Wisconsin Department of Safety and Professional Services
Division of Policy Development
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Tony Evers, Governor
Dan Hereth, Secretary

VIRTUAL/TELECONFERENCE
CONTROLLED SUBSTANCES BOARD
Virtual, 4822 Madison Yards Way, Madison
Contact: Adam Barr (608) 266-2112
September 9, 2022

The following agenda describes the issues that the Board plans to consider at the meeting. At the time of the meeting, items may be removed from the agenda. Please consult the meeting minutes for a description of the actions and deliberations of the Board.

AGENDA

9:30 A.M.
OR IMMEDIATELY FOLLOWING THE REFERRAL CRITERIA WORK GROUP MEETING

OPEN SESSION – CALL TO ORDER – ROLL CALL

A. Adoption of Agenda (1-3)

B. Approval of Minutes July 15, 2022 (4-6)

C. Reminders: Conflicts of Interests, Scheduling Concerns

D. Introductions, Announcements and Recognition

E. Administrative Matters – Discussion and Consideration
1) Department, Staff, and Board Updates
2) Board Members – Term Expiration Dates
   a. Alton, Troy
   b. Barman, Subhadeep – 5/1/2019
   c. Bellay, Yvonne
   d. Bloom, Alan – 5/1/2020
   e. Englebert, Doug
   f. Ferguson, Kris
   g. Koresch, Sandy
   h. Weinman, Robert
   i. Weitekamp, John
3) Alternate Members
   a. Herbert Kaske
   b. Rosalyn McFarland
   c. Michael Parish
   d. Emily Zentz

F. Legislature Agenda Request: Status of Kratom – Discussion and Consideration (7-210)

G. Administrative Rule Matters – Discussion and Consideration (211)

1) Final Rule Draft and Legislative Report
    a. CSB 2.91, Relating to Scheduling 4,4'-Dimethylaminorex **(212-221)**
2) Scope Statements
    a. CSB 2.92, Relating to Scheduling 38 Anabolic Steroids **(222-224)**
    b. CSB 2.93, Relating to Scheduling Daridorexant **(225-226)**
    c. CSB 2.94, Relating to Scheduling 7 Synthetic Benzimidazole-Opioids **(227-229)**
    d. CSB 2.95, Relating to Scheduling Ganaxolone **(230-231)**
    e. CSB 4, Relating to National Provider Identifier Requirement **(232-233)**
3) Pending and Possible Rulemaking Projects **(234-235)**

H. Planning for the 2022 Annual Law Enforcement Hearing – Discussion and Consideration

I. Prescription Drug Monitoring Program (PDMP) Updates – Discussion and Consideration (236)
1) WI ePDMP Operations
    a. Recent and Upcoming Releases **(237-239)**
    b. Status of Grant Projects:
        1. FY 2020 Harold Rogers Prescription Drug Monitoring Program
        2. FY 2021 Harold Rogers Prescription Drug Monitoring Program
    c. Interstate Data Sharing **(240-241)**
    d. EHR Integration Status
2) WI ePDMP Outreach **(242)**

J. Board Member Reports – Discussion and Consideration
1) Medical Examining Board
2) Dentistry Examining Board
3) Board of Nursing
4) Pharmacy Examining Board

K. Liaison Reports

L. Report from the Referral Criteria Work Group – Discussion and Consideration

M. COVID-19 – Discussion and Consideration

N. Deliberation on Special Use Authorizations – Discussion and Consideration

O. Discussion and Consideration of Items Received After Preparation of the Agenda
1) Introductions, Announcements, and Recognition
2) Administrative Matters
3) Election of Officers
4) Appointment of Liaisons and Alternates
5) Delegation of Authorities
6) Informational Items
7) Division of Legal Services and Compliance (DLSC) Matters
8) Education and Examination Matters
9) Credentialing Matters
10) Practice Matters
11) Legislative and Administrative Rule Matters

12) Liaison Reports
13) Appearances from Requests Received or Renewed
14) Speaking Engagements, Travel, or Public Relations Requests, and Reports
15) Consulting with Legal Counsel

P. Public Comments

CONVENE TO CLOSED SESSION to deliberate on cases following hearing (s. 19.85(1)(a), Stats.); to consider licensure or certification of individuals (s. 19.85(1)(b), Stats.); to consider individual histories or disciplinary data (s. 19.85(1)(f), Stats.); and to confer with legal counsel (s. 19.85(1)(g), Stats.).

Q. Deliberation on Special Use Authorizations – Discussion and Consideration

R. Consulting with Legal Counsel

RECONVENE TO OPEN SESSION IMMEDIATELY FOLLOWING CLOSED SESSION

S. Vote on Items Considered or Deliberated Upon in Closed Session if Voting is Appropriate

T. Open Session Items Noticed Above Not Completed in the Initial Open Session

ADJOURNMENT

NEXT MEETING: NOVEMBER 11, 2022

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MEETINGS AND HEARINGS ARE OPEN TO THE PUBLIC, AND MAY BE CANCELLED WITHOUT NOTICE.

Times listed for meeting items are approximate and depend on the length of discussion and voting. All meetings are held virtually unless otherwise indicated. In-person meetings are typically conducted at 4822 Madison Yards Way, Madison, Wisconsin, unless an alternative location is listed on the meeting notice. In order to confirm a meeting or to request a complete copy of the board's agenda, please visit the Department website at https:\\dsps.wi.gov. The board may also consider materials or items filed after the transmission of this notice. Times listed for the commencement of disciplinary hearings may be changed by the examiner for the convenience of the parties. Requests for interpreters for the hard of hearing, or other accommodations, are considered upon request by contacting the Affirmative Action Officer at 608-266-2112, or the Meeting Staff at 608-266-5439.

VIRTUAL/TELECONFERENCE
CONTROLLED SUBSTANCES BOARD
MEETING MINUTES
JULY 15, 2022

PRESENT: Subhadeep Barman, Yvonne Bellay, Doug Englebert, Herbert Kaske, Sandy Koresch, Robert Weinman *(arrived at 9:52 a.m.)*, John Weitekamp

EXCUSED: Troy Alton, Alan Bloom, Kris Ferguson,

STAFF: Adam Barr, Executive Director; Jameson Whitney, Legal Counsel; Nilajah Hardin, Administrative Rules Coordinator; Katlin Schwartz, Bureau Assistant; and other DSPS Staff

Herbert Kaske served as the Dentistry Examining Board Representative at this meeting.

CALL TO ORDER

Doug Englebert, Chairperson, called the meeting to order at 9:31 a.m. A quorum was confirmed with six (6) members present.

ADOPTION OF AGENDA

MOTION: Subhadeep Barman moved, seconded by Yvonne Bellay, to adopt the Agenda as published. Motion carried unanimously.

APPROVAL OF MINUTES OF MAY 13, 2022

MOTION: Subhadeep Barman moved, seconded by Sandy Koresch, to adopt the Minutes of May 13, 2022 as published. Motion carried unanimously.

LEGISLATURE AGENDA REQUEST: STATUS OF KRATOM

MOTION: Subhadeep Barman moved, seconded by John Weitekamp, pursuant to the request of the Wisconsin state legislature, to conduct a review of the current information regarding kratom in its natural form, and to provide a recommendation to the legislature based on the eight-factor analysis outlined in Wis. Stat. §961.11 regarding whether kratom in its natural form should continue to be scheduled as a controlled substance in the State of Wisconsin. Board members shall conduct their review, engaging their respective boards, and return their analysis to the CSB by the CSB's January 2023 meeting. Motion carried unanimously.

ADMINISTRATIVE RULE MATTERS

Adoption Order

CSB 2.80, Relating to Scheduling Oliceridine

MOTION: Subhadeep Barman moved, seconded by John Weitekamp, to approve the Adoption Order for Clearinghouse Rule 21-098 (CSB 2.80), relating to Scheduling Oliceridine. Motion carried unanimously.

(Robert Weinman arrived at 9:52 a.m.)

Final Rule Draft and Legislative Report

MOTION: Subhadeep Barman moved, seconded by Sandy Koresch, to approve the Legislative Report and Draft for the following rules:

- Clearinghouse Rule 22-032 (CSB 2.82), relating to Scheduling Serdexmethlypehnidate,
- Clearinghouse Rule 22-033 (CSB 2.83), relating to Scheduling 10 Fentanyl Related Substances,
- Clearinghouse Rule 22-034 (CSB 2.84), relating to Scheduling Alfaxalone,
- Clearinghouse Rule 22-035 (CSB 2.85), relating to Excluding 6-Beta-Naltrexol,
- Clearinghouse Rule 22-036 (CSB 2.86), relating to Scheduling Fospropofol,
- Clearinghouse Rule 22-037 (CSB 2.87), relating to Scheduling Embutramide,
- Clearinghouse Rule 22-039 (CSB 2.88), relating to Scheduling Lacosamide,
- Clearinghouse Rule 22-038 (CSB 2.89), relating to Scheduling Perampanel,
- Clearinghouse Rule 22-040 (CSB 2.90), relating to Transferring 1-phenylcyclohexylamine and 1- piperidinocyclohexanecarbonitrile, immediate precursors to phencyclidine, also known as PCP,

for submission to the Governor's Office and Legislature. Motion carried unanimously.

Affirmative Action Order

MOTION: Subhadeep Barman moved, seconded by Sandy Koresch, to schedule the following drugs by affirmative action:

- CSB 2.92, Relating to Scheduling 38 Anabolic Steroids
- CSB 2.93, Relating to Scheduling Daridorexant
- CSB 2.94, Relating to Scheduling 7 Synthetic Benzimidazole-Opioids
- CSB 2.95, Relating to Scheduling Ganaxolone

These orders shall take effect on the date they are published in the Administrative Register. Motion carried unanimously.

Possible Scope Statement: CSB 4, National Provider Identifier (NPI) Requirement

MOTION: Subhadeep Barman moved, seconded by Yvonne Bellay, to request DSPS staff draft a Scope Statement revising CSB 4, relating to National Provider Identifier requirement. Motion carried unanimously.

REPORT FROM THE REFERRAL CRITERIA WORK GROUP

MOTION: John Weitekamp moved, seconded by Subhadeep Barman, to accept the recommendations of the Referral Criteria Work Group and refer the specified providers to the appropriate examining boards for further proceedings. Motion carried unanimously.

ADJOURNMENT

MOTION: Subhadeep Barman moved, seconded by Robert Weinman, to adjourn the meeting. Motion carried unanimously.

The meeting adjourned at 10:33 a.m.

State of Wisconsin
Department of Safety & Professional Services

AGENDA REQUEST FORM

1) Name and title of person submitting the request:	2) Date when request submitted:
Adam Barr, Executive Director	9/2/2022
	Items will be considered late if submitted after 12:00 p.m. on the deadline date which is 8 business days before the meeting

3) Name of Board, Committee, Council, Sections:

Controlled Substances Board

4) Meeting Date:	5) Attachments:	6) How should the item be titled on the agenda page?
9/9/2022	☒ Yes ☐ No	Legislature Agenda Request: Status of Kratom – Discussion and Consideration

7) Place Item in:	8) Is an appearance before the Board being scheduled? *(If yes, please complete Appearance Request for Non-DSPS Staff)*	9) Name of Case Advisor(s), if applicable:
☒ Open Session ☐ Closed Session	☐ Yes ☒ No	

10) Describe the issue and action that should be addressed:

Members of the legislature have requested that the Controlled Substances Board conduct an impartial review of existing research and provide the legislature with guidance or act unilaterally if appropriate. Specifically, the board was asked to determine whether kratom in its natural form should continue to be scheduled in Wisconsin. The board passed the following motion at the July 15, 2022 meeting. As noted below, additional materials have been received since that meeting.

MOTION: Subhadeep Barman moved, seconded by John Weitekamp, pursuant to the request of the Wisconsin state legislature, to conduct a review of the current information regarding kratom in its natural form, and to provide a recommendation to the legislature based on the eight-factor analysis outlined in Wis. Stat. §961.11 regarding whether kratom in its natural form should continue to be scheduled as a controlled substance in the State of Wisconsin. Board members shall conduct their review, engaging their respective boards, and return their analysis to the CSB by the CSB's January 2023 meeting. Motion carried unanimously.

Attachments:
First Request from Wisconsin Legislators: Pages 1-2
Second Request from Wisconsin Legislators: Pages 3-6
HHS Letter Rescinding Recommendation to Schedule Kratom: Pages 7-10
HHS Letter to Representative Pocan: Pages 11-12
Request from Representative Pocan: Pages 13-15
Legislators Letter to AMA Opposing a Ban on Kratom: Pages 16-28
AMA Response to Legislators Regarding Withdrawn Proposal: Page 29
2021 Wisconsin Assembly Bill 599 Hearing Testimony: Pages 30-58
Research Article on the Abuse Potential of Kratom (Submitted by American Kratom Association): Pages 59-128
NEW – Submissions from the Department of Health Services: Pages 129-199
NEW – Letter from Jack E. Henningfield, PhD: Pages 200-202

11) Authorization

Adam Barr — 9/2/2022

Signature of person making this request — Date

Supervisor (Only required for post agenda deadline items) — Date

Executive Director signature (Indicates approval for post agenda deadline items) — Date

State of Wisconsin
Department of Safety & Professional Services

Directions for including supporting documents:

1. **This form should be saved with any other documents submitted to the Agenda Items folders.**
2. **Post Agenda Deadline items must be authorized by a Supervisor and the Policy Development Executive Director.**
3. **If necessary, provide original documents needing Board Chairperson signature to the Bureau Assistant prior to the start of a meeting.**

WISCONSIN LEGISLATURE
P.O. BOX 8952 • MADISON, WI 53708

April 28, 2022

Wisconsin Controlled Substances Board
DSPS
PO Box 8366
Madison, WI 53708-8366

Dear Chairperson Engelbart and Members:

The kratom tree is a member of the coffee family and native to Southeast Asia. The kratom leaf in its pure, natural form has been used for centuries for pain relief, alertness, and general well-being in that part of the world. More recently, it has been used as a natural alternative to prescription drugs used for pain relief and anxiety and has been shown to be especially helpful to individuals who experience adverse reactions to prescription medications. The crisis in drug overdoses in the United States has stimulated research into the uses of kratom and other alternative pain management options. This research has shown kratom to have lower addiction and abuse profiles, while showing promising results for users. Unfortunately, nearly a decade ago, kratom was made illegal to possess or use in Wisconsin due to a provision that was included in a bill intended to address the synthetic drug problem. We believe this was done without adequate research and understanding of kratom in its natural form. Therefore, we ask the Board to review the research and provide guidance as to whether natural kratom merits scheduling.

For background, 2013 Wisconsin Act 351 changed the concept of scheduling an analog of a synthetic drug and replaced it with an actual description of the chemical structure of prohibited substances. Two chemical structures included in the long list were mitragynine (MG) and 7-hydroxymitragynine (7H-MG). MG and 7H-MG are alkaloids that are found naturally in the kratom leaf and have acceptable safety profiles in that form. Unfortunately, the change in law made ***any substance*** with MG or 7H-MG in it illegal, and as a result made natural kratom illegal also. We do not believe it was the intent of the Legislature to ban natural kratom; rather the inclusion of these particular alkaloids was intended to address concerns related to synthesized and adulterated products ***marketed*** as kratom. We agree that substances that are synthesized or adulterated with MG or 7H-MG are dangerous and should be scheduled. Kratom, however, in its natural form should not be treated in the same manner.

Since 2013, there has been significant research and discussion on natural kratom and the scientific basis for the decision to schedule kratom here and in the few states where it was indirectly banned, as well as at the federal level. Hundreds of peer-reviewed studies have now been conducted by researchers worldwide, including research sponsored by the National Institute on Drug Abuse (NIDA). These studies confirm that natural kratom is not like opioids in its safety and addiction profile and is actually a harm reduction tool that can enhance public health.

In 2015 and 2018, the Controlled Substances Board had discussions in open session regarding the issue of kratom's scheduling in Wisconsin, but no further action was taken. In August 2018, the US Department of Health and Human Services (HHS) rescinded its recommendation that FDA and DEA begin the process of scheduling MG and 7H-MG, due to insufficient evidence as well as emerging research

suggesting that ***scheduling*** kratom could actually create ***"an unknown and potentially substantial risk to public health"***[1] because it would no longer be available to the millions of Americans that use it**.** Most recently, 2021 Assembly Bill 599 and Senate Bill 958 were introduced in the Wisconsin Legislature which would legalize and regulate the use and sale of natural kratom while keeping synthesized and adulterated kratom products scheduled. AB 599 was given a public hearing and was approved by the standing committee with a bipartisan 9-2 vote.

As a result of the recent evidence, research, and public interest regarding kratom that has been made public since the enactment of 2013 Act 351, we believe it is appropriate for the Board to conduct its own impartial review of existing research and provide the legislature with guidance or act unilaterally if appropriate. We ask the following:

1) That the CSB use its authority under Wis. Stats. Ch. 961.11 to make a determination using the criteria provided in Wis. Stats. Ch. 961(1m) and (1r) as to whether or not kratom in its natural form should be scheduled in Wisconsin; and
2) If natural kratom does not meet the criteria under Wis. Stats. Ch. 961(1m), that the CSB promulgate a rule that would differentiate MG and 7H-MG found in natural kratom from MG and/or 7H-MG contained in other substances so that natural kratom would not violate Wis. Stats. Ch. 961.17(7)(mk) and (ml) of the Wisconsin Controlled Substances Act.

Thank you for your consideration of these requests. We request that the Board please let us know how it intends to proceed.

Sincerely,

Rep. Dave Murphy
56th Assembly District

Sen. Mary Felzkowski
12th Senate District

Speaker Robin Vos
63rd Assembly District

Sen. Jon Erpenbach
27th Senate District

Rep. Rob Brooks
60th Assembly District

Rep. Jonathan Brostoff
19th Assembly District

Rep. Dora Drake
11th Assembly District

Rep. Dan Knodl
24th Assembly District

Rep. John Macco
88th Assembly District

Rep. Michael Schraa
53rd Assembly District

Rep. Christine Sinicki
20th Assembly District

[1] https://www.kratomscience.com/wp-content/uploads/2021/01/dhillon-8.16.2018-response-letter-from-ash-radm-giroir4.pdf

June 24, 2022

Wisconsin Controlled Substances Board
Department of Safety and Professional Services
P.O. Box 8366
Madison, WI 53708-8366

Dear Chairperson Englebert and Honored Board Members,

We write to address the response from the Controlled Substances Board (CSB) to our request that a review be conducted on whether the alkaloid constituents of the kratom plant meet the statutory criteria for scheduling under 961.11 (1m) (a-h). As you are aware, 2013 SB 325, signed by the Governor on April 23, 2014, added kratom's alkaloids, mitragynine (MG) and 7-hydroxymitragynine (7-HMG), to Schedule I. As we clearly stated in our April 28, 2022 letter to the CSB, we believe the characterization in 2013 SB 325 to name chemical structures inappropriately included the natural alkaloids of the kratom plant. The inclusion of kratom's alkaloids in this legislation, however poorly framed, was an action prompted by the various pronouncements by the U.S. Food and Drug Administration (FDA) that federal scheduling of these alkaloids was imminent. The CSB recognized this in its March 15, 2016 Motion that the evidence did not exist to change the schedule for kratom at that time. In the intervening eight years, no such scheduling action has been taken at the federal level and much more research has been conducted. More importantly, based on our review of publicly available documents on kratom, the U.S. Secretary of Health and Human Services (HHS) has determined there is insufficient evidence to propose any federal scheduling of kratom.

The request we made of the CSB was clear—we requested that the Board "conduct its own impartial review of existing research and **provide the legislature with guidance** or **act unilaterally if appropriate**." Instead, the CSB chose to ignore our request to conduct a scientific review of the new research and approved a motion that stated, "the Legislature has scheduled…(kratom alkaloids)…and any change in scheduling should occur at the Legislative level." We consider this response inadequate as this vote did not address the question of the CSB conducting a scientific review.

Additionally, as we reviewed the record, it was perplexing to see that there was discussion by some members of the CSB about the various positions of the medical community and law enforcement entities that were already clearly presented to the legislature in committee hearings and have no basis in the scientific research that is now available. The political views of members of the CSB representing policy positions of groups with whom they are affiliated or purported to speak for raise troubling conflicts, and the proper forum for advocating for such policy positions is before the legislature, not at the CSB. We hope that moving forward, the Board will consider the request not based on policy considerations, but instead on a review of the science that the CSB is **statutorily obligated** to consider in its decision-making.

To clarify our initial request: our question is whether the scientific evidence currently available in 2022 supports the scheduling of kratom under the eight factors set forth in our statutes. We made the request that the CSB review the existing evidence and science to determine if natural kratom meets the criteria to be scheduled under Wisconsin law. The CSB is the only entity in Wisconsin State Government that has the diverse expertise and the statutory responsibility to review scientific data in an impartial manner and provide policymakers with the guidance they need to make good decisions about scheduling substances.

Two separate reviews on this issue at the federal level determined there was insufficient evidence to support the scheduling of kratom. The Wisconsin statute mirrors the same criteria the federal government reviewed, hence our interest in having the CSB re-visit the actions taken by our state in 2014. Additionally, we take note of the fact that the Expert Committee on Drug Dependence (ECDD), at the request of the UN Commission on Narcotic Drugs, conducted an extensive review of all the current science on kratom to determine if kratom should be scheduled internationally. On December 1, 2021, the ECDD voted 11-1 that there was insufficient evidence to recommend scheduling kratom. As members of the health care community, you all know better than we do that science in medicine evolves, and as we gather more evidence and data, it is proper for the state to re-visit old decisions in light of new information.

We restate our specific request that CSB conduct a scientific review and:

1) the CSB provide guidance on whether kratom's alkaloids meet the specific criteria provided in Wis. Stats. Ch. 961 (1m) and (1r) as to whether kratom in its natural form should be scheduled in Wisconsin. We ask that the assessment be made on the science, not the policy views of individual CSB members or organizations they represent; or
2) if the CSB determines natural kratom does not meet the criteria under Wis. Stats. Ch. 961(1m), the CSB promulgate a rule that differentiates natural MG and 7-HMG from any kratom products containing synthesized or chemically altered alkaloids so that natural kratom would not violate Wis. Stats. Ch. 961.17(7)(mk) and (ml) of the Wisconsin Controlled Substances Act.

We once again present our request that the CSB review this same data in an unbiased manner and provide us with your assessment as to whether natural kratom meets the 8-factors necessary for a substance to be scheduled under Wisconsin state law.

We have included several documents that address the scientific reviews conducted at the federal and international levels:

1) *Pinney Associates 8 Factor Analysis of Abuse Potential of Kratom* (The initial analysis was provided to FDA in 2018 prior to their decision to rescind the recommendation to schedule kratom. It has since been updated in August 2021 to include over 100 new peer reviewed published studies).

2) *Department of Health and Human Services Letter to Drug Enforcement Agency 2018* (Rescinding the recommendation to schedule)
3) *HHS Letter to Pocan/Lee* (Describes emerging science and confirms no intent to schedule)

The Controlled Substances Board was created to advise the Legislature, and we are here, asking you, as the experts, for your advice. We hope this second letter clarifies our request to the Board. Please let us know, at your earliest convenience, in writing, how you intend to proceed and feel free to reach out to our Legislative offices with any questions.

Sincerely,

Senator Mary Felzkowski
12th Senate District

Representative Dave Murphy
56th Assembly District

Speaker Robin Vos
63rd Assembly District

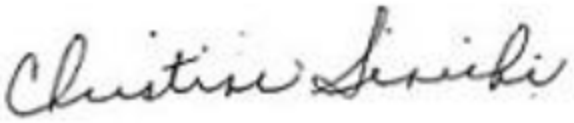
Representative Brostoff
19th Assembly District

Representative John Macco
88th Assembly District

Representative Dora Drake
11th Assembly District

Representative Dan Knodl
24th Assembly District

Representative Rob Brooks
60th Assembly District



Representative Christine Sinicki
20th Assembly District

AUG 16 2018

The Honorable Uttam Dhillon
Acting Administrator
Drug Enforcement Administration
U.S. Department of Justice
8701 Morrissette Drive
Springfield, VA 22152

Dear Mr. Dhillon:

Pursuant to the Controlled Substances Act (CSA), 21 U.S.C. § 811, I am rescinding our prior recommendation dated October 17, 2017, that the substances mitragynine and 7-hydroxymitragynine be permanently controlled in Schedule I of the CSA. HHS is instead recommending that mitragynine and 7-hydroxymitragynine not be controlled at this time, either temporarily or permanently, until scientific research can sufficiently support such an action. Mitragynine and 7-OH-mitragynine are two of the constituents of the plant *Mitragyna speciosa* (*M. speciosa*), commonly referred to as *kratom*. 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. Further research, which I am proposing be undertaken, should provide additional data to better inform any subsequent scheduling decision.

Procedural History

On August 31, 2016, the Drug Enforcement Administration (DEA) issued a Notice of Intent to temporarily schedule the chemicals mitragynine and 7-hydroxymitragynine into Schedule I pursuant to the temporary scheduling provisions of the CSA, 21 U.S.C. § 811(h). *See,* 81 Fed. Reg. 59,929 (Aug. 31, 2016). In response to the Notice of Intent, the DEA received numerous comments from the public on mitragynine and 7-hydroxymitragynine, including comments offering their opinions regarding the pharmacological effects of these substances. To allow consideration of these comments, as well as others received on or before December 1, 2016, the DEA issued a Withdrawal of Notice of Intent and Solicitation of Comments on October 31, 2016.

On October 17, 2017, the then-Acting Assistant Secretary for Health of HHS wrote to then-Acting Administrator of the DEA to indicate that HHS was recommending that the substances mitragynine and 7-OH-mitragynine be permanently controlled in Schedule I of the Controlled

Substances Act. Recently, I became aware of DEA's intent to schedule mitragynine and 7-OH-mitragynine - into Schedule I.

Analysis

The Controlled Substances Act ("CSA") provides in pertinent part that the Attorney General may by rule add to Schedule I any drug or other substance if the Attorney General makes the findings prescribed by subsection (b) of section 812 of the CSA for Schedule I. *See,* 21 U.S.C. § 811(a). Such findings are:

1. The drug or other substance has a high potential for abuse.
2. The drug or other substance has no currently accepted medical use in treatment in the United States.
3. There is a lack of accepted safety or use of the drug or other substance under medical supervision.

The CSA requires that "[i]n making any finding under subsection (a) of this section or under subsection (b) of section 812 of this title, the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules:

(1) Its actual or relative potential for abuse.
(2) Scientific evidence of its pharmacological effect, if known.
(3) The state of current scientific knowledge regarding the drug or other substance.
(4) Its history and current pattern of abuse.
(5) The scope, duration, and significance of abuse.
(6) What, if any, risk there is to the public health.
(7) Its psychic or physiological dependence liability.
(8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter."

21 U.S.C. § 811(c).

Before scheduling a substance, though, the Attorney General must "request from the Secretary (of HHS) a scientific and medical evaluation, and his recommendation, as to whether such drug or other substance should be so controlled or removed as a controlled substance." *Id.* at § 811(b). The Secretary's evaluation should be based on factors (2), (3), (6), (7), and (8), noted above, and the scientific and medical considerations involved in factors (1), (4), and (5). Moreover, the "recommendation of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance." *Id.*

The Secretary has delegated to the Assistant Secretary for Health, in consultation with the National Institute on Drug Abuse and the Food and Drug Administration, the responsibility to make a recommendation under the CSA to the Attorney General. On October 17, 2017, my

predecessor, the Acting Assistant Secretary for Health, forwarded to you his recommendation that mitragynine and 7-hydroxymitragynine be permanently controlled in Schedule I of the CSA. The recommendation included a scientific and medical evaluation prepared by the FDA of the eight factors determinative of control under the CSA. The FDA evaluation also recommended in favor of the three findings that are required for DEA to place a substance in Schedule I.

I have reviewed the Acting Assistant Secretary's earlier recommendation as well as previous and new scientific data. In light of this review, combined with concerns for unintended public health consequences, I now conclude that while mitragynine and 7-hydroxymitragynine have many properties of an opioid, scheduling these chemicals at this time in light of the underdeveloped state of the science would be premature. For example, one recently published peer reviewed animal study indicated that mitragynine does not have abuse potential and actually reduced morphine intake. As such, these new data suggest that mitragynine does not satisfy the first of the three statutory requisites for Schedule I, irrespective of broader considerations of public health. While a single study is rarely dispositive, it strongly suggests that further evaluation is warranted.

Although there remains cause for concern for 7-hydroxymitragynine and potentially mitragynine, the level of scientific data and analysis presented by the FDA and available in the literature do not meet the criteria for inclusion of *kratom* or its chemical components in Schedule I of the CSA at this time. There is still debate among reputable scientists over whether *kratom* by itself is associated with fatal overdoses. Further analysis and public input regarding *kratom* and its chemical components are needed before any scheduling should be undertaken. It is important that we have additional information to justify scheduling, such as:[1]

- A scientific assessment of how many Americans utilize *kratom*, and an understanding of the geographic and demographic distribution of these users (Factors 4, 5);
- A scientific assessment of the actual scale and degree of dependence and/or addiction of Americans utilizing *kratom* (Factors 1, 5, 7);
- A scientific determination based on data whether *kratom* actually serves as a gateway drug that promotes further use of more dangerous opioids (Factors 1, 4, 5);
- A valid prediction of how many *kratom* users will suffer adverse consequences if *kratom* is no longer available, including:
    - Intractable pain, psychological distress, risk for suicide;
    - Transition to proven deadly opioids such as prescription opioids, heroin, or fentanyl; and
    - Transition to other potent or harmful drugs (Factor 6);
- A scientifically valid assessment of causality in the current few deaths in which *kratom* was co-utilized with known lethal drugs such as fentanyl (Factors 1, 2, 3, 5 & 6).

Furthermore, there is a significant risk of immediate adverse public health consequences for potentially millions of users if *kratom* or its components are included in Schedule I, such as:

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[1] I am also concerned about the impact of scheduling *kratom* on our ability to conduct research, especially survey research and our currently inability to routinely test for *kratom* in those brought into an emergency room as a result of a possible overdose.

- Suffering with intractable pain;
- *Kratom* users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with IV drug use;
- Inhibition of patients discussing *kratom* use with their primary care physicians leading to more harm, and enhancement of stigma thereby decreasing desire for treatment, because of individual users now being guilty of a crime by virtue of their possession or use of *kratom*
- The stifling effect of classification in Schedule I on critical research needed on the complex and potentially useful chemistry of components of *kratom*.

Therefore, I conclude at the current time, available evidence does not support mitragynine and 7-hydroxymitragynine being controlled in Schedule I of the Controlled Substances Act. This assessment supersedes the previous recommendation letter from Acting Assistant Secretary Wright dated October 17, 2017. In the meantime, it is recognized that *kratom* may potentially have harmful effects, especially in specific circumstances and/or when used with potent prescription or illicit drugs.

Finally, it is entirely possible that new data and evidence could support scheduling of chemicals in *kratom* at some future time. *Kratom* may have harmful effects, particularly when used with other drugs. As such, I encourage continued enforcement by the FDA against unproven claims by *kratom* manufacturers. I also support enhanced public awareness that *kratom* contains molecules that may potentially be dangerous. I also plan to work expeditiously with colleagues throughout the U.S. government to seek transparent public and scientific input, and to collect data on the critical public health considerations outlined above.

Should you have any questions regarding this recommendation, please contact my office at (202) 690-7694.

Sincerely yours,

Brett P. Giroir, M.D.
ADM, U.S. Public Health Service
Assistant Secretary for Health
Senior Advisor for Opioid Policy

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

March 16, 2022

The Honorable Michael S. Lee
United States Senate
Washington, DC 20510

The Honorable Mark Pocan
U.S. House of Representatives
Washington, DC 20515

Dear Senator Lee and Representative Pocan:

Thank you for your letter about the substance *Mitragyna speciosa*, commonly known as kratom. As your letter notes, efforts to schedule kratom within the United States have not moved forward, and the World Health Organization (WHO) Expert Committee on Drug Dependence concluded that there was insufficient evidence to recommend a critical review of kratom. This means that WHO will take no further action to control kratom under the 1961 or 1971 Conventions at this time.

Your letter also noted that there is emerging science suggesting kratom may have therapeutic health benefits. The Department of Health and Human Services (HHS) is also aware of the emerging research and recent reports indicating that many individuals may be using kratom to self-treat serious health conditions, including, but not limited to, self-medication for managing pain, mental illness, and a substance use disorder. Additionally, there are reports that kratom is used for recreational purposes. Based on the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health, it is estimated that over 2 million Americans 12 years and older used kratom in 2020. However, the prevalence of kratom use is difficult to estimate, and the reason for this prevalence remains unclear.

To that end, HHS and its component agencies are working to address knowledge gaps through research. Both the National Institutes of Health and the Food and Drug Administration (FDA) are supporting studies on the pharmacology of kratom's constituents, their toxicity and addictive liability, as well as their potential therapeutic benefits for pain and substance use disorder. While there are no FDA-approved uses for kratom, the Agency has a proven drug review process involving the evaluation of scientific research and data from rigorous controlled clinical trials to assess the risks and benefits of drugs. This includes a well-developed process for evaluating therapeutic uses of botanical drug products. FDA has also issued guidance on the proper

development of botanical drug products[1] and has a team of medical reviewers who can provide scientific expertise on botanical issues for researchers developing drugs made from plants.

To your final point regarding kratom safety and consumer protections, I agree with your concerns. Indeed, FDA continues to receive concerning reports describing safety concerns associated with kratom, including death. Many kratom-involved overdose deaths have occurred after use of adulterated kratom products or taking kratom with other substances.

While options for scheduling have been discussed, we believe that additional data and information are needed to understand the public health impact of kratom in terms of therapeutic benefits as well as safety risk. Discussions continue within HHS on mitigating actions to best address the various public health concerns presented, including potential unintended consequences that may arise from transitioning to riskier alternatives (for example fentanyl) if kratom were to be scheduled.

Thank you again for contacting me regarding this matter. Should you have further questions, please have your staff contact the Office of the Assistant Secretary for Legislation at (202) 690-7627

Sincerely,

Xavier Becerra

Cc:

Hon. Linda Thomas-Greenfield, United States Ambassador to the United Nations

[1] https://www.fda.gov/files/drugs/published/Botanical-Drug-Development--Guidance-for-Industry.pdf

MARK POCAN
2ND DISTRICT, WISCONSIN
COMMITTEE ON APPROPRIATIONS
COMMITTEE ON EDUCATION & LABOR
JOINT ECONOMIC COMMITTEE
SENIOR WHIP

UNITED STATES
HOUSE OF REPRESENTATIVES

10 EAST DOTY STREET, SUITE 405
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(608) 258-9800

1727 LONGWORTH HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-2906

POCAN.HOUSE.GOV

May 10, 2022

Wisconsin Controlled Substances Board
Department of Safety and Professional Services
PO Box 8366
Madison, WI 53708

Dear Chairperson Engelbart and Members:

As a long-time supporter of legalizing the manufacture, distribution, delivery, and possession of kratom, I write to request your review of research pertaining to kratom and guidance as to whether or not it merits scheduling.

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

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

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

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

Similar to this strong support for kratom from Members of the U.S. House of Representatives and the U.S. Senate – across party lines – the Fiscal Year 2022 Labor, Health and Human Services, Education, and Related Agencies Subcommittee appropriation legislation in the House of Representatives contained the following[3]:

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

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

While testifying before the Appropriations Committee in the U.S. House of Representatives on May 25, 2021, Dr. Nora Volkow, the Director of NIDA, stated: "Kratom, most notably mitragynine, has many interesting properties that could be of value potentially as a medication for pain. Also, interestingly, they could hold value as treatment for addiction […] it is so important to actually do research on this substance."[4] HHS Secretary Becerra went one step further in a letter responding to Senator Lee and me in which he stated: "Discussions continue within HHS on mitigating actions to best address the various public health concerns presented, including potential unintended consequences that may arise from transitioning to riskier alternatives (for example fentanyl) if kratom were to be scheduled."[5]

Clearly, Wisconsin is out of sync with the nation when it comes to kratom, and the results can be devasting. You, however, can contribute to addressing this disparity, and publish guidance that will place Wisconsin one step closer to joining the 44 states that do not restrict kratom in the way

[3] https://www.congress.gov/117/crpt/hrpt96/CRPT-117hrpt96.pdf
[4] https://appropriations.house.gov/events/hearings/fy-2022-budget-request-for-the-national-institutes-of-health
[5] https://www.politico.com/newsletters/prescription-pulse/2022/04/12/fda-combatting-field-mice-at-white-oak-campus-00024563

our state currently does. I hope you will look favorably upon this request.

Sincerely,

Mark Pocan
Member of Congress

June 10, 2022

Gerald E. Harmon, MD
President, American Medical Association (AMA)
AMA Plaza
330 N. Wabash Ave., Suite 39300
Chicago, IL 60611-5885

SENT VIA EMAIL TO: Gerald.Harmon@ama-assn.org

Dr. Harmon:

The undersigned members of state legislatures from 6 states (26 states where legislators supported kratom consumer protections) write to register our strong objection to the consideration of Resolution "Late 1001 (A-22)" submitted by the Mississippi Medical Association at the upcoming AMA House of Delegates meeting in Chicago on June 10-15 entitled: "Banning the Sale of Kratom and Other Related Addictive Substances."

Collectively we represent the eight state legislatures who have passed appropriate regulatory requirements for the sale of kratom products to protect consumers, 18 states that are currently actively considering the Kratom Consumer Protection Act (KCPA). We deem the content of the referenced resolution to present distorted, inaccurate, and in many cases absolutely false information about the current body of science on kratom and its current regulatory status both at the federal and state level.

At the outset, what the proposed Resolution fails to disclose is that the FDA has failed in two separate scheduling recommendations to present evidence that conforms to the requirements for such scheduling under the 8 factors required by the federal Controlled Substances Act (CSA). In the first instance, on October 13, 2016, the Drug Enforcement Administration formally withdrew the Notice of Scheduling submitted by the FDA with the following explanation:

> "In response to the notice of intent, DEA received numerous comments from the public on mitragynine and 7-hydroxymitragynine, including comments offering their opinions regarding the pharmacological effects of these substances. To allow consideration of these comments, as well as others received on or before December 1, 2016, DEA has decided to withdraw the August 31, 2016 notice of intent published at 81 FR 59929. DEA has also requested that the FDA expedite its scientific and medical evaluation and scheduling recommendation for these substances, which DEA previously requested in accordance with 21 U.S.C. 811(b)."[1]

[1] https://www.federalregister.gov/documents/2016/10/13/2016-24659/withdrawal-of-notice-of-intent-to-temporarily-place-mitragynine-and-7-hydroxymitragynine-into

The FDA failed to meet the DEA deadline for submission of the 8-Factor Analysis by December 1, 2016, but independent scientists did submit an 8-Factor Analysis and more that 23,000 public comments were received, with more than 99% opposing the scheduling of kratom. The FDA finally did submit its second scheduling proposal for kratom on October 17, 2017, but that recommendation was summarily withdrawn on August 16, 2018,[2] by the HHS Assistant Secretary of Health, Brett Giroir, M.D., who offered numerous objections to the FDA's proposed scheduling of kratom, including:

> "Pursuant to the Controlled Substances Act (CSA), 21 U.S.C. § 811,1 am rescinding our prior recommendation dated October 17, 2017, that the substances mitragynine and 7-hydroxymitragynine be permanently controlled in Schedule I of the CSA. HHS is instead recommending that mitragynine and 7-hydroxymitragynine not be controlled at this time, either temporarily or permanently, until scientific research can sufficiently support such an action. Mitragynine and 7-OH-mitragynine are two of the constituents of the plant Mitragyna speciosa (M. speciosa), commonly referred to as kratom. 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. Further research, which I am proposing be undertaken, should provide additional data to better inform any subsequent scheduling decision."

We strongly recommend that every member of the AMA House of Delegates read Dr. Giroir's letter in full to see how badly the FDA has missed the mark on its evaluation of kratom, and the importance of the context of the potential harm reduction kratom offers in our collective efforts to reduce the number of drug overdoses that we believe the average AMA member shares our views.

The proposed Resolution also excludes reference to the review of kratom by the Expert Committee on Drug Dependence (ECDD) pursuant to a charge from the UN Commission on Narcotic Drugs to do an exhaustive analysis of current science on kratom and whether it should be scheduled internationally. Following that comprehensive review, the 12-member ECDD released its findings on kratom, on an 11-1 vote, on December 1, 2021[3]:

> "The Committee concluded that there is insufficient evidence to recommend a critical review of kratom. With respect to mitragynine and 7-hydroxymitragynine,

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[2] https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/6014 5eab6df59e7e36a7cfc1/1611947693695/dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf

[3] https://cdn.who.int/media/docs/default-source/controlled-substances/44ecdd_unsg_annex1.pdf?sfvrsn=9c380ac2_5

> the Committee, except for one member, also concluded that there is insufficient evidence to recommend a critical review at this time."

We ask you to consider two additional points that we believe directly address the credibility of the proposed Mississippi Resolution as it is currently drafted. First, HHS Secretary Xavier Becerra responded to inquiries from Congressman Mark Pocan (D-WI) and Senator Mike Lee (R-UT) on the status of the position of HHS on kratom, and Secretary Becerra responded in a letter on March 16, 2022[4] as follows:

> "To your final point regarding kratom safety and consumer protections, I agree with your concerns. Indeed, FDA continues to receive concerning reports describing safety concerns associated with kratom, including death. **Many kratom-involved overdose deaths have occurred after use of adulterated kratom products or taking kratom with other substances.** While options for scheduling have been discussed, **we believe that additional data and information are needed to understand the public health impact of kratom in terms of therapeutic benefits as well as safety risk**. Discussions continue within HHS on mitigating actions to best address the various public health concerns presented, **including potential unintended consequences that may arise from transitioning to riskier alternatives (for example fentanyl) if kratom were to be scheduled** [emphasis added]."

Second, we ask that you consider the response by the Director of the National Institutes on Drug Abuse (NIDA), Nora Volkow, M.D., to U.S. Senator Patty Murray's (D-WA) question during the May 17, 2022, Senate Labor HHS Appropriations Subcommittee on what overdose mitigation strategies NIDA and HHS hope to roll out in the next few months:

> **"**. . . There's also interest in the community to test other products that may serve as harm reduction. For example, the use of kratom which is sold as tea and that contains a drug/molecule that has effects that are similar to a dose of buprenorphine but could be utilized also for decreasing withdrawal or depression. So, these are more novel and we don't have sufficient data, but those are things that are being discussed."

If the Mississippi Resolution on scheduling kratom were to be adopted by the AMA House of Delegates, and a subsequent federal Schedule I classification of kratom were adopted, it would

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[4] https://www.dropbox.com/s/m7c87cu47667ec3/TAB%2014%20HHS%20Becerra%20Letter%20Lee%20and%20Pocan.pdf?dl=0

literally halt all research on the harm reduction potential of kratom. Such an action would directly contradict your own statement on the overdose epidemic[5]:

> "To make meaningful progress towards ending this epidemic, a broad-based public health approach is required. This approach must balance patients' needs for comprehensive pain management services, including access to non-opioid pain care as well as opioid analgesics when clinically appropriate, with efforts to promote appropriate prescribing, reduce diversion and misuse, promote an understanding that substance use disorders are chronic conditions that respond well to evidence-based treatment, and expand access to treatment for individuals with substance use disorders."

The potential value of kratom as a harm reduction tool as referenced by Dr. Girior and Dr. Volkow, and that you recognized as a needed resource, is highlighted in a survey conducted by researchers at Johns Hopkins University that concluded their "findings underscore the need for research and regulation, but not on outright ban on sales [on kratom]."[6] The survey revealed that 87% of adult kratom users who self-treated for opioid dependence reported relief from withdrawal symptoms, and 35% were free from opioids within >1 year.

NIDA-funded research on a kratom tea as a therapeutic option for opioid dependence revealed the following:

> **Results:** Oral administration of LKT resulted in dose-dependent antinociception (≥1 g/kg, p.o.) absent in mice lacking the mu-opioid receptor (MOR) and reduced in mice lacking the kappa-opioid receptor. These doses of LKT did not alter coordinated locomotion or induce conditioned place preference, and only briefly reduced respiration. Repeated administration of LKT did not produce physical dependence, but significantly decreased naloxone-precipitated withdrawal in morphine dependent mice.
>
> **Conclusions:** The present study confirms the MOR agonist activity and therapeutic effect of LKT for the treatment of pain and opioid physical dependence.[7]

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[5] https://www.ama-assn.org/delivering-care/overdose-epidemic/physicians-progress-toward-ending-nation-s-drug-overdose-epidemic

[6] https://www.hopkinsmedicine.org/news/newsroom/news-releases/natural-herb-kratom-may-have-therapeutic-effects-and-relatively-low-potential-for-abuse-or-harm-according-to-a-user-survey

[7] Wilson LL, Harris HM, Eans SO, Brice-Tutt AC, Cirino TJ, Stacy HM, Simons CA, León F, Sharma A, Boyer EW, Avery BA, McLaughlin JP, McCurdy CR. Lyophilized Kratom Tea as a Therapeutic Option for Opioid Dependence. Drug Alcohol Depend. 2020 Nov 1;216:108310. doi: 10.1016/j.drugalcdep.2020.108310. Epub 2020 Sep 22. PMID: 33017752. https://pubmed.ncbi.nlm.nih.gov/33017752/

For the record, we ask you to consider the following statements on the content of the Mississippi Resolution that are factually incorrect:

MISSISSIPPI RESOLUTION: Whereas, The US Food and Drug Administration (FDA) is warning consumers not to use Mitragyna speciosa, commonly known as Kratom and is concerned that Kratom, which affects the same opioid brain receptors as morphine, appears to have properties that expose users to the risks of addiction, abuse, and dependence; and

RESPONSE: NIDA concurrently funded two independent studies on the addiction liability of kratom's alkaloids that were published in June and July 2018, and those conclusions directly address why kratom is not scheduled today by the DEA because it does not meet the scheduling criteria in the CSA:

- Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine, Hemby, et. al., that concluded "present findings indicate that MG does not have abuse potential and reduces morphine intake, desired characteristics of candidate pharmacotherapies for opiate addiction and withdrawal . . . "[8]

- Abuse liability of mitragynine assessed with a self-administration procedure in rats, Yue, et. al., that concluded "these results suggest a limited abuse liability of mitragynine and potential for mitragynine treatment to specifically reduce opioid abuse. With the current prevalence of opioid abuse and misuse, it appears currently that mitragynine is deserving of more extensive exploration for its development or that of an analog as a medical treatment for opioid abuse.[9]

MISSISSIPPI RESOLUTION: Whereas, The following jurisdictions have already banned the sale of Kratom: Alabama, Arkansas, Indiana, Tennessee, Vermont, Wisconsin, Rhode Island, Vermont, New Jersey and the District of Columbia as well as the communities of Union County, Mississippi, Sarasota, Florida, San Diego, CA, Denver, CO and at least four cities in the state of Illinois, and various other restrictions pending or being considered around the country; and

RESPONSE: Alabama, Arkansas, Indiana, Vermont [referenced twice], Wisconsin, Rhode Island, and Vermont – and most of the local

[8] https://onlinelibrary.wiley.com/doi/abs/10.1111/adb.12639
[9] https://pubmed.ncbi.nlm.nih.gov/30039246/

jurisdictions -- all enacted bans following the requests by the FDA when the agency initially filed its first scheduling recommendation on kratom in 2016. No state has banned kratom since Rhode Island in 2017. The KCPA has passed in Utah (2019), Georgia (2019), Arizona (2019), Nevada (2019), Oklahoma (2021), Oregon (2022), Colorado, (2022), and Missouri (2022). In addition, the KCPA has been filed in Vermont, Wisconsin, and Rhode Island to overturn the current bans and replace them with the KCPA.

There is no ban in effect in New Jersey, and the KCPA has been filed there. Tennessee enacted a ban on synthetic kratom, not the natural plant, and a full ban proposal was defeated in 2022.

MISSISSIPPI RESOLUTION: Whereas, There are efforts in Kentucky to add Kratom to the list of controlled substances that are unlawful to traffic and additionally to add it to the list of controlled substances that are unlawful for a person to possess; and

RESPONSE: The bill to ban kratom in the 2022 session was withdrawn by the sponsor and replaced with the KCPA, and the bill was subsequently referred for interim study.

MISSISSIPPI RESOLUTION: Whereas, This year, Washington State is attempting to designate Kratom as a controlled substance; and

RESPONSE: The bill to ban kratom in the 2022 session in Washington was withdrawn and the sponsor replaced with the KCPA, and the bill was subsequently referred for interim study.

MISSISSIPPI RESOLUTION: Whereas, The Ohio Board of Pharmacy recently recommended that Kratom be classified as a Schedule 1 controlled substance, and this follows on the heels of the FDA research, which has been considering similar measures, and refers to Kratom as having a “high potential for abuse”, “no accepted medical use”, and lacking “accepted safety for use in treatment under medical supervision”; and

RESPONSE: The proposed recommendation by the Ohio Board of Pharmacy to classify kratom as a Schedule I controlled substance was withdrawn in 2020, and the issue was deferred to the Ohio Legislature for action. The Ohio House of Representatives passed the KCPA earlier this year on a vote of 82-10 and the KCPA has had the first of three hearings in the Ohio Senate.

It is interesting to note that the Mississippi Resolution fails to disclose that a kratom ban was proposed in the 2022 legislation session in Mississippi but failed to be enacted. The Resolution also fails to disclose that the Nevada Board of Pharmacy also opened a review of kratom whether it should be scheduled and formally ended that review by removing the recommendation from their April 14, 2022, agenda.

The reason these Boards of Pharmacy have removed scheduling of kratom from their reviews, why the Mississippi and numerous other state ban bills have failed, and the reason the FDA has failed in its efforts to schedule kratom at both the national in international levels, is that the science on kratom clearly demonstrates it simply does not meet the criteria for scheduling. Without appropriate regulations, bad-actors adulterate kratom products with dangerous substances, including fentanyl, heroin, and morphine. The AMA House of Delegates would better protect the public by endorsing our efforts to pass the KCPA to protect consumers.

Any decision on whether kratom or its principal alkaloids, mitragynine or 7-hydroxymitragynine, should be banned should be based on current science. We recommend that every member of the AMA House of Delegate review the 8-Factor Analysis[10] published in January 2022 the addresses the more than 100 research articles on kratom that have been published since Dr. Girioir's August 16, 2018 letter withdrawing kratom from consideration for scheduling.

Here is a list of state legislators who have sponsored consumer protections for kratom consumers in their individual states:

Senator Sonny Borelli
Arizona Senate

Representative Leo Biasiucci
Arizona House of Representatives

Representative John Kavanagh
Arizona House of Representatives

Representative Walt Blackman
Arizona House of Representatives

Representative Kevin Payne
Arizona House of Representatives

Representative Tony Rivera (former)
Arizona House of Representatives

Senator Joann Ginal
Colorado Senate

Senator Don Coram
Colorado Senate

[10] Henningfield JE, Wang DW, Huestis MA. Kratom Abuse Potential 2021: An Updated Eight Factor Analysis. *Front Pharmacol*. 2022;12:775073. Published 2022 Jan 28. doi:10.3389/fphar.2021.775073

Representative Tom Sullivan
Colorado House of Representatives

Representative Quentin Phipps
Connecticut House of Representatives

Representative Travis Simms
Connecticut House of Representatives

Representative Ken Gucker
Connecticut House of Representatives

Senator Bobby Powell
Florida Senate

Representative Alex Andrade
Florida House of Representatives

Senator Joe Gruters
Florida Senate

Speaker Scott Saiki
Hawaii House of Representatives

Senator Ron Kouchi
President, Hawaii Senate

Senator Elgie Sims
Illinois Senate

Representative Marcus Evans
Illinois House of Representatives

Senator Adrienne Southworth
Kentucky Senate

Representative Josh Calloway
Kentucky House of Representatives

Representative Daniel Elliott
Kentucky House of Representatives

Representative Derrick Graham
Kentucky House of Representatives

Representative Lori Stone
Michigan House of Representatives

Representative Keven Hertel
Michigan House of Representatives

Representative Padma Kuppa
Michigan House of Representatives

Representative Rich Steenland
Michigan House of Representatives

Representative John Cherry
Michigan House of Representatives

Representative Julie Brixie
Michigan House of Representatives

Representative Regina Weiss
Michigan House of Representatives

Representative Jim Headsma
Michigan House of Representatives

Representative Donna Lasinski
Michigan House of Representatives

Representative Brenda Carter
Michigan House of Representatives

Representative Sue Allor
Michigan House of Representatives

Representative Abraham Alyash
Michigan House of Representatives

Representative Rachel Hood
Michigan House of Representatives

Representative Bill Sowerby
Michigan House of Representatives

Representative Aisha Gomez
Minnesota House of Representatives

Representative Nolan West
Minnesota House of Representatives

Representative Ron Roberson
Mississippi House of Representatives

Senator Joey Fillingame
Mississippi Senate

Senator Jeff Tate
Mississippi Senate

Representative Phil Christofanelli
Missouri House of Representatives

Representative Dru McDaniel
Missouri House of Representatives

Senator Holly Rehder
Missouri Senate

Representative Hershel Nunez
New Hampshire House of Representatives

Representative Aidan Ankarberg
New Hampshire House of Representatives

Assemblywoman Carol Murphy
New Jersey Assembly

Senator Leroy Comrie
New York Senate

Representative Donna Lupardo
New York Assembly

Representative Mark Fraizer
Ohio House of Representatives

Representative Scott Lipps
Ohio House of Representatives

Representative Gary Click
Ohio House of Representatives

Representative David Leland
Ohio House of Representatives

Representative Michele Lepore-Hagen
Ohio House of Representatives

Representative Mary Lightbody
Ohio House of Representatives

Representative Beth Liston
Ohio House of Representatives

Representative Bill Seitz
Ohio House of Representatives

Representative Monique Smith
Ohio House of Representatives

Representative Daniel Pae
Oklahoma House of Representatives

Representative Lonnie Paxton
Oklahoma House of Representatives

Representative Bill Post (former)
Oregon House of Representatives

Representative John Lively
Oregon House of Representatives

Representative David Brock Smith
Oregon House of Representatives

Representative Chelly Boshart Davis
Oregon House of Representatives

Representative Vikki Breese-Iverson
Oregon House of Representatives

Representative Maxine Dexter
Oregon House of Representatives

Representative Paul Evans
Oregon House of Representatives

Representative Cedric Hayden
Oregon House of Representatives

Representative Gary Leff
Oregon House of Representatives

Representative Bobby Levy
Oregon House of Representatives

Representative Raquel Moore-Green
Oregon House of Representatives

Representative Ron Noble
Oregon House of Representatives

Representative Mark Owens
Oregon House of Representatives

Representative Rachel Prusak
Oregon House of Representatives

Representative Eric Werner-Reschke
Oregon House of Representatives

Representative Tawna Sanchez
Oregon House of Representatives

Representative Greg Smith
Oregon House of Representatives

Representative Tim Knopp
Oregon House of Representatives

Representative Tracy Pennycuick
Pennsylvania House of Representatives

Representative Christina Sappey
Pennsylvania House of Representatives

Representative Susan C. Helm
Pennsylvania House of Representatives

Representative Jennifer M. O'Mara
Pennsylvania House of Representatives

Representative Timm Hennessey
Pennsylvania House of Representatives

Representative Mike Schlossberg
Pennsylvania House of Representatives

Representative Doyle Heffley
Pennsylvania House of Representatives

Representative Chris Quinn
Pennsylvania House of Representatives

Representative Tina Davis
Pennsylvania House of Representatives

Representative Brian Patrick Kennedy
Rhode Island House of Representatives

Representative Jay Edwards
Rhode Island House of Representatives

Representative Grace Diaz
Rhode Island House of Representatives

Representative Sam Azzinaro
Rhode Island House of Representatives

Representative Joe Towns
Tennessee House of Representatives

Senator Sara Kyle
Tennessee Senate

Senate Judith Zaffrini
Texas Senate

Representative J.M. Lozano
Texas House of Representatives

Representative Brad Daw (former)
Utah House of Representatives

Senator Curt Bramble
Utah Senate

Representative Brian Cina
Vermont House of Representatives

Representative Kate Donnally
Vermont House of Representatives

Representative Heather Surprenant
Vermont House of Representatives

Representative Tristan D. Toleno
Vermont House of Representatives

Representative Buddy Fowler
Virginia General Assembly

Senator Jim Honeyford
Washington Senate

Speaker Robin Vos
Wisconsin House of Representatives

Representative Dave Murphy
Wisconsin House of Representatives

Representative Rachael Cabral-Guevara
Wisconsin House of Representatives

Representative Christine Sinicki
Wisconsin House of Representatives

Representative Chuck Wichgers
Wisconsin House of Representatives

Representative Dora Drake
Wisconsin House of Representatives

Representative Jonathan Brostoff
Wisconsin House of Representatives

Senator Mary Felzkowski
Wisconsin Senate

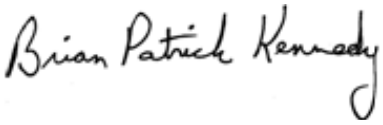
Senator Lena Taylor
Wisconsin Senate

We look forward to engaging in positive discussions on this topic with a focus on science, and request that the AMA House of Delegates defer any action on the proposed Mississippi Resolution until the science supports such an action. We would welcome the invitation for one or more of us to formally present our case for the KCPA at your upcoming House of Delegates meeting in Chicago when the Mississippi Resolution is discussed.

Respectfully submitted,

Senator Curt Bramble
Utah State Senate
Former President of the
National Conference of
State Legislatures

Speaker Robin Vos
Wisconsin House of
Representatives
Former President of the
National Conference of
State Legislatures



Representative Brian Patrick
Kennedy
Speaker Pro-Tempore
Rhode Island House of
Representatives
Vice President of the
National Conference of
State Legislatures

Representative Nolan West
Minnesota House of Representatives

Representative Tracy Pennycuick
Pennsylvania House of
Representatives

Assemblywoman Carol Murphy
New Jersey General Assembly
Majority Whip

June 11, 2022

Utah State Senator Curt Bramble
Rhode Island State Representative Brian Patrick Kennedy
Wisconsin State Assembly Speaker Robin Vos
Minnesota State Representative Nolan West
Pennsylvania State Representative Tracy Pennycuick
New Jersey Assemblywoman Carol A. Murphy

Dear Mr. Bramble, Mr. Kennedy, Mr. Vos. Mr. West, Ms. Pennycuick and Ms. Murphy:

Thank you for your letter regarding a proposed resolution submitted to the American Medical Association House of Delegates regarding kratom, and its potential inclusion as a Schedule 1 substance under the Controlled Substances Act.

This resolution was submitted by the Mississippi State Medical Association and it has withdrawn it from consideration at the AMA House of Delegates, which opened June 10 in Chicago and will continue through June 15, 2022. I want to personally thank you for taking the time to share your views on this matter with us. You can rest assured that, should this issue come before us in the future, your input will be given full consideration.

Thank you for contacting us.

Sincerely,

Gerald E. Harmon
President, American Medical Association

DAVE MURPHY

State Representative • 56th Assembly District

Assembly Committee on State Affairs

Public Hearing, December 8, 2021

Assembly Bill 599

Testimony of State Representative Dave Murphy

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

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

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

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

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

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

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

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

MARK POCAN
2ND DISTRICT, WISCONSIN

COMMITTEE ON APPROPRIATIONS
COMMITTEE ON EDUCATION & LABOR
JOINT ECONOMIC COMMITTEE
SENIOR WHIP

UNITED STATES
HOUSE OF REPRESENTATIVES

10 EAST DOTY STREET, SUITE 405
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POCAN.HOUSE.GOV

December 6, 2021

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

Dear Chair Swearingen:

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

Mark Pocan
Member of Congress

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for your efforts and the opportunity to comment.

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Wisconsin Medical Society

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

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

DATE: December 8, 2021

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

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

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

> There are no FDA-approved uses for kratom, and the agency has received concerning reports about the safety of kratom. FDA is actively evaluating all available scientific information on this issue and continues to warn consumers not to use any products labeled as containing the botanical substance kratom or its psychoactive compounds, mitragynine and 7-hydroxymitragynine. FDA encourages more research to better understand kratom's safety profile, including the use of kratom combined with other drugs.

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

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

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

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

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

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

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

Continuing Research into Kratom Use Shows Troubling Effects

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

> The increasing consumption of kratom (Mitragyna speciosa) is emerging as a public health concern among Americans, and forecasting models indicate its use will continue to rise. Aside from the Food and Drug Administration (FDA) reports of concern and adverse effects exhibited through increased calls to poison control centers and overdose deaths, the notion of addiction is rapidly emerging.

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

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

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

WISAM WISCONSIN SOCIETY of ADDICTION MEDICINE

07/14/2021

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

Dear Mr. Grapentine,

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

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

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

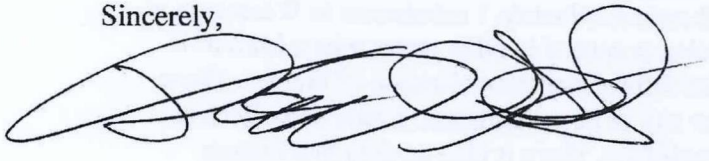
Finally, any attempt to introduce this bill as part of the HOPE legislation under the guise of treatment for OUD is anti-scientific and harmful. The FDA has issued warning letters to

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

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

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

Sincerely,



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

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A Case Report of Kratom Addiction and Withdrawal

David Galbis-Reig, MD

ABSTRACT

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

CASE PRESENTATION

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

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CME available. See page 53 for more information.

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

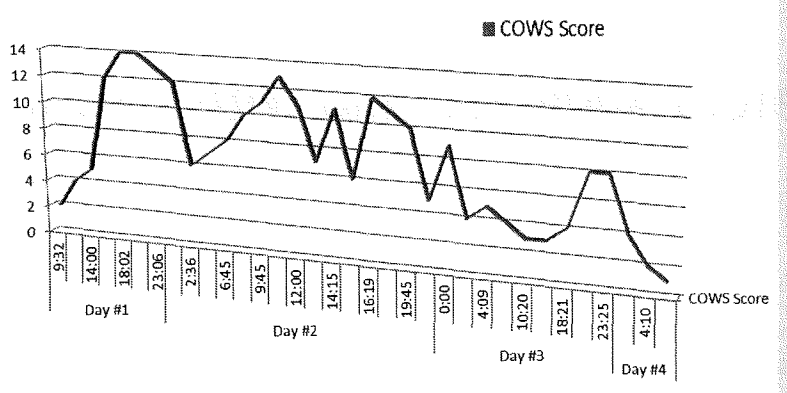
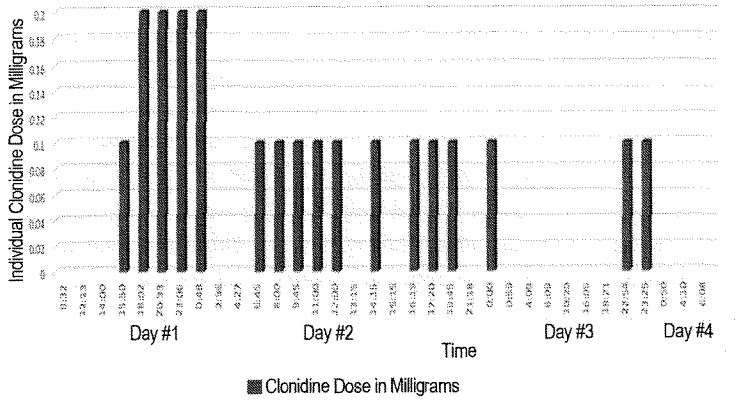


Figure 2. Kratom Withdrawal Clonidine Dose Requirements



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

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

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

DISCUSSION

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

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

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

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

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

CONCLUSION

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

Funding/Support: None declared.

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

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

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

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

ABSTRACT

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

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

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

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

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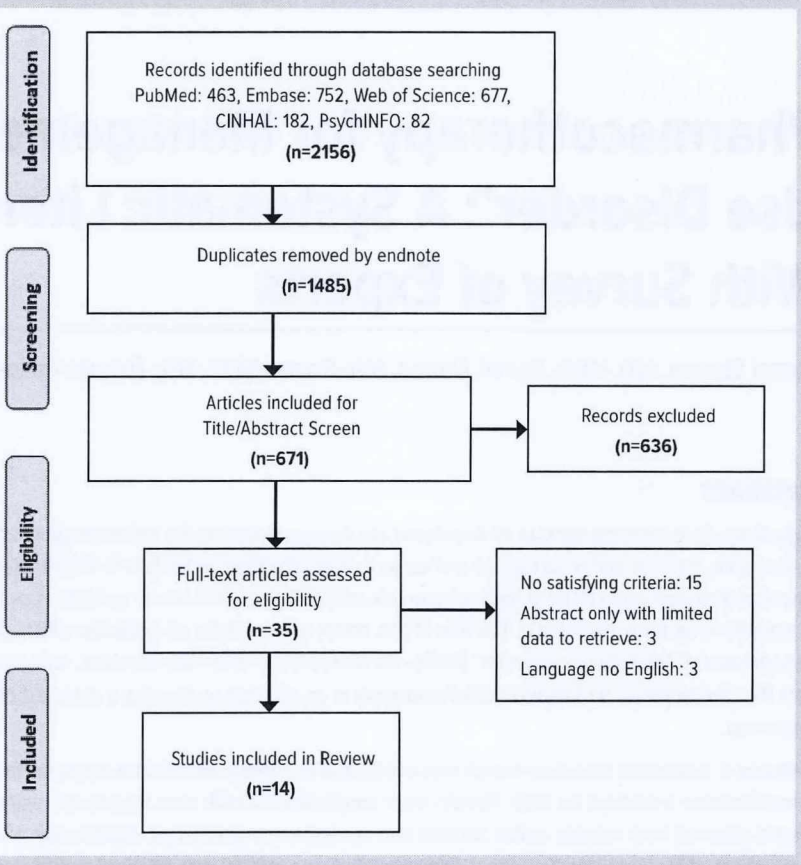
INTRODUCTION

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.

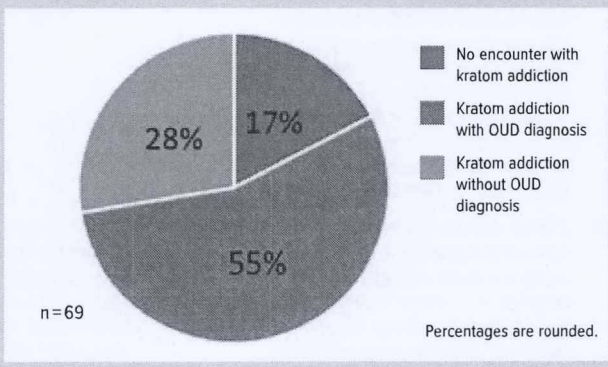
There is a clear need to establish a consensus on how to manage KUD independent of an OUD. As demonstrated in this review, there has been success with treating KUD using the same pharmacological agents as those approved for OUD. In the cases included here that did not involve a comorbid OUD diagnosis,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

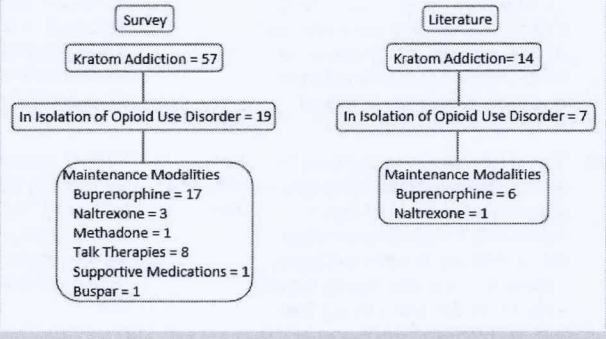
The cases resulting from the literature search and included in the analysis/comparison have a significant amount of heterogeneity in the descriptions, information provided (ie, kratom dose, route, etc), toxicology screens used for abstinence monitoring, reporting of maintenance follow-up duration, etc.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

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

Funding/Support: None declared.

Financial Disclosures: None declared.

Appendices: Available at www.wmjonline.org.

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

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

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

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

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

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

Sincerely,

Heidi Sykora RN, DNP

8 December 2021

Written Comment by Jack E. Henningfield, PhD

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

Bethesda, Maryland

To The

Wisconsin Committee on State Affairs Hearing on AB 599

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pinney Associates

Leading Edge Kratom Science

Addressing Abuse Potential, Safety, Patterns of Use, Reasons for Use, and New Studies of Mitragynine, 7-hydroxymitragynine, and Other Kratom Alkaloids

September 2, 2021

An annotated update of the 2018 published review article:

The Abuse Potential of Kratom According to the 8 Factors of the Controlled Substances Act:

Implications for Regulation and Research

By

Jack Henningfield, Reginald Fant & Daniel Wang

This report was developed by

Dr. Jack Henningfield and colleagues at PinneyAssociates

For the American Kratom Association to inform and update policy makers, health and regulatory officials, and public health and medical experts on kratom safety and abuse potential

August 6, 2021

Acknowledgement and disclosure. This update of the Henningfield et al. 2018 kratom abuse potential assessment review is required to account for the significant number of new research studies that have been completed that collectively adds to the body of scientific evidence about the kratom plant and its constituent alkaloids. The American Kratom Association (AKA) and its affiliate, the Center for Plant Science and Health that funds new research into kratom, have supported an independent assessment of the current research landscape. This update followed a request for partial support of the time and effort for Dr. Henningfield and his colleagues at PinneyAssociates to develop the report. The purpose was to provide a state-of-the-art report to inform policy makers, health and regulatory officials, and public health and medical experts on kratom safety and abuse potential. AKA did not contribute to or influence the conclusions of Dr. Henningfield and colleagues at PinneyAssociates.

Through PinneyAssociates, Dr. Henningfield and his colleagues provide scientific and regulatory consulting to support new drug applications (NDAs) and risk management programs for a broad range of CNS active substances and drug products including psychedelic substances, new chemical entities, and alternative formulations and routes of delivery, as well as dietary ingredient notifications, cannabinoid assessment, and noncombustible tobacco/nicotine products for FDA regulation.

PinneyAssociates scientific experts who contributed to this report include: Rachel Beck, PhD; August Buchhalter, PhD; Yolanda Green; Marilyn Huestis, PhD, HonD; Mark Sembower, MS; and Daniel Wang.

We also acknowledge the thinking embodied in this document by our former colleague and co-author of the 2016 kratom Abuse Potential Assessment submitted to the DEA and FDA and its updated published version in 2018. Dr. Fant died in September 2020, and we miss him dearly. See more about our team and Dr. Fant at www.pinneyassociates.com.

Preface and Main Findings

Background: The 2018 Henningfield, Fant & Wang kratom abuse potential assessment was based on a 2016 assessment developed by Dr. Henningfield and colleagues at PinneyAssociates to inform the United States (US) Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA) in their assessment as to the most appropriate regulatory approach to kratom and whether listing kratom (specifically, its alkaloids mitragynine [MG] and 7-hydroxymitragynine [7-OH-MG]) in Schedule I of the Controlled Substances Act (CSA) was warranted and in the interests of public health.

In brief, we concluded there was no evidence of an imminent threat to public health (a requirement for temporary or emergency scheduling) and that kratom was not like opioids in its safety and addiction risks. Furthermore, there was evidence that millions of people were using kratom for reasons associated with health and well-being, including in place of opioids they had been using for pain and/or addiction, and that thousands of people would be at risk of relapse to opioids and overdose if sale of kratom were banned and possession considered a narcotic criminal offense. We also concluded that banning kratom would foreseeably lead to the emergence of a deadly illicit market that would worsen what appeared to be the main problems with kratom, namely contaminated, adulterated, and inappropriately marketed products. We concluded that these problems could be addressed by continuing to allow legal sale of kratom but with FDA oversight providing standards for product quality, labeling, and other issues that FDA routinely addresses.

Overview of main findings: This update reaffirms all of the conclusions of the 2018 report. The more than 100 new peer-reviewed published studies by researchers worldwide and many laboratory studies in the US with funding from the National Institute on Drug Abuse (NIDA), sustain those earlier findings. These studies provide a much fuller characterization of how kratom works and how it provides the benefits that many people report as their reason for use, but without narcotic-like addiction and overdose risks. The studies include the state-of-the-art types of animal abuse and physical dependence/withdrawal studies that FDA requires for new medicines and which DEA relies on for drug scheduling decisions. New clinical studies in humans provide initial assessments of kratom's physiological health and safety related effects on liver, kidney, and cardiovascular function, as well as brain function, using magnetic resonance imaging techniques.

Conclusions based on new studies since January 1, 2018

- *Since the Henningfield, Fant & Wang (2018) 8-FA, there have been over 100 new published scientific studies, reviews, and commentaries by leading kratom experts, and an accelerating research pipeline funded in part by the US National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA). These studies provide an increasingly strong evidence base for regulation and policy.*

- *Nature got it right. There is a convergence of studies showing that the main natural constituent of kratom that accounts for the reasons people use kratom is MG, which carries relatively low abuse and health risks (See below). 7-OH-MG naturally occurs at*

very low levels and product standards should prevent marketing of products with levels higher than those that appear to carry little risk.

- *Evidence does not support the conclusion that kratom is an imminent public health threat or that it is fueling the opioid and drug overdose epidemic that led to more than 93,000 deaths in 2020. Rather, the evidence supports the conclusion that for many people kratom is a path away from opioids and other drugs to help self-manage craving and withdrawal for people who find kratom more effective, accessible, acceptable, tolerable, and/or prefer natural products.*

- *Animal drug self-administration, physical dependence, and withdrawal studies show low abuse potential and withdrawal risks of kratom relative to opioids. Furthermore, these studies also show that MG administration can reduce self-administration of morphine and heroin as well as withdrawal from morphine. These findings are consistent with human surveys and studies showing that addiction risks for kratom are overall low as compared to opioids.*

- *Numerous surveys and field studies of kratom users have been conducted in the US and Malaysia. These new studies largely confirm the earlier large US survey on kratom consumer usage patterns published by Dr. Grundmann (2017). Most US kratom users are 30-50 years old, employed, have some college education, and have health insurance. Leading reasons for use are to self-manage pain, depression, anxiety, to increase focus and alertness analogous to caffeinated beverage use, and to self-manage opioid and other substance use disorders to relieve craving and withdrawal and often the pain that motivates such drug use.*

- *Surveys also show that users fear a kratom ban and the risks of resumption of opioid and other drug use, and/or turning to illicitly marketed kratom. This makes it foreseeable that thousands of people would be at risk of opioid overdose and other mortality risks associated with illicit drug use, injection drug use, and adulterated kratom products.*

- *Studies of kratom's alkaloids support the conclusion that that MG and other alkaloids are not appropriately categorized as opioids, as they are diverse in their activity, effects, and mechanisms of action. Moreover, the primary active constituent of kratom, MG, does not produce the signature powerfully rewarding and lethal respiratory depressant effects that characterize morphine-like opioids.*

- *Kratom PK and safety studies include examination of the pharmacokinetics (PK) and pharmacodynamics (PD) in rats and dogs by oral and intravenous administration of many kratom alkaloids in addition to MG. MG, at human dose equivalents many times higher than humans take, are without acute serious adverse effects and there is little evidence of a respiratory depressant effect.*

- *Six clinical studies evaluated the effects of long term kratom use on a variety of physiological parameters including kidney and liver function, hematological parameters, cognition, and brain function by magnetic resonance imaging. Although these were*

relatively small studies, none suggest serious adverse consequences of long term kratom use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies.

- *New medicine innovation efforts are developing new molecules as analogs of MG and other kratom alkaloids as possible safer and/or more effective treatments for pain, addiction, depression, and other disorders, due to the promising findings with kratom and its naturally occurring alkaloids. These efforts are also contributing to knowledge about kratom safety and effects; however, New Drug Applications (NDAs) typically require a decade or more of research at costs often exceeding one billion dollars before they can be submitted for review and potential approval by the FDA.*

- *The pipeline of research and new science has been enhanced in quantity and quality not only by funding from the US National Institutes of Health (NIH) and other organizations but as well by regular scientific conferences that are fostering global collaboration and cooperation in an exciting new frontier in search of safer and more effective ways to manage health and well-being. Such efforts are working and should be expanded.*

- *These scientific findings taken together have implications for consideration of kratom regulation by the Controlled Substances Act (CSA). The CSA is intended to protect the public health from substances that pose as imminent threat to public health, and in the case of medicines with a potential for abuse to ensure that they are appropriately regulated if the science supports placement in the CSA. Kratom is not a new drug but rather is a naturally occurring substance with decades of history of use in the US and much longer in Southeast Asia where it grows in abundance and is used by many more people. The scientific evidence does not indicate a profile of meaningful abuse potential or physiological dependence potential of its primary active constituent, mitragynine. This review supports the key findings and action by Assistant Secretary of Health, Dr. Brett Giroir (Giroir, 2018) to rescind the 2017 recommendation (FDA, 2017a) to place MG and 7-OH-MG in Schedule I of the CSA. Specifically, it supports the conclusions that "mitragynine does not satisfy the first of the three statutory requisites for Schedule I", and that "there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I" and that the very research that all parties agree is needed would be severely stifled by CSA scheduling.*

- *Kratom regulation would be better informed by scientific and public health information exchange and active collaboration among CDC, DEA, FDA, NIDA, and the Substance Abuse and Mental Health Services Administration. Kratom science should be accelerated by increased kratom research funding to NIDA, as well as to support increased surveillance that is specific to kratom. As in other areas of science and public health, progress and process would likely be improved if federally funded kratom*

research had input and possibly oversight by a multi-agency task force and with an annual report developed with updates on the state of kratom science and annual surveillance, perhaps led by NIDA.

- *An important development that relates to overall safety, health benefits and risks of kratom use is a regulatory and policy update and is not included in the science updates: at the time of this writing, five states, Arizona, Georgia, Nevada, Utah, and Oklahoma, have enacted laws referenced as the Kratom Consumer Protection Act (KCPA). The KCPA establishes a regulatory framework to protect consumers from unsafe and adulterated kratom products that by requiring manufacturers strict adherence to good manufacturing standards (GMP) to ensure purity; requires testing for contaminants; prohibits adding any dangerous substances to kratom products; forbids boosting the alkaloid levels of MG and 7-OH-MG over those present in the natural kratom plant; bars synthesizing any of the alkaloids; requires registration and product testing; prohibits any therapeutic health claims; and forbids sales to minors. These KCPA laws provide needed consumer protections for consumers. To illustrate the kratom regulatory framework for the Utah KCPA, the Utah Department of Agriculture rule on kratom can be found at https://ag.utah.gov/businesses/regulatory-services/kratom/ . For updates on the status of KCPA legislation in other states, visit the American Kratom Association website at https://www.americankratom.org/advocacy/aka-in-your-state.html .*

Contents

1 Introduction

This is a scientific update to “The abuse potential of kratom according to the 8 factors of the Controlled Substances Act: implications for regulation and research”, by Jack Henningfield, Reginald Fant, and Daniel Wang (Henningfield, Fant & Wang, 2018). Primarily findings and conclusions quoted directly from kratom-related scientific research since December 2017 are included.

Seven of the eight factors of the Controlled Substances Act were affected by new research and survey data. The eighth factor did not change, as neither kratom nor any of the constituents in kratom or its alkaloids are controlled substances, nor are they immediate precursors of controlled substances.

This update includes several new studies employing a variety of state-of-the-art animal models of abuse potential, physical dependence, and withdrawal potential as compared to opioids and other classic drugs of abuse. The understanding of kratom’s mechanisms of action and its safety profile help explain not only why it differs from opioids with respect to safety but also its relatively low potential for abuse and dependence.

1.1 Comments on Efficacy, Risk, and Drug Scheduling According to the Controlled Substances Act

Therapeutic efficacy standard by FDA. This research update includes additional evidence that the major reasons for kratom use for millions of people in the US are for health and well-being including for self-management of pain, addiction, depression, and other disorders. The evidence includes peer reviewed surveys and field studies in the US and Southeast Asia (SEA), some clinical studies, and many animal studies that show that the mechanisms of action of MG are consistent with such effects. Moreover, several animal models used to predict efficacy for treating opioid use disorder, opioid withdrawal, and pain, demonstrated efficacy.

However, none of this research meets FDA’s standard for therapeutic efficacy which is typically determined by evaluation of a New Drug Application (NDA) (whether NDA is based on a new chemical entity or botanical substance). The NDA must be supported by “substantial evidence of effectiveness,” and is defined as “evidence consisting of adequate and well-controlled investigations” (Dabrowska & Thaul, 2018; Katz, 2004). The time and cost to develop and achieve FDA approval of a product as therapeutically effective and acceptably safe varies widely but is often approximately ten years and 1 billion dollars (DiMasi, Grabowski & Hansen, 2016; Wouters, McKee & Luyten, 2020). Only two botanical substances have been developed as drug products consistent with FDA’s Botanical Drug Guidance (FDA, 2016).

Thus, by FDA’s standard for efficacy, no kratom product or kratom alkaloid or derivative is recognized as therapeutically efficacious or “safe and effective”. This report does not endorse or recommend therapeutic use. However, terms such as therapeutic use are used in many of the articles cited and by many consumers of kratom who report using it for and obtaining therapeutic benefits. Denial of this would not be consistent with the science regardless of whether it meets the FDA standard. Neither should it be denied that studies estimate that over ten million people in the US (AKA, 2019; Henningfield, Grundmann, Garcia-Romeu & Swogger, 2021) use kratom products and find them acceptable, and sometimes preferred over

other products. For this population, kratom is perceived as effective, accessible, tolerable, and preferable as a natural product compared to conventional medicines.

1.1.1 Comment on Risk

Risk is a relative concept. This report discusses many risks and benefits of kratom, particularly as compared to morphine-like opioids which carry far greater risks of addiction and overdose death as discussed in the report (see also Henningfield, Grundmann, Babin, et al., 2019). This research does not suggest that kratom consumption is without risk. It is also important to recognize that kratom is not approved for therapeutic use by the FDA. Therefore, surveys showing that individuals use kratom to improve personal health and wellbeing, and for self-management of disease should not be taken as endorsements of such use or that use is without risk.

1.1.2 Comment on Drug Scheduling

Drug scheduling in the US is guided by the Controlled Substances Act (CSA). For new drugs, scheduling recommendations are developed by FDA, with input from NIDA and transmitted to DEA by the Assistant Secretary of Health (ASH) to the Administrator of the DEA (FDA, 2017a; Giroir, 2018). The same process can be applied to substances that are not approved as drugs and this process was followed for the 2017 FDA recommendation that MG and 7-OH-MG be permanently placed in Schedule I of the CSA, although it was concluded in a critique of the FDA recommendation that there was no evidence of actual NIDA input into the FDA 8-Factor Analysis (FDA 2017a; Henningfield, Babin, Boyer, et al. 2018).

By law and in practice, following FDA's 2017 Guidance (FDA, 2017b), scheduling decisions are guided by analysis of the eight factors of the CSA, which include three factors (nos. 4, 5 and 6) that address public health implications of scheduling including whether it is in the interest of public health to schedule a substance and, if so, which schedule is most appropriate. Regardless of the actual level of abuse potential and public health risk, if it is determined that a substance warrants CSA scheduling and it is not approved for therapeutic use by FDA (i.e., as an approved drug), only Schedule I (C-I) is an option. If the substance or product is approved for therapeutic use and is recommended for CSA scheduling then it will be placed in Schedule II, III, IV or V, in which V is least restrictive (e.g., lacosamide, pregabalin, and low dose codeine plus acetaminophen) and Schedule II is most restrictive (e.g., amphetamine, fentanyl, morphine) supported by the 8-factor analysis. For discussions and examples of the process and how public health considerations including risks and benefits related to scheduling are considered, see FDA's 2017 Guidance and review articles (Belouin & Henningfield, 2018; FDA, 2017b; Giroir, 2018: Johnson, Griffiths, Hendricks & Henningfield, 2018; Spillane & McAllister, 2003).

The science update supports the conclusion that kratom is providing a public health benefit by enabling millions of people in the US to self-manage their health and well-being and that it is foreseeable that banning sales and criminalizing those who possess kratom could lead to thousands of opioid overdose deaths among people who reverted to opioid use. We believe that individuals and public health would be better served by regulations that ensure that lawfully marketed products are pure, uncontaminated, and unadulterated by other harmful substances, drugs, or unnaturally high levels of kratom's naturally occurring alkaloids, and that

kratom products are appropriately marketed, packaged, and labeled and unsubstantiated health claims are not made.

1.2 Approach

This update is based on a review of studies published primarily since January 1, 2018 to update the science cited in the Henningfield, et al. (2018) 8-Factor Analysis which was completed and accepted for publication in December 2017.

Published literature was obtained by internet searches and a direct request for the most recent published and "accepted for publication" studies of more than twenty of the leading kratom research centers and research leaders worldwide. Conclusions were also influenced by the several national and international meetings in which new kratom research findings were presented and discussed each year (including virtual meetings from March 2020 to the present).

We do not represent this as a consensus report but have made every effort to reflect the thinking of other leading kratom science and policy experts. The approach to our study summaries is to rely heavily on direct quotes from the authors of articles or brief summaries that we feel accurately represented the articles. We provide the references and will make available the library of the more than 100 articles on request. It is our intent that this transparent process will also facilitate efforts to contact researchers for more information about their research and thinking.

A review of this body of evidence strengthens the conclusions of the 2018 8-FA that the public health benefits of continued access to kratom (ideally, with a regulatory framework developed by FDA with input from stakeholders and experts and other agencies including NIDA) outweigh the risks.

Kratom and its primary alkaloid, mitragynine, is not without risks or devoid of abuse potential; however, those risks are overall relatively small as compared to the serious risks of a kratom ban. The abuse potential of kratom and mitragynine do not rise to the level of abuse potential or risk that would be effectively or appropriately mitigated by placement in the CSA. This takes into consideration the overall public health impact, as required by consideration of factors 4, 5 and 6.

Thus, this update does not fundamentally change the following conclusion of the 2018 8-FA:

> "The overarching public health and policy question is not could kratom be regulated as a controlled substance but rather should kratom be so regulated. From a pharmacological perspective, this review suggests, as concluded by Henningfield (2015) and Pinney Associates (2016) that a case could be made to place kratom in the CSA. In fact, if MG, for example, was a newly discovered active chemical entity in a medicine submitted for approval by FDA, and hence without decades of use in the community, it would certainly be evaluated for potential scheduling according to the CSA and FDA's guidance (FDA 2017b), and it might be recommended for scheduling following its approval as a therapeutic medicine." (Henningfield, Fant & Wang, 2018, p. 585)

1.3 Comment on Current State of Research

There have been extensive new scientific advances since 2018 on the impact of kratom on substance use disorders and rehabilitation. This includes many thoughtful integrative reviews. We provide an example of one of these that we think provides a useful framing from this report.

Drs. Veltri and Grundmann (2019) concluded as follows:

> "Throughout its history of use, Kratom has been known to exert stimulant- and opioid-like effects that is raising concerns with regulatory agencies and resulted in scheduling actions in various countries. Although knowledge from clinical studies is limited, epidemiological data obtained from Southeast Asia, Europe, and the United States indicate that Kratom has a distinct user profile and presents with discrete effects from other stimulants or opioids. A substance-dependent opioid user does not prefer Kratom over another opioid but instead would utilize Kratom as a harm reduction or mitigation agent. This has been the conclusion from studies in Malaysia and the United States although the current information is preliminary in scope based on the small sample sizes and regional limitation of the surveys. The findings do align with preclinical observations in rodents that report a reduction in morphine self-administration with the use of mitragynine. This current knowledge points to a potential for further development of mitragynine or use of Kratom as a harm reduction agent similar to methadone or buprenorphine….While a majority of regular Kratom users in Southeast Asia and the West alike do not experience acute or chronic adverse effects, the incidence of unwanted side effects remains unknown and can include both stimulant and opioid-like sedative effects….a direct causative link between the fatalities in which Kratom was detected cannot be drawn because nearly all of them involved poly-drug exposures. The toxicity of Kratom in various animal species is variable and has not been determined for most of them following acute and chronic exposure. The only clinical pharmacokinetic study in humans that provides blood concentrations of mitragynine does not correlate with post-mortem blood mitragynine concentrations thus not allowing for the determination of a toxic or lethal cut-off level…. Reports and studies of the dependence potential to Kratom are of serious concern given the current opioid crisis in the United States and rising abuse of opioids in other countries. It appears that most Kratom-dependent users had a prior substance use disorder or were seeking relief from a chronic pain condition but wanted to avoid opioid use. The severity of Kratom dependence symptoms appears to be milder compared to opioid use disorder…" (pg. 29)

Note that research is rapidly expanding in the US and SEA, especially at the Center for Drug Research (CDR), Universiti Sains Malaysia, in part due to increased support of kratom related research by NIDA. For nearly a decade, NIDA has supported research into potentially safer and less abusable medicines for pain and treatments derived from kratom alkaloids for opioid use disorder. This is among the more rapidly expanding areas of research providing new facts and insights to characterize the benefits and risks of kratom use and how appropriate regulation could minimize risks.

Along with this accelerated research, NIDA has also supported conferences in the US and internationally which have been important in the facilitation of research sharing. This has also fostered global collaborative efforts that are evident in many of the published articles in this update in which authorship represents multiple research centers, sometimes from three or four countries.

Two conferences in particular are important to note for their important research stimulating effects. The first was the 2018 NIDA International Forum: Building International Collaborative Research on Drug Abuse, June 8–11, as a satellite meeting of the annual College on Problems of Drug Dependence meeting, which itself included a major kratom symposium and several individual presentations by researchers whose work is included in this update.[1,2]

The second major international meeting that accelerated research and fruitful cross disciplinary, global collaborations was the NIDA supported Second International Kratom Symposium convened by the University of Florida Clinical and Translational Science Institute and the Department of Pharmacodynamics from February 8-10,2019.[3] See more about their program and efforts to accelerate kratom science at the University of Florida Kratom Resource page[4].

An additional influence on the conclusions of the present report were policy efforts that involved more than a dozen kratom and substance abuse research leaders developing three reports in the form of open letters to update FDA, DEA, NIDA, the White House, and Congressional leaders[5,6,7] . These reports were also developed with support from the AKA. Each of these reports were co-authored and signed by nine or more contributors with eight contributing to all of them.

As the safety and effects of kratom and its primary active alkaloid MG have become increasingly studied over the past 5-10 years there have been a growing number of articles and scientific meetings exploring the diverse potential public health and therapeutic benefits of kratom that are already evident (Grundmann, Brown, Henningfield, et al., 2018; Prozialeck et al., 2020; Sharma & McCurdy, 2021). All of these articles recognized that the FDA standard for therapeutic benefit, which is generally approval of a new drug application (NDA) for therapeutic use, has not been met.

To date, there has not been an NDA submission to FDA for a kratom product and it is not clear that there ever will be. However, kratom-related potential new drug development efforts are already underway as some companies have announced on their websites (e.g., Kures

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[1] https://www.drugabuse.gov/international/2018-nida-international-forum-building-international-collaborative-research-drug-abuse
[2] https://www.drugabuse.gov/international/kratom-research-presented-nida-international-forum-promotes-international-cooperation
[3] https://www.leg.state.nv.us/App/NELIS/REL/80th2019/ExhibitDocument/OpenExhibitDocument?exhibitId=41965&fileDownloadName=0403ab303c_gasr_symposium.pdf
[4] https://pd.pharmacy.ufl.edu/research/kratom/
[5] February 2018 Letter to White House and DEA at http://www.americankratom.org/images/file/Document%2019%20Science%20Letter%20on%20Kratom%20Sent%20to%20WH%20and%20DEA%20Feb%208%202018.pdf
[6] June 2018 Letter to Leaders of Congress at https://www.americankratom.org/images/16_Kratom_Scientist_Letter_to_Congressional_Leaders_June_21_2018_FINAL.pdf
[7] November 2018 letter to DHHS, FDA, DEA, and NIDA critiquing the FDA's kratom 8 Factor Analysis at https://www.americankratom.org/images/file/Scientists-Response-to-FDA-Kratom-8FA--28-Nov-2018-FINAL.pdf

Therapeutics, Inc[8] and Sparian Biosciences[9]). The foregoing efforts include scientists on their teams who have been researching kratom alkaloids, with support from NIDA, as part of NIDA's efforts to foster research to stimulate the development of new medicines to treat substance use disorders as well as medicines for other disorders for which the present leading medicines carry addiction and safety risks.

2 Summary of Findings

For each factor, this report will begin with a short summary of the main finding of the 2018 8-Factor Analysis (8-FA), followed by key scientific updates, and finally conclusions. Mitragynine is abbreviated "MG" and 7-hydroxy-mitragynine "7-OH-MG". Unless specified, "opioids" means morphine, heroin, oxycodone and fentanyl, and other full opioid agonists, and not opioid antagonists such as naloxone (Narcan®) or naltrexone, or the partial opioid agonist buprenorphine.

2.1 Factor 1 – Actual or Relative Potential for Abuse

2.1.1 Summary of 2018 Findings

Henningfield, Fant & Wang (2018) did not have the benefit of classic animal self-administration and withdrawal studies of kratom's alkaloids; however, other data suggested relatively low abuse potential as compared to opioids and other drugs of abuse. Survey data from the US and field studies in SEA observed most kratom use was for health-related benefits, including management of drug dependence and drug withdrawal, primarily for opioid related dependencies but also for alcohol and stimulant use disorders. Initial drug discrimination and conditioned place preference (CPP) studies with rats suggested weak opioid-like discriminative effects and weak rewarding effects at extremely high human dose equivalents that might not be tolerable in humans. Taken together, the 2018 Factor 1 evidence suggested that kratom was not without abuse potential but that its potential for individual and societal harm was relatively low as compared to opioids and other drugs of abuse.

2.1.2 Factor 1 Science Updates

2.1.2.1 Intravenous (IV) Self-administration Studies of Abuse Potential

Two 2018 studies provided assessment of kratom's abuse potential in the IV rat self-administration model, the most predictive animal model for reinforcing effects and abuse potential (FDA, 2017b). In addition, MG's brain rewarding effects were evaluated in the intracranial self-stimulation model and the CPP procedure.

Hemby, MacIntosh, Leon, et al. (2019) summarized the reinforcing effects of MG and 7-OH-MG compared to morphine, and also evaluated pretreatment of animals with MG or 7-OH-MG on morphine self-administration:

> "The present findings indicate that MG does not have abuse potential and reduces morphine intake, desired characteristics of candidate pharmacotherapies for opiate

[8] https://www.kures.life/
[9] https://www.sparianbiosciences.com/

addiction and withdrawal, whereas 7-HMG should be considered a kratom constituent with high abuse potential that may also increase the intake of other opiates." (p. 1)

It is important to note that the reinforcing human dose equivalents of 7-OH-MG in the rat were many times higher than would be tolerable for humans, and that 7-OH-MG is present at or near de minimis levels in kratom leaves and most marketed products. Their findings support recommendations that marketed kratom products should not contain more than 1-2% 7-OH-MG, the highest concentration found naturally in plants and that does not provide reinforcing or harmful effects. This is the approach adopted by states that passed Kratom Consumer Protection Act laws to regulate kratom.[10]

Yue, Kopajtic and Katz (2018) compared MG's reinforcing effects to heroin and methamphetamine and evaluated MG pretreatment of animals prior to the opportunity to self-administer heroin or methamphetamine. Their conclusions:

> "In rats trained to self-administer methamphetamine, saline substitutions significantly decreased the number of responses, whereas different doses of methamphetamine (0.002–0.068 mg/kg/injection) or heroin (0.001–0.03 mg/kg/injection) maintained self-administration with maximal responding at 0.022 or 0.01 mg/kg/injection, respectively. In contrast, no dose of mitragynine maintained response rates greater than those obtained with saline. Presession mitragynine treatment (0.1 to 3.0 mg/kg) decreased response rates maintained by heroin but had little effect on responding maintained by methamphetamine across the same range of doses. These results suggest limited abuse liability of mitragynine and the potential for mitragynine treatment to specifically reduce opioid abuse. With the current prevalence of opioid abuse and misuse, it appears currently that mitragynine is deserving of more extensive exploration for its development or that of an analog as a medical treatment for opioid abuse." (p. 2823)

2.1.2.2 Intracranial Self-Stimulation (ICSS) Study of Abuse Potential

Another classic model for assessing the brain rewarding effects and drug abuse potential is the intracranial self-stimulation (ICSS) model. In the ICSS model, rats are equipped with electrodes in brain regions that lead animals to press a lever to self-deliver rewarding electrical brain stimulation (Negus & Miller, 2014). Opioids, amphetamine-like stimulants, cocaine, and other classic drugs of abuse reduce the threshold of stimulation and increase the strength of the rewarding effect of brain stimulation that delivers small electrical stimulations.

Behnood-Rod, Chellian, Wilson, et al. (2020) compared the potential brain rewarding effects of MG to morphine and found that morphine robustly and dose-dependently decreased the stimulation threshold consistent with other opioids, cocaine, amphetamine, and other drugs with high abuse potential (see also, Negus & Miller, 2014). In contrast, MG produced only a weak reduction in threshold with higher doses increasing the threshold. 7-OHMG did not reduce thresholds. Behnood-Rod, et al. (2020) concluded:

[10] https://www.americankratom.org/media/attachments/2021/01/25/kcpastates.pdf

"These initial findings indicate that mitragynine and 7-hydroxymitragynine are not rewarding in the ICSS procedure. The present results suggest that these kratom alkaloids do not have abuse potential." (p. 7)

2.1.2.3 Conditioned Place Preference Studies of Abuse Potential

Four studies employing various preparations of MG on CPP observed mixed effects across studies and some evidence suggestive of abuse potential at high doses. Japarin, Yusoff, Hassan, et al. (2021) evaluated cross-reinstatement of MG and morphine place preference in rats.

Another study found that baclofen pretreatment could prevent the acquisition and expression of MG-induced CPP (Yusoff, Mansor, Müller et al., 2018).

CPP also was demonstrated in mice but at high doses of a methanolic extract of kratom leaves (Vijeepallam, Pandy, Murugan, et al., 2019). The relevance of the high dose CPP studies to humans is not clear but is an example of the importance of diverse scientific approaches to better profile the overall safety including abuse potential of substances.

In the fourth study, described in greater detail I Factor 2, Wilson, Harris, Eans, et al. (2020) evaluated lyophilized (freeze-dried) kratom tea (LKT) as a potential treatment for pain and opioid dependence in a mouse model in which mice (referred to as knockout mice) were absent various drug receptors. The effects of oral LKT were examined in a warm water tail assay for nociception (pain relief), locomotor effects, respiratory depression, conditioned place preference, and to determine if it would reduce withdrawal signs in mice that were made physically dependent to on morphine by chronic morphine administration.

LKT did not induce conditioned place preference. See Factor 2 for summary of results on other measures.

Taken together these seven studies found no evidence of rewarding effects of MG in the IV self-administration and ICSS models, and weak evidence of potential reward in the CPP procedure.

2.1.2.4 Physical Dependence and Withdrawal Studies

The CDR at University Sains, Malaysia is actively evaluating MG's potential to produce physical dependence and withdrawal, as well as how its effects differ from those of classic opioids in animal physical dependence models evaluating substances under development as potential new medicines.

Harun, Johari, Mansor & Shoaib (2020) performed a series of studies comparing withdrawal following chronic MG and chronic morphine administration. Physical dependence with naloxone challenge tests and MG's effectiveness at reducing morphine withdrawal were evaluated. These studies found little evidence of physical dependence or withdrawal as compared to morphine and evidence of potential therapeutic benefits of MG for treating opioid withdrawal, consistent with human reports. Harun et al. (2020) concluded:

> "…the discontinuation of MG was not associated with the disruption of schedule-controlled behaviour in rats. This suggests that MG or analogs might be further investigated as potential therapeutic drugs for treating OUD and opioid withdrawal…The findings from this study suggest that discontinuation of MG is not associated with overt withdrawal effects, a finding that supports published studies using other behavioural models. For example, Hemby et al. (2019) and Yue et al. (2018) found that MG administration reduced IV morphine self-administration in rats but that MG itself did not maintain self-administration. The findings may suggest that MG possesses the desired characteristics of candidate pharmacotherapies for opioid dependence and withdrawal…. Although mitragynine may possess some addictive properties on its own, it may, in low-medium doses, in which humans voluntarily use it, help to manage opiate addiction." (p. 864)

In a follow-up study to Harun, et al. 2020, Johari, Harun, Sofian & Shoaib (2021) compared mitragynine to morphine withdrawal using the pentylenetetrazol (PTZ) discrimination mode for evaluating anxiogenic signs in rats. Although there are qualitative similarities in kratom withdrawal signs with opioid withdrawal signs, they are not only weaker for kratom but also may be distinct in several respects and this model can be helpful in characterizing the profile. The administration of PTZ produces a rodent model of anxiety that is used in pharmaceutical development. Morphine dependent rats press levers associated with PTZ administration when withdrawal is precipitated by naloxone administration. A recent study showed that MG withdrawal was not associated with such a response.

Twenty rats were treated with either MG at doses known to produce some physical dependence and withdrawal in rats and morphine. Then they were challenged with naloxone. Johari, et al. (2021) concluded as follows:

> "Unlike morphine that produced dose-related PTZ-like stimulus, MG at 3, 10, 30 and 45 mg/kg doses showed no substitution to the PTZ discriminative stimulus. In contrast to morphine which produced a time-dependent generalization to the PTZ stimulus, naloxone did not precipitate withdrawal effects in MG-treated rats as they selected the vehicle lever at three withdrawal time points. These results demonstrate that MG produces a very different response to morphine withdrawal that is not associated with anxiogenic-like subjective symptoms. These characteristics of MG may provide further support for use as a novel pharmacotherapeutic intervention for managing opioid use disorder." (p. 1)

Hassan, Pike See, Sreenlivasan, et al. (2020) compared the efficacy of MG to methadone for treating morphine withdrawal in a rat model of physical dependence and withdrawal. Hassan, et al. (2020) concluded:

> "…the morphine withdrawal model induced withdrawal signs for 16 days in rats. Four-day replacement treatment with mitragynine attenuated the withdrawal symptoms significantly, suggesting that mitragynine is able to reduce morphine withdrawal symptoms similar to methadone and buprenorphine. ...The present study suggests that mitragynine may serve as an alternative treatment for opiate withdrawal effects as they occur in opiate addiction. Although mitragynine may possess some addictive properties

on its own, it may, in low-medium doses, in which humans voluntarily use it, help to manage opiate addiction. The current report details the efficacy in comparison to methadone and buprenorphine. While mitragynine is equally effective in reducing opiate withdrawal effects in rats, it may be the safer drug with less undesired side-effects." (p. 9-10)

Although withdrawal signs in rats are weak as compared to morphine withdrawal, there does appear to be evidence of some degree of physical dependence. Other studies have explored brain proteins that might serve as more sensitive biomarkers for physiological dependence in rats (Hassan, Othman, Mansor, et al., 2021). Another study examined the attenuation of MG withdrawal signs in rats with clonidine (Hassan, Sreenivasan, Müller et al., 2021). Another study examined potential signs of naloxone precipitated withdrawal in rats (Harun, Johari, Japarin, et al., 2021a). Overall, such research is consistent with human reports that kratom withdrawal is generally more modest and more readily self-manageable than that produced by opioids.

2.1.2.5 Real World Evidence of Abuse and Dependence

As reported in 2018, there is kratom recreational use; however, all surveys in the US and SEA indicate that its euphoriant effects are relatively low as compared to opioids and other recreational drugs. Also, for opioids, stimulants, and other drug use there is a strong tendency to increase euphoria by smoking, injecting, and/or insufflating the drug. Electronic vaping devices can also be employed. This is notably less common for kratom, as raising the dose produces little increase in euphoria and increases undesirable effects including nausea. These factors limit kratom doses, as reported by kratom users in public hearings and internet discussion groups and may contribute to kratom's overall safety profile. Rapid delivery of high doses by non-oral routes contributes to the morbidity and mortality of opioids, stimulants, and other recreational drugs.

Several new surveys from the US and SEA and conclusions from leading kratom researchers worldwide in consensus-type review articles support the conclusions of the 2018 8-FA. The new survey data are summarized in Factors 4, 5 and 6. Several reviews and studies confirm that chronic high daily intake can lead to kratom dependence and withdrawal in some kratom users, but these are substantially less likely to interfere with family, social and occupational life and commitments as compared to opioid dependence. Moreover, kratom is widely viewed as a healthier and less life-impairing substance to replace opioids and other drugs including alcohol and stimulants (Galbis-Reig, 2016; Prozialeck, et al., 2019; Singh, et al., 2014; Swogger & Walsh, 2018).

A variety of reports confirm kratom use to self-manage opioid withdrawal and also that abstinence from high chronic kratom use is typically associated with milder symptomatology than abstinence from classical opioids as documented in surveys and discussed on the internet in websites and discussion groups such as Erowid and Reddit (See survey and internet discussion data in the following: Coe, et al., 2019; Prozialeck, et al., 2019; Singh, et al., 2014; Singh, et al., 2016; Singh, Narayanan, Müller, et al., 2018; Grundmann, et al., 2017 Garcia-Romeu, et al., 2020; Henningfield, et al., 2020; Smith, et al., 2017; Swogger, et al., 2015; Veltri & Grundmann, 2019).

The conclusions by Prozialeck, et al. (2020) and Grundmann, et al. (2018) were further strengthened by two published US surveys, which found that the overwhelming majority of kratom consumers use for health benefits and not to get high or for other recreational purposes (Coe, et al., 2019; Garcia-Romeu, et al., 2020). A third survey of over 12,000 kratom consumers presented at the 2020 annual meeting of the American College of Neuropsychopharmacology by Henningfield, Barr, Wang & Huestis (2020) showed that approximately 8300 respondents were using kratom to manage some "ailment" other than a substance use related disorder and approximately 3800 (32%) respondents were using kratom to manage "drug" withdrawal.

These three surveys were generally consistent with the Grundmann (2017) survey that reported most US kratom users were approximately 30-50 years old, had some college education and healthcare, were employed and consumed kratom for health and well-being. Leading reasons for use were pain, self-management of opioid and other substance use disorders and withdrawal, and mood disorders including depression, anxiety, and post-traumatic stress disorder. Dependence and withdrawal can occur but are generally reported as more tolerable, less disruptive to work and social function, and more readily self-manageable than opioid and other classic drugs of abuse, dependence, and withdrawal.

While this update on science related to the abuse potential and regulatory status was under development by Dr. Henningfield and colleagues at PinneyAssociates, several of the world's leading kratom researchers, Drs. Harun, Johari, Japarin, Suhaimi, Hassan, & Shoaib (2021b), published a new review article addressing similar scientific issues and reached generally similar conclusions. Harun, et al. (2021b) also described needed research, particularly for development of MG and/or analogs for submission for FDA regulatory approval as new drugs.

2.1.3 Factor 1 Updated Conclusions

Two rat intravenous self-administration studies showed no evidence of morphine or heroin like abuse potential by MG (Hemby et al. 2018 and Yue et al. 2018). Those same studies showed that MG pretreatment of animals reduced subsequent self-administration of morphine (Hemby et al., 2018) and heroin (Yue et al., 2018). These findings are consistent with human reports that kratom is useful in the management of opioid craving and withdrawal and to support opioid abstinence (Grundmann et al., 2018; Prozialeck et al., 2020; Coe et al., 2019; Garcia-Romeu et al., 2020).

Taken together, the new research suggests an overall abuse potential that is relatively low as compared to morphine and morphine-like opioids. Several models revealed little abuse potential, whereas the CPP model suggested weak but not zero abuse potential. This contrasts with opioids, stimulants and other classic drugs of abuse that demonstrate robust rewarding effects across all such abuse potential models. Similarly, MG's potential to produce physical dependence and withdrawal appears relatively low, but not absent, as compared to opioids in animal models. It is worth noting that the animal self-administration studies were published during the summer of 2018 when the Department of Health and Human Services was reviewing the FDA's 2017 recommendation (FDA, 2017a) that DEA permanently list MG and 7-OH-MG as CSA Schedule I drugs (see discussion below in Factors 4, 5 & 6) and one of the studies was cited as a new finding supporting the decision to withdraw the scheduling recommendation (Giroir, 2018).

The relevance and importance of such animal model data are well established, and in the case of kratom, was recognized in the formal FDA rescission of the kratom scheduling request submitted to the DEA in which Assistant Secretary Giroir stated:

> "One recently published peer reviewed animal study indicated that mitragynine does not have abuse potential and actually reduced morphine intake. As such, these new data suggest that mitragynine does not satisfy the first of the three statutory requisites for Schedule I, irrespective of broader considerations of public health."

These animal model findings are generally consistent with human reports that MG has a relatively low abuse potential as compared to Schedule II opioids but can reduce opioid self-administration and withdrawal. Surveys indicate that reducing opioid self-administration and withdrawal are among the most common reasons for kratom use in the US.

Not discussed above because they are not published articles are the tens of thousands of comments by kratom users and others interested in kratom policy to the DEA (approximately 20,300 in 2016) discussed in the Henningfield, Fant & Wang (2018) 8-FA, and many more in public hearings by FDA and NIDA (April, 2018), and public hearings convened by cities and states across the nation since 2018, in which kratom regulatory laws and policies were under consideration. These comments largely focused on the reasons that people use kratom which primarily fall into the category of health and well-being consistent with the surveys discussed in Factors 4, 5, and 6, and relatively rare reports of use to get high, or reporting addiction or serious harm.

2.2 Factor 2 – Scientific Evidence of its Pharmacological Effect

2.2.1 Summary of 2018 Findings:

"More research is clearly needed to elucidate receptor binding profiles and the diverse and probably complex mechanisms of action of the kratom alkaloids singly, in combination, and as commonly occurs in marketed products and brewed extracts." (Henningfield, Fant & Wang, 2018, p. 589).

2.2.2 Factor 2 Science Updates

Since 2018, pharmacological research characterizing kratom's effects and the mechanisms of action of its alkaloids rapidly advanced. For example, as discussed in Factor 1, the impact of drugs such as methadone, buprenorphine, and clonidine on rats that show evidence of MG withdrawal was studied (Hassan, Sreenivasan, Müller et al., 2021). This research documents the lower mortality risks of kratom compared to opioids based upon its mechanisms of action including its biased partial agonist effects that are lower in beta-arrestin recruitment, and thus also relatively low in producing physical dependence and respiratory depression.

There were also rapid advances in characterizing many of kratom's alkaloids in addition to MG and 7-OH-MG. Although most were insufficiently abundant in kratom leaves to contribute to its effects, some may be model analogs for potentially more effective and safe medicines for a variety of medical disorders. Whereas new medicines based on kratom's alkaloids may be ten years in the future, they are attracting increasing attention from leading researchers and pharmaceutical developers.

An important international clinical study collaboration between researchers at Yale School of Medicine and the Center for Drug Research Malaysia investigated kratom efficacy and safety for the treatment of pain (Vicknasingam, Chooi, Rahim, et al., 2020). As reported in 2018, animal models demonstrated MG's analgesic antinociceptive effects consistent with kratom's widespread use globally to self-manage pain; however, clinical evidence was lacking. The Vicknasingam et al. (2020 study employed the classic cold pressor task to evaluate the effects of kratom concoctions on pain tolerance by assessing how long research participants could tolerate the pain of inserting their hands into an ice water bath. Kratom produced significantly increased tolerance for pain as compared to placebo in long term daily kratom users, an important advancement in understanding kratom's therapeutic potential. The authors concluded:

> "These study findings provide the first objectively measured evidence obtained in controlled research with human subjects that are preliminarily supporting or confirming previously published reports of kratom pain relieving properties based on self-reports collected in observational studies." (p. 235-236).

In a study mentioned in Factor 2, Wilson, Harris, Eans, et al. (2020) evaluated lyophilized (freeze-dried) kratom tea (LKT) as a potential treatment for pain and opioid dependence in a mouse model in which mice (referred to as knockout mice) were absent various drug receptors. The effects of oral LKT were examined in a warm water tail assay for nociception (pain relief), locomotor effects, respiratory depression, conditioned place preference, and to determine if it would reduce withdrawal signs in mice that were made physically dependent on morphine by chronic morphine administration. Wilson, et al. (2020) reported the following results:

> "Oral administration of LKT resulted in dose-dependent antinociception (pain relief) in mice lacking the mu-opioid receptor (MOR) and reduced in mice lacking the kappa-opioid receptor. These doses of LKT did not alter coordinated locomotion or induce conditioned place preference, and only briefly reduced respiration. Repeated administration of LKT did not produce physical dependence, but significantly decreased naloxone-precipitated withdrawal in morphine dependent mice. The present study confirms the MOR agonist activity and therapeutic effect of LKT for the treatment of pain and opioid physical dependence." (p. 1)

Obeng, Wilkerson, Leon, et al. (2021) compared MG and 7-OH-MG in in vitro receptor binding affinity studies and in vivo studies of morphine discrimination, antinociception in the model pain "heated plate" test, and naloxone challenge tests to understand the role of endogenous morphine opioid receptors. This series of studies concluded:

> "At human m-opioid receptor (MOR) in vitro, mitragynine has low affinity and is an antagonist, whereas 7-hydroxymitragynine has 9-fold higher affinity than mitragynine and is an MOR partial agonist. In rats, intraperitoneal mitragynine exhibits a complex pharmacology including MOR agonism; 7-hydroxymitragynine has higher MOR potency and efficacy than mitragynine. These results are consistent with 7-hydroxymitragynine being a highly selective MOR agonist and with mitragynine having a complex

pharmacology that combines low efficacy MOR agonism with activity at nonopioid receptors." (p. 412)

Todd, Kellogg, Wallace, et al. (2020) investigated the functional selectivity of MG and 7-OH-MG to produce biased G-protein signaling, with little recruitment of β-arrestin. They concluded:

> "…To evaluate the biological relevance of variable speciofoline levels in kratom, we compared the opioid receptor binding activity of speciofoline, mitragynine, and 7-hydroxymitragynine. Mitragynine and 7-hydroxymitragynine function as partial agonists of the human μ-opioid receptor, while speciofoline does not exhibit measurable binding affinity at the μ-, δ-, or ƙ-opioid receptors. Importantly, mitragynine and 7-hydroxymitragynine demonstrate functional selectivity for G-protein signaling, with no measurable recruitment of β-arrestin. Overall, the study demonstrates the unique binding and functional profiles of the kratom alkaloids, suggesting potential utility for managing pain, but further studies are needed to follow up on these in vitro findings. All three kratom alkaloids tested inhibited select cytochrome P450 enzymes, suggesting a potential risk for adverse interactions when kratom is co-consumed with drugs metabolized by these enzymes." (p.1)

Kruegel, Uprety, Grinell, et al. (2019) examined this possibility in a series of studies and concluded:

> "…preliminary research has provided some evidence that mitragynine and related compounds may act as atypical opioid agonists, inducing therapeutic effects such as analgesia, while limiting the negative side effects typical of classical opioids. Here we report evidence that an active metabolite plays an important role in mediating the analgesic effects of mitragynine. We find that mitragynine is converted in vitro in both mouse and human liver preparations to the much more potent mu-opioid receptor agonist 7-hydroxymitragynine and that this conversion is mediated by cytochrome P450 3A isoforms. Further, we show that 7-hydroxymitragynine is formed from mitragynine in mice and that brain concentrations of this metabolite are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of mitragynine. At the same time, mitragynine is found in the brains of mice at very high concentrations relative to its opioid receptor binding affinity, suggesting that it does not directly activate opioid receptors". (p. 1)
>
> "Further, it suggests a possible explanation for the seemingly improved safety profile of mitragynine compared to classical opioid agonists. However, the critical involvement of hepatic metabolism also complicates our understanding of mitragynine's pharmacology and introduces the possibility of interindividual variability in the compound's potential therapeutic effects and side effects. We believe mitragynine and related compounds have great potential as future therapeutics, but metabolic processes must be carefully considered as the field continues to advance". (p. 7)

The Kruegel et al. studies provided the foundation for their new pharmaceutical company to develop new kratom derived molecular entities for the treatment of pain, depression, and substance use and other disorders[11].

Reeve, Obeng, Oyola, et al. (2020) evaluated the discriminative stimulus properties of MG in a series of studies to determine the pathway that primarily mediates these effects since it only partially generalizes to opioids. They found full generalization to lofexidine and phenylephrine suggesting that its discriminative effects are primarily mediated by adrenergic and not opioid receptors.

Hiranita, Sharma, Oyola, et al. (2020) investigated the hypothesis that MG exerts opioid agonist activity, in part, through metabolic conversion to 7-OH-MG. The authors concluded:

> "Though the conversion rate of 7-hydroxymitragynine from p.o. mitragynine is low, 7-hydroxymitragynine is a more potent and efficacious μ-opioid receptor agonist than mitragynine, suggesting that conversion to this metabolite may contribute to the in vivo μ-opioid activity of mitragynine." (p. 1)

Multiple investigators' research characterizing MG alkaloids receptor binding profiles and pharmacologic activities also supports pursuit of kratom alkaloid-based substances for the treatment of alcohol use disorder, pain, opioid withdrawal, and other disorders (Chakraborty, Uprety, Daibani, et al., 2021; Gutridge, Robins, Cassell, et al., 2020). Chakraborty, Uprety, Daibani, et al. (2021) concluded:

> "In conclusion, we report a thorough and complete in vitro pharmacological characterization of five kratom based minor alkaloids. Given their low abundance, it seems unlikely that these alkaloids play a major mediating role in the biological actions of kratom consumed by humans. However, these alkaloids represent novel starting points for optimizing probes to better understand opioid receptor function.
>
> There are three major findings from this present work. First, we identify three new templates present in kratom with antinociceptive activity in mice, with corynoxine being equipotent to morphine. Second, we identify ligands with an array of pharmacological profiles, ranging from the partial opioid agonism displayed by corynantheidine and mitraciliatine and full agonism of corynoxine and KOR agonism with isopaynantheine. Finally, we identify corynoxine and mitraciliatine to be structurally unique natural products with safer, MOR dependent antinociception, and we identify isopaynantheine as the first kratom alkaloid with KOR mediated antinociceptive actions." (p. 11)

Animal models are also employed to assess potential cognitive effects of kratom. Although kratom is commonly taken to enhance occupational performance and as a coffee substitute for energy at low doses, it would not be surprising to see performance decrements at high doses. Indeed, in an animal model of special learning and memory, high doses impaired memory in this model (Hassan, Suhaimi, Ramanathan, et al., 2019). The relevance of the results to

[11] https://www.kures.life/

humans cannot be assessed based on this study but it suggests that more research is warranted.

Suhaimi, Hassan, Mansor & Müller (2021) studied brain electroencephalogram (EEG) activity after acute and chronic exposure to chronic MG in rats. Suhaimi, et al. (2021) summarized their findings as follows:

> "… the changes in brain electroencephalogram (EEG) activity after acute and chronic exposure to mitragynine in freely moving rats. Vehicle, morphine (5 mg/kg) or mitragynine (1, 5 and 10 mg/kg) were administered for 28 days, and EEG activity was repeatedly recorded from the frontal cortex, neocortex and hippocampus. Repeated exposure to mitragynine increased delta, but decreased alpha powers in both cortical regions. It further decreased delta power in the hippocampus. These findings suggest that acute and chronic mitragynine can have profound effects on EEG activity, which may underlie effects on behavioral activity and cognition, particularly learning and memory function." (p. 1)

Gutridge, Robins, Cassell, et al. (2020) pharmacologically characterized kratom extracts, kratom alkaloids, and synthetic carfentanil-amide opioids interactions with G proteins and beta-arrestin at mu, delta and kappa opioid receptors *in vitro* and assessed the degree to which opioids reduced alcohol intake and whether they had rewarding properties. The authors stated:

> "In conclusion, we found that kratom alkaloids do not recruit β-arrestin 2 at the μOP, δOP and κOP and can significantly reduce both moderate and binge alcohol intake in male and female mice. This pharmacological profile and effect on alcohol intake in rodents may explain why some find kratom useful to self-medicate for alcohol use disorder. Yet, as we observed that kratom extract and 7-hydroxymitragynine exhibited reinforcing properties, our study also highlights the risks associated with kratom use. Our results indicate that δOPs contributed to the efficacy of the kratom alkaloids to reduce alcohol intake, whereas the lack of efficacy for the G protein-biased μOP agonist TRV130 to decrease alcohol intake argued against a major role for the μOP in this behavioral response. The ability of MP102, a synthetic G protein-biased opioid with a preference for δOP, to reduce alcohol intake without affecting general locomotion or inducing (δOP-mediated) CPP provides support for future efforts to produce G protein-selective, δOP-selective opioids for the treatment of alcohol use disorder, some of which could be plant-derived still as well". (p. 1510)

Hiranita, Leon, Felix, et al. (2019) compared the effects of MG to morphine in behavioral and antinocioception assays in rat models. They wrote:

> "Morphine and mitragynine dose-dependently decreased schedule-controlled responding; the ED50 values were 7.3 and 31.5 mg/kg, respectively. Both drugs increased thermal antinociception (the ED50 value for morphine was 18.3). Further, doses of naltrexone that antagonized morphine did not antagonize mitragynine. Mitragynine (17.8 mg/kg) did not alter the rate-decreasing or antinociceptive effects of morphine. …The antinociceptive effects of mitragynine and morphine occur at doses larger than those that disrupt learned behavior. Opioid receptors do not appear to mediate the disruptive effects of mitragynine on learned behavior. Mitragynine had

lesser antinociceptive effects than morphine, and these did not appear to be mediated by opioid receptors. The pharmacology of mitragynine includes a substantial non-opioid mechanism." (p. 1)

2.2.2.1 Studies of Kratom Minor Alkaloids and their Metabolites

While kratom contains many alkaloids (more than 50 identified to date and more likely to be discovered), only one or a few of these account for most of the effects produced in humans. This is a trait also found in other psychoactive plants, such as coffee, tea, and cannabis.

Most of these alkaloids are likely at what may be de minimis levels with respect to the human experience, effects, and safety. However, it is also possible that while the majority of the effects produced by natural plant-based preparations are mediated by MG, one or more of these minor alkaloids may also play a minor role. This may account for possible differences in strains of kratom products. Increasingly, it appears that 7-OH-MG, long considered a substance of potentially greater concern than MG from a safety perspective may occur naturally at functionally de minimis levels (Chear, Leon, Sharma, et al., 2021; Kruegel, Uprety, Grinell, et al., 2019).

These molecules are also of interest as potential new drug candidates or as templates for novel synthesized molecules. It has been estimated that up to one third to one half of FDA approved medicines are based on natural plant product substances that provided the novel structures utilized in development of the final approved medicines or which at least were critical in the drug development process (Newman & Cragg, 2016; Domnic, Narayanan, Mohana-Kumaran & Singh, 2021).

Chear, et al. (2021) reported the results of an extensive study in which:

> "Ten indole and oxindole alkaloids were isolated from the freshly collected leaves of Malaysian Mitragyna speciosa (Kratom). The chemical structures of these compounds were established on the basis of extensive 1D and 2D NMR and HRMS data analysis. The spectroscopic data of mitragynine oxindole B (4) are reported herein for the first time. The spatial configuration of mitragynine oxindole B (4) was confirmed by single-crystal X-ray diffraction. Simultaneous quantification of the isolated alkaloids in the M. speciosa leaf specimens collected from different locations in the northern region of Peninsular Malaysia was also performed using UPLC-MS/MS. The oxindole alkaloids (1−4) and the indole alkaloid (10) were assessed for binding affinity at opioid receptors. Corynoxine (1) showed high binding affinity to μ-opioid receptors with a Ki value of 16.4 nM. Further, corynoxine (1) was 1.8-fold more potent than morphine in rats subjected to a nociceptive hot plate assay. These findings have important implications for evaluating the combined effects of the minor oxindole alkaloids in the overall therapeutic activity of *M. speciosa*." (p. 1).

Domnic, Chear, Rahman, et al. (2021) showed that combinations of kratom alkaloids may inhibit cell proliferation and migration of nasopharyngeal carcinoma cells suggesting potential for the development of the substances themselves or possibly new analogs as new treatments for cancer. As discussed by the authors, these are early-stage findings but certainly findings that merit further study. Regarding 7-OH-MG, they also reported that 7-OH-MG was only

present at very low levels in all samples, supporting other reports which suggest that it is a postharvest artifact resulting from MG.

Kruegel, et al. (2019) has also suggested that the effects of kratom are not produced by exogenously ingested 7-OH-MG but that the metabolism of MG to small amounts of 7-OH-MG may modulate and contribute to some of the desired effects such as pain relief.

Sharma, Kamble, Leon, et al. (2019) employed a method to simultaneously quantify ten key kratom alkaloids in kratom leaf extracts and commercial products using ultra-performance liquid chromatography–tandem mass spectrometry. They summarized their results as follows:

> "…an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method was developed and validated for the quantification of ten key alkaloids, namely: corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine, mitragynine, mitraphylline, paynantheine, speciociliatine, and speciogynine… After successful validation, the method was applied for the quantification of kratom alkaloids in alkaloid-rich fractions, ethanolic extracts, lyophilized teas, and commercial products. Mitragynine (0.7%–38.7% w/w), paynantheine (0.3%–12.8% w/w), speciociliatine (0.4%–12.3% w/w), and speciogynine (0.1%–5.3% w/w) were the major alkaloids in the analyzed kratom products/extracts. Minor kratom alkaloids (corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine) were also quantified (0.01%–2.8% w/w) in the analyzed products; however mitraphylline was below the lower limit of quantification in all analyses." (p. 1)

Kamble, Berthold, King, et al. (2021) developed and validated a bioanalytical method for the simultaneous quantification of 11 kratom alkaloids in rats following oral administration of lyophilized kratom tea (LKT) and a marketed kratom product, Optimized Plant Mediated Solutions (OPMS). The authors concluded:

> "In the present study, OPMS liquid showed an extended exposure of kratom alkaloids as compared to LKT. Among the tested alkaloids, only MTG, 7-HMG [7-OH-MG], COR, and SPC showed measurable systemic exposure following an oral dose. Having an understanding of the pharmacokinetics of individual kratom alkaloids following the oral administration of kratom products in preclinical species will facilitate the design of clinical trials evaluating kratom products. Additionally, the developed bioanalytical method can be implemented for the analysis of plasma samples obtained from a variety of animal species including humans using standardized kratom products". (p. 6)

Bhowmik, Galeta, Havel, et al. (2021) mapped the neuropharmacology of Mitragyna alkaloids. The authors concluded

> "In summary, we describe a systematic examination of late-stage functionalization of kratom alkaloids, which provided efficient access to MG analogs and identified 11-F-7OH (22) as an important lead compound for further investigations". (p.11)

2.2.2.2 MG Metabolism and Metabolite Profiling.

Another rapidly advancing area of research is understanding the metabolic pathways and modulating enzymes including profiling of MG's metabolites, and identification of enzymes modulating MG metabolism.

Kamble, Sharma, King, et al. (2019) included the following summary in their abstract:

> "Metabolic pathways of MG were identified in human liver microsomes (HLM) and S9 fractions. A total of thirteen metabolites were identified, four oxidative metabolites and a metabolite formed by demethylation at the 9-methoxy group were the major metabolites of MG. 3. The cytochrome P450 enzymes involved in the metabolism of MG were identified using selective chemical inhibitors of HLM and recombinant cytochrome P450. The metabolism of MG was predominantly carried out through the CYP3A4 with minor contributions by CYP2D6 and CYP2C9. The formation of five oxidative metabolites (Met2, Met4, Met6, Met8 and Met11) was catalyzed by the CYP3A4. 4. In summary, MG was extensively metabolized in HLM primarily to O-demethylated and monooxidative metabolites. The CYP3A4 enzyme plays a predominant role in the metabolic clearance of MG and also in the formation of 7-hydroxyMG (Met2), a known active minor alkaloid identified in the leaf material." (p. 1)

Another study by Kamble, Sharma, King, et al. (2020) examined the potential interactions in metabolism of MG and other alkaloids that may occur with other substances including pharmaceutic products. This is also early work but fundamental in understanding potential interactions that could increase risk of use and may thereby at some point be included in warning labels for kratom and/or future potential kratom based drug products.

A systematic metabolic study evaluated how metabolism alters opioid mediated effects, possibly without increasing harmful respiratory effects. Kamble, León, King, et al. (2020) reported:

> "…in human plasma 7-HMG is converted to mitragynine pseudoindoxyl, an opioid that is even more potent than either mitragynine or 7-HMG. This novel metabolite is formed in human plasma to a much greater extent than in the preclinical species tested (mouse, rat, dog, and cynomolgus monkey) and due to its μ-opioid potency may substantially contribute to the pharmacology of kratom in humans to a greater extent than in other tested species." (p. 1)

Such research may explain potential human effects and benefits that may not be predicted in animal studies alone.

2.2.3 Factor 2 Updated Conclusions

Scientific advances in understanding the pharmacology and mechanisms of action of kratom's primary active alkaloid, MG, as well as 7-OH-MG, and increasingly the minor alkaloids that appear to contribute relatively little to the effects of kratom in kratom consumers may ultimately contribute to safer and more effective new medicines for a variety of disorders as well as for general health and well-being. Development and approval of such products may be a decade or more in the future, but in the meantime, this rapidly advancing science is helping to explain

how kratom works, and why its pain relieving and other benefits occur with relatively low levels of abuse, dependence, and harmful decreases in respiration as compared to opioids.

2.3 Factor 3 – The State of Current Scientific Knowledge Regarding the Drug

2.3.1 Summary of 2018 Findings:

The 2018 8-FA highlighted kratom's pharmacodynamic effects described in earlier investigations and reviews (e.g., Prozialeck, et al., 2012; Warner, et al., 2016). In one PK study involving oral MG administration to ten healthy male volunteers, a two-compartment model best described MG's pharmacokinetics (Trakulsrichai, et al., 2015). Preclinical and clinical pharmacokinetic data are limited, with significant variability within and between species. There was little clinical study of human physiological effects and health parameters to draw on.

2.3.2 Factor 3 Science Updates

Several new preclinical pharmacokinetic studies also provide important safety data, as animals were closely monitored over 12 h or more for adverse events associated with MG and 7-OH-MG plasma concentrations.

2.3.2.1 Pharmacokinetics and Pharmacodynamics Findings Related to Safety (MG and 7-OH-MG)

Most human consumption in the US and SEA is in traditional tea-like decoctions containing 0.5-1 mg/kg MG per serving; however, more intense users managing chronic pain or suffering from opioid use disorder may consume four or more servings per day and in some cases, larger serving sizes, totaling 20 mg/kg/day.

Avery, Boddu, Sharma, et al. (2019) studied the pharmacokinetics of mitragynine in rats following oral administration of a variety of preparations. One of the many important findings was summarized as follows:

> "The results provide evidence that an equivalent oral dose of the traditional preparation (lyophilized kratom tea) and formulated/manufactured products (organic fraction) of kratom leaves provide better systemic exposure of mitragynine than that of mitragynine dosed alone." (p. 1)

Maxwell, King, Kamble, et al. (2020) evaluated MG's safety and pharmacokinetics in beagle dogs following 5 mg/kg oral MG (equivalent to approximately 3 mg/kg in humans) and 0.1 mg IV MG. The authors summarized:

> "The dose of 7-HMG used in this study was well tolerated with no adverse events or major abnormalities in clinical parameters…Derived pharmacokinetic parameters of 7-HMG from this study can be scaled allometrically along with the pharmacokinetic parameters of mitragynine to predict the dose of mitragynine while designing the first in human study." (p. 462)

No life threatening or serious adverse events were reported.

The Hiranita, Sharma, Oyola, et al. (2020) study discussed in Factor 2 also evaluated the pharmacokinetics of 55 mg/kg oral MG in rats. As reported:

> "Following p.o. administration of mitragynine (HCl salt, 55 mg/kg), the Cmax value of 7-hydroxymitragynine (85 ng/mL) was 14-fold less than that of mitragynine. The Tmax values of 7-hydroxymitragynine and mitragynine were 30 and 84 minutes, respectively… drug discrimination was used as a pharmacologically selective measure of μ-opioid receptor agonism *in vivo*. In rats discriminating morphine (3.2 mg/kg, i.p.) from vehicle, the discriminative stimulus effects of mitragynine were assessed 90 minutes after p.o. administration to correspond to its Tmax. Mitragynine (up to 178 mg/kg) produced 76% morphine-lever responding (ED50=51 mg/kg). Though the conversion rate of 7-hydroxymitragynine from p.o. mitragynine is low, 7-hydroxymitragynine is a more potent and efficacious μ-opioid receptor agonist than mitragynine, suggesting that conversion to this metabolite may contribute to the *in vivo* μ-opioid activity of MG." (p. 1)

2.3.2.2 Pharmacokinetic and Pharmacodynamic Findings Related to Safety (Minor Alkaloids)

In addition to studies of MG and 7-OH-MG pharmacokinetics, there is increasing attention to the pharmacokinetics and other effects of other alkaloids from traditional kratom tea decoctions and commercial products.

Kamble, Berthold, King, et al. (2021) characterized the pharmacokinetics of eleven alkaloids given orally to rats. As described by the authors, they:

> "…developed and validated a bioanalytical method for the simultaneous quantitation of 11 kratom alkaloids (mitragynine, 7-hydroxymitragynine, corynantheidine, speciogynine, speciociliatine, paynantheine, corynoxine, corynoxine-B, mitraphylline, ajmalicine, and isospeciofoline) in rat plasma. The validated method was used to analyze oral pharmacokinetic study samples of lyophilized kratom tea (LKT) and a marketed product, OPMS liquid shot, in rats. Among the 11 alkaloids, only mitragynine, 7-hydroxymitragynine, speciociliatine, and corynantheidine showed systemic exposure 8 h post dose, and the dose-normalized systemic exposure of these four alkaloids was higher (1.6−2.4-fold) following the administration of the commercial OPMS liquid. Paynantheine and speciogynine levels were quantifiable up to 1 h post dose, whereas none of the other alkaloids were detected. In summary, the method was successfully applied to quantify the exposure of individual kratom alkaloids after an oral dose of traditional or commercial products. This information will contribute to understanding the role of each alkaloid in the overall pharmacology of kratom and elucidating the pharmacokinetic differences between traditional and commercial kratom products." (p. 1)

Berthold, Kamble, Raju, et al. (2021) studied the pharmacokinetics of the minor indole kratom alkaloid, speciociliatine. They summarized:

> "An ultra-performance liquid chromatography tandem mass spectrometry method was developed and validated to quantify speciociliatine in rat plasma. The quantitation range

was 3−600 ng/mL. The validated method was applied to a preclinical pharmacokinetic study in male Sprague-Dawley rats after 2.5 mg/kg intravenous (I.V.) and 20 mg/kg oral (P.O.) dosing. The plasma was analyzed to obtain concentration-time profiles and results were subjected to non-compartmental analysis to determine pharmacokinetic parameters including volume of distribution (6.2 ± 2.3 L/kg I.V.), clearance (0.7 ± 0.2 L/h/kg), and absolute oral bioavailability (20.7%). Speciociliatine had higher systemic exposure and lower clearance compared to the other kratom alkaloids mitragynine and corynantheidine. The speciociliatine pharmacokinetic parameters described here will help to better understand the overall effects reported with kratom product use." (p. 1)

These data suggest why natural kratom leaf based kratom products, extracts, and tea-like decoctions might differ in the effects experienced by kratom users from more refined extracts, as explained by the authors:

> "Interestingly, the exposure of mitragynine when it is dosed orally in rats as lyophilized kratom tea or the organic fraction obtained from lyophilized kratom tea increases by 1.5- and 1.8-fold, respectively [18]. The lyophilized kratom tea and organic fraction contains all the alkaloids that would be present in the plant, including speciociliatine. These results indicate that the presence of other alkaloids found in the traditional preparation have influence on the pharmacokinetics of mitragynine. Similarly, the pharmacokinetic parameters of speciociliatine, when dosed in combination with the other naturally occurring alkaloids, may be altered. Further research into the pharmacokinetics of minor indole alkaloids after administration of a lyophilized kratom tea product must be investigated to determine which alkaloids' parameters are affected by the presence of other compounds." (p. 2)

This is not to imply that chewing kratom leaves, kratom tea like decoctions or more simplified extracts are more beneficial or safer than other MG products, but that they may differ in the effects that users seek, desired and undesired. It supports the conclusion that since none were demonstrated to be more beneficial or harmful than others, with the exception of adulterated products in which other substances are added or possibly an individual alkaloid's concentration is boosted to unnaturally high levels (e.g., 7-OH-MG), that there is yet no safety basis for banning such products from the marketplace.

A published abstract by Jagabalan, Zainal, Ganaby, et al. (2019) reported:

> "Estimated typical clearance (CL/F) value was 2.21 L/hr, absorption rate (Ka) of 0.82/hr, and volume of distribution (Vd) of 30.8L. . . . Based on the single dosing experimental rat data, the model [2-compartment distribution with 1st order absorption] provides a useful tool to quantify the pharmacokinetic parameters to propose an optimal dosing regimen in rats. Subsequently, the pharmacokinetics parameter can be modeled to the pharmacodynamics of MG for extrapolation into human use." (p. 1)

King, Sharma, Kamble, et al. (2020) developed bioanalytic methods to study the PK of corynanthidine, which is a minor kratom alkaloid that binds to opioid receptors and acts as a functional opioid antagonist (e.g., with some naloxone-like properties). This study was important both for its methods development as well as characterization of the PK of corynanthidine given intravenously and orally to rats.

2.3.2.3 Safety Assessments from Preclinical and Clinical Studies

Currently, there are no validated assessments of the lethal dose for humans or animals, mainly due to the unreliability and difficulty in studies that have attempted to determine lethal doses in animals, and the fact that most human deaths in which kratom use was verified were more likely caused by other substances (e.g., Olsen et al. 2019; Henningfield, Grundmann, Babin, et al. 2018, Babin, 2019).

Smith et al., 2019 conducted a study comparing oral and intravenous MG and 7-OH-MG to establish the lethal doses (LD_{50} doses) in mice. They were able to produce death by an oral dose of 547.7 mg/kg MG, though were unable to produce death by oral 7-OH-MG administration. Large intravenous doses of MG (27.8mg/kg), 7-OH-MG (24.7 mg/kg), and heroin (23.7 mg/kg) were also lethal. Some of their observations are inconsistent with those from other laboratories (e.g., Kruegel, Gassaway, Kapoor et al., 2016 and see also Kruegel et al., 2019), though not consistent with rat toxicity study data summarized in Henningfield, Fant & Wang, 2018; thus, this study awaits replication.

It should be noted that human use of kratom alkaloids by intravenous injection is not practiced for several reasons. First, rapid administration (e.g. smoking) does not produce as pleasurable effects or desired effects compared to oral use (Henningfield, Fant and Wang, 2018). Additionally, MG and 7-OH-MG are not soluble in water and must be prepared using specialized laboratory preparations involving a tween/DMSO based vehicle (as used in Smith et al., 2019). Thus, this study represents another line of research that will be important to continue but its relevance to real world kratom safety and toxicity is not clear.

To better understand potential health and safety related effects related to kratom use, Leong Bin Abdullah, Tan, Mohd, et al. (2020) studied the lipid profiles, liver function and other parameters in 100 chronic kratom users compared to 100 healthy nonusers in Malaysia. Although the study was acknowledged by the authors to be relatively small and exploratory, their preliminary findings will be useful in the design of future studies. They found:

> "The liver parameters of the study participants were within normal range. The serum total cholesterol and LDL of kratom users were significantly lower than those of healthy subjects who do not use kratom. There were no significant differences in the serum triglyceride and HDL levels. However, higher average daily frequency of kratom use and increasing age were associated with increased serum total cholesterol among kratom users. Other kratom use characteristics such as age of first kratom intake, duration of kratom use, and quantity of daily kratom intake were not associated with increased serum triglyceride, total cholesterol, LDL, and HDL levels. Our findings suggest regular kratom consumption was not linked to elevated serum lipids, except when there is a higher frequency of daily kratom intake. However, the study was limited by the small sample size, and hence a more comprehensive study with larger sample size is warranted to confirm the findings." (p. 1)

A preliminary study of the impact of kratom use on brain function (as assessed by brain magnetic resonance imaging) among chronic kratom users in Malaysia was conducted by Singh, Chye, Suo, et al. (2018). In brief, they reported:

> "A total of 14 subjects (7 regular kratom users and 7 non-kratom users) voluntarily participated in this cross-sectional study…. There were no significant differences ($p>0.05$) in the intracranial volume (ICV), cortical volumes (frontal, parietal, temporal, occipital, or cingulate lobe), or subcortical volumes (striatum, hippocampus, or amygdala), as well as in the diffusion tensor imaging (DTI) metrics, fractional anisotropy (FA) and mean diffusivity (MD) between kratom users and the controls.
>
> Conclusion: This preliminary study showed long-term consumption of kratom decoction is not significantly associated with altered brain structures in regular kratom users in traditional settings. However, further study is needed to establish more data for kratom use and its effects." (p. 1)

Singh, Müller, Murugaiyah, et al. (2018) studied various hematological and clinical-chemistry parameters of kratom users in Malaysia. In brief, Singh, et al. (2018) summarized their results as follows:

> "A total of 77 subjects (n=58 regular kratom users, and n=19 healthy controls) participated in this cross-sectional study. All the surveys were conducted through face-to-face interview to elicit subject's sociodemographic characteristics and kratom use history. A full-blood test was also administered. Laboratory analysis was conducted using GC-MS to determine mitragynine content in the acquired kratom samples in order to relate mitragynine consumption with possible alterations in the blood parameters of kratom users. Findings showed that there were no significant differences in the hematological and clinical-chemistry parameters of traditional kratom users and healthy controls, except for HDL and LDL cholesterol values; these were found to be above the normal reference range for the former. Similarly, long-term kratom consumption (> 5 years), and quantity of daily kratom use (≥3 ½ glasses; mitragynine content 76.3–114.8 mg) did not appear to alter the hematological and biochemical parameters of kratom users. These data suggest that even long-term and heavy kratom consumption did not significantly alter the hematological and clinical-chemistry parameters of kratom users in a traditional setting." (p. 1)

Singh, Narayanan, Grundmann, et al. (2020), studied the long-term effects of kratom use in thirteen people in Malaysia who had used kratom longer than 20 years in a cross-sectional pilot study. They summarized their results as follows:

> "Respondents were required to undergo a blood-test and laboratory analysis was conducted to determine the mitragynine content in an acquired street sample of kratom. The regular, long-term consumption of brewed kratom decoction did not cause any significant alterations in haematological, kidney, liver, thyroid, inflammatory and gastrointestinal analytes in a cohort of kratom users who had no history of substance misuse. However, those who had a higher intake (>3 glasses per day) of kratom exhibited higher lipid values (except for HDL-cholesterol), and a moderate elevation of homocysteine level. Long-term (>20 years with a daily intake of ≥87.54mg of mitragynine) kratom consumption was not associated with altered biochemical levels, although prolonged and heavy use (>3 glasses daily) may result in cardiovascular risks. The latter finding, however, requires further investigation." (pg. 1)

Singh, Narayanan, Müller et al. (2019) studied potential long-term cognitive effects associated with kratom use in kratom uses in Malaysia. Singh, et al. (2019) summarized their results as follows:

> "We assessed the cognitive function of 70 regular kratom users and 25 control participants using the Cambridge Neuropsychological Test Automated Battery. Participants performed six neuropsychological tasks that assessed motor, learning and memory, attention and executive function. Relative to control participants, higher consumption (>3 glasses daily or mitragynine doses between 72.5 mg and 74.9 mg) of kratom tea was selectively associated with impaired performance on the Paired Associates Learning task, reflecting deficits in visual episodic memory and new learning. Overall, the performance of kratom users compared to control participants, and the performance of high (>3 glasses per day) as well as low (≤3 glasses per day) kratom using groups, were comparable on all neuropsychological domains. Higher intake of kratom juice (>3 glasses daily) did not appear to impair motor, memory, attention or executive function of regular kratom users." (p. 1)

Increasing attention to safety related signals is evident in much ongoing kratom research. For example, Leong Abdullah, Tan, Narayanan, et al. (2021) studied the prevalence of ECG abnormalities and QTc intervals in kratom users without histories of illicit drug use. They found:

> "…the odds of having ECG abnormalities did not differ between kratom users and non-kratom-using control subjects, except for higher odds of sinus tachycardia in kratom users. Torsades de pointes was not reported among kratom users, but greater age at first kratom use, longer duration of kratom use, the higher daily quantity of kratom use, and intake of kratom less than 3 h before an assessment could increase the QTc interval with an estimated daily mitragynine intake of 434.28 mg (7.06 mg/kg/day). Hence, we found that regular daily kratom consumption led to borderline QTc intervals, but it was not associated with prolonged QTc intervals. However, further controlled clinical studies are needed to confirm our findings." (p. 1)

2.3.3 Factor 3 Updated Conclusions

Among the most important data in assessing product safety is investigation of the patterns of exposure and associated safety in pharmacokinetics and other studies. As described, the science advanced considerably in this domain. It shows that over a broad range of doses, dosage form and within two species (rat and dog) MG can be safely given. This includes oral doses that are many multiples of those consumed by humans.

Additionally, six clinical studies evaluated the effects of long-term kratom use on a variety of physiological parameters including kidney and liver function, blood chemistry hematological parameters, cognition, cardiac parameters including ECG, and on brain function by brain magnetic resonance imaging. Although these were relatively small studies, none suggest serious adverse consequences of use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies.

2.4 Factors 4, 5, and 6 – History and Current Patterns of Abuse; The Scope, Significance and Duration of abuse; What, if any, Risk is there to the Public Health

Note that for this update, Factors 4, 5 and 6 are considered together because they all contribute to understanding nonmedical use, recreational use and abuse, and public health impact, relying on some of the same surveys across factors.

These factors address public health considerations which include the impact of various regulatory approaches on individual and public health risks and benefits of CSA scheduling versus not scheduling, as well as the most appropriate schedule if the substance or product is approved for therapeutic use. Substances that are considered to merit control in the CSA but which are not approved for therapeutic use can only be placed in Schedule I regardless of their actual abuse potential.

For temporary scheduling (also known as “emergency” scheduling) only factors 4, 5, and 6 must be considered. Temporary scheduling lasts for two years and can be recommended by the FDA or conducted by DEA without recommendation from FDA.

The key conclusion of analysis of Factors 4, 5 and 6 that must be drawn to support temporary scheduling is that the substance poses an imminent risk to public health related to its abuse. For poisons and toxins not used for psychoactive and abuse related effects, such as contaminated food products, etc. public health interventions and sometimes regulations other than the CSA are employed as appropriate.

2.4.1 Summary of 2018 Findings:

Survey and public health data are the most important sources of information to determine if a substance merits temporary scheduling. Only Factors 4, 5 and 6 must be considered for temporary scheduling. If these factors together support the conclusion that a substance poses imminent risk to public health related to its abuse and apparently addictive use, then the substance or product can be placed in the CSA. Schedule I is the only option if there is no FDA approved therapeutic use (i.e., approval as a medicine). Note for poisons and toxins that are not used for psychoactive and abuse related effects, the CSA is not considered the appropriate regulatory tool to protect public health.

Factors 4, 5 and 6 of the 2018 8-FA documented several decades of kratom use in the US that began before the 1980s. In contrast to opioids, kratom use in SEA and the US was almost exclusively by the oral route with use primarily for health and well-being including self-management of pain, opioids and other addictions, improvement of mood in people with depression and anxiety disorders, and for many people as an alternative or complement to coffee to improve occupational performance. Use for recreational purposes, e.g., to get “high” was not a major category of use. Major US federal surveys including the Drug Abuse Warning Network (DAWN) (until 2011 when it was discontinued), the Monitoring the Future Survey (MTFS), Treatment Episodes Data Set (TEDS), and the National Survey on Drug Use and Health (NSDUH) showed little evidence of kratom use, abuse, addiction or harm.

Although the DEA’s National Forensic Laboratory Information System (NFLIS) began detecting MG use and reporting it in 2010 as a potential emerging trend, overall reports remained low (less than 200 of 1,549,313) in 2015, and apparently below the threshold for continued

reporting when the 2018 8-FA was written. The Henningfield, Fant & Wang (2018) 8-FA summarized Factor 4 as follows

> "As confirmed by NFLIS, kratom is available to persons who have been found with substances of abuse, yet kratom has not emerged as a substance of abuse by any of the federal surveillance systems. Nonetheless, as MG identifications were a new category, the DEA placed MG on its "watch list," meaning essentially that laboratories and investigators are encouraged to be alert for products potentially containing MG and to be testing for MG....The relative absence of apparent abuse of kratom as measured by national surveys does not mean there is no abuse, but certainly the signal is very weak compared to many other substances that people seek help for to achieve abstinence.…As mentioned earlier, the very low risk of overdose poisoning and serious adverse events does not mean that they have not and will not occur. However, given the two decades during which consumption has increased to an estimated two or more million consumers in the US, in addition to far more extensive consumption in SE Asia, this is a substance and category of product with a remarkable safety record." (p. 580)

2.4.2 Factor 4, 5, and 6 Science Updates

2.4.2.1 Prevalence of Kratom Use in the US

One of the most important questions in public health assessments relevant to a drug's health risks and benefits is the number of users. The surveys and more than 20,000 comments to the DEA in 2016 define the demographics of kratom users and their reasons for use. Although estimates vary across surveys, together they suggest that most kratom users are 30-50 years of age, more male than female, with some college education, employed, have health care, and are a diverse ethnic/racial mix with somewhat more kratom users identifying as White than other ethnicities (Coe et al., 2019; Covvey, Vogel, Peckham, et al., 2020; Garcia-Romeu, et al., 2020; US DHHS, 2020; Palamar et al., 2021). Surveys that focused on kratom use and opioids (e.g., Coe, et al., 2019; Garcia-Romeu, et al., 2020) or kratom use and pain find high rates of opioid use motivated in large part to replace opioids. The Grundmann (2017) survey found that most kratom users were not opioid users, and similarly the survey presented by Henningfield et al. at the American College of Neuropsychopharmacology meeting with more than 14,000 respondents found that most people used for reasons that were not related to opioids or addiction (Henningfield, et al., 2020).

But there still is no reliable estimate of the actual number of kratom users and surveys vary widely in their estimates, as shown in Table 5 below. There is consensus from 2014 that the American Botanical Education Alliance estimate of 3-5 million was credible and consistent with kratom suppliers and marketers estimates, and that kratom sales and use steadily increased. Thus, the American Kratom Association estimate of approximately 10-15 million based on Indonesian kratom export data, and with input from US marketers appears plausible.

The Covvey, et al. (2020) nationally representative online survey estimated past year use to be approximately 10.5 million kratom consumers. Informal marketer estimates suggest that kratom consumption also increased during the COVID-19 epidemic, which is not surprising due to frequent use of kratom to self-manage opioid use disorder, anxiety, stress, and depression.

2.4.2.1.1 National Survey on Drug Use and Health (NSDUH)

Prior to 2019, NSDUH did not include kratom/MG-specific items. From 2010 through 2018, there were a total of nine (9) lifetime kratom mentions (unweighted – not nationally representative), although five of those were in the last two years (2017 and 2018). By contrast, and over the same time frame, lifetime mentions (unweighted) of oxycodone, heroin, cocaine, amphetamine, marijuana, and other prototypic substances of abuse were in the many thousands. Lifetime aspirin mentions ranged from 7 to 23 per year, while lifetime diphenhydramine mentions ranged from 11 to 46 per year. See Table 1.

Table 1: Number of Unweighted Lifetime Cases of Kratom, Aspirin, Diphenhydramine, and Other Substances Reported to the National Survey on Drug Use and Health (2010-2018)

	NSDUH – Lifetime Number of Unweighted Cases								
	2010	*2011*	*2012*	*2013*	*2014*	*2015*	*2016*	*2017*	*2018*
Kratom/Mitragynine†	1	0	0	0	1	1	1	3	2
Oxycodone§	2,068	2,097	2,017	1,877	1,835	*	*	*	*
Heroin§	771	826	829	842	946	956	961	1,029	962
Cocaine§	6,464	6,260	6,009	5,653	6,636	6,740	6,580	6,748	6,646
Amphetamine§	3,916	4,136	4,113	4,171	4,179	*	*	*	*
Marijuana§	22,842	22,994	22,238	22,163	23,462	24,302	23,789	24,225	24,280
Aspirin†	17	22	18	18	19	7	7	18	23
Diphenhydramine†	29	21	19	20	12	18	11	21	46

† Unweighted non-medical/illicit use case mentions from open-ended response items only
§ Unweighted non-medical/illicit use case mentions from drug-specific and open-ended response items
** Estimate suppressed by SAMHSA*

In 2019, NSDUH added a series of kratom-related items to the survey, allowing for nationally representative estimates of lifetime, past-year, and past-month kratom use vs. comparators. In 2019, an estimated 3.9 million (1.4%) Americans aged 12 and older had used kratom in their lifetime, with 1.9 million (0.7%) using in the past year and 0.8 million (0.3%) using in the past month. In comparison, 4.5 million (1.6%) had misused prescription amphetamine products and 3.2 million (1.2%) had misused oxycodone in the past year, while illicit drugs such as marijuana (48.2 million [17.5%]) and cocaine (5.5 million [2.0%]) were also used more frequently than kratom. As shown in Table 2, the majority of kratom use is kratom only or kratom with alcohol which is different from the “polypharmacy” that is increasingly normal in recreational drug users; the exception is the common use of kratom by users of opioids, alcohol, stimulants, and other drugs as an aid to reducing and/or stopping use of those drugs and/or managing withdrawal when use of those drugs was discontinued.

Table 2: Lifetime, Past Year, and Past Month Use of Kratom vs. Misuse or Illicit Use of Comparators (Numbers in 1,000s), NSDUH (2019)

	Use / Misuse / Illicit Use N in 1,000s (%)		
	Lifetime	*Past Year*	*Past Month*
Kratom/Mitragynine	3,909 (1.4%)	1,919 (0.7%)	825 (0.3%)
Oxycodone†	*	3,185 (1.2%)	N/A
Heroin§	5,696 (2.1%)	745 (0.3%)	431 (0.2%)
Cocaine§	41,445 (15.1%)	5,468 (2.0%)	1,998 (0.7%)
Amphetamine†	*	4,486 (1.6%)	N/A
Marijuana§	127,139 (46.2%)	48,242 (17.5%)	31,606 (11.5%)

All estimates (N and %) are weighted to be nationally representative
N/A Data not collected by NSDUH
† Misuse of prescription or OTC product
§ Illicit use
** Estimate suppressed by SAMHSA*

Past month kratom use alone and in combination with other substances are presented in Table 3 below.

Table 3: Past Month Kratom Use Among Adults 18+: Overall, Kratom Only Use, and In Combination with Misuse or Use of Other Substances, NSDUH (2019)

	Past Month Kratom Use	
	% of US Adults 18 Years of Age or Older	*% of Adult Past Month Kratom Users*
Overall	0.32%	100.00%
Kratom and Pain Reliever Misuse	0.02%	7.04%
Kratom and Sedative Misuse	<0.01%	1.05%
Kratom and Alcohol	0.23%	71.87%
Kratom and Stimulant Misuse or Cocaine Use	0.04%	12.38%
Kratom Only	0.08%	24.41%

** All estimates are weighted to be nationally representative*
***Categories are not mutually exclusive (e.g., Kratom and Pain Relievers includes all respondents using both kratom and pain relievers, regardless of whether they were using other substances listed here)*
****The Kratom Only category excludes only those substances listed in this table. A respondent using Kratom and a substance not included in this table would be considered a kratom only user for the purposes of this analysis*

However, the NSDUH survey appears to greatly underestimate kratom use (see estimates in **Error! Reference source not found.**), just as it apparently does for many new psychoactive s ubstances (NPS). This deficiency was discussed by Palamar et al. (2015), who called for “new survey methods to prevent underreporting”. Similarly, the RADARS survey (Schimmel, et al., 2021) may have similar deficiencies. Both of these surveys include large panels who are interviewed, and it is possible that panel selection and/or interview approaches that provide realistic assessments of traditional recreationally used drugs and prescription opioids may underestimate use of novel products, and products taken for health and well-being and not for recreational purposes. These hypotheses require examination as the answers are not clear; however, kratom experts and marketers agree that that the NSDUH and RADARS surveys substantially underestimate the number of kratom users in the US.

Table 4: Kratom use prevalence estimates across studies in the United States

Year	Source	Method	Prevalence
2019	NSDUH 2020	• US Federal survey by SAMHSA (N=67,625) • Nationally representative multi-stage probability sample with face-to-face interviews • % estimates of US population aged 12+ (18+ presented in this slide)	Lifetime: 1.5% Past year: 0.7% Past month: 0.3% Past year adult users estimate: 1,790,000
2018-2019	Schimmel et al. 2020	• US survey by RADARS System panel (N=59,714) • Non-probability sample with online self-administration • % estimates of US population aged 18+	Lifetime: 1.3% Past year: 0.8% Past year adult users estimate: 2,040,000
2019	Covvey et al. 2020	• US survey via Qualtrics Panels (N=1,842) • Non-probability sample with online self-administration • % estimates of US population aged 18–59	Lifetime: 6.1% Past year: 4.1% Past month: 3.5% Past year adult users estimate: 10,500,000
2019	American Kratom Association	• Southeast Asian survey of commercial kratom exporters • Average monthly volume of kratom exported to US ÷ average volume of kratom used by US kratom consumer = approximate number of US kratom consumers	estimated US kratom consumers: 15,600,244
2014-2016	Botanical Education Alliance	• US survey of kratom venders	Estimated 3–5 million kratom consumers

2.4.2.1.2 Treatment Episode Datasets (TEDS) and Monitoring the Future (MTF)

There are no updates to the TEDS and MTF data sets since the 2018 report. Note that the lack of reports does not mean there were no instances of treatment seeking or recreational use by young people. In fact, there are internet and media reports that suggest some recreational use by youth, and there are self-reports of addiction in some kratom users on internet discussion groups and in internet surveys of adults. However, the signals from TEDS and MTF are apparently small enough not to warrant reporting.

2.4.2.1.3 Drug Abuse Warning Network (DAWN)

A new iteration of DAWN began collecting data from a sample of hospitals in April 2019. While some preliminary data were released (April 2019-October 2020), data related to kratom are not yet available.

2.4.2.1.4 American Association of Poison Control Centers' National Poison Data System (AAPCC-NPDS)

From 2011-2017, a total of 1,807 exposures involving kratom were reported to AAPCC, with about two-thirds of those occurring in 2016-2017 (Post, Spiller Chounthirath & Smith, 2018). *Kratom* is listed as a separate product in the AAPCC annual reports since 2016; however,

Plants-Mitragyna and *Mitragyna speciosa korthals* are not listed separately in the reports (they are included in broader categories). Thus, only the generic-coded *Kratom* cases are available when using the AAPCC annual reports as a data source. Table 5 below shows those calls listed under the generic *Kratom* code, as well as widely used substances that are readily available without prescription as comparators, for the years 2016-2019. Nicotine gum, lozenge and patch and the lessor used prescription nicotine nasal spray and oral inhaler all carry dependence potential, are used off-label by some people, and can sustain dependence. Abrupt discontinuation is not recommended due to the possibility of a withdrawal syndrome, but these comparators are not listed in the Controlled Substances Act because their abuse potential is lower than the products they replace (namely cigarettes) and it was considered in the interest of public health to make them more readily available (FDA, 1995, 1996).

Table 5: Exposure Cases by Product, (AAPCC-NPDS, 2016-2019)

	2016	2017	2018	2019
Kratom	1	372	1,146	1,357
Diphenhydramine*	55,740	55,075	53,842	53,121
Aspirin**	17,882	18,089	17,380	16,317
Nicotine Pharmaceuticals***	1,571	1,582	1,741	1,809

*Diphenhydramine alone or in combine
**Aspirin only; does not include combination products
***Nicotine gum, patch, and lozenge

2.4.2.1.5 National Forensic Laboratory Information System (NFLIS)

There are no updates to the NFLIS data set since the 2018 report.

2.4.2.2 Reports of Overdose and Death

In FDA's February 6, 2018 report by Commissioner Scott Gottlieb[12], in which FDA stated that it had documented 44 kratom associated deaths (worldwide over nearly ten years), it included the following acknowledgement:

> "Overall, many of the cases received could not be fully assessed because of limited information provided; however, one new report of death was of particular concern. This individual had no known historical or toxicologic evidence of opioid use, except for kratom. We're continuing to investigate this report, but the information we have so far reinforces our concerns about the use of kratom."

About six months later, the Assistant Secretary of Health of the US Department of Health and Human Services (DHHS) reviewed the FDA-prepared 8-FA submitted to the US Drug Enforcement Administration (DEA) in October of 2017 with a recommendation to Schedule MG and 7-OH-MG as Schedule I drugs in the CSA (thus, effectively banning legal sales and possession of kratom). The Secretary discovered that the death highlighted in Commissioner

[12] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds

Gottlieb's report due to the apparent absence of other substances was caused by an automobile crash, and there was no evidence that kratom use was a contributing factor.

Babin (2018) evaluated all deaths reported by the FDA as potentially related to kratom. She concluded:

> "None of the case reports released to date support the evidentiary standard required by the CSA to prove there is a risk to the public health that relies primarily on the FDA claim of numerous deaths associated with kratom.
>
> In fact, the data show only that a relatively small number of individuals died from a variety of actual causes related to underlying health issues, abuse of prescription or illicit drugs either at toxic doses or taken in combination when contraindicated. The use of kratom by these individuals has no medical or statistical significance in assessing the safety signal required for scheduling." (p. 8).

Olsen, O'Donnell, Mattson, et al. (2019) commented on 152 unintentional drug overdose deaths listed as associated with kratom, out of 27,338 deaths listed in the State Unintentional Drug Overdose Reporting System (SUDORS). The authors included the following statements supporting their concerns about potential kratom risks, as well as uncertainties about the actual contribution of kratom to deaths reported by medical examiners as "kratom caused" and/or "kratom associated":

> "Data on 27,338 overdose deaths that occurred during July 2016–December 2017 were entered into SUDORS, and 152 (0.56%) of these decedents tested positive for kratom on postmortem toxicology (kratom-positive). Postmortem toxicology testing protocols were not documented and varied among and within states. Kratom was determined to be a cause of death (i.e., kratom-involved) by a medical examiner or coroner for 91 (59.9%) of the 152 kratom-positive decedents, including seven for whom kratom was the only substance to test positive on postmortem toxicology, although the presence of additional substances cannot be ruled out (4)." (p. 1)

Gershman, Timm, Frank, et al. (2019) reviewed autopsy reports and performed additional analyses on available blood samples from 15 death cases that mentioned kratom from 1999 to 2017. They reported:

> "Autopsy reports were reviewed for all 15 deaths, which included 13 men and 2 women, with a median age of 28 years (range, 24 to 53). On the basis of toxicology testing, 11 cases involved multidrug ingestion (two to six drugs), and 8 persons had positive test results for other opioids. Four deaths were reported to involve mitragynine only, and coroners attributed each to mitragynine toxicity. We further investigated the 4 deaths that appeared to be due to mitragynine only, reviewing police investigation records for all 4 and performing comprehensive toxicology screening with high-performance liquid chromatography with tandem mass spectrometry for the 3 cases for which residual blood was available (Table 1). In our investigation of all 15 kratom-related deaths, we determined that 14 deaths clearly involved multiple drugs. Mitragynine levels varied widely, from 16 to 4800 ng per milliliter. Residual blood was not available for confirmatory testing in the remaining kratom-related death." (p. 1)

The Olsen, et al. (2019) and Gershman, et al. (2019) reports are consistent with the evaluation of Dr. Babin (2018) and the position of NIDA (2019) on its website that suggests that in the vast majority of kratom associated deaths, it cannot be ruled out that other substances or conditions were contributing, if not the primary, cause of death.

NIDA's Kratom Facts webpage states:

> "Can a person overdose on kratom? There have been multiple reports of deaths in people who had ingested kratom, but most have involved other substances. A 2019 paper analyzing data from the National Poison Data System found that between 2011-2017 there were 11 deaths associated with kratom exposure. Nine of the 11 deaths involved kratom plus other drugs and medicines, such as diphenhydramine (an antihistamine), alcohol, caffeine, benzodiazepines, fentanyl, and cocaine. Two deaths were reported following exposure to kratom alone with no other reported substances, but the extent of toxicological testing is unknown.* In 2017, the FDA identified at least 44 deaths related to kratom, with at least one case investigated as possible use of pure kratom. The FDA reports note that many of the kratom-associated deaths resulted from intake of adulterated products or taking kratom with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there are reports of kratom packaged as dietary supplements or dietary ingredients laced with other compounds that caused deaths. People should check with their health care providers about the safety of mixing kratom with other medicines." (NIDA, 2019)

NIDA's position is consistent with the conclusion drawn by Assistant Secretary of Health Brett P. Giroir, MD, ADM who stated:

> "There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses" (Giroir, 2018).

Palamar (2021) examined data from the 2019 National Survey on Drug Use and Health that included 56,136 respondents. The author concluded:

> "Kratom use is particularly prevalent among those with opioid use disorder but is also prevalent among people who use other drugs. Use has been associated with numerous adverse events, although most have involved use of other drugs." (p. 5)

Gershman, Timm, Frank, et al. (2019) reviewed autopsy reports and performed additional analyses on available blood samples from 15 death cases that mentioned kratom from 1999 to 2017. They reported:

> "Autopsy reports were reviewed for all 15 deaths, which included 13 men and 2 women, with a median age of 28 years (range, 24 to 53). On the basis of toxicology testing, 11 cases involved multidrug ingestion (two to six drugs), and 8 persons had positive test results for other opioids. Four deaths were reported to involve mitragynine only, and coroners attributed each to mitragynine toxicity. We further investigated the 4 deaths that appeared to be due to mitragynine only, reviewing police investigation records for all 4 and performing comprehensive toxicology screening with high-performance liquid chromatography with tandem mass spectrometry for the 3 cases for which residual

blood was available (Table 1). In our investigation of all 15 kratom-related deaths, we determined that 14 deaths clearly involved multiple drugs. Mitragynine levels varied widely, from 16 to 4800 ng per milliliter. Residual blood was not available for confirmatory testing in the remaining kratom-related death." (p. 1)

Henningfield, Grundmann, Babin, et al. (2019) summarized animal toxicology data, surveys and mortality data associated with opioids and kratom to provide a basis for estimating relative mortality risk. Related to safety, the authors concluded:

> "Kratom is not without risk, but the risk estimates as calculated by any of the approaches used, relative to opioids, suggest that morphine-like opioids carry an overdose risk of a thousand or more times greater than kratom. This conclusion has the limitation that some kratom users inherently carry or assume factors that might greatly increase the risk of kratom-associated mortality, e.g., use in combination with opioids, sedatives, alcohol or other drugs, or some preexisting disease states that may make kratom use especially risky. The fact that deaths associated with kratom use varied widely and included liver disease, homicide, suicide, trauma, and overdose with clearly lethal other drug concentrations (Babin, 2018; Henningfield et al., 2018b), cannot form the basis for concluding that co-existing conditions make kratom use more or less risky compared to opioids."
>
> "In fact, while the contribution of kratom to death in some cases cannot be ruled out, there has yet to be an overdose death from kratom alone in either the US or South East Asia where heavy kratom use is common (Prozialeck et al., 2019)."
>
> "Because many deaths possibly involving kratom appear to have also involved opioids and other drugs that are known to carry a high risk of overdose death, a regulatory approach that establishes standards for kratom product purity, packaging, labeling, and alkaloid content is urgently needed to reduce the risks for persons who purchase lawfully marketed products." (p. 2-3)

2.4.2.3 US and International Survey Data

In all of the surveys reporting reasons for use, despite descriptions by some authors with terms such as "therapeutic use", it is important to note that reasons for kratom use provide some basis for establishing benefits, though these do not imply FDA approved therapeutic claims.

Leong Abdullah, Tan, Narayanan, et al. (2021) conducted an analytical cross-sectional study of 200 participants (100 kratom users and 100 control subjects) in Malaysia, where kratom grows in abundance, leaves and marketed products are widely available, and use is widespread despite its illegality. The authors cardiovascular safety conclusions were:

> "The odds of having ECG abnormalities did not differ between kratom users and non-kratom-using control subjects, except for higher odds of sinus tachycardia in kratom users." (p. 7-8)

Leong Bin Abdullah, Yuvashnee & Singh (2021) conducted a cross-sectional study including data from 200 respondents (100 subjects who use kratom and 100 healthy controls) in Malaysia. The authors concluded:

> "The results of this study have some clinical implications to healthcare professionals. People who use kratom may experience some impairment of physical health, psychological, and environment QoL. Longer duration of kratom use may impair the physical health QoL, whereas greater severity of kratom dependence may impair all domains of QoL except for social relationship QoL. Hence, it is necessary to adequately treat kratom dependence in order to achieve better QoL in people who use kratom." (p. 5)

Garcia-Romeu, Cox, Smith, et al. (2020) conducted a MG survey of 2798 respondents. Related to safety, the authors concluded:

> "This study supports the results of previous studies (Coe et al., 2019; Grundmann, 2017; Smith and Lawson, 2017; Swogger et al., 2015) by suggesting that kratom has a relatively benign risk profile compared to typical opioids, with only a minority of respondents endorsing kratom related adverse effects, withdrawal symptoms, or problematic use. Adverse effects reported here were most commonly rated as mild and lasted ≤1 day, and less than 1% of the total sample found the effects of kratom to be severe enough to seek medical treatment. Adverse effects of kratom use were related to a number of demographic, health, and drug use variables including age, sex, education, income, depression, pain severity, and past 12-month alcohol and opioid use. Therefore, younger individuals or people with depression or more severe pain may experience more kratom-related adverse effects, potentially related to co-use with alcohol or other opioids. However, daily kratom users among the current sample were unlikely to meet criteria for a kratom related SUD, or report substantial problems or concerns related to their kratom use. Logistic regression models additionally found that greater kratom-related SUD symptoms predicted negative effects of kratom use, kratom withdrawal, and seeking treatment for kratom use, but not kratom use for the purposes of opioid reduction. Thus, kratom may differ in important respects from typical opioids, and may have significant therapeutic potential in light of the present opioid crisis." (p. 6)

Smith, Rogers, Schriefer, et al. (2021) analyzed 280 kratom subreddit posts and concluded:

> "Ultimately, kratom subreddit posts contained complicated narratives that do not make for simple characterizations. For some, kratom was lifesaving and for others it was ruinous, or yet another substance to which they had become beholden. Like other findings, the (provisional) takeaway is that it is premature to laud kratom as a cure-all and equally premature to demonize it as a dangerous substance with risk that outweighs benefit. At base, this stems from insufficient information, but also from the fact that "kratom" in the US constitutes many different products with variability in alkaloid content, composition, and purity, some of which is an artifact of factors related to the geographic region of the tree, kratom harvesting, post-harvesting handling, or other agricultural or horticultural conditions and practices (Fowble and Musah, 2019; Griffin et al., 2016; Mudge and Brown, 2017; Zhang et al., 2020). Findings here reinforce current scientific consensus, which is that kratom is a highly varied psychoactive substance being used in different doses and for different reasons among a diverse group of people that we are only beginning to understand." (p. 7)

Swogger & Walsh (2018) conducted a systematic review of kratom use and mental health including 13 studies addressing kratom use in the US, SEA, and other countries and regions of the world. Most mental health related uses were for harm reduction as a substitute for less desirable substances including opioids, alcohol, and other drugs, or for modulation of mood including energizing effects to counteract fatigue and self-management of mood disorders including anxiety, depression, and posttraumatic stress. The authors stated:

> "In conclusion, kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids." (p. 139)

The Garcia-Romeu, et al. (2020) survey mentioned earlier concluded:

> "Most respondents endorsed using kratom for pain relief (91.3%), and/or to treat mood-related issues such as anxiety (67.2%), and depression (64.5%). Among these, the majority said they would recommend kratom for pain relief (98.7%), and mood-related issues (96.7%). Mean (SD) efficacy ratings of kratom for treating pain on a scale from 0 (not at all) to 100 (extremely) were 83.3 (18.5); for anxiety were 76.7 (24.3); and for depression were 76.5 (25.4). Subgroups also reported using kratom for post-traumatic stress (29.6%) or bipolar mood (24.6%), with mean (SD) efficacy ratings of 60.2 (38.2), and 51.4 (39.9), respectively." (p. 3-4)

Covvey, et al. (2020) conducted an online cross-sectional survey including data from 1,842 respondents, of which 112 (6.1%) reported lifetime kratom use. The authors concluded:

> "Similar to existing data, the presence of emotional and mental health conditions, including concurrent substance use, was ubiquitous for individuals reporting kratom use compared to others. Anxiety, depression, and chronic pain were the most reported medical conditions among both groups, with significantly higher rates among respondents reporting kratom use. Previous surveys of individuals who use kratom cite treatment of pain and mental health conditions as the primary motivations for use. Coe and colleagues identified treatment of pain (48%) or mental health conditions (21.5%) as the most common reasons for use, while Grundmann identified even higher percentages reporting use for pain (68%) or mental health (66%) conditions. While the present study was not able to directly ascertain reasons underlying the use of kratom, these conditions were found with higher frequency among individuals reporting kratom use, suggesting a possible connection." (p. 5)

Singh, Grundmann, Murugaiyah, et al. (2020) conducted a field face-to-face survey including data from 92 respondents (long-term male kratom users). The authors stated:

> "Seventy-two participants (78%) reported using kratom to enhance sexual performance, and 71 of them (71/72, 99%) reported experiencing improved sexual performance. Of those who reported not using kratom to enhance sexual performance, 7/20 (35%) also experienced improved sexual performance after kratom use. The reported enhancements of sexual performance included: more energy during sex (75/92), delayed ejaculation (71/92), help to maintain erection (70/92), longer climax (51/92),

increased sexual desire (44/92), and reduced sex organ sensitivity (43/92). The mean (SD) Mal-BMSFI score was 33.9 (7.1) and 78/92 (85%) reported overall high satisfaction with their sex life in the past 30 days." (p. 1)

Singh, Narayanan, Müller, Swogger, et al. (2019) studied the motives for using kratom among regular kratom users in Malaysia. Singh, et al. (2019) summarized their results as follows:

> "A total of 116 regular kratom users were recruited for this cross-sectional survey. The Drinking Motives Questionnaire (DMQ) was administered to measure kratom use motives. Our results indicate that heavy (> 3 glasses daily, each glass contains 48.24–50.4 mg of mitragynine) kratom use was associated with coping ($t87.09 = 3.544$, $p < 0.001$), and enhancement ($t114 = 2.180$, $p=003$). Single subjects had higher mean scores on the coping domain, relative to married subjects ($t113.89 = 3.029$, $p < 0.003$), while those earning more than RM1500 per month had higher mean scores on the enhancement domain, compared to those earning less than RM1500 per month ($t107 = 2.151$, $p < 0.034$). Higher scores on the coping domain were significantly associated with higher (> 3 glasses daily) kratom consumption ($p < 0.0045$). Coping was associated with high (> 3 glasses daily) kratom consumption among regular kratom users in traditional, rural settings." (p.1)

Singh, Chear, Narayanan, et al. (2020) studied patterns of use and reasons for use by current and former opioid poly-drug users in Malaysia. They summarized their findings as follows:

> "A total of 204 opioid poly-drug users (142 current users vs. 62 former users) with current kratom use history were enrolled into this cross-sectional study. A validated UPLC-MS/MS method was used to evaluate the alkaloid content of a kratom street sample. Results from Chi-square analysis showed that there were no significant differences in demographic characteristics between current and former opioid poly-drug users except with respect to marital status. Current users had higher odds of being single. Similarly, there were no significant differences in the duration, daily quantity, or frequency of kratom use between current and former opioid poly-drug users. While both current and former opioid users reported using kratom to ameliorate opioid withdrawal, current users had significantly higher likelihood of using kratom for that purpose. In contrast, former opioid users were more likely to be using kratom for its euphoric (mood elevating) effects. Results from the UPLC-MS/MS analysis indicated the major alkaloids present in the representative kratom street sample (of approximately 300 mL of brewed kratom) were mitragynine, followed by paynantheine, speciociliatine and speciogynine, as well as low levels of 7-hydroxymitragynine. Both current and former opioid poly-drug users regularly used kratom (three glasses or about 900 mL daily or the equivalent of 170.19 mg of mitragynine) to overcome opioid poly-drug use problems." (p. 1)

2.4.2.4 Public Health and Individual Benefits of Kratom.

In a systematic review of the global mental health effects of kratom, Swogger & Walsh (2018) stated:

> "In conclusion, kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects

relative to that of opioids. More and better research, including well-controlled, prospective studies is necessary to further elucidate kratom's potential for good and harm and the moderators of its effects." (p. 139)

2.4.2.4.1 Kratom Use for Pain Management and Managing Opioid Use/Withdrawal

Coe, Henningfield, Pillitteri, et al. (2019) conducted an anonymous online survey of 3,024 kratom users (2867 current users and 157 former users). The authors wrote:

> "Kratom was used primarily to relieve pain (endorsed by 48% of respondents), for anxiety, PTSD, or depression (22%), to increase energy or focus (10%) and to help cut down on opioid use and/or relieve withdrawal (10%). Over 90% of respondents who used it in place of opioids indicated that it was helpful to relieve pain, reduce opioid use, and relieve withdrawal." (p. 24)
>
> "In contrast to the well-documented and serious risks associated with opioids (Baldini et al., 2012; Benyamin et al., 2008), respondents reported kratom effects as relatively minor, with few requiring medical attention. The rates and severity of "bad reactions" were generally similar to those reported previously (Grundmann, 2017), occurring in approximately 13% of respondents. The reported incidence of bad adverse reactions was 13%, and reactions were overwhelmingly mild and self-managed." (p.24)
>
> "The findings from this survey indicate that many individuals are taking kratom for conditions that often involve the prescribing of or self-medication with opioids (i.e., pain, withdrawal relief). Survey respondents overwhelmingly reported that kratom was helpful for these conditions and that bad effects from kratom, including those leading them to seek medical care, were uncommon." (p. 29).
>
> "Results of this survey and others (Grundmann, 2017) suggest that kratom may be a useful alternative to opioids for some persons with pain, and this would be consistent with what is known about kratom pharmacology (Kruegel et al., 2016; Raffa et al., 2018; Takayama et al., 2002)." (p. 29)
>
> "Although severity and relatedness of the bad reactions to kratom were not assessed, only 0.8% of respondents stopped using kratom because of a bad reaction or because they didn't like the way it made them feel." (p. 30)
>
> "The rates and severity of "bad reactions" were generally similar to those reported previously (Grundmann, 2017), occurring in approximately 13% of respondents." (p. 30)
>
> Müller, Hillemacher & Müller (2020) illustrates the realities of pain management that are typical in the real world. In this case, illustrated by a patient who benefited at times satisfactorily and at others less so. A summarized by the authors:
>
> "We present the case of a 26-year-old man in Substitol-assisted treatment of excessive Kratom and Tilidin use expressing the wish for a drug-free management of a chronic pain condition. After an accidental calcaneus impression fracture, the patient was suffering from severe chronic pain and anxiety of further accidents. This was managed initially with Tilidin. Resulting from the wish to self-manage the pain condition in a way that permitted continuation of a job, the patient searched for a 'natural' treatment

> alternative obtained from an Internet vendor. He successfully instrumentalized Kratom for 3 years with daily consumption intermixed with occasional Tilidin for pain management. However, the dose of Kratom was increased considerably up to a level of effect reversal, when no analgesic and behaviorally activating effects occurred any more, but only intense drowsiness. The patient was treatment seeking and subsequently detoxified from Kratom and Tilidin. Pain management was shifted to retarded morphine." (p. 1)

Note that in the foregoing report by Müller et al. (2020) (and another below by Müller et al., 2021), as in some other studies from the Malaysia Center for Drug Research reviewed by Henningfield, Fant & Wang (2018), the term "instrumentalized" and "instrumentalization" or "instrumental use" elsewhere, is approximately interchangeable with terms such a "therapeutic" and "beneficial" used in other studies and reviews.

Although the surveys indicate that a major reason for kratom use is the self-management of pain, it is also important to understand that kratom, like other pain management approaches, whether FDA-approved medicines or any other therapeutic approach, is not a panacea for all types of pain, people or pain sufferers (see Henningfield, Ashworth, Gerlach, et al., 2019; Kroenke, Alford, Argoff, et al., 2019).

A harm reduction benefit of replacing opioids and other drugs with kratom is the absence of opioid-like respiratory depressant effects and substantially lower overdose potential of kratom as compared to opioids. Considering the more than 93,000 drug overdose deaths in 2020, the majority of which are due to opioid intoxications, kratom use provides an alternative to opioid use and withdrawal (CDC, 2021). Kratom also has a low risk of inducing psychopathological states or aggression. Swogger & Walsh (2018) concluded:

> "Apart from kratom dependence, available studies give no indication that kratom causes psychopathology…. We searched for scientific information on kratom use and self-and-other directed aggression. Although few studies directly assessed aggression, reports of this outcome were notably absent from studies that indirectly enabled such reporting (e.g., Anwar et al., 2016; Saingam et al., 2012; Swogger et al., 2015; Trakulsrichai et al., 2013). No studies indicated increased self-or-other directed aggression following acute kratom ingestion. Approximately 1% of Malaysian interviewees indicated being aggressive or experiencing hostility while in kratom withdrawal (Ahmad and Aziz, 2012)." (p. 5)

An international consortium of leading kratom researchers (Prozialeck, Avery, Boyer et al., 2019) conducted a scientific and policy analysis of kratom and concluded:

> "The many positive user comments on Erowid.org (Erowid, 2016), SageWisdom.org (Wisdom, 2016), Reddit.com/r/kratom (Reddit, 2018) and Speciosa.org (speciosa.org, 2016) comprise an extensive collection of anecdotal data documenting kratom use. Scientific analyses of such user reports clearly indicate that the therapeutic potential of kratom is too large to be ignored (Swogger et al., 2015). The 23,000+ comments submitted to the federal register in response to the DEA's proposed scheduling action also provide a vast collection of anecdotal data suggesting profound therapeutic benefits for kratom (DEA, 2016a). Another piece of evidence suggesting that kratom

may have significant therapeutic potential is that US patents have been issued for companies and individuals who are interested in developing kratom-based drugs (Heyworth, 1964; Takayama, Kitajima, Matsumoto, & Horie, 2008). Together, these observations provide evidence that kratom may have potentially useful therapeutic effects, and that well-controlled clinical trials are urgently needed to evaluate the safety and efficacy of kratom and its principal alkaloid mitragynine." (p. X)

2.4.2.4.2 Kratom Use During the COVID-19 Pandemic

Müller, Hillemacher & Müller (2021) published a case history of the use of kratom to self-manage anxiety and depression during the COVID-19 pandemic. They reported:

> "Altogether, the present report may add evidence for long-term instrumentalization of Kratom for self-management of major depression and general anxiety disorder and Morbus Meniere. It also evidences the boundaries of drug instrumentalization when environmental conditions change, such as during increased psychological stress in the COVID-19 pandemic." (p. 3)

In the first half-year of the COVID-19 pandemic, Singh, Brown, Cinosi, et al. (2020) discussed how the pandemic may have affected kratom supply and use drawing on observations from researchers globally as well as kratom suppliers and marketers from the SEA region. Their observations included the following:

> "The widespread use of kratom and consistent reports of its benefits or therapeutic value that are important to users raises the question: would sudden decreases in the availability of the plant have negative impacts on kratom users? Various internet studies found that some kratom users are concerned about the possibility of relapsing to opioids and/or seeking alternative, possibly questionable, sources of kratom if products become less readily available. This is a serious concern as kratom, not currently regulated as a dietary supplement, may be adulterated by unscrupulous traders and cause users to relapse to opioid use and inevitably experience a significant increase in overdose risk (7, 9, 14–17). Indeed, there is evidence to suggest that the COVID-19 pandemic has been associated with increased drug overdose deaths and that the reduced access to conventional treatment, as well as mutual-aid groups, is a plausible contributing factor (18), though it is unknown whether diminished access to kratom has explicitly contributed to any overdose deaths." (p. 1)

Note that similar concerns as expressed above were also discussed by US DHHS, Assistant Secretary of Health Dr. Giroir in his August 2018 formal rescission of the October 2017 recommendation developed by the FDA to permanently list MG and 7-OH-MG as Schedule I drugs, which would have abruptly banned legal consumer sales and possession (see below).

As of 2021, it has already been estimated by the US Centers for Disease Control and Prevention (CDC) that total drug overdose deaths rose nearly 30% in 2020 to more than 93,000 in the US (Ahmad, Rossen & Sutton, 2021). The actual impact on kratom use and supply related to the COVID-19 pandemic may not be understood for a year or more to come but would seem to merit further study. Given that a major use of kratom is as a less harmful substitute for opioids and the absence of evidence suggesting that it has contributed to the opioid epidemic (see Factors 4, 5 and 6 and Henningfield, Raffa, Garcia-Romeu & Doshi,

2018), it is hypothesized that kratom access may have prevented many deaths. Regardless of the actual and probably complex relationship, this merits study.

2.4.2.4.3 Potential Effects of Inappropriate Regulation

Public health risks of regulation, including decisions as to where public health is better served by scheduling or not scheduling substances and products, must consider the risks and benefits of decisions. For example, the leading nicotine replacement medicines (gum, lozenge and patch) were not listed in the CSA despite meeting all criteria for CSA control and other risks. Additionally, they were converted to over-the-counter status due to their lower abuse potential and addiction risk and better safety profile than cigarettes (FDA, 1995, 1996; Henningfield, 2011). Similarly, common cough, cold and allergy products (e.g., diphenhydramine and dextromethorphan and caffeine), substances that lead to dependence and withdrawal, are not scheduled in the US or globally. This illustrates the point that drug scheduling and control actions in the US and internationally consider the public health risks and benefits of scheduling actions in the determination of whether drugs are scheduled or not and if they are controlled, which schedule they are placed in (Spillane & McAllister, 2003)

Survey findings and internet monitoring provided no compelling evidence that kratom was fueling the opioid epidemic but provided substantial evidence that kratom offered a life-saving path away from opioids. It appeared that DEA shared similar concerns and that US DHHS agreed. Although DEA proposed scheduling kratom in August 2016, within approximately one month they withdrew the proposal inviting public comment and FDA input (DEA, 2016). This was in response to thousands of comments from kratom consumers describing kratom's health benefits, its use as an opioid replacement, and fear of a relapse to opioids if kratom was scheduled. The DEA Administrator, Chuck Rosenberg, explained that withdrawing kratom from the market could pose risks to people who used kratom to abstain from opioids and a relapse could put them at risk of an overdose death. Assistant Secretary of DHHS, Dr. Giroir, in his MG and 7-OH-MG scheduling rescission letter stated:

> "Furthermore, there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I, such as:
>
> - Suffering with intractable pain;
> - Kratom users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with IV drug use;
> - Inhibition of patients discussing kratom use with their primary care physicians leading to more harm, and enhancement of stigma thereby decreasing desire for treatment, because of individual users now being guilty of a crime by virtue of their possession or use of kratom;
> - The stifling effect of classification in Schedule I on critical research needed on the complex and potentially useful chemistry of components of kratom."

Assistant Secretary Giroir also noted:

> "I am also concerned about the impact of scheduling kratom on our ability to conduct research, especially survey research and our current inability to routinely test for kratom in those brought into an emergency room as a result of a possible overdose."

Concerns about these foreseeable risks if kratom was banned for sale and criminalized for consumer possession were expanded in several published articles (e.g., Grundmann, Babin, Henningfield, et al., 2021; Grundmann, Brown, Henningfield, et al., 2018), and joint expert report/letters to the DEA, DHHS, FDA, NIDA, White House and Congressional leaders (Henningfield, Swogger, Walsh, Kruegel, et al., 2018a, 2018b). A critique of FDA's own 8-FA (FDA, 2017a) by kratom and substance abuse experts and those experienced in drug scheduling was also published (Henningfield, Babin, Boyer, et al., 2018). These analyses raised concerns in addition to those raised by Assistant Secretary Giroir. These included the foreseeable consequence of a rapidly developing kratom black market increasing the problems of product adulteration and quality, instead of gaining the benefits of legally regulated kratom with standards for purity, packaging, labeling, marketing, and claims.

2.4.2.5 Factor 4, 5, and 6 Updated Conclusions

The most important finding from substantially more survey evidence in the US is that the surveys do not support the conclusion that kratom products and kratom's primary active alkaloid, MG, pose a "serious imminent threat to public health". This extensive survey update supports the Henningfield, Fant & Wang (2018) conclusion:

> "There has been no documented threat to public health that would appear to warrant emergency scheduling of the products and placement in Schedule I of the CSA carries risks of creating serious public health problems…. Although kratom appears to have pharmacological properties that support some level of scheduling, if it was an approved drug, placing it into Schedule I, thus banning it, risks creating public health problems that do not presently exist".

Conversely, the evidence is affirmative that millions of people in the US purchase and use kratom products for the health benefits they provide and are preferred to FDA approved medicines because for them, kratom products are more effective, accessible, and tolerable. Furthermore, many prefer managing health problems with natural products.

For those using kratom products in place of opioids, which appears to be approximately 1/3 of all kratom users, it is foreseeable that removing kratom from the legal marketplace would put many at risk of returning to opioid use and risking opioid overdose death. This was clearly stated in comments to the DEA and public hearings as reported in the 2018 8-FA, and in surveys. As stated by Assistant Secretary Dr. Giroir, as noted earlier:

> "Furthermore, there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I, such as: … Kratom users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with IV drug use…" (Giroir, 2018).

As noted in Factor 1, the survey data are consistent with comments by kratoms users to DEA[13,14,15,16] and FDA[17],[18] that were summarized in the Henningfield, Fant & Wang, 2018 kratom 8-FA, as well as with comments in public hearings in cities and states that have been considering, and in many cases, implementing kratom regulations, to ensure access to kratom and provide some regulatory oversight over products and marketing. Although some commentors describe addiction to kratom, the most common themes are used for health and well-being, including to stay off opioids. Although not scientific surveys, these comments from real world kratom users provide an important complement to the scientific findings.

2.5 Factor 7 – The Psychic or Physiological Dependence Liability

2.5.1 Summary of 2018 Findings:

Psychic dependence has been commonly referred to in recent years simply as "dependence" (APA, 1994; WHO, 1994) or by the 5th edition of the APA's Diagnostic and Statistical Manual as "substance use disorder" and more commonly as "addiction" though definitions of addiction vary widely. Physiological dependence is often used interchangeably with the most common measure of physiological dependence, namely "withdrawal" which is also considered a clinical disorder (APA, 2013). In the 2018 8-FA, Henningfield, Fant & Wang (2018) concluded:

> "There have not been laboratory studies of physical or psychological dependence or abuse potential in humans caused by kratom." Nor had classic animal studies of employing the drug self-administration and physical dependence/withdrawal model been conducted as have been conduct since 2018 (see Factor 2 in this report)." (p. 584)

Nonetheless, the real-world evidence in the published literature supported the following conclusions:

> "…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. However, such reports make it difficult to disentangle the emergence of preexisting symptoms that had been mitigated by kratom use from those

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[13] See 22,232 comments to the DEA in 2016 at https://www.regulations.gov/document/DEA-2016-0015-0006/comment

[14] An Excel file of the comments is available at https://www.dropbox.com/s/6txmv91536oujhq/DOCKET_DEA-2016-0015.xlsx?dl=0

[15] An analysis of the comments where a comment ID allowed for a classification of the source of the comment (conducted on 19,419 of the comments) is available at https://www.dropbox.com/s/h1b4qz36lzqm1d5/KratomCommentProject_DataSet%20-%20STATISTICS_VERIFIABLE_DATA.pdf?dl=0

[16] A general summary news release of the foregoing analysis is available at https://www.prnewswire.com/news-releases/review-of-dea-kratom-public-comments-shows-strong-support-among-vets-doctors-cops-and-seniors-for-coffee-like-herb-300401575.html

[17] Public comments concerning the benefits of kratom as life-saving assets with respect to the opioid epidemic were also made orally and in written submissions to the FDA and NIDA April 17, 2018 Public Meeting on Patient-Focused Drug Development for Opioid Use Disorder at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/public-meeting-patient-focused-drug-development-opioid-use-disorder.

[18] Written comments for the docket are at https://www.regulations.gov/document/FDA-2018-N-0987-0001/comment

that occur as a physiological rebound accompanying the abrupt discontinuation of kratom use in kratom-dependent people. More studies of kratom's potential to produce physical dependence, tolerance, and withdrawal are needed to characterize the nature and severity, and determinants of abstinence-associated symptoms." (p.584)

2.5.2 Factor 7 Science Updates:

There have been new research findings, a systematic review, and a review by an international consortium of kratom experts that contribute to a significant advance in knowledge on the psychic and physiological dependence potential of kratom.

The systematic review of kratom use and mental health discussed earlier in Factors 4, 5 and 6 by Swogger & Walsh (2018) provided additional perspectives related to kratom's potential to produce dependence or addiction (also referred to as a substance use disorder, APA, 2013), and physical dependence and withdrawal. The researchers concluded:

> "Kratom withdrawal symptoms resemble the opioid withdrawal syndrome (Miranda and Taca, 2017). Extant data suggest that kratom's withdrawal syndrome is uncomfortable, but generally milder and of shorter duration than is characteristic of opioid withdrawal (Singh et al., 2015; Swogger et al., 2015)." (p. 137).

Regarding dependence, Swogger & Walsh (2018) concluded:

> "There is good evidence that kratom dependence is typically less severe than opioid dependence, with which kratom shares some mechanisms of action (Hassan et al., 2013). Moreover, unlike opioids, kratom use does not appear to result in significant respiratory depression (Kruegel et al., 2016) and is thus far less likely to cause fatal overdose. The perception that kratom is a milder and less dangerous opioid-like psychoactive substance is supported by the uptake of kratom use as an opiate substitute (Vicknasingam et al., 2010) and is consistent with data on the unimpaired social functioning of regular kratom users (Singh et al., 2015). For future research on the effects of heavy kratom use, a scale designed to measure kratom dependence has shown good preliminary reliability and validity (Scale; Saingam et al., 2014)." (p. 138)

The international consortium of leading kratom researchers mentioned earlier in Factors 4, 5 and 6 also assessed dependence and withdrawal associated with kratom use. According to Prozialeck, et al., 2019):

> "Regular use of kratom, particularly at higher doses, can lead to tolerance and dependence (Galbis-Reig, 2016; Singh et al., 2014; Swogger & Walsh, 2018; Yusoff, et al., 2016)." (p. 73)

However, available human reports suggest that abstinence from kratom is typically associated with milder symptomatology than abstinence from classical opioids (Erowid, 2017; Henningfield, et al., 2020; Singh, et al., 2014, Singh, et al., 2016; Singh, Narayanan, Müller, et al., 2018; Swogger, et al., 2015). At the same time, although these reports indicate that the effects of kratom can, in some ways, resemble those of opioids, many individuals report that the subjective effects of kratom are quite different from those of opioids. As noted previously, low to moderate doses of kratom tend to be somewhat stimulating, rather than sedating, and

do not produce the “high” or strong euphoric effects associated with opioids, although some users have reported intoxication and euphoria after using higher doses (Erowid, 2017; Henningfield, et al., 2020; Singh, et al., 2016; Swogger, et al., 2015). This distinct spectrum of effects, including attenuated euphoria and abuse potential, is supported by two recent preclinical studies, which found that mitragynine is not self-administered by rats (Hemby, McIntosh, Leon, Cutler & McCurdy, 2019; Yue, Kopajtic & Katz, 2018). Further, even at high doses, kratom does not appear to severely depress respiration as do classical opioids (Singh, et al., 2014, 2016). Thus, even though kratom has some potential for abuse and dependence, several investigators have concluded that kratom has both less abuse liability and much lower risk of fatal overdose than traditional opioids and that the potential benefits of kratom in the treatment of OUD may outweigh these risks (Henningfield, Fant & Wang, 2018; Singh, et al., 2014, 2015, 2016; Swogger, et al., 2015). This does not mean that kratom is not sometimes used by people to get high and/or intoxicated because such use has been documented (Swogger, et al., 2015). Such findings were also considered by Henningfield, Fant & Wang (2018).

The Vicknasingam, et al. (2020) study included in Factor 2 that evaluated kratom’s effects on pain tolerance in a clinical trial also assessed potential withdrawal signs using the Clinical Opiate Withdrawal Scale (COWS) comparing scores on days that the participants were administered placebo to days that participants were administered a kratom concoction (Vicknasingam, et al., 2020). Although this study was not designed to be a definitive withdrawal assessment study, and did not include an opioid comparator, it would have been likely that people who were using opioids multiple times per day for many years would have experienced pronounced withdrawal symptoms. In this study the authors concluded as follows:

> “None of the participants reported withdrawal symptoms either using spontaneous self-report or had significant withdrawal symptoms based on the COWS scores. All urine toxicology screens conducted at the end of the testing day were negative.” (p. 236)
>
> “All participants reported long histories of daily kratom consumption, with high frequency of daily consumption and substantial amounts consumed. It is not possible to quantify these reports into markers that could be used to approximate amounts of plant material or active ingredients consumed. However, despite the reported long duration and high levels of daily kratom consumption, during documented kratom discontinuation lasting from 10 to 20 hours, no participant reported or displayed discomfort, symptoms, or signs of potential withdrawal symptoms.” (p. 236)

Leong Bin Abdullah, Yuvashnee & Singh (2021) studied kratom users in Malaysia to assess potential symptoms related to kratom dependence and withdrawal. They concluded:

> “In the context of regular kratom use, most people with kratom use experience some anxiety and depressive symptoms during kratom withdrawal. . .
>
> Greater Kratom Dependence Scale (KDS) score and longer duration of kratom use were significant predictors of physical health Quality of Life (QoL), while only greater KDS score significantly predicted psychological and environment QoL scores. Prolonged kratom use and kratom dependence may negatively impact the QoL of people who use kratom, hence kratom addiction has to be treated adequately.” (p. 1)

Garcia-Romeu, Cox, Smith, et al. (2020) conducted a survey that specifically asked questions about potential withdrawal symptoms associated with discontinuation of kratom use. They concluded as follows

> "Kratom-related withdrawal symptoms were reported by 9.5 % of respondents with another 17.5 % reporting possible kratom-related withdrawal." (p. 4)
>
> "This study supports the results of previous studies (Coe et al., 2019; Grundmann, 2017; Smith and Lawson, 2017; Swogger et al., 2015) by suggesting that kratom has a relatively benign risk profile compared to typical opioids, with only a minority of respondents endorsing kratom-related adverse effects, withdrawal symptoms, or problematic use." (p. 6)

The survey by Coe, Henningfield, Pillitteri, et al. (2019) also asked questions related to potential kratom use associated dependence and discontinuation related withdrawal. They concluded as follows:

> "The survey did not address whether respondents experienced any physical dependence or craving as a result of kratom use, but it appears likely that chronic kratom use is associated with physical dependence and withdrawal, albeit both are reportedly milder and more readily self-managed compared to opioid dependence and withdrawal (Singh et al., 2014, 2016; 2018). Furthermore, kratom use and dependence reportedly do not interfere with social, family, and occupational functioning (Singh et al., 2014, 2016; Swogger and Walsh, 2018; Vicknasingam et al., 2010) to the extent that conventional opioids do." (p. 30) This conclusion is similar to Grundmann's (2017) findings.
>
> The foregoing conclusions are also consistent with those of Grundmann, Babin, Henningfield, et al. (2021) who stated as follows "Some user reports suggest that regular kratom consumption carries risks of dependency and addiction, though with generally self-manageable withdrawal (12)." (p. 1)

Another study employed widely used psychiatric instruments (Beck Depression Inventory and Beck Anxiety Inventory) to assess potential symptoms of anxiety and depression that may accompany abrupt discontinuation of kratom use in chronic kratom consumers in Malaysia. (Singh, Narayanan, Müller et al., 2018). Singh, et al. (2018) concluded:

> "Most respondents (70%) experienced symptoms of mild anxiety, while 81% experienced symptoms of mild depression during kratom cessation. Those who consumed higher quantities of kratom tea daily (≥4 glasses) had higher odds of reporting longer duration of kratom use history…, higher frequency of daily kratom use (≥4 times) …, and were more likely to experience moderate symptoms of depression during kratom cessation than those who consumed between one and three glasses of kratom tea per day. Cessation from regular and long-term kratom tea consumption was not associated with symptoms of high anxiety or depression." (p.1)

Nonetheless, it is evident that some fraction of chronic heavy kratom users exhibit strong dependence or use disorder, albeit with generally moderate withdrawal symptoms (Singh, Narayanan, Müller et al., 2018). In many such cases, the people had preexisting opioid or

other substance use disorders and/or were using kratom to self-manage chronic pain. It is not known what fraction of kratom users experience what might be termed a kratom use disorder (even though this term is not an APA, 2013 recognized term). Surveys by Grundmann (2017), Coe, et al. (2019), and Garcia-Romeu, et al. (2020) suggest that 5-10% of kratom users report some level of dependence with evidence suggesting that it is tolerable, manageable and not disruptive to life demand for most people. However, as noted in the 2018 scheduling recission letter by Assistant Secretary of Health Giroir, the number is not known and is important to know, particularly before any effort to substantially restrict kratom access.

Swogger & Walsh (2018) concluded as follows "In conclusion, kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids." (p. 139)

2.5.3 Factor 7 Updated Conclusions

Several surveys in the US, field studies in Malaysia, and a clinical trial of pain relief efficacy that included assessment of withdrawal support the conclusions of the 2018 8-FA. The main findings are that some people report dependence/addiction and/or withdrawal. The likelihood is generally related to higher levels of chronic daily consumption. In general, it is more readily self-managed and less likely to interfere with occupational, social and family activities and responsibilities as dependencies to opioids, alcohol, stimulants and other drugs of abuse. Many users had histories of opioids and/or other addictive drug use and so the degree to which their addiction to kratom is a new addiction cannot readily be ascertained.

For some people for whom kratom use is considered by themselves and/or others to be a serious problem, they should have the same access to treatment as anyone else with a substance use disorder. Many addiction treatment providers already advertise and offer kratom use disorder treatment assistance. Use of opioids such as methadone and buprenorphine should be used judiciously with people seeing help to manage their kratom use disorder and/or withdrawal. If they were formerly and perhaps still using opioids, then the possibility of treatment with buprenorphine or methadone may be more helpful and appropriate if kratom is not satisfactory. However, for people without prior histories of recreational opioid use and dependence, using buprenorphine or methadone as a treatment may be introducing them to opioids and may not be the best option. For some people that might be like treating unwanted caffeine dependence with amphetamine to replace the caffeine.

3 Conclusions Based on New Studies since January 1, 2018

- *Since the Henningfield, Fant & Wang (2018) 8-FA, there have been over 100 new published scientific studies, reviews and commentaries by leading kratom experts, and an accelerating research pipeline funded in part by the US National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA). These studies provide an increasingly strong evidence base for regulation and policy.*

- *Nature got it right. There is a convergence of studies showing that the main natural constituent of kratom that accounts for the reasons people use kratom is MG which carries relatively low abuse and health risks. 7-OH-MG naturally occurs at very low*

levels and product standards should prevent marketing of products with levels higher than those that appear to carry little risk.

- *Evidence does not support the conclusion that kratom is an imminent public health threat or that it is fueling the opioid and drug overdose epidemic that led to more than 93,000 deaths in 2020. Rather, the evidence supports the conclusion that for many people, kratom is a path away from opioids and other drugs to help self-manage craving and withdrawal for people who find kratom more effective, accessible, acceptable, tolerable, and/or prefer natural products.*

- *Animal drug self-administration and physical dependence/withdrawal studies show low abuse potential and withdrawal risks of kratom relative to opioids. Furthermore, these studies also show that MG administration can reduce self-administration of morphine and heroin as well as withdrawal from morphine. These findings are consistent with human surveys and studies showing that addiction risks for kratom are overall low as compared to opioids.*

- *Numerous surveys and field studies of kratom users have been conducted in the US and Malaysia. These studies largely confirm the large US survey published by Dr. Grundmann (2017). Most US kratom users are 30-50 years old, employed and have some college education and healthcare. Leading reasons for use are to self-manage pain, depression, anxiety, to increase focus and alertness analogous to caffeinated beverage use and to self-manage opioid and other substance use disorders to relieve craving and withdrawal and often the pain that motivates such drug use.*

- *Surveys also show that users fear a kratom ban and the risks of resumption of opioid and other drug use, and/or turning to illicitly marketed kratom. This makes it foreseeable that thousands of people would be at risk of opioid overdose and other mortality risks associated with illicit drug use, injection drug use, and adulterated kratom products.*

- *Studies of kratom's alkaloids support the conclusion that that MG and other alkaloids are not appropriately categorized as opioids, as they are diverse in their activity, effects, and mechanisms of action. Moreover, the primary active constituent of kratom, MG, does not produce the signature powerfully rewarding and lethal respiratory depressant effects that characterize morphine-like opioids.*

- *Kratom PK and safety studies include examination of the pharmacokinetics (PK) and pharmacodynamics (PD) in rats and dogs by oral and intravenous administration of many kratom alkaloids in addition to MG. MG, at human dose equivalents many times higher than humans take, are without acute serious adverse effects and little evidence of respiratory depressant effect.*

- *Six clinical studies evaluated the effects of long term kratom use on a variety of physiological parameters including kidney and liver function, hematological parameters, cognition, and on brain function by brain magnetic resonance imaging. Although these were relatively small studies, none suggest serious adverse consequences of long term*

kratom use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies.

- *New medicines development efforts are developing new molecules as analogs of MG and other kratom alkaloids as possible safer and/or more effective treatments for pain, addiction, depression and other disorders, due to the promising findings with kratom and its naturally occurring alkaloids. Though, it is likely that it may be a decade or more before they result in New Drug Applications to the FDA.*

- *The pipeline of research and new science has been enhanced in quantity and quality not only by funding from the US National Institutes of Health (NIH) and other organizations but as well by regular scientific conferences that are fostering global collaboration and cooperation in an exciting new frontier in search of safer and more effective ways to manage health and well-being. Such efforts are working and should be expanded.*

- *Kratom regulation would be better informed by scientific and public health conversation by active collaboration among CDC, DEA, FDA, NIDA, and the Substance Abuse and Mental Health Services Administration. Kratom science should be accelerated by increased kratom research funding to NIDA, as well as to support increased surveillance that is specific to kratom. An annual report should be provided by multi-agency committee with updates on the state of kratom science and annual surveillance, perhaps led by NIDA.*

- *An important development that relates to overall safety and health benefits and risks that is a regulatory and policy update and is not included in the science updates: at the time of this writing, five states (Arizona, Georgia, Nevada, Utah, and Oklahoma) have enacted laws referenced as the Kratom Consumer Protection Act (KCPA). The KCPA establishes a regulatory framework to protect consumers from unsafe and adulterated kratom products that require adherence to good manufacturing standards (GMP) to ensure purity; requires testing for contaminants; prohibits adding any dangerous substances to kratom products; forbids boosting the alkaloid levels of MG and 7-OH-MG over those present in the natural kratom plant; bars synthesizing any of the alkaloids; requires registration and product testing; prohibits any therapeutic health claims; and forbids sales to minors. These KCPA laws provide needed consumer protections for consumers. To illustrate the kratom regulatory framework for the Utah KCPA, the Utah Department of Agriculture rule on kratom can be found at https://ag.utah.gov/businesses/regulatory-services/kratom/ . For updates on the status of KCPA legislation in other states, visit the American Kratom Association website at https://www.americankratom.org/advocacy/aka-in-your-state.html .*

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Kratom

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Cite as: *CMAJ* 2019 October 7;191:E1105. doi: 10.1503/cmaj.190470

1 Kratom (*Mitragyna speciosa* Korth.) is a herbal product from Southeast Asia with opioid agonist properties

Kratom is a herbal product that is most commonly obtained as a powder and consumed as a beverage.[1–3] Kratom contains the indole alkaloid compounds mitragynine and 7-hydroxymitragynine, which are opioid receptors agonists.[2,3] They reduce pain, cause dose-dependent stimulant and sedative effects, and have an adverse effect profile consistent with opioid activity.[2] Kratom is not detected on conventional urine drug-screening tests.[2]

2 Kratom use is increasing

Avoidance of drug withdrawal, treatment of chronic pain and recreation are common reasons for kratom use.[1,2] American poison centres saw an increase in kratom-related calls, from 18 exposures in 2011 to 357 in the first 7 months of 2018.[4] The US Centers for Disease Control and Prevention identified 91 cases in which kratom was identified as a potential cause of death from July 2016 to December 2017.[5]

3 Effects of kratom use appear to be dose dependent

Kratom use is associated with stimulant effects at low doses (1–5 g), and sedative effects at higher doses (5–15 g).[2] Negative adverse effects most commonly include gastrointestinal symptoms and agitation, and are reported to be dose dependent.[1,4]

4 Kratom users may experience withdrawal with cessation

Moderate to heavy daily users of kratom (≥ 3 doses/d) commonly have cravings and withdrawal symptoms similar to those of opioid withdrawal with cessation.[2,5] Of kratom users, 43% reported negative adverse events if they abstained for more than 48 hours.[1]

5 Management of kratom ingestion is supportive

Doses in excess of 15 g may mimic an opioid toxidrome. Naloxone should be given for drowsiness and respiratory depression.[3] Severe adverse events, including death, have been reported with kratom use in conjunction with opioids, benzodiazepines, modafinil and other medications.[2,5] Supportive management and toxicology consultation are indicated for cases of overdose or intoxication.

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Competing interests: None declared.

This article has been peer reviewed.

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Pain Ther (2020) 9:55–69
https://doi.org/10.1007/s40122-020-00151-x

REVIEW

Kratom—Pharmacology, Clinical Implications, and Outlook: A Comprehensive Review

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Received: November 25, 2019 / Published online: January 28, 2020

ABSTRACT

Kratom, or *Mitragyna*, is a tropical plant indigenous to Southeast Asia, with unique pharmacological properties. It is commonly consumed by preparing the leaves into decoction or tea, or by grinding them into a powder. Recent evidence has revealed that kratom has physiological effects similar to opioids, including pain relief and euphoria, as well as stimulant properties, which together raise potential concern for dependence and addiction. Moreover, growing evidence suggests that the prevalence of kratom use is increasing in many parts of the world, raising important considerations for healthcare providers. This manuscript will discuss the most current epidemiology, pharmacology, toxicity, and management related to kratom, while seeking to provide a contemporary perspective on the issue and its role in the greater context of the opioid epidemic.

Keywords: Drug abuse; Drug addiction; Kratom; Mitragynine; Opioid; Stimulant

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.11567916.

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Key Summary Points

Kratom (*Mitragyna speciosa*) is a botanical supplement with unique psychoactive properties.

The prevalence of kratom use appears to be increasing in Europe and North America, raising concerns for its possible development into a significant public health threat.

The body of scientific literature concerning kratom is expanding, but has not yet sufficiently characterized the nature and extent of the potential risks posed by kratom.

There is an increasing need for healthcare providers to be familiar with kratom and the management of patients who abuse it.

INTRODUCTION

Mitragyna speciose (Korth) is a tree-like herb consumed for its distinctive psychotropic properties [1]. Commonly known as "kratom"—a term referring to both the plant itself and the botanical products derived from its leaves—the *M. speciosa* tree is a tropical evergreen indigenous to the southeastern Asia-Pacific region, sharing close phylogeny with the coffee plant in the *Rubiaceae* family [2]. The consumption of kratom has been commonplace within this region for centuries, but has also recently gained popularity in the West [3, 4].

Kratom is primarily sought out for its stimulant and opioid-like properties, and may be used either for its perceived therapeutic effects or as a recreational drug. In either case, there is considerable uncertainty regarding the safety of ingesting kratom products. Consequently, it is important that healthcare providers be familiar with the subject, as it represents a growing public health concern. There are multiple aspects for the medical field to consider in addressing the problem of kratom, including reducing interest and accessibility, optimizing management of toxicity and dependence, and investigating its prospective use in research and therapeutics (Fig. 1).

Fig. 1 Key considerations regarding kratom in the medical field. Figure is original and was produced by the authors for this particular publication

The purpose of this review is to provide an in-depth discussion of these points, framing them within the greater context of the opioid crisis at large. Specifically, the article seeks to address the current epidemiology, pharmacology, and toxicity associated with kratom. In addition, we provide a synopsis on the clinical management of kratom in order to assist caretakers as they address patients suffering from overdose, addiction, and withdrawal related to the drug. To achieve these objectives, we have conducted an extensive and detailed literature review of the subject, incorporating both preclinical studies and clinical case reports in order to provide a fuller perspective on the matter.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

KRATOM: BACKGROUND, PREVALENCE, AND LEGAL STATUS

Kratom use has been customary in countries such as Thailand, Malaysia, and Myanmar for several hundred years [5]. Depending on the specific region, kratom is alternatively known as ketum, biak–biak, ithang, or thom [6]. Although raw leaves can be chewed or smoked for the

effects, more frequently the leaves are boiled in water to produce decoctions or teas, which contain multiple biologically active phytochemicals, accounting for its psychoactive properties [3, 7]. In addition to these more traditional methods of preparation, the leaves may be dried and processed into powders, capsules, and extracts, especially in western countries [8].

Historically, kratom has been used in traditional folk remedies for treating a range of ailments, for example, to mitigate symptoms of opiate addiction and withdrawal, or for weaning off dependence [9, 10]. It is also frequently used to relieve pain, produce euphoria, and stave off fatigue, especially among laborers in rural areas [11]. Its potential for dependence and addiction has long been apparent, and led to its categorization as a banned substance in both Malaysia and Thailand in the mid-twentieth century (of note, the Thai National Assembly has recently made it legal for medical purposes) [12, 13]. Nevertheless, the illicit use of kratom remains common; for instance, a survey conducted in Thailand in 2011 estimated the nationwide prevalence (lifetime) to be 2.9%, with nearly half of those admitting to daily kratom use, making it among the most commonly used illicit substance in the country [14].

In recent years, commercial preparations of kratom have become increasingly available in regions far beyond its local origins. Large-scale epidemiological studies evaluating the prevalence of kratom use are scarce, but available evidence indicates that its prevalence is on the rise in the United States [15], Europe [16], and developed eastern countries such as Japan [17]. In the USA, over 1800 total calls related to kratom ingestion were received by US poison centers in the 7-year interval from 2011 through 2017, with nearly two-thirds of these occurring in the last 2 years of the period, signifying the rapid rise in the use of the substance [18]. Moreover, a recent synopsis on kratom estimated the number of users in the USA to be in the range of 3–5 million based on membership numbers obtained from the American Kratom Association [19]. If accurate, this would correspond to approximately 0.9–1.5% of the US population reportedly using kratom. This trend is also reflected in the expanding scientific literature, where the number of case reports describing kratom intoxication continue to accumulate [20–23].

Particularly in the West, kratom is often used as a recreational drug, where it is perceived as a safe, "legal high" [12]. This reputation led to the proposed categorization of kratom as a Schedule I drug by the US Drug Enforcement Administration (DEA) in 2016, but it garnered little interest among policymakers. Thus, a key contributor to the problem is that kratom remains unrecognized as a controlled substance by the DEA and is therefore not subject to regulation by the US Controlled Substances Act [24]. Although it is currently listed on the DEA's Drugs of Concern registry, this is mostly a symbolic measure and does little to prevent its sale. However, as of 2019, six states legislatures (Alabama, Arkansas, Indiana, Wisconsin, Rhode Island, and Vermont) have successfully passed statutes criminalizing kratom possession [25]. In the rest of the USA, it remains legal and is easily obtained in stores or through numerous online retailers. Its sale is permitted throughout Europe as well, with the exception of Poland, Ireland, and Romania, as well as most of the Nordic and Baltic states [26].

To be sure, its unscheduled status and widespread availability have contributed to the expansion of kratom within Western markets [27]. However, in the USA, the more fundamental issue underlying the growing demand for kratom is the current opioid abuse epidemic [28]. As prescribers are pressured to cut back on supplying opioid medications, patients with opioid dependence often resort to alternatives like kratom to support their habit as traditional opioids become scarce [29]. Kratom is also sought out by those who wish to self-medicate for health conditions such as chronic pain or opioid withdrawal/dependence, and it has been heralded as a legal, inexpensive alternative to opioid replacement regimens [30]. The efficacy of kratom for such purposes remains highly questionable, and more research is needed to establish a conclusive answer.

PHARMACOLOGY OF KRATOM AND PROSPECTS IN THERAPEUTICS AND RESEARCH

Kratom does not denote a single, specific compound, but rather a cocktail of the psychoactive alkaloids occurring naturally in the plant. More than 40 of these compounds have been identified to date, although only four are known to be pharmacologically active: mitragynine, 7-hydroxymitragynine (7-OH- mitragynine), speciociliatine, and corynantheidine [31]. The most prevalent is mitragynine, which accounts for approximately 2% of kratom preparations by mass, but up to 66% of the total alkaloid content [32]. Its highly active oxidized metabolite, 7-OH-mitragynine, is present in far lower quantities, generally under 0.02% [33]. Other indole alkaloids present in significant concentrations include speciogynine, paynantheine, and mitraphylline [34]. Like the remaining trace alkaloids, these compounds are not known to be pharmacologically active; however, it is possible they may contribute synergistically to the overall effect of kratom in an unknown manner. Given the diversity of alkaloids present in kratom extracts and the unique potential pharmacodynamic properties of each, the net physiological effect of the substance is complex, intermixing stimulant and opiate-like properties in a dose-dependent manner (primarily stimulant-like at low amounts, with opioid effects predominating at higher doses) [35, 36].

Both mitragynine and 7-OH-mitragynine target opioid receptors, albeit with significant differences in binding affinity [37]. In fact, while the affinity of mitragynine for opioid receptors is less than that of morphine, 7-OH-mitragynine is far more potent than either, approximately 46 times that of mitragynine and 13 times that of morphine [38, 39]. Despite considerable investigation, the precise manner in which kratom alkaloids act at each of the receptors remains disputed. For example, Takayama and colleagues have produced a sizeable body of work on the subject, indicating that both mitragynine and 7-OH-mitragynine behave as agonists, with mitragynine acting primarily on μ- and δ-receptors and 7-OH-mitragynine more selective for μ- and κ-receptors [39–41]. However, competing evidence suggests a different model; rather than acting as simple agonists, mitragynine and 7-OH-mitragynine appear to demonstrate variable effects depending on the receptor. Specifically, the data show that both mitragynine and 7-OH-mitragynine are mixed opioid receptor agonists/antagonists, behaving as partial agonists at μ-receptors and competitive antagonists at δ-receptors, with negligible effects on κ-receptors [42].

Importantly, the indole alkaloids in kratom are structurally and pharmacodynamically distinct from their opioid counterparts, producing partially overlapping but nonidentical effects. Accordingly, these compounds have been called *atypical opioids* to distinguish them from morphine, semisynthetic opioids, and endogenous ligands [43]. Like the opioids, binding of the indole alkaloids to opioid receptors initiates G-protein-coupled receptor (GPCR) signaling; however, unlike traditional opioids, the activation of GPCRs by indole alkaloids does not initiate the β-arrestin pathway [44]. This phenomenon, known as biased agonism or ligand-directed signaling, enables a single receptor to mediate multiple different intracellular effects by selectively disengaging the various signaling cascades coupled to the receptor [45]. Interestingly, β-arrestin recruitment is responsible for most of the symptomology associated with opioid use (e.g., respiratory depression, sedation, constipation) [46, 47]. Thus, the selective inactivation of β-arrestin represents a desirable feature for an opioid, and suggests that mitragynine might be a useful template for designing novel opioids with more tolerable side effect profiles.

In addition to its opioid-like analgesic effects, mitragynine appears to block pain signaling through other mechanisms as well, suggesting a multimodal role in regulating pain perception. For instance, mitragynine shares considerable structural homology with yohimbine, another indole alkaloid, which has well-known adrenergic properties [37]. Like yohimbine, experimental evidence indicates that mitragynine activates α-2 adrenergic postsynaptic receptors [48]. This is significant for

mitragynine's analgesic effects, as α-2 receptors are present in modulatory "descending" pain pathways [49]. The importance of these pathways has only recently become apparent, and represent a major advancement in the complex neurobiological understanding of pain [50]. A third anti-nociceptive mechanism has been proposed in light of evidence that mitragynine impairs neuronal pain transmission via blockade of Ca^{2+} channels [51]. Additionally, indirect analgesic properties have been attributed to mitragynine's putative anti-inflammatory effects, secondary to the inhibition of COX-2 and prostaglandin E_2 mRNA expression [52, 53]. In addition to these anti-nociceptive functions, mitragynine bears some affinity for receptors in the central nervous system, including the 5-HT_{2C} and 5-HT_7 serotonin receptors, D_2 dopamine receptors, and A_{2A} adenosine receptors, but the physiological significance of these interactions is unclear [41].

The metabolism of kratom alkaloids is primarily hepatic, with several cytochrome P450 (CYP) isoforms involved, including CYP3A4, with lesser contributions from CYP2D6 and CYP2C9 [54]. It demonstrates linear pharmacokinetics and has a biphasic elimination pattern from the plasma when ingested orally, suggesting a two-compartment model of distribution [55]. The half-life of mitragynine has been reported to be as short as 3 hours, although some studies suggest it may be much longer [56, 57]. A major development in the understanding of kratom pharmacology has been the recognition that mitragynine is converted into 7-OH-mitragynine by hepatic metabolism in vivo [58–60]. Consequently, it has been postulated that 7-OH-mitragynine actually represents the active metabolite of mitragynine, accounting for most or all of the effects traditionally attributed to the mitragynine precursor. This hypothesis was first described by a trio of 2019 publications conducted by three separate groups [58–60]. These studies provided evidence that the activation of mitragynine occurs by CYP34A-mediated dehydrogenation—a process analogous to the activation of opiates such as codeine, which is converted into is active metabolite by CYP2D6. Although 7-OH-mitragynine is present in kratom extracts, it occurs at trace concentrations, leaving the authors to conclude that any ingested 7-OH-mitragynine is inconsequential relative to the endogenous generation of 7-OH-mitragynine derived from mitragynine. As current work is limited to animal models, future studies will need to confirm the relevance of this discovery in human physiology.

EFFECTS OF KRATOM ALKALOIDS IN PRECLINICAL STUDIES

Concern for the potential adverse effects associated with kratom has led to numerous preclinical investigations on the subject, such as the risk for dependence and addiction posed by mitragynine and related alkaloids. For instance, both mice and rat models have demonstrated addiction potential and cognitive impairment particularly in the setting of chronic mitragynine ingestion [61–63]. Studies also have found that the development of addiction and toxicity is specifically dependent on 7-OH-mitragynine, with mitragynine posing a minor risk [61, 64]. Moreover, chronic use has been associated with enhanced punishment tolerance and reward-seeking behavior [65]. Despite these adverse properties, animal model studies have also identified possible benefits; for example, mitragynine appears to slow the development of opioid tolerance when co-administered with morphine in mice, an observation which raises interesting possibilities for clinical applications [66].

Kratom has also been implicated as a cause of organ dysfunction and toxicity [67]. Animal studies have indicated a risk for drug–drug interactions, namely through modulating hepatic P450 activity and drug metabolism [68, 69]. Mitragynine also appears to inhibit hepatic demethylases and transferases, as well as glucuronidation by UDP-glucuronosyltransferases (UGT) such as UGT2B7 and UGT1A1 [70–73]. This bears important implications for a possible interaction when kratom is co-administered with other drugs known to be UGT substrates (e.g., buprenorphine and ketamine, metabolized by UGT2B7) [73]. Such findings have been used as a potential explanation for cases of

toxicity following co-ingestion of kratom with other medications, including a reported fatality secondary to toxicity from supratherapeutic levels of a prescribed antipsychotic concurrent with kratom ingestion [74]. The authors attribute this outcome to a drastic reduction in clearance of quetiapine (a CYP3A4 substrate) secondary to the acute suppression of hepatic metabolism by kratom.

Clearly, the basic science literature raises legitimate concerns regarding the potential for drug toxicity and behavioral risks following kratom ingestion. However, a major limitation of the preclinical literature is that many of the experiments were conducted using either chemically synthesized mitragynine or 7-OH-mitragynine rather than actual kratom (although a few studies utilized kratom leaf methanolic extracts) [75–77]. Consequently, such evidence likely represents an oversimplified and incomplete portrayal of the possible effects attributable to actual kratom consumption. This fundamental distinction must be considered prior to drawing any conclusions about patient safety from preclinical investigations.

POTENTIAL FOR ADDICTION AND TOXICITY

As alluded to earlier, the historical record concerning kratom's potential for dependence and addiction in humans raises strong concerns about its safety [41, 62, 78]. However, in many cases the primary motivation among regular users may simply be as a means to prevent exhaustion, and improve energy or mood. In such cases, routine use may not constitute dependence or addiction per se, but rather merely the desire to improve productivity [9]. This is in alignment with "drug instrumentation" theories, in which a substance is utilized in a purposeful, goal-directed manner [79, 80]. Such theories may account for the low incidence of kratom use disorder and other side effects among traditional users in Southeast Asia [81–85]. Nevertheless, the successful instrumentation of kratom does not preclude the potential for prolonged drug use, which under certain circumstances can degenerate into outright addiction [78]. It has also been proposed that a significant amount of kratom use occurs as a substitute for more harmful substances (namely narcotics) in patients with existing substance abuse, in which case kratom use represents a sort of harm reduction rather than drug abuse [79, 86]. Yet, while there is convincing evidence that kratom has significantly less potential for dependence and overdose than traditional opioids, the use of kratom in place of established medical opioid replacement regimens has little basis in evidence [30, 87, 88].

Aside from its potential for abuse, kratom poses numerous others risks to patients, largely a consequence of its status as an unregulated supplement. Without regulatory oversight, there is little to ensure the authenticity, purity, quality, potency, and safety of commercially available kratom preparations [89]. Consequently, it is difficult to know for certain what is actually present within commercially available kratom preparations, and the concentration of mitragynine contained can vary considerably [90]. For instance, it has been reported that kratom products may be altered by artificially increasing levels of 7-OH-mitragynine to enhance potency [91]. In addition, multiple instances of deliberate adulteration of kratom have been documented, for instance, by adding synthetic substances such as phenylethylamine (PEA) or *O*-desmethyltramadol, both of which have resulted in patient deaths [92, 93]. Other risks include product contamination (intentional or otherwise). For example, laboratory and epidemiological evidence identified kratom as the source of a multi-state salmonella outbreak in 2018 [94, 95]. There have also been cases describing the sale of kratom products later found to contain harmful heavy metal contaminants [96]. As there is considerable disparity between reported kratom toxicities in the West and in Southeast Asia (where it is comparatively uncommon), it has been suggested that misinformation regarding the content and potency of kratom may be largely responsible for the apparent danger attributed to kratom use [36].

CLINICAL PRESENTATIONS OF KRATOM ABUSE

Seeking to gauge the spectrum of possible symptoms associated with kratom toxicity, a 2019 retrospective review of cases reported to the National Poison Data System and New York City Office of the Chief Medical Examiner identified a wide variety of presenting symptoms, with agitation being the most common at 18.6%, followed by tachycardia at 16.9%, drowsiness at 13.6%, and confusion at 8.1% [97]. Serious neurological sequelae included seizures in 6.1% of cases, and hallucinations in 4.8%, with 2.3% progressing to coma. Toxicity occurred in a dose-dependent manner, particularly when doses of kratom powder exceeded 8 g. The study also determined kratom to be a contributing factor in at least four deaths. Consequently, the authors concluded that kratom supplements pose a public health risk and should not be presumed safe despite being legal for purchase.

Case studies reveal that a wide range of organ systems are susceptible to kratom-mediated injury (Table 1). For example, instances of kidney injury [67], cardiotoxicity and arrhythmia [98, 99], thyroid injury and hypothyroidism [100] lung injury/acute respiratory distress syndrome (ARDS) [101, 102], neonatal abstinence syndrome, [103–107] and hepatic injury [23, 108–116] have all been linked to kratom. Hepatic injury is an especially common presentation, and often presents with a cholestatic hepatitis pattern similar to other drug-related injuries: transaminitis (usually with levels above 100 units/L) along with an elevated alkaline phosphatase (> 200 units/L) and total bilirubin (> 1.2 mg/dL). A variety of neurological complications due to kratom toxicity have also been described, including acute brain injury and coma [21], along with the risk of seizures in both the acute and chronic setting [117, 118]. Long-term cognitive impairment may develop after long-term chronic users [81].

In certain severe cases, kratom toxicities have resulted in death. In fact, the incidence of kratom-related mortality appears to be rising, according to reporting by the Centers for Disease Control and Prevention (CDC), which linked kratom to 152 deaths between 2016 and 2017 [96]. Importantly, the existence of polysubstance abuse is a key risk factor predisposing patients to toxicity and death and has been estimated to occur in 87% of cases [119]. This has led to the belief that death resulting solely from ingestion of kratom is exceedingly rare, even impossible. However, in a 2019 article assessing kratom-related mortality in the state of Colorado, the authors reported that at least 4 of the 15 total deaths between 1999 and 2017 were attributable exclusively to mitragynine toxicity, a result which the authors confirmed using an extensive toxicological and

Table 1 Spectrum of organ system involvement and corresponding injuries associated with kratom use as identified in the case study literature

Organ system	Presentation signs and conditions	References
Hepatic	Acute liver failure, hepatitis, transaminitis, intrahepatic cholestasis, hepatomegaly	[23, 108–116, 131]
Endocrine	Hypothyroidism, hypogonadism	[26, 100]
Renal	Acute kidney injury	[67]
Cardiac	Cardiotoxicity, arrhythmia	[98, 99]
Pulmonary	Acute lung injury, ARDS	[101, 102]
Obstetric	Neonatal abstinence syndrome	[103–107]
Neurological	Acute brain injury, seizure, coma, cognitive impairment	[21, 81, 117, 118]

ARDS acute respiratory distress syndrome
Table is original and was produced by the authors for this particular publication

biochemical workup [120]. Nevertheless, it remains probable that most kratom-related deaths are the result of kratom toxicity superimposed upon the effects of some other noxiousness factor, such as adulterants or contaminants within the kratom product itself, or in conjunction with the ingestion of another illicit substance.

CONSIDERATIONS FOR TREATMENT AND MANAGEMENT

The management of patients abusing kratom can be divided according to three objectives, each addressing a different scenario: (1) stabilization and prevention of organ injury in the setting of intoxication/overdose; (2) alleviation of the symptoms during acute withdrawal; and (3) long-term maintenance of sobriety for behavioral addiction. While there are no published guidelines specifically indicated for kratom, it is reasonable to begin management in a manner similar to that employed for patients presenting with opioid abuse. However, kratom may pose greater potential risk for drug toxicity and organ injury than might be expected with opioids.

In cases of kratom overdose, management is largely supportive. While reversal agents are standard of care for opioid overdose, their efficacy in cases of kratom overdose has not yet been evaluated in clinical trials. However, anecdotal evidence from various case studies supports its use, and it is widely speculated to be beneficial [121, 122]. This has led several experts to recommend it [123, 124]. Depending on the organ system(s) involved, certain additional interventions may also be warranted. Acute hepatitis can be managed with *N*-acetylcysteine in a manner analogous to other cases of drug-induced hepatitis [125]. If seizures or neurological symptoms are present, appropriate management with anti-epileptics is warranted [21]. Kidney injury, cardiovascular events, or other emergency presentation should be similarly addressed with the appropriate measures. The symptomology of kratom overdose can mimic the opioid toxidrome, particularly when patients consume more than 15 g of kratom [125]. Given the absence of any effective therapies, primary prevention is the ideal method for lowering a patient's long-term risk for morbidity and mortality. However, screening is dependent upon patient disclosure, as kratom is not detectable with any commercially available toxicology screens.

Patients presenting with symptoms of kratom withdrawal tend to exhibit a clinical picture similar to that seen in opioid withdrawal [126]. This includes somatic complaints such as nausea/vomiting, chills, diarrhea, sialorrhea/rhinorrhea, body aches, restlessness, and irritability [78]. Physical exam findings include mydriasis, hypothermia, tremors, and diaphoresis. Additionally, a significant number of patients report psychiatric symptoms, most commonly nervousness, anxiety, and depression [33, 127]. Patients in acute withdrawal are managed conservatively, although there is some evidence to suggest that the combination of buprenorphine and naloxone can alleviate both the physical and mental symptoms associated with kratom withdrawal [128]. Additional evidence suggests positive results using high-dose clonidine or other α-2 agonists in combination with hydroxyzine [129].

For patients with chronic kratom addiction and drug cravings, long-term pharmacological replacement therapy may be warranted. Kratom addiction often begins in the setting of patients suffering from opioid dependence, in part because it is perceived as a cheaper, more natural alternative to buprenorphine or methadone in those who wish to cease their abuse of narcotics. However, as previously stated, there is currently no reliable clinical evidence that kratom is an effective alternative for achieving this purpose [30, 88]. Consequently, such patients risk developing habitual kratom use as well, while leaving their underlying chronic addiction inadequately addressed. For motivated kratom-dependent patients actively seeking long-term control of drug cravings in the medical setting, treatment regimens are identical to those employed for traditional opioid dependence, given the lack of empirical treatment guidelines for kratom specifically. However, presumptive management using opioid-

replacement therapy with methadone, buprenorphine, or buprenorphine-naloxone regimens have reportedly been effective [128, 130]. Lastly, consideration should also be given to referral of patients for counseling or enrollment in 12-step addiction treatment programs.

CONCLUSIONS

Although not an epidemic in its own right, the current trends in kratom use are cause for steadily growing concern, and it is likely to become a significant public issue in the near future if it continues on its current trajectory. In seeking to address it, the problem must be understood within the greater context of the current epidemic of opioid abuse, as the desire to alleviate opioid withdrawal symptoms is a critical factor accounting for patients who seek out and abuse kratom. Because it is primarily a consequence of the opioid crisis, it will be difficult to adequately address this issue until the larger opioid problem is resolved. Even then, use of kratom will continue among non-addicts who wish to abuse it for recreational purposes. In this regard, taking actions to limit access may be warranted. But even in the event that kratom is scheduled as a controlled substance, it will likely remain available through clandestine dealings, just as many currently controlled illicit substances are. Given the likelihood of protracted demand for kratom use, health providers and medical educators should take efforts to improve awareness of this still relatively unknown drug.

In addition to promoting awareness among healthcare professionals, there is a great need for more extensive, high-quality studies to better understand the mechanism of its toxicity and to formulate specific and credible guidelines for the management of kratom ingestion. Patients should be made aware of the potential harm kratom poses, including predictable risks such as dependence and toxicity, and unpredictable risks related to product quality and contamination. However, the rising importance and interest in this issue presents new opportunities for research on kratom in the context of opioid pharmacology, and ultimately will support the development of new and improved analgesic agents.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Steven C. Eastlack and Elyse M. Cornett have nothing to disclose. Alan David Kaye is a member of the journal's Editorial Board.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable for this article, as no data sets were generated or analyzed during the current study.

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Journal of Perinatology (2021) 41:1236–1243
https://doi.org/10.1038/s41372-021-00952-8

REVIEW ARTICLE

Outcomes of mothers and newborns to prenatal exposure to kratom: a systematic review

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Received: 21 May 2020 / Revised: 18 November 2020 / Accepted: 21 January 2021 / Published online: 15 February 2021

Abstract
Kratom is a legal, widely available substance that contains opioid agonist alkaloids. Due to the marketing of kratom as an opioid alternative for treatment of pain, anxiety, depression, or to reduce opioid withdrawal symptoms, the use of kratom has increased among persons in the USA including pregnant women. This systematic review of the peer-reviewed literature regarding kratom in relation to maternal and infant outcomes resulted in analysis of six case reports of prenatal kratom exposure. Maternal and infant withdrawal from kratom exposure was described in each case, resulting in pharmacologic treatment for both mothers and infants.

Introduction

The opioid epidemic has brought attention to perinatal substance exposures and the resulting effects on pregnancy, maternal, and newborn outcomes. Besides the substances of use that are identified by routine history and toxicology, novel psychoactive substances (NPS) often are not routinely part of the health history obtained and remain undisclosed or undetected during pregnancy. NPS are legally sold on the internet and in retail locations such as gas stations, herbal stores, and "head shops" [1]. From 2000 to 2017, the United States poison control reported roughly 67,500 calls reporting exposure to NPS [2]. Kratom was one of the four leading substances that had the highest rates of hospitalization and serious medical outcomes. While most exposures to natural psychoactive substances have decreased over the years, exposures to kratom have increased drastically, by 4948.9%, from 2011 to 2017 [2].

cKratom, a derivative of *Mitragyna speciosa*, is in the coffee plant family and originated from Southeast Asia. Kratom is sold as tea, capsules, tablets, raw leaves, and concentrated extracts. The two main alkaloid substances found in kratom are mitragynine pseudoindoxyl and 7-hydroxymitragynine. Mitragynine is an opioid agonist with a small affinity for receptors. Conversely, 7-hydroxymitragynine has a much smaller presence in kratom, yet an increased potency as an opioid agonist [3, 4]. The alkaloid 7-hydroxymitragynine has been reported to have a higher potency than morphine [5]. A major challenge in understanding the actions and effects of kratom is the varying dosage of the alkaloids, additives, or alterations of kratom, the variability of dosage, and simultaneous polysubstance use by consumers [6, 7].

Metabolites of kratom will not appear on a standard urine toxicology. Standard analytical screening techniques for mitragynine and its metabolites, as with other NPS, require a more sophisticated liquid chromatography–mass spectrometry [8–10].

The primary reasons for use of kratom given by persons with past or present substance use disorder include pain, anxiety, depression, and to stop or reduce opioid use by reduction of withdrawal symptoms [11–13]. Kratom is popularly used and marketed in the USA as an opioid substitute and for the reduction of withdrawal symptoms [14–18]. In 2016, the Food and Drug Administration (FDA) attempted to list kratom as a Schedule 1 controlled substance [19], which generated a massive response from pro-kratom advocates. In 2018, the FDA released a report of 36 kratom-related overdose deaths with potential deadly interactions with other substances [20]. In the same year, the FDA released a warning of kratom

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contamination with multiple strains of Salmonella, which resulted in 199 people infected across 41 states and 38% of infected individuals were hospitalized [21]. A subset of states and cities in the USA has banned kratom (Alabama, Arkansas, Tennessee, San Diego, California, Indiana, Rhode Island, Vermont, Wisconsin). The debate on the benefits of kratom versus the risks continues, and highlights the need for research to inform clinical practice guidelines [22].

Prenatal use of kratom incidence is not fully known. The specific effects on pregnant women and their infants/children are unknown. The purpose of this systematic review was to analyze the current evidence published in peer-reviewed journals of the effects of kratom on human mothers and infants.

Methods

The peer-reviewed literature including prenatal kratom exposure and effects on mothers and newborns was analyzed using the following databases: PubMed, Cochrane Review, CINAHL, EBSCOhost, and Google Scholar. Search terms included kratom and pregnancy, kratom, kratom and neonatal effects, kratom and neonatal abstinence syndrome, kratom and infancy, kratom and newborn, and kratom and perinatal exposure. Inclusion criteria for the studies included: (1) the literature using English language; (2) peer-reviewed journals; (3) research studies; (4) studies of kratom when the use was during pregnancy; (5) studies that included effects on the mother and/or infant associated with use of kratom prenatally; and (6) case reports that included prenatal use of kratom and effects on the mother and/or infant. Exclusion criteria for the studies included: (1) non-English language literature; (2) journals that are not peer-reviewed; (3) the literature that was not research; (4) studies of kratom that did not include use during pregnancy; and (5) studies of kratom that did not include effects on the mother and/or the infant.

A total of 31 articles were found in the search of the databases using the search terms described (Fig. 1). Eighteen of the articles were duplicate and were excluded from the review. Abstracts of the remaining 13 articles were reviewed. Five of the articles did not pertain to infant or maternal outcomes relating to kratom prenatal exposure. The remaining eight articles were reviewed in full text. Three articles were excluded due to not being research or case reports in addition to not pertaining to infant or maternal outcomes related to prenatal kratom exposure. Five published case reports in peer-reviewed journals that pertained to prenatal kratom use and maternal/infant outcomes were included in the review (Fig. 1).

Results

The review of the five case reports of prenatal kratom use and maternal and infant outcomes are summarized in Table 1. The five articles included six mothers with an age range of 39–37 years and used kratom during pregnancy [23–27]. The reasons mothers reported using kratom for included: (1) pain relief such as fibromyalgia, back pain, and restless leg syndrome; (2) anxiety; (3) relief of opioid withdrawal symptoms; and (4) desired opioid-like effects. Four of the six mothers used kratom 3–4 times per day for the entire pregnancy [23–27]. The cost of the kratom was reported by one mother as $40.00 per day [24]. Two mothers were treated with prescribed buprenorphine or buprenorphine and naloxone after weaning off kratom during pregnancy [27].

Descriptions of the mothers' withdrawal symptoms from kratom use were reported in the case studies and included anxiety, piloerection, diaphoresis, and restlessness. Symptoms of withdrawal were described as severe resulting in returning to kratom use or being treated with buprenorphine or buprenorphine and naloxone. One mother had to go to the emergency department due to the initial severity and presentation of her withdrawal symptoms when discontinuing kratom use [27]. Prior to pregnancy, one mother reported that if she missed a kratom dose for 4–6 h or if she tried to taper her kratom dose, she experienced symptoms that included diaphoresis, rhinorrhea, myalgia, anxiety, nausea, diarrhea, and piloerection [24]. Psychological dependence was also described by a mother as not being able to function at home or work without taking kratom [24].

Polysubstance use was reported in four cases and included prescribed substances for comorbid conditions [23, 25] (Table 1). Two cases had no other substances identified except kratom [24, 26].

The gestational age of five of the infants ranged between 37 weeks and 5 days to description of full term [23–27]. Infant outcomes included symptoms of neonatal abstinence syndrome in five out of six infants in the case reports, including the two infants that were only exposed to kratom prenatally. Symptoms of neonatal abstinence syndrome appeared to begin as early as 6–8 h after birth and could be detected up to 4 days after birth. The average length of stay in the hospital was ~10 days with a minimum stay of 3 days and a maximum stay of 12 days [23–27].

The five infants that exhibited withdrawal symptoms were pharmacologically treated with a morphine weaning protocol. One of the five was started on morphine then switched to clonidine after signs of over sedation. The infant developed sinus bradycardia on both morphine and clonidine and had no reported prenatal substance exposures other than kratom [26]. A Finnegan score of 18, prior to

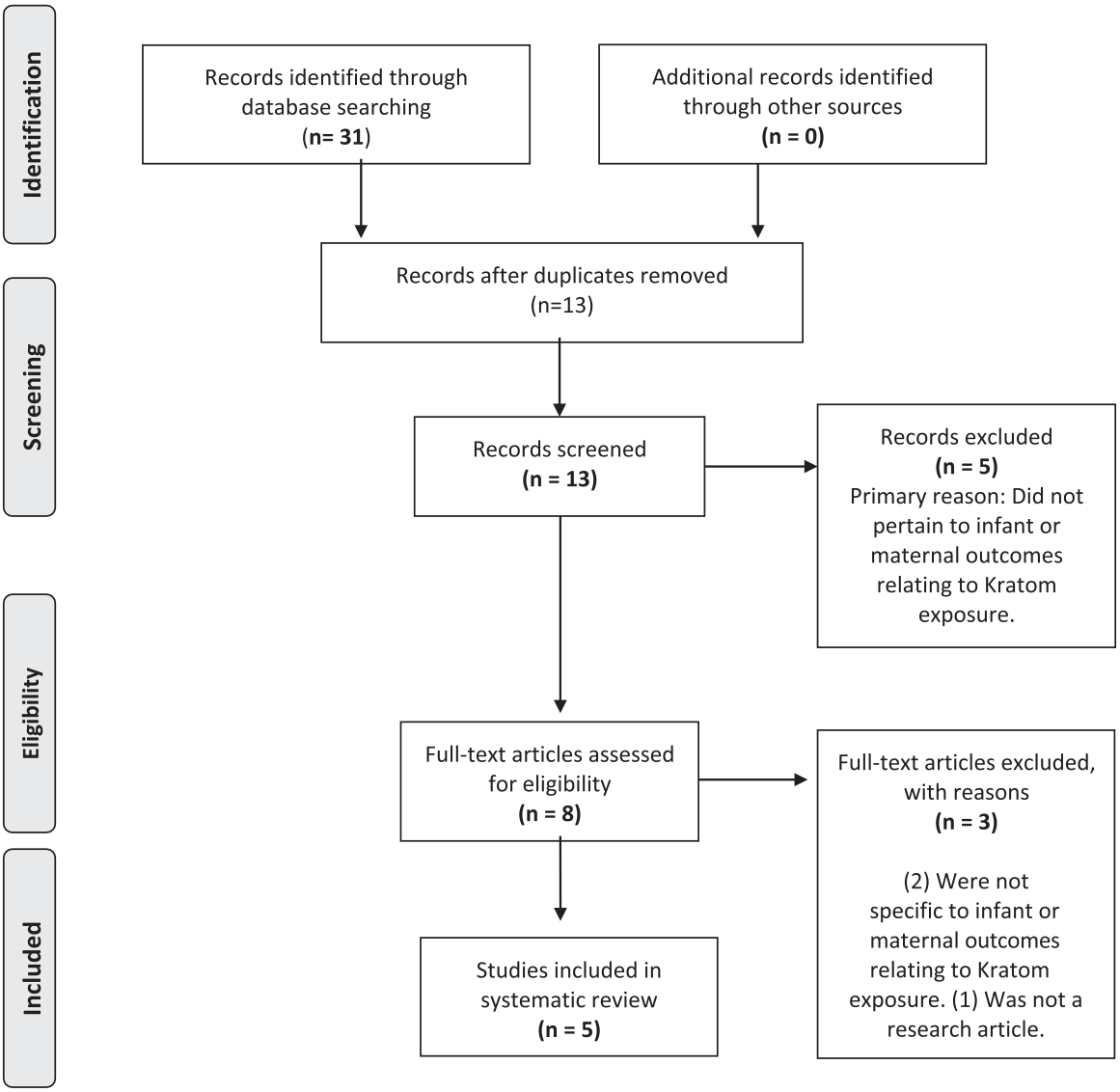

Fig. 1 Prisma flow diagram. Databases used: PubMed, CINAHL, Cochrane Review Google scholar, and EBSCOhost. Key search terms: "Kratom and neonatal abstinence syndrome," "Kratom and neonatal effects," and "Kratom and pregnancy".

morphine treatment, was reported for the infant exposed to kratom (tea used 3–4 times per day), selective serotonin reuptake inhibitors, acetaminophen-methocarbamol, diphenhydramine, valacyclovir, ranitidine, loratadine, salbutamol, and citalopram [25]. One of the infants who was only exposed to kratom, with a maternal daily use pattern of kratom 18–20 g three times per day, developed abstinence symptoms day 2 postpartum. Symptoms included feeding intolerance, jitteriness, irritability, and emesis requiring IV morphine 10 mg/kg/h and was switched on day 7 to oral morphine when able to tolerate oral intake [24].

The one infant that did not exhibit neonatal withdrawal symptoms was not exposed to kratom at the end of pregnancy, but instead the mother was given 2 mg of buprenorphine to alleviate maternal symptoms of withdrawal [27]. In addition, this baby was discharged from the hospital when 3 days old without evidence of withdrawal symptoms and there was no without report in the case study of follow-up of the infant to monitor symptoms post discharge from the hospital.

Discussion

The systematic review of the literature of prenatal kratom use and effects on maternal and infant outcomes revealed case reports of both maternal and infant withdrawal symptoms after kratom use in pregnancy. The majority of mothers in the case studies were using kratom daily prior to their pregnancy. All mothers reported consumption of

Table 1 Prenatal kratom exposure literature on maternal and infant outcomes.

Case study	Maternal characteristics	Other substances during pregnancy	Maternal outcomes	Infant outcomes	Comments
Davidson et al. [23]	29-year-old female	Other substances during pregnancy:	Delivery: Spontaneous vaginal delivery	Gestational age:	Call for research
	Chronic smoker	Gabapentin	Mother's treatment: Maternal treatment not specified in case study	Full term	Safety and efficacy of kratom for prenatal maternal use and effects on the fetus during pregnancy.
	Second pregnancy	Clonazepam		Feeding: Formula Fed	Polysubstance exposure complicates the causal relationship of kratom and withdrawal.
	Mother's kratom use pattern: Chronic kratom user				Further research is needed on polysubstance exposures.
	Reasons for kratom use:	Prenatal vitamins		Signs/symptoms of infant withdrawal: Symptoms 24 h after birth	Clinicians understanding specific spectrometry to identify kratom, routine toxicology will not identify kratom.
	Chronic low back pain, fibromyalgia, and anxiety			Included:	
		Daily over the counter herbal supplements		Reduced oral intake, jitteriness, sneezing, hypertonia, excessive crying. Intermittent tachypnea, excessive suck, hyperthermia.	
		Penicillin prophylaxis		Finnegan 10 and above	
		Nicotine		Pharmacologic Wean: Yes, morphine	
				Length of hospital stay: 14 days	
Mackay and Abrahams [24]	29-year-old female	Other substances during pregnancy:	Delivery: Delivered 37 weeks 5 days	Gestational age: 37 weeks and 5 days	Clinicians need to ask patients about kratom use and observe infants exposed for neonatal withdrawal.
	Gravida 4	No other substances described	Unremarkable pregnancy	Signs/symptoms of infant's withdrawal: On postpartum day 2, exhibited feeding intolerance, jitteriness, irritability, and persistent vomiting	Maternal withdrawal needs to be assessed and treated.
	Para 1-3-0-0		Mother's length of stay in the hospital:	Pharmacologic treatment for infant withdrawal:	Authors suggest the nonpharmacologic measure of rooming-in with mother and breastfeeding for infant withdrawal.
	Mother's kratom use pattern:		4 weeks in perinatal addiction unit	IV then oral morphine	
	18–20 g three times per day prior to and during pregnancy.		Mother's treatment:	Length of infant's stay in the hospital:	
	Reasons for kratom use:		Postpartum day 2 oral morphine	NICU 2 days	
	Back pain		moderate withdrawal symptoms anxiety, piloerection, diaphoresis and restlessness Improved over 2 days	Tertiary NICU 7 days	
	Functioning		4 weeks slow taper	Total length of stay not specified	
	Withdrawal symptoms if dose delayed 4–6 h			Feeding: Breastfed Infant was breastfed at the beginning of day 7	
	Symptoms included				
	anxiety, piloerection, diaphoresis, and restlessness				
Murthy and Clark [25]	37-year-old female	Other substances during pregnancy:	Mother's length of stay in the hospital:	Gestational age:	Maternal kratom demonstrated
	Gravida 2	Selective serotonin reuptake inhibitors	7 days after delivery	Term	withdraw symptoms with clinical features similar to narcotic withdraw.
	Reasons for kratom use:	Acetaminophen-methocarbamol	Delivery:	Feeding: Breastfed	Demonstrates importance of maternal history and practitioners' familiarity of kratom and kratom with polysubstance use.
	Anxiety	Diphenhydramine	C-section		Management principles for managing NAS with maternal kratom use are needed.

Table 1 (continued)

Case study	Maternal characteristics	Other substances during pregnancy	Maternal outcomes	Infant outcomes	Comments
				Signs/symptoms of infant's withdrawal: Within 6–8 h after birth jittery and increased tone	
	Restless leg syndrome	Valacyclovir	Mother's treatment (postpartum): Rapid 7 day detoxification program	12 h, excessive sucking and irritability	Prolonged withdrawal symptoms in infant need further evaluation.
	Mother's kratom use pattern:	Ranitidine		22 h, irritability, sleeplessness between feeds and excessive sucking Finnegan score of 18	
	Kratom tea was used daily 3–4 times per day	Loratadine		Pharmacologic treatment for infant withdrawal:	
		Salbutamol		Morphine with two unsuccessful weans of morphine	
		Citalopram		Length of hospital stay:	
				Discharged home on day 12 on oral morphine. Total wean off morphine took 2 months	
Eldridge et al. [26]	Mother's kratom use pattern: Daily drank kratom tea during pregnancy, which she purchased at a smoke shop, to self-treat opioid dependence	Other substances during pregnancy:	Delivery: Uncomplicated C-section	Signs/symptoms of infant's withdrawal: 33 h post birth, sneezing, jitters, excessive suck, facial excoriations, irritability, resting tremors, high pitched cry	Pediatricians should be aware of the increasing use of kratom as a self-treatment and "opioid alternative" in pregnant mothers and should expect to see more babies with NAS.
	Reasons for kratom use:	No other substances reported during pregnancy	Mother's length of stay in the hospital:	Pharmacologic treatment for infant's withdrawal: Morphine	Pediatricians need to ask mothers specifically about this drug when taking histories because it does not show up in urine samples.
	Opioid withdrawal symptoms	Maternal urine toxicology:	Not reported in case report	Appeared overly sedated and developed sinus bradycardia. Discontinued morphine after 3 days. Finnegan scores rose to 11–13	There is a lack of literature to guide pediatricians in management of babies with NAS due to kratom and more research needs to be done.
	Sleep	Negative	Mother's treatment:	Clonidine for 2 days until sinus bradycardia reoccurred so weaned off day 5	
			Not reported in case report	Length of infant's stay in the hospital: 8 days	
Smid et al. [27]	**Case One**	Other substances during pregnancy:	Delivery: Scheduled repeat C-section	Gestational age:	Kratom exposure in beginning of pregnancy switched to buprenorphine for remaining of pregnancy at a decreased dose.
	32-year-old woman	Buprenorphine:	Mother's length of stay in the hospital: After giving birth, mother remained in the hospital for 3 additional days (infant with her)	39 weeks	Infant was discharged on day 3 postpartum after prenatal exposure to buprenorphine but suggest follow-up if symptoms develop.
	Gravida 4 Para 2-0-1-2	8 mg after period of abstinence from kratom, tried to self-wean in pregnancy with severe depression so began 2 mg of buprenorphine for remainder of pregnancy	Mother's treatment (postpartum):	Signs/symptoms of infant's withdrawal: No evidence of neonatal abstinence syndrome, however child was discharged on day 3 after exposure to buprenorphine	Obstetricians should be aware of kratom use among individuals with opioid use disorders including pregnant women.
	Medical history:	Other substances during pregnancy:	Oxycodone for post cesarean pain	Length of infant's stay in the hospital: 3 days	Suggests that buprenorphine or methadone may be viable options for opioid replacement pharmacotherapy.
	Hodgkin's lymphoma	Switched from kratom to prescribed buprenorphine 16 mg and naloxone 4 and 2 mg, respectively	Buprenorphine	Feeding: BreastfedBreastfeeding:	Further studies should be done on prenatal use of kratom.
				Feeding: Breastfed	

Table 1 (continued)

Case study	Maternal characteristics	Other substances during pregnancy	Maternal outcomes	Infant outcomes	Comments
	Hx of oxycodone use for pain weaned in prior pregnancy	At 36 weeks gestation due to withdrawal symptoms switched to 20 mg buprenorphine and 3 mg naloxone daily			
	Reasons for kratom use:	Escitalopram, lamotrigine, and quetiapine (to treat bipolar disorder)	Length of mother's stay in the hospital:	Signs/symptoms of infant's withdrawal: Diagnosed with neonatal abstinence syndrome on day 4 after birth	
	Used to treat chronic pain and anxiety	Quit smoking cigarettes and switched to using an e-cigarette two to six times daily	2 days after giving birth	Treatment for infant's withdrawal: Treated with morphine	
	Mother's use pattern: Daily use for 7 months prior to discovering she was 16 weeks pregnant. She initially discontinued use, to self-wean, but was unsuccessful so she continued use of kratom		Delivery: Induced vaginal delivery	Length of infant's stay in the hospital: After being weaned off morphine, was discharged after 12 days after birth	
	Case Two		Mother's treatment (prenatal): Maintained 4 mg of buprenorphine and 2 mg of naloxone four times per day, switched to e-cigarettes, increased to 20 mg buprenorphine and 3 mg naloxone daily at 36 weeks of gestation for increased withdrawal symptoms	Feeding: Breastfed	
	28-year-old woman		Mother's treatment (postpartum): Maintained on same dosage of buprenorphine and naloxone until discharge	Infant was breastfed	
	Gravida 5			Gestational age:	
	Para 3-0-1-3			39 weeks	
	Presented to emergency department at 19 weeks gestation with withdrawal symptoms secondary to kratom. After 10–12 h of abstinence from kratom experienced opioid-like withdrawal symptoms			Apgar scores:	
	Past medical history:			8 and 8 at 1 and 5 min	
	History of intravenous methamphetamine and heroin use. Last use 6 months prior to presentation at emergency department			Finnegan scores:	
	Hospitalized several times for suicide attempts, but denied any active suicidal ideation			Not reported in case study	
	Reasons for kratom use: Desired opioid-like effects				
	Mother's use pattern: Smoking kratom for 4 months until reaching 19 weeks of gestation				

kratom because of its opioid-like effects and 66.67% of mothers reported previously being dependent on opioids. Although the previous drug history of all mothers was unclear in the case studies, the women who attempted to decrease or stop their kratom usage reported symptoms similar to opioid withdrawal and expressed psychologic dependence on kratom. Women of childbearing age are using kratom and becoming pregnant without knowing or being advised of consequences of continued use during pregnancy.

Of the case reports that included toxicology results, the results were negative. The presence of kratom metabolites needs specific spectrometry [22] and the standard toxicology testing would be negative if not specifically ordered. Clinicians need to review toxicology panels and understand the limitations of routine testing to detect NPS such as kratom.

Polysubstance exposure was described in the case studies. One mother reported taking prescribed gabapentin during her pregnancy along with a variety of other drugs. Gabapentin while taking opioids has shown an increase in the opioid's effects, and it is unknown whether kratom produces these same effects [28, 29]. The severity of the symptoms could not be fully analyzed due to inconsistent reporting of Finnegan scores in the case study reports; however, pharmacologic wean was needed whether or not the infants had polysubstance exposure or single exposure to kratom.

The treatment plan for the mothers was similar to typical opioid treatment plans. The various treatments performed to discontinue kratom usage included prenatal medically assisted therapy using buprenorphine or buprenorphine and naloxone, partial replacement of kratom with oral morphine (which both were completely weaned off after 4 weeks), and a rapid detoxification program with assistance of psychiatry and an addiction program. All of the treatment plans reported successfully weaning the women off kratom.

Infants experienced withdrawal symptoms that created a need for pharmacologic wean using morphine and in one case clonidine and morphine. In the only case report that did not require pharmacologic treatment, the mother was only using prescribed buprenorphine during the last months of pregnancy [27]. The infant was sent home 3 days after birth, which makes it possible that symptoms may have developed after discharge. Timing of infant withdrawal to prenatal kratom exposure is an area of research that is needed to guide timing of postbirth observation for withdrawal in infants.

Clinicians are educated to take a medical history that includes any drugs or other substances taken by a patient, especially during pregnancy. The public impression that herbal substances do not fall into the category of needing to be disclosed is based on the principal that these substances are "natural" and therefore do not need any special consideration. Due to marketing of kratom that claims it is a nonaddictive alternative for opioids without risk, mothers do not know the potential of risk if they use kratom [30]. In a qualitative study of pregnant or parenting mothers with substance use disorder, mothers expressed their concern on effects of substance use on their infant and were motived to discontinue use for the sake of their child(ren) [31]. Kratom use is not reported to child protective services because it is "legal." All of these factors may lead to misinterpretation of the safety of prenatal exposure to kratom and other legal psychoactive substances. Clinicians providing services to childbearing age, pregnant, or parenting women should specifically ask about the use of any substance. It should be explained to mothers that any substance exposure for the growing fetus may have effects—some that are known and some that are just being discovered as different substances become more available. The lack of incidence data is a result of the current state of undiscoverable use of kratom in pregnancy. Adoption of a validated tool, such as the kratom dependence scale, may assist in screening for the increasing use of psychoactive substances [32]. Understanding the presence of exposure to psychoactive substances during pregnancy assists in anticipating the observation of withdrawal symptoms for both mother and infant in the postpartum period, and scheduling the appropriate timing of discharge to home. Offering substance use treatment, such as detoxification, counseling that includes motivational interviewing, trauma informed care, and medically assisted therapy, is a standard of practice to address substance use disorders and should be made available to all childbearing age and pregnant women.

Research is needed to study the potential impacts of prenatal kratom in maternal and infant outcomes. In order to study the effects of perinatal kratom use, foundational areas of research are needed that include: (1) patterns of maternal use during pregnancy; (2) reasons for use in pregnancy; (3) maternal symptomatology; and (4) reactions to self-weaning during pregnancy. Infant outcomes need to address the crossing of kratom through the placenta, the determination of toxicology identification of kratom exposure, the amount of kratom in breast milk transmission to infants, and the timing, severity, and signs of infant withdrawal from prenatal exposure. Kratom combined with other prescribed and nonprescribed substances is an area of research needed to determine if there is an increased severity of negative maternal and infant outcomes.

Acknowledgements The project was partially supported by the Clemson Creative Inquiry Program.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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PHARMACOTHERAPY

BRIEF REPORT

Kratom Use and Toxicities in the United States

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Background Kratom is an herbal supplement containing alkaloids with opioid properties. This review was conducted to determine toxicities associated with kratom use in the United States in order to provide insight into its safety as a dietary supplement.

Methods We conducted a retrospective review of kratom exposures reported to the National Poison Data System to determine the toxicities associated with kratom use. We also reviewed records from a county medical examiner's office in New York State to identify kratom-associated fatalities.

Results A total of 2312 kratom exposures were reported, with 935 cases involving kratom as the only substance. Kratom most commonly caused agitation (18.6%), tachycardia (16.9%), drowsiness (13.6%), vomiting (11.2%), and confusion (8.1%). Serious effects of seizure (6.1%), withdrawal (6.1%), hallucinations (4.8%), respiratory depression (2.8%), coma (2.3%), and cardiac or respiratory arrest (0.6%) were also reported. Kratom was listed as a cause or contributing factor in the death of four decedents identified by the county medical examiner's office.

Conclusions Kratom use is increasing and is associated with significant toxicities. Our findings suggest kratom is not reasonably expected to be safe and poses a public health threat due to its availability as an herbal supplement.

Key Words opioid use disorder, opioids, kratom.
(Pharmacotherapy 2019;39(7):775–777) doi: 10.1002/phar.2280

Kratom, available as an unregulated herbal supplement in the United States, is prepared from the leaves of the Southeast Asian plant *Mitragyna speciosa*. The plant has been used for centuries in Southeast Asia by manual laborers for its stimulatory and analgesic effects.[1] In the United States, kratom has been predominantly used for self-treating pain or mood disorders.[2] Recently, kratom has gained acceptance among patients with opioid use disorder (OUD) as a practical alternative to evidence-based medication-assisted treatment, such as buprenorphine or methadone.[3,4] Anecdotal reports have posited that kratom is a safe treatment alternative to relieve opioid withdrawal, but clinical evidence to support this claim is lacking. Although a clear dose-response relationship has not been established, preliminary data suggest that lower doses of kratom produce stimulant-like effects and higher doses produce sedative effects.[5]

Mitragynine, the active component of kratom, has agonist activity at mu opioid receptors, and itself may lead to dependence and addiction.[6] Hydroxymitragynine, a minor component of kratom, also has opioid activity and is thought to be more potent than morphine. The addition of synthetic 7-hydroxymitragynine to kratom as an adulterant is thought to produce a product with more profound opioid effects.[7] A myriad of

Conflict of interest: The authors have no conflicts of interest to declare.

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other alkaloids, with activity at adrenergic, serotonergic, and adenosine receptors, may produce other clinical effects, but their potency and activity are poorly understood.[5] We conducted a retrospective review of kratom exposures and associated clinical effects reported to the United States National Poison Data System (NPDS), along with a retrospective review of kratom-associated fatalities identified by a county medical examiner's office in New York State.

A kratom case was defined as any call to the NPDS reporting a human kratom exposure between January 1, 2011, and July 31, 2018. Exposures that included substances in addition to kratom in the substance list (multiple substance exposures) were excluded and the remaining exposures (single substance exposures) were reviewed for demographics and associated clinical effects. All case data, including the substance list, clinical effects, and demographics, were extracted based on NPDS case coding. A kratom death was defined as any decedent identified by the county medical examiner's office during the same time period, with kratom listed as a cause or contributory factor to the death. Postmortem toxicology results were reviewed for all decedents. Both reviews were determined to be exempt from review by our Institutional Review Board.

A total of 2312 kratom exposures were reported to the NPDS during the time frame reviewed, with an increase from 18 exposures in 2011 to 357 exposures in the first 7 months of 2018 (Figure 1). After excluding cases involving multiple substances, 935 single substance exposures to kratom were identified for review. A majority of exposures (56.5%) reported kratom being used as a tablet, capsule, or powder and nearly all exposures identified oral ingestion as the route of exposure (86.2%). Most cases reported the reason for the exposure as intentional abuse or misuse (61.6%). The most commonly reported adverse effects were agitation (18.6%), tachycardia (16.9%), drowsiness (13.6%), vomiting (11.2%), and confusion (8.1%). Severe adverse effects included seizure (6.1%), withdrawal (6.1%), hallucinations (4.8%), respiratory depression (2.8%), coma (2.3%), and cardiac or respiratory arrest (0.6%). Four cases of neonatal abstinence syndrome and two deaths were reported to the NPDS during this time frame.

A total of four decedents with kratom listed as a cause or contributing factor to the death were identified by the county medical examiner's office during the time frame evaluated. Kratom alone was identified as the cause of death in two decedents, a combination of kratom and ethanol was identified as the cause of death in one decedent, and mixed drug toxicity with kratom, clonazepam, and cocaine was identified as the cause of death in the fourth decedent. Postmortem blood mitragynine concentrations of 260 and 1400 ng/ml were reported in the two decedents where kratom was the only substance identified. These concentrations are higher than those reported in Thai individuals consuming traditional kratom tea without adverse effects.[1]

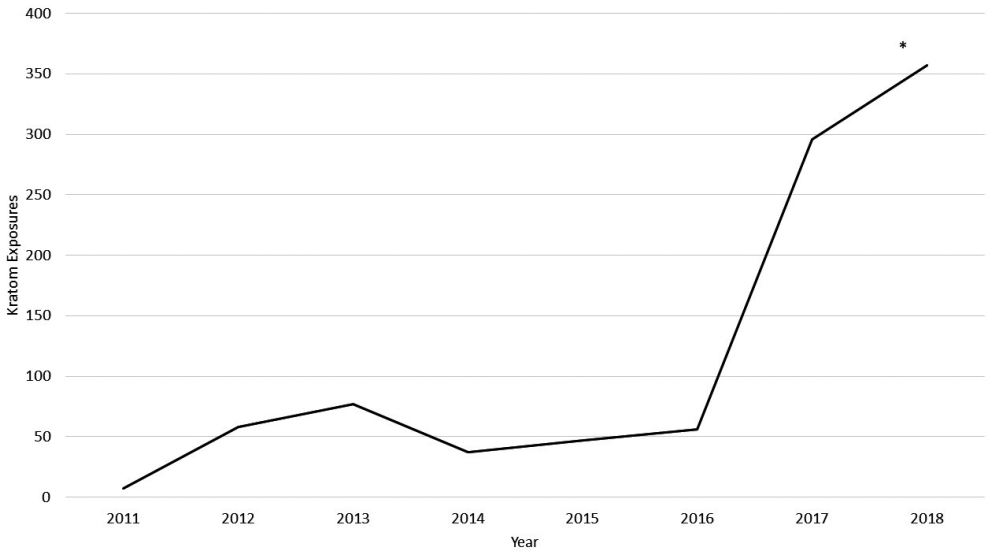

Figure 1. Kratom exposures reported to the National Poison Data System from January 1, 2011, to July 31, 2018. *Data for 2018 is partial and includes exposures from January 1, 2018, to July 31, 2018.

However, there are insufficient pharmacokinetic and postmortem data in patients using kratom for OUD to draw definitive conclusions. In the decedent with kratom and ethanol identified on postmortem analysis, a blood mitragynine concentration of 200 ng/ml and a blood ethanol concentration of 181 mg/dl were reported. In the decedent with mixed drug toxicity, a postmortem blood mitragynine concentration of 540 ng/ml was reported along with qualitative positives for blood cocaine and clonazepam.

Despite kratom's growing popularity as a safe and natural self-treatment option for patients with OUD, our findings suggest there are concerns for significant toxicity. Reports of kratom exposures to the NPDS are rising and have already been associated with serious opioid toxicities, including seizures, agitation, and death. Our county medical examiner's office has also identified four cases where kratom use appeared to contribute to the cause of death. Additionally, reports of withdrawal and neonatal abstinence syndrome suggest that kratom, similar to other opioids, can produce dependence. According to the United States Dietary Supplement Health and Education Act of 1994, herbal and dietary supplements must contain ingredients that are reasonably expected to be safe.[8] Our findings repudiate the idea that kratom meets this criterion. Kratom's opioid effects put patients at risk for withdrawal, respiratory depression, and death.

We concede that further research is needed to determine what role, if any, kratom may have in the treatment of OUD or chronic pain, and to identify the extent of kratom abuse in the United States. Of note, these data were derived from voluntarily reported exposures collected by the NPDS and a single medical examiner's office. We were not able to determine the incidence or prevalence of kratom use from this data set, and due to the voluntary nature of the reporting system, the data likely underrepresent the total number of exposures, toxicities, and deaths associated with kratom use. Data from NPDS are obtained from Poison Center coding and do not provide sufficient details to determine the circumstances surrounding the patient's reason for using kratom. Last, although examining only single substance exposures provides insight into kratom's clinical effects, it limits information on kratom's potential synergistic toxicity when taken with other substances. However, given these serious patient safety concerns and the 44 kratom-related deaths in the United States reported by the Food and Drug Administration, we agree with the United States Department of Health and Human Services that kratom's availability as an herbal supplement should be reconsidered.[9] Furthermore, kratom's rapid rise in popularity in the United States highlights the urgent need to expand access to evidence-based medication-assisted treatment for patients with OUD and to address the complex symptoms of chronic pain.

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Drugs (2020) 80:263–283
https://doi.org/10.1007/s40265-019-01242-6

REVIEW ARTICLE

Kratom (*Mitragyna Speciosa*) Liver Injury: A Comprehensive Review

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Published online: 9 January 2020

Abstract
Kratom (*Mitragyna speciosa*) leaves contain the mu opioid partial agonists mitragynine and 7-hydroxymitragynine. The US Drug Enforcement Agency considers it a 'drug of concern', and the US FDA is reviewing kratom, but there is a paucity of information regarding health effects. Liver injury is often cited as a potential health consequence, however the same few case reports are repeatedly referenced, without a broader context. Furthermore, reports have largely lacked standardized causality assessment methods. The objective is to evaluate causality in kratom liver injury, through a comprehensive scoping review of human cases, and by reviewing epidemiologic, animal, and mechanistic reports that relate to kratom liver injury. Hepatotoxicity causality was systematically examined using the Roussel Uclaf Causality Assessment Method (RUCAM) for case reports. Biopsy findings, potential pathophysiologic mechanisms, and management options are discussed. This review identified 26 case reports and abstracts, in addition to 7 cases reported from the Drug-Induced Liver Injury Network, 25 in FDA databases, and 27 in internet user forums. Latency periods to symptom onset had a median of 20.6 days and mean of 21 days (range 2–49). Common presenting signs and symptoms were abdominal discomfort, jaundice, pruritis, and dark urine. Histologic findings were predominantly cholestatic, although, biochemically, the condition was heterogenous or mixed; the median R ratio was 3.4 and the mean was 4.6 (range 0.24–10.4). Kratom likely causes liver injury based on the totality of low-quality human evidence, and, in the context of epidemiologic, animal, and mechanistic studies. It remains unclear which subgroups of users are at heightened risk.

1 Introduction

Mitragyna speciosa is a tropical tree native to Southeast Asia. Known colloquially as 'kratom' in Thailand and 'ketum' in Malaysia, the tree has large leaves that contain the partial mu opioid receptor agonists mitragynine and 7-hydroxymitragynine, among other alkaloids. While these compounds bind opioid receptors and have classical mu opioid effects, they are functionally biased, with unique downstream effects compared with classical opioids [1, 2]. The plant is anecdotally popular as a home remedy for opioid withdrawal and opioid use disorder, and few studies have formally investigated this popularity [3]. It is available as powder, extract, tea, tablets, or capsules with ground leaves. In the US and Thailand, regional poison centers have experienced increasing call volumes for kratom exposure [4, 5].

Kratom is illegal in numerous countries, and while sales in the US have been banned in several cities and states, it is not federally scheduled as a controlled substance. In 2016, the US Drug Enforcement Administration (DEA) declared its intention to list kratom as schedule I using emergency scheduling powers, but due to pressure from kratom advocacy groups, the public, and members of congress, scheduling was postponed [6]. The DEA considers kratom a 'drug of concern', and the US FDA is actively reviewing kratom, repeatedly expressing concern for abuse potential and harms associated with use [7, 8].

There is a paucity of information regarding kratom's health effects. Liver injury is cited as a potential health consequence, yet the same few case reports are repeatedly referenced, without a broader context. Furthermore, prior reports have largely lacked standardized methods of causality assessment for drug/herb-induced liver injury. The

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Key Points

Kratom likely causes liver injury based on the totality of low-quality human evidence in the form of case reports, US FDA databases, and online user forums, and in the context of epidemiologic, animal, and mechanistic studies.

Most users do not experience clinically apparent liver injury, and it is unknown which user subgroups are at heightened risk.

Laboratory parameters show heterogenous or mixed liver injury, while liver biopsies show predominantly cholestatic injury.

review evaluates the strength of causality in kratom-induced liver injury by performing the first comprehensive review of human cases, and reviewing the epidemiologic, animal, and mechanistic reports that relate to kratom-induced liver injury.

2 Methods

A scoping review was performed to broadly examine the current heterogenous evidence for kratom causing hepatotoxicity. A literature search for human cases was performed from inception through 20 November 2019, using the PubMed, Scopus, Embase, and Google Scholar electronic databases. The searched keywords were (kratom OR ketum OR Mitragyna OR mitragynine) AND (liver OR hepatic OR hepatotoxic OR hepatotoxicity OR hepatitis OR DILI OR HILI OR cholestatic OR cholestasis OR transaminitis OR transaminases OR LFT OR jaundice OR hepatomegaly). An additional search was performed in the National Health Institute (NIH) LiverTox database.

A literature search for relevant animal studies was also performed using the above timeframes and databases, based on (kratom OR ketum OR Mitragyna OR mitragynine) AND (animal OR model OR rat OR rats OR rodent OR rodents OR mouse OR mice) AND (toxicity OR toxic OR liver OR hepatic OR hepatotoxic OR hepatotoxicity OR hepatitis OR DILI OR HILI OR cholestatic OR cholestasis OR transaminitis OR transaminases OR LFT OR jaundice OR hepatomegaly).

For human and animal studies, only English-language articles were identified. A manual search of relevant article references was performed to further expand the search. Articles were included if they described a unique human exposure or animal study with suspected liver injury.

Causality of hepatotoxicity was systematically examined by calculating Roussel Uclaf Causality Assessment Method (RUCAM) scores for all case reports, and by utilizing a global approach to interpret RUCAM scores in the context of these alternate avenues of evidence.

3 Causality Assessment of Drug-Induced Liver Injury

Drug-induced liver injury (DILI) and herb-induced liver injury (HILI) are terms for a heterogenous group of disorders. The primary mechanisms for DILI are mitochondrial dysfunction, oxidative stress, and altered bile acid homeostasis [9]. Cholestatic DILI likely involves either direct injury of canalicular membranes or cholangiocytes by cytotoxic substances excreted in bile, or inhibition of transporter proteins. Heterogeneity between substances and people complicates attribution of causation.

A number of systems have been developed to evaluate causality, including the Naranjo Adverse Drug Reactions Probability Scale and World Health Organization-Uppsala Monitoring Center (WHO-UMC) criteria, which were not designed specifically for liver injury [10]; the Maria and Victorino scale, which does not account for liver injury pattern [11]; the Digestive Disease Week-Japan scale, which includes specific lymphocyte tests [12]; and a structured expert opinion process used by the Drug-Induced Liver Injury Network (DILIN) [13].

The RUCAM score has also been referred to as the Council for International Organizations of Medical Sciences (CIOMS) score [14]. When compared with the complex structured expert opinion process, the RUCAM tends to underestimate causality [15]. The RUCAM performed well when validated against re-exposure liver injury as the gold standard [16]. RUCAM is ideally used prospectively to ensure completeness of data collection, but has frequently been applied retrospectively, including in the validation study of the original RUCAM [16–18]. The drawback of retrospective use is the risk of incomplete information, resulting in a lower probability estimate.

The RUCAM criteria were modified in 2016 to define the degree of alcohol intake as a risk factor and to shift hepatitis E virus testing from group II to group I of nondrug causes for exclusion [17]. The RUCAM has several drawbacks, as noted by García-Cortés et al. and Shapiro and Lewis, which were only partially addressed by the updates [19, 20]. These obstacles include handling of incomplete data, atypical presentations, changing patterns of liver injury during the illness course, exclusion of histologic information, and subjectivity of some data elements. The RUCAM also has problematic test–retest and interrater reliability [21]. Overall, the

RUCAM remains the most commonly used method of causality assessment for DILI and HILI [17].

While the term DILI is often used to refer to herbal etiologies, HILI is a more specific term. Evaluating causality form herbal drugs has additional complexities that do not exist with pharmaceutical good manufacturing practices [22]. Herbal products can vary significantly, with unknown source harvesters and manufacturers, inconsistent plant parts used, variable solvents and impurities, varying chemical composition and active ingredient strength, and potentially the inclusion of multiple plant species. This multifactorial confounding does not negate the importance of causality assessment, but conclusions must be considered in this context. The RUCAM score has not been specifically validated for HILI but is commonly used to assess causality for herbal etiologies and is considered of value.

4 Epidemiologic Studies

Epidemiologic and cross-sectional studies have reported limited details regarding liver injury, making conclusions difficult to impossible. In 1975, a report on kratom users in Thailand noted that long-term users develop "an appearance similar to a hepatic face", and describes a 55-year-old male with "an appearance similar to a hepatic face", however no jaundice was reported and no laboratory studies were performed [23].

In Malaysia, a structured interview on kratom use in 562 subjects found six subjects who responded 'yes' to "Have you had a medical problem as a result of your Ketum use (e.g. memory loss, hepatitis, convulsions, bleeding, etc.)" [24]. No further details were reported, and it is unknown if these were cases of kratom-induced liver injury.

In a Malaysian cross-sectional study comparing 58 male regular kratom users with 19 nonusing male controls, there was no difference in transaminases [25]. The authors defined regular kratom use as self-reported consumption at least twice daily for at least 2 years, and subjects were excluded if they had ethanol or illicit drug use, nonalcoholic fatty liver disease, viral hepatitis, cirrhosis, coronary artery disease, or diabetes. Snowball sampling allowed authors to identify eligible subjects but may limit generalizability.

Between 2011 and 2017, among 1807 calls to US poison centers for kratom, 59 were for aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 100 (5%), 30 were for increased bilirubin (2.6%), and 18 were for other liver test abnormalities (1.5%) [4]. No further details are available and causality cannot be estimated. A retrospective, single poison center study from 2002 to 2016 examined calls from healthcare facilities for kratom exposure. Of 12 included patients, one was found to have elevated transaminases and bilirubin after presenting with nausea, abdominal pain, and jaundice [26]. The patient had underlying nonalcoholic steatohepatitis, and 1 month prior he discontinued lupus medications and started using kratom three times daily. Unclear evaluation by gastroenterology did not uncover alternate etiologies to explain his acute presentation. Laboratory values are unknown and transaminases improved after a 21-h course of N-acetylcysteine (NAC).

5 Human Case Reports

Articles state that only a few kratom liver injury cases have been described; however, searching revealed a total of 26 formally described cases: 11 case reports [27–37], 13 conference abstracts representing 12 unique cases [38–50], 1 case not formally published [51], and 2 cases in the NIH LiverTox database (Table 1) [52, 53]. In instances of data omission, we contacted authors to determine whether missing data were available.

The median age was 31.5 years, mean 35.4 years (range 19–70), and 65% of patients were male. Kratom formulations were powder (37%), unknown (37%), tea (15%), capsules (7%), and crushed leaves (3.7%). Among 18 cases with clearly reported latency periods from the start of kratom use to symptom onset, the median was 20.6 days and the mean was 21 days (range 2–49). Common presenting signs and symptoms were abdominal discomfort, jaundice, pruritis, and dark urine. Many cases also had chills and light-colored stools. Dosing amounts and frequency varied significantly and were poorly reported on, preventing dose–response estimation. The latency findings in the above cases are consistent with the separate seven-patient series produced by the DILIN, in which median latency to onset was 22 days (range 15–49).

A RUCAM score could not be calculated for three cases due to an unknown interval between initiating kratom and the onset of liver injury (latency) [29, 36, 41]. One of these cases may have involved re-exposure, which would otherwise likely have had a high RUCAM score [41]. RUCAM separately could not be calculated for one case owing to a lack of documented alkaline phosphatase (ALP), which is required to calculate an R ratio for RUCAM [44, 47].

Most case reports met the laboratory criteria for DILI based on consensus case definitions [54]. Three cases did not meet the DILI criteria; two further cases had insufficient documentation and were excluded [41, 44], and one was included due to an otherwise suggestive case [27, 44]. The included case that did not meet the DILI criteria had mild elevation in transaminases and ALP, and a direct hyperbilirubinemia of 28.6 mg/dL. Isolated hyperbilirubinemia is not considered a DILI; however, we chose to include this case because DILI consensus criteria are based on level 2b evidence, and given the otherwise suggestive elements of

Table 1 Summary of published cases

Article	Description	Diagnostics
Kupferschmidt 2011 [38]	A 30-year-old female used kratom powder 5 g with ethanol (unknown amount), 2 days apart. One day after the second use, the patient had fever and myalgias, which resolved in 1 day. Five days after the second use, the patient had pruritis and jaundice. Pruritis was treated with an antihistamine and a corticosteroid. At 35 days, transaminases and bilirubin normalized	Peak bilirubin total 9.4, ALP 174, ALT 482, AST 271. Unremarkable ultrasound, MR cholangiography, serum electrophoresis, ceruloplasmin, iron, ferritin, autoimmune antibodies, viral hepatitis, EBV, CMV
Kapp et al. 2011 [27]	A 25-year-old male used kratom powder twice daily for 2 weeks, and servings increased from approximately 3 g to approximately 12 g. 2 days after cessation, the patient had chills, and by day 8 had abdominal pain and dark urine. Bilirubin remained markedly elevated for 3 weeks after presentation, then gradually fell	Initial bilirubin total 30.9 (direct 28.6), ALP 173, ALT 94, AST 66. Negative viral hepatitis, ANA. Ultrasound and CT showed steatosis. Detectable urine/serum mitragynine. Biopsy found cholestatic injury
Rivera et al. 2011 [44]	A 26-year-old male used kratom, and had fever, abdominal pain, and jaundice. LFTs normalized over 1 month after stopping kratom	Bilirubin total 7.8, ALT 97, AST 57. Negative ANA, AMA, SMA, hepatitis serologies, CMV, herpes simplex virus, EBV. Negative studies for hemochromatosis and Wilson's disease. Ultrasound was normal
Kesar et al. 2013 [39]	A 34-year-old female used kratom half-spoon (unknown formula) on 2 adjacent days. Within 1 week, the patient had pruritis, dark urine, and light stools. The patient was treated with N-acetylcysteine for possible APAP toxicity, then started on ursodiol and hydroxyzine. At 40 days, tests normalized	Initial bilirubin total 10.6, ALP 298, ALT 93, AST 61. Negative viral hepatitis, EBV, CMV. Excluded autoimmune hepatitis, Wilson's disease, AAT deficiency, hemochromatosis, and primary biliary cholangitis. Ultrasound and hepatobiliary scan found no common bile duct obstruction
Dorman et al. 2015 [28]	A 58-year-old male used kratom powder daily for 1 month, stopped when he had jaundice and dark urine. The patient also had grade I hepatic encephalopathy. 1-year prior, the patient had jaundice after using kratom powder 1 tablespoon daily for 3 months, with bilirubin 9.7 that resolved with discontinuation	Initial bilirubin total 25.6 (direct 17.1), ALP 790, ALT 106, AST 49, ammonia 161 µmol/L Negative viral hepatitis, ANA, SMA. Ultrasound showed irregular liver texture without obstruction
Arens et al. 2015 [48]	A 26-year-old male with no past medical history, ingested, in 24 h, ethanol 15–20 drinks and kratom 15 g. Two days later, the patient had chills and right upper quadrant pain, and 2 weeks later presented again with dark urine. In the hospital, the patient had fever to 38.6 °C and tachycardia and was treated symptomatically. Transaminases peaked at ALT 703 and AST 483. The patient then improved and was discharged on hospital day 3. The time course of transaminase improvement was unknown	Initial bilirubin total 2.3, ALP 171, ALT 448, AST 483, undetectable APAP. Ultrasound found diffuse gallbladder wall thickening and pericholecystic fluid, without cholelithiasis or sludge. Negative acute viral hepatitis, normal ceruloplasmin, and 24-h urine copper. Initial serum mitragynine 13 ng/mL and urine mitragynine 356 ng/mL
Sullivan 2016 [51]	A 19-year-old female used kratom tea made by friends; however, the next morning, the patient had emesis, epigastric pain, fever, and myalgias. By day 6, the patient had pruritis, pale stools, and 'neon yellow' urine. On day 7, the patient had jaundice and went to hospital. Her friends had no ill effect. She had used kratom once approximately 3 weeks earlier without issue. Throughout the illness, the patient took 6 × 325 mg APAP tablets. She had been taking oral contraceptives for > 1 year, and was an occasional binge drinker, but not recently. Symptoms rapidly improved, and 2 weeks later the laboratory tests normalized, and were still normal at follow-up > 1 year later	Initial bilirubin total 5.8, ALP 181, ALT 215, fasting serum bile acids 225 µmol/L (normal < 10). Acute viral hepatitis tests negative, ultrasound normal, ANA 1:80, which may be present in healthy patients. Negative SMA, AMA, and liver kidney microsomal antibodies. Normal ceruloplasmin and AAT

Table 1 (continued)

Article	Description	Diagnostics
Drago et al. 2017 [37]	A 23-year-old male used kratom powder over 6 weeks (estimated 85 g in total). 1 week after the last use, the patient presented with 4 days of jaundice, pale stools, and dark urine. He used 'moderate' alcohol. Over 2 weeks, the liver tests normalized	Initial bilirubin total 7.4, direct bilirubin 5.8, ALP 225, ALT 210, AST 129, INR 0.9 Unspecified tests for viral and autoimmune hepatitis were negative. Biopsy "was entirely consistent with cholestatic liver injury"
Bernier et al. 2017 [40]	A 41-year-old female used kratom 1 teaspoon, twice daily for 1 week. Ten days after stopping, the patient had jaundice, pruritus, diarrhea, and subsequently went to hospital	Initial bilirubin total 15, ALP 245, ALT 144, AST 66. Viral (including E) and autoimmune hepatitis tests negative. Biopsy showed cholestatic overload with discrete destruction of interlobular bile ducts compatible with cholestatic hepatitis. On recheck 51 days later, bilirubin total 6, ALP 126 (Le Boisselier, R, personal communication, 26 June 2019)
Shah et al. 2017 [41]	A 30-year-old female used kratom tea and presented with a few weeks of abdominal pain, jaundice, dark urine, and pruritis. The patient was admitted with similar complaints and similar laboratory test abnormalities as previously. The abstract does not describe timing between use and onset, or whether ethanol or other medications are used, and it is unclear if this was a case of re-exposure	Initial bilirubin total 18, ALP 100, ALT 47, AST 48. Unknown extensive work-up for liver disease was negative, including viral etiologies. MRI and endoscopic ultrasound excluded mechanical biliary obstruction. Biopsy showed intrahepatic cholestasis
Riverso et al. 2018 [29]	A 38-year-old male used kratom and then presented with 5 days of chills and was subsequently discharged with likely viral illness. The patient used five doses of APAP and continued kratom. He initially improved, then returned with dark urine and pale stools. Unknown time interval between kratom use and onset	Initial bilirubin total 5.1 (direct 4.0), ALP 304, ALT 389, AST 220. Unremarkable serum APAP, and serum AAT and phenotype. No active viral hepatitis. Biopsy showed mild centrilobular hepatocellular and canalicular cholestasis
Griffiths et al. 2018 [30]	A 21-year-old male used kratom for 2 weeks, up to 12 capsules daily, and 10 g in the 2 days before admission. The patient had emesis, fatigue, abdominal pain, and dark urine. He drinks 2 beers 3×/week, and uses hallucinogenic mushrooms, last used 2 weeks prior. Discharged after 2 days, lost to follow-up	Initial bilirubin total 2.9, ALP 193, ALT 319, AST 294. Undetectable serum APAP, negative viral hepatitis panel. MRI showed moderate hepatosplenomegaly and small ascites. Ultrasound showed common bile duct dilation per the article, but it was only 6.4 mm, with no cholelithiasis or other abnormality (Olin JL, personal communication, 4 June 2019)
Tayabali et al. 2018 [36]	A 32-year-old male used 60 kratom tablets over 1 week, in addition to powder. Two weeks before presenting, the patient had jaundice, nausea, fatigue, arthralgias, night sweats, pale stools, and dark urine. He used kratom for > 2 weeks, and symptom onset occurred while still using kratom, but unclear latency from the start of kratom use to onset (Tayabali K, personal communication, 22 November 2019). The patient occasionally used APAP for chronic pain, drank alcohol occasionally; neither were quantified. He was treated with NAC 150 mg/kg/h, but had anaphylaxis so therefore stopped	Initial bilirubin total 6.3, ALP 391, ALT 365, AST 222. Negative tests for APAP, hepatitis A, B, C, HIV. Normal ceruloplasmin and AAT. Serum mitragynine 47.8 ng/mL, and detectable metabolite 7-hydroxymitragynine Ultrasound normal
Mousa et al. 2018 [31]	A 31-year-old male used kratom tea for 2 weeks and presented with 4 days of dark urine and malaise. He was treated with 18 doses of NAC (140 mg/kg load then 70 mg/kg every 4 h) and discharged on day 4	Initial bilirubin total 2.2, ALP 191, ALT 578, AST 191. Negative viral hepatitis panel and ANA, unremarkable abdominal CT and ultrasound (Mousa MS, personal communication, 20 June 2019)

Table 1 (continued)

Article	Description	Diagnostics
Mackenzie and Thompson, 2018 [49] De Francesco et al. 2019 [50]	A 27-year-old male ingested kratom powder purchased online. Several weeks after using it multiple times weekly, typically 3–4 tablespoons, the patient had 2 days of 'heavy' alcohol consumption, then developed vomiting, diarrhea, and epigastric pain. The next 3 days he ingested APAP 4 g/day, then presented with liver injury. On day 5 of admission, a liver transplant was performed	Initial bilirubin total 0.98, ALP 109, ALT 330, AST 1,431, APAP 2.6 µg/mL. Liver tests peaked 48 h later, with bilirubin total 11.2, ALP 162, ALT 6969, AST > 14,000, INR 8.8. Comprehensive urine toxicology screen was negative, except APAP and caffeine. Blood culture grew *Salmonella javiana*. Negative tests for viral hepatitis, Wilson disease, and extensive unspecified other causes. Biopsy found extensive hepatocellular necrosis with extracellular cholestasis. Gas chromatography–mass spectrometry of two of the kratom bags found mitragynine, paynantheine, and speciogynine (mitragynine isomer), without chemical adulterants. The kratom was confirmed to have *S. javiana*
Antony and Lee 2019 [32]	A 70-year-old male used kratom twice daily for 4 days and 2–3 weeks later presented with jaundice, nausea, and a 9-kg weight loss, as well as hepatitis that improved. He was readmitted 3 days later for worsening pruritis, melena, and syncope. At that time, Hgb was 4.8, creatinine was 2.9, and the patient had a red blood cell transfusion. Kidney injury of unclear etiology was thought to be as a result of acute tubular necrosis due to pigment nephropathy from hyperbilirubinemia. Three months later, laboratory tests normalized, except creatinine 1.8	Unclear documentation of laboratory test timing between admissions. Bilirubin total 27, ALP 230, ALT 59, AST 53, creatinine 2.27, BUN 80. Negative viral hepatitis, negative for 'various liver diseases', and unremarkable CT and MR cholangiography
Fernandes et al. 2019 [34]	A 52-year-old male used APAP 800 mg twice daily plus kratom for 2 months. He used kratom 1 teaspoon of crushed leaf initially twice daily for a few days, then daily for 2 months. Approximately 2 weeks after starting kratom, scleral icterus and jaundice began that slowly progressed. 16 days after stopping kratom, the patient presented with jaundice. He was treated with ursodiol for 1 month, at which time bilirubin improved but was not normal, and transaminases were rising. Not followed further	Initial bilirubin total 23.2 (peaked 10 days later at 28.9), ALP 255, ALT 66, AST 55, INR normal. MRI showed patent biliary ducts. Negative unknown work-up for alternate causes of liver disease. Biopsy showed acute cholestatic injury Laboratory tests on day 27 (last follow-up) showed bilirubin total 4, AST 71, ALT 78, ALP 183
Osborne et al. 2019 [33]	A 47-year-old male used kratom capsules for 3 weeks, not daily, then developed a few days of dark urine, pruritis, chills, and nausea. He took APAP < 3 g/day for symptoms, and denied any other new drugs, including herbals. The patient was managed as an outpatient. At 16 days, laboratory tests were still slightly abnormal; at 58 days, the only abnormality was ALT 60, possibly from underlying nonalcoholic fatty liver disease given obesity, dyslipidemia 9 months later, the patient presented again with 2 days of pruritis and anorexia, after rechallenge with kratom powder for 1 day. Bilirubin total 3.2, AST 185, ALT 566, ALP 211, and laboratory tests "trended toward normal 3 weeks following re-challenge"	Initial bilirubin total 5.8 (direct 4.3), ALP 170, ALT 265, AST 108. Laboratory tests peaked on day 2 then started downtrending. Undetectable serum APAP, negative EBV and viral hepatitis, normal AAT and ceruloplasmin levels, negative ANA. CMV IgM antibody index 1.7. Ultrasound showed steatosis (in the setting of obesity)
Ricardo et al. 2019 [42]	A 33-year-old female used kratom tea 1–2 small cups for 1 month; she had a history of chronic hepatitis C. The patient presented with 3 days of abdominal pain, jaundice, pruritis, and dark urine. Occasional alcohol use (unquantified). The patient was discharged after 3 days, when jaundice resolved and liver tests downtrended (unknown to what degree)	Initial bilirubin total 5.1 (direct 4.4), ALP 387, ALT 1134, AST 4624, normal INR. Undetectable APAP, ultrasound normal. Hepatitis C antibody reactive, hepatitis C RNA 31,100 IU/mL (Ricardo J, personal communication, 24 June 2019)

Table 1 (continued)

Article	Description	Diagnostics
Desai et al. 2019 [47]	A 36-year-old female used kratom for a few weeks, and was transferred for perinephric abscess. She drank a few beers weekly and used APAP < 10 g/week. ALT and AST more than doubled within a few hours. Started NAC intravenously. Liver enzymes improved to ALT < 300 and AST < 1000. NAC was stopped, but within 16 h, ALT/AST increased again therefore NAC was restarted. Peaked at ALT > 3800 and AST > 12,000; on discharge ALT was 352 and AST was 56. During admission, the perinephric abscess was drained and ciprofloxacin was administered (Desai P, personal communication, 25 November 2019)	Initial bilirubin total 2.4, ALP 239, ALT 592, AST 1482. Unremarkable viral hepatitis panel, ceruloplasmin, autoimmune antibodies, serum APAP, and ultrasound
Bøgevig et al. 2019 [43]	A 56-year old male used kratom powder 1 teaspoon daily. He had obstipation for 10 days and jaundice for 5 days, then presented 14 days after starting kratom. The patient had a history of mild 'liver enzyme' elevation that was normal 6 months prior, and no history of substance abuse, including ethanol. Bilirubin and ALT normalized in 3 weeks	Initial bilirubin total 17.3, ALP 392, ALT 887, AST unlisted. Negative viral hepatitis and CMV Gas chromatography–mass spectrometry of the kratom powder found mitragynine content 0.590 mg/g; there is no description of potential contaminant analysis
Aldyab et al. 2019 [35]	A 40-year-old female used kratom weekly for 1 month, then had abdominal pain and fever, and presented for care. The patient had also started a ketogenic diet 1 month before symptom onset. She had been taking an oral contraceptive and a nettle leaf supplement for a few years. She stopped kratom, contraceptives, and supplements, but started ursodiol, prednisone. The authors questioned if the discrepancy between cholestatic histology and hepatocellular biochemical tests may have been from prebiopsy corticosteroids that reduced lobular hepatitis more than bile duct injury	Initial bilirubin total 5.1, ALP 162, ALT 875, AST 462. Negative viral hepatitis, Wilson's disease, AAT deficiency, ANA, SMA, AMA. CT and MR cholangiopancreatography found mild periportal edema. Biopsy showed bile duct injury with few vague granulomas, and portal tract inflammation
Pronesti et al. 2019 [45]	A 30-year-old male used kratom powder with water for 4–6 weeks at night. He presented with 1 week of dark urine and pale stools, and one day of scleral icterus. The patient had a history of diabetes mellitus. No drug or APAP use. At 1 month, laboratory tests normalized	Bilirubin total 5.7, direct bilirubin 4.5, ALP 556, ALT 308, AST 125. Normal CT, hepatitis A, B, C, iron studies, ceruloplasmin, AAT, AMA, liver–kidney microsomal antibody, except ferritin 405 and SMA 1:20. Ultrasound found coarsened liver texture Biopsy showed inflammation with focal prominent eosinophils, and hepatocellular and canalicular cholestasis without fibrosis
Kaur et al. 2019 [46]	A 42-year-old female used kratom for 4 months, with the last use 4 weeks before presenting. One week before presenting, the patient had subjective fever, fatigue, nausea, anorexia, and dark urine (Kaur R, personal communication, 16 November 2019). No prior liver disease, alcohol use, or APAP use. Jaundice and AST/ALT improved at discharge, and at 1 month had normalized	Initial bilirubin total 3.3, ALP 298, ALT 371, AST 171, INR 0.97. ALT peaked at 606 Ultrasound found thickened gallbladder wall and normal liver. Negative autoimmune liver panel, viral hepatitis, HIV, EBV, CMV. Normal AAT, iron, ceruloplasmin
LiverTox Case 6972 [52]	A 29-year-old male used kratom powder daily, and 23 days after starting, the patient had jaundice, dark urine, pruritis, abdominal pain, and fever. He also used herbs Ma Huang (ephedra), kava kava, and *Sida cordifolia* for 2 days prior to starting kratom. The patient had a history of ethanol and injection drug use, and no history of liver disease. The illness was complicated by hemolysis and acute kidney injury	Initial bilirubin total 22.4, ALP 428, ALT 272, AST 70, INR 1.1. Negative viral hepatitis (including E) and ANA. CT and ultrasound found no biliary obstruction but showed gallbladder wall thickening and increased lymph nodes. Biopsy showed "cholestatic changes with mild necrosis and inflammation", but did not suggest chronic alcoholic liver disease or viral hepatitis

Table 1 (continued)

Article	Description	Diagnostics
LiverTox Case 8332 [53]	A 25-year-old male began using kratom every third day for five doses. 25 days after starting use, he developed jaundice, dark urine, pruritis, and abdominal pain. Documentation is conflicting on whether the patient had excess ethanol intake, but, in scoring, excess intake was used. The patient had no history of liver disease. He had started venlafaxine 3 months prior, and consumed a psilocybin mushroom once	Initial bilirubin total 5.6, ALP 218, ALT 126, AST 73, INR 0.9. Negative viral hepatitis (including E) and negative ANA. Ultrasound showed no biliary obstruction

AAT α-1-antitrypsin, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AMA* antimitochondrial antibodies, *ANA* antinuclear antibody, *APAP* acetaminophen, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CMV* cytomegalovirus, *CT* computed tomography, *EBV* Epstein–Barr virus, *Hgb* hemoglobin, *IgM* immunoglobulin M, *INR* international normalized ratio, *LFTs* liver function tests, *MR* magnetic resonance, *MRI* magnetic resonance imaging, *NAC* N-acetylcysteine, *SMA* smooth muscle antibody

Units are bilirubin, mg/dL; aminotransferases and alkaline phosphatase, units/L

the case with liver biopsy showing cholestatic injury. For one additional case, it was unclear whether the DILI criteria were met as ALP was 230 U/L but a reference range was not provided [32].

Six cases involved acetaminophen and although onset times were compatible for the RUCAM, reported doses were nontoxic and there was no suspected self-harm intent; therefore, as a concomitant drug, acetaminophen was considered not compatible with liver injury. One case used < 2 g/day × 3 days [39], one case used < 3 g/day for several days to treat symptoms of liver injury that were already present [33], one case used 1.6 g/day for 2 months [34], one case used 4 g/day for 3 days (and had serum acetaminophen 2.6 µg/mL [49], one case used < 10 g/week [47], and one case used acetaminophen 'occasionally' without quantification and the authors felt it was noncontributory [36]. Furthermore, Kesar et al. [39] and Fernandes et al. [34] had pure cholestatic patterns, which is inconsistent with acetaminophen toxicity. One case that used five doses of an unknown acetaminophen strength was excluded for lack of documentation [29]. It is unknown if therapeutic dosing of acetaminophen alters the risk for kratom liver injury.

A separate case was noteworthy for sonographic gallbladder wall thickening with pericholecystic fluid, in the absence of cholelithiasis or sludge [48]. The patient reported a single kratom use 2 weeks prior, but, based on serum mitragynine, likely used kratom more recently, and it is unclear to what extent the patient's ethanol use contributed. The patient recovered without cholecystectomy. One case was presented at two conferences, and a combination of the two abstracts was used to calculate the RUCAM [49, 50]. This case was notable for the positive *Salmonella javiana*, with liver failure requiring transplant. It is unclear to what extent kratom use was directly responsible, relative to *S. javiana* infection.

6 Human Reports in the Drug-Induced Liver Injury Network (DILIN)

Using data from 2004 to 2018, a study by Navarro et al. found eight cases of liver injury associated with kratom, out of 404 cases associated with herbal and dietary supplements [55]. There were two cases in 2008, one in 2016, and five in 2018. Rather than RUCAM, the DILIN uses a structured, expert opinion process for causality assessment. The expert opinion process determined a causal association in seven of eight cases, in which the median age was 46 years. The authors reported that "products were used for a median of 22 days (range 15–49) before onset of injury; 5 had jaundice, 6 itching, 5 abdominal pain, 3 fever, and none had rash" [55]. All cases had ethanol use. Hospitalization occurred for six of eight patients, and all recovered. The study did not describe whether NAC or other treatments were administered.

Table 2 Cases in FAERS [57]

Case no	Description	Diagnostics
15346316	A 24-year-old male used kratom 15 capsules on back-to-back days, 1 week apart (total of 4 days). The patient had an unknown pre-existing liver disease. He went to a hospital for routine liver biopsy, diagnosed with unknown staphylococcus infection, determined he would need a liver transplant. FAERS report by the patient's mother, who said his liver failure was thought to be from kratom	No diagnostics listed
14367521	A 25-year-old male used kratom two times on different days, and presented with hepatotoxicity 8 days after the initial use. No past medical history	Initial bilirubin total 4.2, ALP 141, ALT 684, AST 449
14180919	A 26-year-old male used kratom tea for 2 weeks, and had jaundice and lethargy. No past medical history. Treated with N-acetylcysteine	Initial bilirubin total 5.8, ALP 297, ALT 466, AST 214
14345738	A 35-year-old male used kratom for 3 weeks, and had jaundice, dark urine, and pruritis. No other drugs or herbs, 'drinks socially'. No past medical history. The patient was admitted and treated by discontinuing kratom	ALT 461, AST 189
15680525	A 35-year-old male used kratom two to three times over 1 month. The patient had severe abdominal pain. He was treated with N-acetylcysteine and transaminases normalized; surgery for potential cholecystitis was deferred	'Elevated LFTs' with no further laboratory results. Radiographic findings of cholecystitis
15346315	A 35-year-old male developed yellow skin when withdrawing from 2 years of significant daily kratom use, however it was unclear if this was jaundice	No diagnostics listed
15561348	A 45-year-old male presented for a few weeks of malaise, myalgias, and fatigue. He had pneumonia, acute kidney injury, and liver injury. His family found bags of kratom and thought he may have used it for 2–3 months. The patient had a history of hepatitis C and alcohol abuse, and had recent use of over-the-counter cold and flu products. FAERS report by the patient's sibling	ALT 300, AST 1900 at an unclear point in the illness. Undetectable acetaminophen. Thrombocytopenia. Creatinine 2.1. Ammonia 135 (unknown unit)
14347379	A 46-year-old male used kratom for a 'few weeks', and presented with 1 week of jaundice, lethargy, and confusion. He had a history of presumed alcoholic cirrhosis without decompensated events. Per family, no heavy ethanol intake for 1.5 years. Prior laboratory tests showed normal bilirubin, ALT, and AST. Medications were citalopram, lisinopril, metoprolol. Liver failure progressed to death	Initial bilirubin total 12.8, ALT 2426, AST 2609 Last laboratory tests were bilirubin total 24.6, ALT 1162, AST 802, INR 5.4
15373449	A 54-year-old female used an unknown amount of kratom powder. Two days later, the patient presented for unstated reasons. She used kratom once several months prior without effect. She had a history of hepatitis C, tobacco use, myocardial infarct, dilated cardiomyopathy, hypertension, dyslipidemia, and methadone dependence. Medications were aripiprazole, escitalopram, mirtazapine, lorazepam, methadone, aspirin, atorvastatin, losartan, and metoprolol	Initial ALP 114, ALT 2747, AST 3062. CT showed normal liver size/morphology. Ammonia reached 110 μmol/L
15744592	A male of unknown age used kratom tea for an unknown period. He presented for hematuria and bleeding with shaving. The patient was not receiving anticoagulants, gets regular testosterone injections, and the only new medication was meloxicam for 1 month	INR 12. Unremarkable mixing studies and fibrinogen, and factor X, II, and V levels. No other diagnostics

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CT* computed tomography, *FAERS* US FDA Adverse Event Reporting System, *LFTs* liver function tests, *INR* international normalized ratio
Units are bilirubin, mg/dL; aminotransferases and alkaline phosphatase, units/liter

The following cases were reviewed and considered unlikely to be kratom-induced liver injury: 14212085, 14356493, 14554619, 14995024, 14554565

7 Human Reports to the US FDA

A total of 25 cases of kratom hepatotoxicity have been reported to the FDA, which maintains the Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS) as a database of adverse event reports for food, dietary supplements, and cosmetics. A related database, the FDA Adverse Event Reporting System (FAERS), collects adverse event reports on drugs.

CAERS was queried from 2004 through June 2018, using the terms 'kratom', 'Mitragyna', and 'mitragynine'. This yielded 132 cases, of which 15 were related to liver injury [56]. This attribution was based on reports of 'acute hepatitis', 'drug-induced liver injury', 'acute liver/hepatic failure', 'hepatotoxicity', etc. Case details are unknown and causality was not estimated.

FAERS was queried from 2008 through March 2019, and a total of 408 reports under 'Mitragynine/Herbals' were identified [57]. Of these, 15 were considered potential hepatotoxicity, and case details were obtained from the FDA. Reviewing case notes excluded a further five cases as unlikely to be kratom liver injury. The remaining 10 cases are described in Table 2 and are of varying quality. Some are unlikely to be from kratom, but the lack of documentation prevented this determination.

FAERS has several potential drawbacks, including incomplete reports and lack of information verification. Case overlap between CAERS and FAERS is possible, however there is no overlap of ages between included CAERS and FAERS cases, or of case details between FAERS and LiverTox or published case reports and abstracts.

8 Human Reports in Internet Forums

The internet has numerous drug user forums, with intent ranging from risk reduction to high enhancement. Reports of kratom hepatotoxicity were queried on two popular harm reduction websites—Erowid and Bluelight—from the earliest available through March 2019 [58, 59]. Erowid allows for user posts but is curated by the website's operators, while Bluelight is a traditional user forum. Notably, although the first case report of kratom hepatotoxicity was published in 2011, these two websites have reports from 2004, 2007, 2008, and 2009. This underscores the value of user communities in detecting and reporting potential toxicity prior to identification by the medical community. A total of 27 posts were identified that are suggestive of kratom hepatotoxicity, listed in abbreviated form in Table 3. The reports vary in quality, with some listing specific test results and timeframes, while others omit important information. Given the number of online venues for drug use discussion, these 27 posts likely represent a fraction of online user-generated kratom hepatotoxicity reports. Reports include differing kratom formulations such as powdered kratom and concentrated extract, with frequency of use spanning from daily to weekly or less, and with variable intervals to hepatotoxicity onset. Diagnostic testing included three liver biopsies, and there were no reported deaths (although the majority are self-reports). Causality for user reports was not formally evaluated with RUCAM due to the high rate of omitted information. Despite limitations inherent to data from non-medical user forums, this adjunctive data source has value in demonstrating variations in formulations, time to onset, and frequency of use.

9 Human Biopsies

Twelve human liver biopsies have been described in case reports, not inclusive of internet forums. Kapp et al. found pure cholestatic injury without hepatocellular damage, with bile precipitations and canalicular cholestasis [27]. Kesar et al. found cholestasis, lobular inflammation, and increased eosinophils in sinusoids [39]. Drago et al. noted histology that was "entirely consistent with cholestatic liver injury" [37]. Shah et al. found intrahepatic cholestasis [41], and Bernier et al. found cholestatic overload with discrete destruction of interlobular bile ducts [40]. One of two cases in the LiverTox database showed "cholestatic changes with mild necrosis and inflammation" [52]. Riverso et al. found normal lobular architecture, mild portal tract inflammatory infiltrate with predominantly eosinophils, mild bile duct injury with rare apoptotic bodies and lymphocytic infiltration, and mild duct proliferation [29]. There was also focal steatosis and focal hepatocyte dropout, with mild centrilobular hepatocellular and canalicular cholestasis. Fernandes et al. found marked canalicular cholestasis, portal tract inflammatory infiltrate with lymphocytes, eosinophils, and some neutrophils, and bile duct injury with epithelial disarray [34]. Lobules showed injury with mild sinusoidal mononuclear infiltrate and Kupffer cell hyperplasia, and rare spotty necrosis without steatosis. Aldyab et al. found portal tract inflammatory infiltrate with predominantly nonplasma cells, bile duct injury, and scattered ballooned hepatocytes and endotheliitis [35]. Also noted were a few vaguely formed granulomas encasing interlobular bile ducts. Lastly, Pronesti et al. showed inflammation with focal prominent eosinophils, and hepatocellular and canalicular cholestasis without fibrosis [45]. Two biopsies performed in the DILIN (below) showed cholestasis.

Table 3 Self-reports through March 2019 in the Erowid Experience Vaults and Bluelight forum [58, 59]

Year	Post title (Author); website	Description
2004	Kratom—First time–Another Kratom Success (m#########n); Bluelight	Male used kratom for 3 weeks, and, over 1 week, developed jaundice, weakness, nausea, and dark urine; he suspected it was from kratom. Unknown if he stopped kratom use, it improved. History of prior significant ethanol use
2007	Extreme abdominal pain (PB); Erowid	Male used kratom weekly for several months, then had abdominal pain, malaise, and dark urine. Resolved 1 day later. Used kratom again 2 weeks later with identical symptoms. Not medically evaluated
2008	Kratom-induced hepatotoxicity (Sly); Erowid	25-year-old male used kratom extract every other day. After dose number 4, the patient had abdominal pain, dark urine, and jaundice. He was diagnosed with cholestatic hepatitis, which resolved in 2 weeks
2009	Kratom Health Issues (M#####h); Bluelight	Used kratom 10 g two to three times per week; after an unclear interval, the patient had jaundice, ALP 447–570, AST 375–460, ALT 685–834, urine bilirubin 6
2011	Kratom-induced hepatitis? (nlogn); Erowid	22-year-old female used crushed leaf almost daily for 2 weeks; had jaundice and pruritis. Previously healthy, no heavy ethanol use. Peak ALT 1400, AST 300, Tbili 6, ALP unknown. Ruled out viral and autoimmune hepatitis
2011	Kratom and liver damage (K################e); Bluelight	On day 1 used 10 × kratom extract 2.5 g and that night had abdominal pain. Over the next 2 weeks, the patient had jaundice and pruritis. On day 15, the patient went to hospital and was diagnosed with liver failure. Many tests were performed, including liver biopsy, and the patient was diagnosed with drug-induced cholestasis. Five weeks later, the patient was improving but had not returned to baseline
2012	Trip to the ER (SobeDog); Erowid	A 37-year-old male used kratom extract for first time, then the next day had abdominal pain and malaise that lasted 1 week. Two weeks later, he used kratom extract again, and awoke that night with abdominal pain and went to hospital. ALT 340, AST 250, unknown bilirubin and ALP. Liver tests trended down the next day, and normalized in 3 weeks
2012	Kratom-induced liver issues (Mark); Erowid	A 38-year-old female used kratom then had dyspnea and chest discomfort. In the Emergency Department, she had elevated liver function tests and was discharged. Over the next 5 days, the patient had progressive jaundice and pruritis
2013	Liver issues after very little use of kratom (l#####r); Bluelight	"I developed hepatitis around the same time I was taking kratom fairly often"
2013	Liver issues after very little use of kratom (a########l); Bluelight	Used kratom extract six times over 2 weeks (daily for 3 days, then three times in 1.5 weeks). 1 week after starting, the patient had nausea, and, 1 week after stopping, the patient had jaundice, pruritis, and dark urine, and was admitted. Liver enzymes, which were previously normal, were elevated. Negative hepatitis C. Ultrasound deferred. Previously healthy, no other drug use in 1.5 years, including OTC. Diagnosed as drug-induced cholestasis, which doctors thought was from kratom. Jaundice and pruritis improved but were still present 2 weeks after the last dose. Two years later, the patient used kratom again a few times over 1 week and 'liver symptoms' started returning. The patient stopped immediately, and was not medically evaluated
2013	Liver issues after very little use of kratom (J##########n); Bluelight	Used kratom 9 g daily for 2 weeks. After 1 week, the patient had dark urine, went to hospital, and had ALT > 500, "with other enzymes elevated as well". The patient stopped kratom and urine gradually normalized at the time of the online post; awaiting repeat tests. "I personally think that is [53] was the kratom, but given the other medicines I was taking to ease the [suboxone] withdrawal, I can't be sure."
2013	A warning to new Kratom users (J##########m); Bluelight	Used kratom approximately six times, then had jaundice; unclear timeline. The first four times were 3–10 g, the fifth time was 10 g; the patient had fever and nausea. The patient took an additional 10 g that night, and the next day had jaundice and pale stools. The patient had "elevated liver enzymes that of 6–8 times the normal levels". Further unknown tests were performed. The patient had also recently started the anabolic steroid methylepitiostanol

Table 3 (continued)

Year	Post title (Author); website	Description
2013	Kratom-induced liver injury? (s#########r); Bluelight	A 26-year-old male used powdered kratom 3 g, then a further few grams a few days later. Three weeks later, he drank kratom tea, and a few nights later repeated it. Over the next 2 weeks, he used kratom 5 times, 10 g each time, but never more than once in 2 days. He woke with emesis, went to the doctor, and "liver enzymes were through the roof". He was discharged, but a few days later had jaundice, pruritis, and dark urine, and was admitted. He had "extensive blood tests and several ultrasounds, I tested negative for all common liver diseases and showed no signs of gallstones, bile duct obstruction or anything else likely to cause such a reaction". He had detectable serum mitragynine. In addition, 18 months prior, he had a history of elevated liver enzymes for 3 weeks, which resolved and was attributed to acetaminophen. He used ethanol but not heavily, and marijuana was the only other drug used in this period. "Samples of the powdered kratom showed no obvious contaminants". The patient was diagnosed with "drug-induced hepatic injury causing severe biliary cholestasis", which doctors thought was from kratom. One month later, jaundice resolved, with residual fatigue and elevated liver enzymes
2013	Kratom-induced liver injury? (W######1); Bluelight	Began using daily kratom 1–3 teaspoons of crushed leaf. Five weeks later, the patient had abdominal pain, pruritis, and mild flu-like symptoms. One week later, the patient had scleral icterus, and tests showed "liver enzymes through the roof". The patient was admitted for 4 days, "no infection was detected, had many blood tests and abdominal ultrasound. Doctors thought from kratom". Diagnosed with drug-induced hepatitis. No other drugs were used, drinks "a couple of glasses of wine" in an evening, and abstains at least two nights weekly. 10 weeks later, the patient was back to baseline, and was awaiting repeat tests at the time of the online post
2013	A warning to new Kratom users (M####m); Bluelight	Used kratom daily for 1.5 weeks. The patient had vomiting and was admitted since "enzymes were severely elevated"; discharged after several days. One month later "enzyme levels were only a few points above normal". The patient then used kratom again for 1 week and had identical symptoms. The patient stopped use, did not seek medical care, and improved
2014	Hepatitis-like jaundice (FakeName); Erowid	Used kratom daily for 1 week, then had malaise, jaundice, pale stools, and very elevated 'liver enzymes'. Viral hepatitis tests were negative. Liver biopsy showed "blockage of the bile duct". started ursodiol, resolved over 1.5 months
2014	Killing my liver (happygent1236); Erowid	A male used kratom daily for several months, then suddenly had chills and jaundice. He was diagnosed with 'liver toxicity'. Previously healthy, no ethanol use
2014	Hard to Ignore: Kratom is extremely dangerous for some users (b################t); Bluelight	Used kratom for 3–4 weeks, 2–3 teaspoons of powder once daily. The patient had fever, abdominal pain, and dark urine, then scleral icterus and vomiting. The patient had leukopenia and "enzymes elevated to six times a normal level" with 'intrahepatic cholestasis'. No other hepatotoxic drug use, no pre-existing liver condition or hereditary concern. Doctors thought from kratom. Three weeks after being admitted, liver enzymes fell to slightly above normal. Symptoms gradually improved, starting 8 h after the last dose
2014	Hard to Ignore: Kratom is extremely dangerous for some users (C#######c); Bluelight	Used tramadol for 1 year and stopped, then started kratom six capsules daily. The patient had gradual pruritis, abdominal pain, and 3–4 weeks later stopped kratom. After 2–3 days of stopping, the symptoms resolved. The patient tried kratom again and severe symptoms returned. Did not seek medical care either time
2015	Almost Destroyed My Liver (sammers); Erowid	A 26-year-old previously healthy male (unclear duration of kratom use) awoke with nausea, and outpatient "liver enzymes were through the roof". Several days later, he had worse jaundice, no alternate etiology based on ultrasound, and "extensive blood tests". He was admitted for 1 week, and jaundice resolved over 1 month, with liver tests gradually improving but still elevated at the time of the online post

Table 3 (continued)

Year	Post title (Author); website	Description
2015	Induced hepatoxicity? (EkbatDeSebat); Erowid	A 26-year-old female used kratom once, then a few weeks later began daily use for 2 weeks. She had nausea, dark urine, and pale stools. ALT was approximately 400, Tbili 4.6, ALP unknown. She was admitted for a few days until laboratory tests downtrended. She had a CT scan, HIDA scan, ultrasound, and blood tests. The patient had a history of heavy ethanol use, with unclear frequency
2015	Kratom—Second time–hepatotoxic, ER with liver problems (h##########n); Bluelight	Used kratom once previously, then 2–3 teaspoons twice daily. The patient had abdominal pain, but continued to use for 1–2 days, then stopped use. The patient went to hospital and was diagnosed with hepatitis; had negative viral hepatitis tests. A repeat test showed downtrending liver enzymes. Abdominal pain peaked 2 days after stopping kratom, and improved within 1 week of abstinence. Repeat liver tests showed normalization
2017	Kratom and liver damage (H##########n); Bluelight	A few days after starting kratom, the patient had jaundice, pruritis, lower extremity edema, and vomiting. No other drugs were used in this time. The patient stopped kratom for an unknown period. There was no other drug use during this time, including OTC. The patient began using kratom again 2 weeks later, at a lower dose (1 teaspoon), but redeveloped vomiting and lower extremity edema. Did not seek medical care either time
2018	Bilirubin levels were through the roof (San Salvador); Erowid	A 23-year-old previously healthy male with no heavy ethanol use, used kratom for the first time. He awoke that night with abdominal pain, dark urine, and jaundice. A clinic said he had "drug-induced hepatoxicity and that my bilirubin levels were through the roof"
2018	Shooting liver pains and two trips to the ER (actual_ carrot); Erowid	A 20-year-old female used kratom for first time, but later that night had nausea and malaise. She suspected viral illness. 2 weeks later, she used kratom again, and awoke that night with chills, abdominal pain, and pale stools that progressed over 1 week. CT scan showed hepatomegaly, Tbili 3.9, elevated ALT. Negative viral hepatitis tests and ultrasound, and no heavy ethanol use. Bilirubin normalized over 2 weeks, and symptoms resolved over 2 months
2018	Kratom and liver damage (M########s); Bluelight	A male used kratom and had severe pruritis and elevated liver enzymes for 3 weeks. He also had liver biopsy. No further details are available
2019	Kratom, drug interactions prescription/OTC (a####n); Bluelight	Used kratom concurrent with ethanol, and developed 'severe hepatitis', but recovered

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ALP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CT* computed tomography, *ER* emergency room, *HIDA* hepatobiliary iminodiacetic acid, *OTC* over-the-counter, *Tbili* total bilirubin

10 Animal Studies

While the majority of animal studies have had neurobehavioral or other focuses, numerous animal studies have evaluated hepatotoxicity. In 1972, Macko et al. conducted the first mitragynine animal toxicity studies, in rats and dogs [60]. Biochemical parameters of liver injury were not tested, however hepatic changes were found on sacrifice. Liver weight actually decreased overall in rats administered mitragynine 5 or 50 mg/kg/day most days per week for 6 weeks. In dogs administered 20 mg/kg/day most days of the week, 3/4 developed diffuse increased sinusoidal cellularity, which did not occur at 5 mg/kg/day.

In a 2010 rat study by Harizal et al. of acute kratom toxicity, methanolic *M. speciosa* extract was ingested at 100, 500, or 1000 mg/kg over 14 days [61]. A positive control group ingested high-dose morphine, and a negative control group received 1% methanol. All three experimental groups and the positive control group had higher mean transaminases versus negative controls, while total bilirubin and γ-glutamyltransferase (GGT) did not differ. Rats in the highest-dose experimental group and the positive control group

also developed severe sinusoidal congestion, centrilobular necrosis, lipid accumulation, hepatocyte hemorrhage, and Kuppfer cells.

In 2012, Kamal et al. administered a single oral dose of *M. speciosa* extract to rats at 175–2000 mg/kg [62]. When measured at 14 days, there was no significant change in ALP or ALT compared with controls; however, histology demonstrated steatosis in all treatment groups, and the 2000 mg/kg group had centrilobular necrosis.

In a 2013 study by Sabetghadam et al. rats received oral mitragynine at 1, 10, or 100 mg/kg for 28 days [63]. A control group received vehicle alone (propylene glycol, Tween-80, water). There was no difference in transaminases versus controls at mitragynine 1 or 10 mg/kg, but the 100 mg/kg group had significantly higher mean transaminases, with higher mean relative liver weights. Bilirubin was not assessed. Histology in the 10 and 100 mg/kg mitragynine groups demonstrated hepatocyte hypertrophy, hemorrhage, and sinusoidal dilation. Centrilobular necrosis and inflammatory cell infiltration were absent in all groups.

In 2013, Fakurazi et al. administered mitragynine at 15 and 25 mg/kg intraperitoneally to mice with and without morphine [64]. There was no change from controls in AST, ALT, or GGT among treatment groups, with the exception of elevated ALT in the mitragynine 25 mg/kg group.

In a 2014 study by Sakaran et al. 32 rats were administered either control 15% Tween-80 on an acute or subacute basis, or administered *M. speciosa* methanolic extract [65]. The two *M. speciosa* groups received either a single oral dose of 1000 mg/kg for 14 days (acute group), or repeated doses of 500 mg/kg daily for 28 days (subacute group). The control groups had normal liver parenchyma. The acute *M. speciosa* group developed hypertrophy of hepatocytes with mild cytoplasmic vacuolation and sinusoidal congestion, while the subacute group demonstrated severe hepatocyte hypertrophy with numerous vacuoles and severe sinusoidal congestion.

A 2014 study by Ali et al. administered oral *M. speciosa* chloroform-methanolic extract to 70 rats, at doses of 10, 30, or 100 mg/kg [66]. One group of rats was additionally exposed to immobilization stress conditions for 2 h daily, and there was also a placebo group. On liver histology, slight and moderate hyperemia were noted in the 100 mg/kg non-stressed and 30 mg/kg stressed groups, respectively.

A 2015 rat study by Ilmie et al. administered oral methanolic *M. speciosa* extract for 28 days at 100, 200, or 500 mg/kg, while controls received water [67]. There was no difference in ALT between groups. Compared with controls, mean AST was significantly higher in the 100 mg/kg group only (lowest dose). The authors noted that "total bilirubin … showed statistically significant differences when compared to the control group", but this data is not provided. Histology in the 200 mg/kg group showed portal inflammation and bile duct proliferation.

In 2018, Haslan et al. investigated *Piper betle* as a hepatoprotective herb in rats with kratom [68]. Controls received oral 15% Tween-80 *or P. betle* methanolic extract dissolved in Tween-80. Experimental groups received *M. speciosa* methanolic extract 500 mg/kg/day in Tween-80 for 28 days, or *M. speciosa* extract with *P. betle* extract. Control groups demonstrated normal liver histology. The *M. speciosa* group developed severe sinusoidal congestion with disrupted central veins, scattered focal necrosis with inflammatory cell infiltrate, 'drop out' lesions, and acidophilic bodies. Some hepatocytes had ballooning degeneration and microvesicular steatosis, and a few areas showed fibrous portal expansion and bridging fibrosis. The *M. speciosa* group with *P. betle* had minimal focal necrotic and acidophilic bodies, and only a few portal triads with fibrous portal expansion. The authors concluded *P. betle* reduced *M. speciosa* liver injury in this animal model.

A 2019 mouse study by Guenther et al. administered oral kratom tea at varying doses, found increased liver size on day 11 in the kratom tea group compared with controls [69]. Kratom was then discontinued and, at 4 weeks after kratom cessation, liver size was similar in the kratom-treated mice and controls. However, after 4 weeks of cessation, the kratom-treated group was noted to have adhesions of the liver to adjacent intraperitoneal organs. Biochemical parameters of liver injury were not measured, and the authors concluded kratom can cause reversible hepatomegaly in as few as 10 days in a murine model.

Overall, animal studies tend to show increased histologic and biochemical marker effects of liver injury at higher doses, however this is not consistent. Pathohistological patterns have included centrilobular necrosis and bile duct proliferation, among other findings. Most studies used *M. speciosa* methanolic extract at doses far higher than typical users are exposed to.

11 Mechanisms of Kratom Hepatotoxicity

Kratom metabolism is primarily hepatic, but its effects on hepatic transporters and enzymes remain poorly studied. Based on current evidence, we propose a multifactorial pathophysiologic mechanism involving pregnane X receptor (PXR) activation and cytotoxicity, but this is likely an incomplete model. The effects on UDP glucuronosyltransferases (UGTs), glutathione S-transferases (GSTs), and P-glycoprotein (PgP) may also play a role. These mechanisms may also reduce the threshold for hepatotoxicity from other substances.

PXR is a nuclear ligand-gated transcription factor that upregulates hepatic expression and activity of multiple

drug-metabolizing enzymes and transporters [70]. PXR activation has been linked to DILI, and postulated mechanisms involve either increased toxic metabolite formation due to upregulated drug-metabolizing enzymes and transporters, or altered homeostasis leading to increased endogenous toxic substances [71]. In general, drugs with significant hepatic metabolism cause DILI at a rate higher than other drugs, likely by generation of local toxic metabolites [72]. A single study has examined the in vitro effect of kratom on PXR. It found that at 0.37 μM for 48 h, mitragynine increased PXR activity 1.2-fold and several other *M. speciosa* alkaloids had increased effect [70]. This in vitro concentration must be considered in the context of plausible human plasma concentrations. A single study examined maximum concentration (C_{max}) in human volunteers and found the highest C_{max} was 0.105 μg/mL (0.26 μM) [73]. This study administered varying concentrations and volumes of kratom tea to regular kratom users, and the highest C_{max} was reached in the subject taking the largest loading dose of 23 mg. In rats, C_{max} has been reported as 1–1.8 μM [74]. Kratom in vitro studies are challenging to extrapolate clinically. Human C_{max} may reach higher levels since those using kratom recreationally often consume doses larger than those reported by Trakulsrichai et al.; however, free mitragynine is likely much lower, since the authors measured total mitragynine, which does not account for high protein binding [74]. Additionally, users often consume kratom for a longer duration than the 48 h studied in vitro by Manda et al. [70].

Cytotoxicity may play a role in kratom liver injury, causing hepatocellular injury or selectively damaging canalicular membranes, with specific pathways unelucidated. Saidin et al. found *M. speciosa* extract and mitragynine cytotoxic in vitro to human neurons, and cytotoxicity was enhanced by cytochrome P450 (CYP) 2E1 [75]. Separately, cytotoxicity and genotoxicity of mitragynine and methanolic *M. speciosa* extract were tested in vitro on human intestinal epithelial and neuronal cells after 4 and 6 h [76]. There was concentration-dependent reduced viability in both intestinal and neuronal cells. Genotoxicity was noted from extract but not pure mitragynine, suggesting it may be mediated by non-mitragynine plant constituents.

Kratom undergoes metabolism by several phase I CYP450 enzymes, in addition to phase II sulfation and glucuronidation [74, 77]. Kratom has been variably shown to affect UGTs, GSTs, and CYP450 enzymes, however these effects lack a clear link to hepatotoxicity, unless there is a resultant increase in an unidentified toxic metabolite.

Mitragynine affects several CYP450 enzymes, particularly CYP1A2, CYP2D6, and CYP3A4. Findings on whether induction or inhibition occurs, and the concentration at which it occurs, have varied among studies [74]. Similar to phase II enzyme inhibition, these effects may reduce the ability of the liver to detoxify metabolites or endogenous substances.

UGTs perform glucuronidation. A 2013 study found *M. speciosa* extracts weakly inhibited UGT activity in vitro, at concentrations too high for clinical relevance [78]. The same study administered *M. speciosa* extract to rats for 2 weeks, and UGT activity actually increased, possibly from an unidentified mechanism not present in the in vitro system. Another in vitro study assessed the effects of mitragynine and 7-hydroxymitragynine on human liver microsomes expressing recombinant human UGTs, and found inhibition only at concentrations too high for clinical relevance [79]. Separately, GST inhibition was demonstrated in rat liver cytosol in vitro by high concentration *M. speciosa* extract, yet the same study found, in rats, an in vivo trend toward GST induction rather than inhibition [80]. The cause for the discrepancy is unclear and may relate to *M. speciosa* metabolites only present in vivo.

Lastly, it is unknown if the effects on PgP may contribute to kratom hepatotoxicity. Mitragynine is not a PgP substrate and has been found to inhibit PgP in three studies and to induce PgP in one study [74, 81].

Several transport proteins strongly implicated in cholestatic liver injury have not been studied with kratom and future research should focus on the bile salt export pump, multidrug resistance proteins 2 and 3, and farnesoid X receptor [82, 83]. Further research may reveal a single protein effect as the dominant pathophysiologic mechanism.

12 Clinical Course

Due to the small number of cases described, the clinical course of kratom liver injury is unclear. There have been no clear deaths from kratom liver injury and a single case in the FAERS database died without sufficient exclusion of alternate etiologies and with likely underlying alcoholic cirrhosis. Hepatic coagulopathy has not been described; one case in the FAERS database had severe coagulopathy, but no conclusions could be drawn due to poor documentation. Hepatic encephalopathy grade I was described in a single case report [28] and two cases in the FAERS database had elevated serum ammonia with no documentation of encephalopathy. Kidney injury was described in two cases, but one had unclear chronicity and was complicated by a duodenal ulcer requiring transfusion [32], and the other in the FAERS database was likely from hemolysis of unknown etiology.

Latency to onset of liver injury is unclear. Several case reports and online self-reports had seemingly fast onset within 1 day. However, some of these may have been re-exposure cases, with subclinical liver injury from prior use that increased to a clinically apparent threshold after re-use [51]. Some reports of liver injury occurred after varying

periods of regular use, while others developed without regular use [38, 39, 51]. The cases in this review had a median latency of 20.6 days (range 2–49), and these findings are similar to the seven-patient series by the DILIN. The cause for latency to clinical manifestations may relate to the half-life of the parent compound and metabolites. This may be supported by Kapp et al. [27] noting detectable urine mitragynine 2 weeks after cessation of use, and by the finding that many cases have laboratory abnormalities that peak following initial tests.

13 Management

Optimal management of kratom liver injury remains unstudied. The majority of cases resolved with discontinuation, and it is unknown if the treated cases would have self-resolved without intervention. Several cases utilized antihistamines for symptomatic treatment of cholestatic pruritis.

Seven cases were treated with NAC, five published cases [26, 31, 36, 39, 47] and two cases in the FAERS database. NAC has classically been used for acetaminophen hepatotoxicity, although it has multiple therapeutic mechanisms and has been used with varying success in other hepatic conditions [84]. In one case, NAC was discontinued due to anaphylaxis [36]. Its utility for kratom liver injury is unknown; however, given the low risk of harm, it may be a reasonable therapeutic option if the etiology in the setting of a hepatocellular injury pattern is unclear.

Three cases were treated with ursodiol (ursodeoxycholic acid) [34, 35, 39]. The mechanisms of ursodiol include protecting cholangiocytes from hydrophobic bile acid cytotoxicity, stimulating hepatobiliary secretion via insertion of transporters into the canalicular membrane, and protecting hepatocytes against apoptosis from bile acids [85]. Anticholestatic effects have been described in a number of conditions, and while there are no data on efficacy for kratom liver injury, ursodiol may be reasonable if a cholestatic pattern is not readily resolving with discontinuation.

Two cases were treated with glucocorticoids and their role in the management of kratom-induced liver injury is unknown [35, 38]. This treatment is occasionally used in severe cases of cholestatic pruritis. A single case underwent lier transplantation, however it is unclear to what extent liver failure was directly due to kratom use, relative to Salmonella infection [49, 50].

In cases of suspected kratom liver injury, after initial tests to exclude common alternate etiologies, pursuing outpatient management for select patients may be reasonable. This depends on the extent of hepatic injury, degree of symptomology, ability to tolerate oral hydration, and resources and follow-up capabilities. Outpatient management was followed by resolution in one case report [33] and for two patients in the DILIN [55]; several others had brief admissions followed by outpatient management.

14 Limitations

The available evidence has several limitations. The total number of cases remains a limited dataset relative to estimated prevalence of use. Furthermore, many of the case reports and abstracts lack the necessary information to calculate accurate RUCAM scores. These omissions range from nonreporting of known data, historical variables that were not asked of the patient, or diagnostic tests that were not performed. In several cases, the patient was not followed for a long enough period for biochemical parameters to improve to the degree dictated by the RUCAM. Many of the cases that did not score higher were due to a lack of information, such as lost to follow-up, laboratory tests not rechecked early enough, or unknown timing. Omitted information overall risks RUCAM scores underestimating causality, given the score penalty for lack of information. We contacted authors in an attempt to obtain instances of missing data.

Additionally, the RUCAM dictates that those receiving treatment for liver injury, such as ursodiol or corticosteroids, must receive a score of 0 for course (dechallenge period), since treatment may mask the natural course [17]. This resulted in a total of five cases each being penalized 2 points on the RUCAM.

Hepatotoxicity from a contaminant cannot be excluded but is less likely given the standardized extracts used in animal studies and the kratom gas chromatography–mass spectroscopy analysis in five cases [27, 49, 55].

R ratios were calculated based on initial laboratory testing when available, however some were based on laboratory testing later in the illness course. Due to variability in both patient presentation timing and report documentation, *R* ratio timing could not be standardized and may have changed during the illness course. This is a recognized drawback of the RUCAM, therefore using the initial values when available is recommended [17].

15 Discussion

This review identified 26 case reports and abstracts, in addition to 7 cases reported from the DILIN, 25 in FDA databases, and 27 in internet user forums. Although evaluation by clinical gestalt is an accepted method of judging causation, its lack of standardization or rigor should preclude its application to a wider cohort. Attributing causation in DILI and HILI is of paramount importance as it affects the drugs a patient can receive and informs policy decisions regarding drug availability. Determination of a substance's

Table 4 Calculation of RUCAM scores

	Liver injury type	Time to onset (days)	Risk factor (ethanol, pregnancy)	Age, years	Course	Concomitant drugs	Nondrug causes ruled out	Prior hepatotoxicity	Re-exposure response	Modified RUCAM
Kupferschmidt, 2011 [38]	R ratio 8.0 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	≥ 50% improved > 30 days [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Kapp et al. 2011 [27]	R ratio 1.4 Cholestatic	5–90 [+2]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
Rivera et al. 2011 [44]	No ALP for R ratio									Cannot calculate
Kesar et al. 2013 [39]	R ratio 0.5 Cholestatic	≤ 15 from last use [+1]	Absent [0]	< 55 [0]	Corticosteroid/ ursodiol [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	2
Dorman et al. 2015 [28]	R ratio 0.24 Cholestatic	1–90 for second exposure [+2]	Absent [0]	≥ 55 [+1]	Unknown [0]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Positive [+3]	7
Arens et al. 2015 [48]	R ratio 7.5 Hepatocellular	< 5 [+1]	Present [+1]	< 55 [0]	Unknown [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Sullivan 2016 [51]	R ratio 3.4 Mixed	5–90 [+2]	Present [+1]	< 55 [0]	≥ 50% improved in 180 days [+2]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	6
Drago et al. 2017 [37]	R ratio 2.7 Mixed	≤ 15 from last use [+1]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	4
Bernier et al. 2017 [40]	R ratio 1.7 Cholestatic	≤ 15 from last use [+1]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	None [0]	Groups I and II [+2]	Published, unlabeled [+1]	Unknown [0]	6
Shah et al. 2017 [41]	R ratio 1.4 Cholestatic	Insufficient documentation								Cannot calculate
Riverso et al. 2018 [29]	R ratio 4.0 Mixed	Insufficient documentation								Cannot calculate
Griffiths et al. 2018 [30]	R ratio 4.8 Mixed	5–90 [+2]	Absent [0]	< 55 [0]	Unknown [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Tayabali et al. 2018 [36]	R ratio 2.7 Mixed	Insufficient documentation								Cannot calculate
Mousa et al. 2108 [31]	R ratio 8.7 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	N-acetylcysteine [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Mackenzie and Thompson, 2018 [49] De Francesco et al. 2019 [50]	R ratio 8.7 Hepatocellular	5–90 [+2]	Present [+1]	< 55 [0]	Liver transplant [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	4
Antony and Lee 2019 [32]	R ratio 0.7 Cholestatic	≤ 15 from last use [+1]	Absent [0]	≥ 55 [+1]	≥ 50% improved in 180 days [+2]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
2019, Fernandes et al. 2019 [34]	R ratio 0.7 Cholestatic	5–90 [+2]	Absent [0]	< 55 [0]	Ursodiol [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3

Table 4 (continued)

	Liver injury type	Time to onset (days)	Risk factor (ethanol, pregnancy)	Age, years	Course	Concomitant drugs	Nondrug causes ruled out	Prior hepatotoxicity	Re-exposure response	Modified RUCAM
Osborne et al. 2019 [33]	R ratio 5.2 Hepatocellular	1–15 rechallenge [+2]	Absent [0]	< 55 [0]	> 50% improved in 30 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Positive [+3]	7
Ricardo et al. 2109 [42]	R ratio 8.4 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	Unknown [0]	None [0]	< 5 in group I [− 2]	Published, unlabeled [+1]	Unknown [0]	1
Desai et al. 2109 [47]	R ratio 7.1 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	*N*-Acetylcysteine [0]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	3
Bøgevig et al. 2019 [43]	R ratio 6.5 Hepatocellular	5–90 [+2]	Absent [0]	≥ 55 [+1]	> 50% improved in 30 days [+2]	None [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	6
Aldyab et al. 2019 [35]	R ratio 10.4 Hepatocellular	5–90 [+2]	Absent [0]	< 55 [0]	Ursodiol [0]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
Pronesti et al. 2019 [45]	R ratio 1.6 Cholestatic	5–90 [+2]	Absent [0]	< 55 [0]	≥ 50% improved in 180 days [+2]	Time incompatible [0]	5–6 in group I [0]	Published, unlabeled [+1]	Unknown [0]	5
Kaur et al. 2109 [46]	R ratio 3.6 Mixed	> 15 from last use								Cannot calculate
LiverTox Case 6972 [52]	R ratio 2.1 Mixed	Calculated by NIH LiverTox								5
LiverTox Case 8332 [53]	R ratio 2.1 Mixed	Calculated by NIH LiverTox								8

Interpretation: 9–10 highly probable, 6–8 probable, 3–5 possible, ≤ 0 excluded

Notes on scoring: for *R* ratios, upper limits of normal in the manuscript were used, but, if unavailable 40 was used for ALT and 115 was used for ALP. For Kapp et al. [27], serum mitragynine of 20 ng/mL at 12 days was not considered toxic due to the lack of reference ranges for toxicity. Griffiths et al. [30] describe common bile duct dilation, however 6.4 is within the normal limits. Antony and Lee [32] calculated RUCAM based on + 1 for alcohol risk factor, however the above calculation uses 0 because there was not excess ethanol consumption (Antony A, personal communication, 28 February 2019). For Osborne et al. [33], CMV hepatitis was unlikely given immunocompetency, but possible given + CMV IgM. For Ricardo et al. [42], the patient 'occasionally drank alcoholic beverages' that were unquantified, therefore the above calculation conservatively used ≤ 2 drinks/day (0 points). For nondrug causes, AST/ALT > 2 raised the possibility of alcoholic hepatitis, and hepatitis C RNA was moderately elevated, therefore hepatitis C flare is possible (Ricardo J, personal communication, 24 June 2019). Tayabali et al. [36] calculated a RUCAM score, however the latency period was unknown. In cases by Arens et al. [48] and Mackenzie and Thompson [49], ethanol is considered both a risk factor and a possible group I nondrug cause. For Kesar et al. [39] and Fernandes et al. [34], corticosteroid and/or ursodiol were administered, therefore although ≥ 50% improvement in 180 days would be [+2], the course had 0 points. For Mousa et al. [31], Aldyab et al. [35], and Desai et al. [47], N-acetylcysteine or ursodiol was administered, therefore although ≥ 50% improvement in 30 days would be [+2], the course had 0 points

ALP alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CMV* cytomegalovirus, *IgM* immunoglobulin M, *NIH* National Institutes of Health, *RUCAM* Roussel Uclaf Causality Assessment Method

hepatotoxicity based on pooling RUCAM scores has not been well-described but is instructive regarding the confidence in causation attribution. Among the 20 scorable case reports in this review, modified RUCAM scores had a median of 5 and a mean 4.5 (range 1–8) [Table 4]. Using the original RUCAM scoring criteria, the median was 6.0 and the mean was 6.0 (range 1–9). This difference is primarily due to the 2016 RUCAM modifications that emphasize Hepatitis E testing as only a single case report assessed hepatitis E beyond the two cases in the LiverTox database. Unless explicitly reported, it was assumed hepatitis E was not tested for. The updated RUCAM considers hepatitis E a group I nondrug cause due to a low percentage of cases previously attributed to DILI subsequently being attributed to hepatitis E [86, 87]. The 2016 modified RUCAM criteria are the current standard but have not undergone revalidation despite significant score changes due to the inclusion of hepatitis E.

The modified RUCAM scores suggest possible causality, while original RUCAM scores suggest probable causality. Overall, the above RUCAM scores likely underestimate causality, given the score penalty for lack of information, including testing and clinical course. Kratom likely causes liver injury based on the totality of low-quality human evidence in the form of case reports, FDA databases, and online user forums, and in the context of epidemiologic, animal, and mechanistic studies.

The R ratio assists in distinguishing cholestatic liver injury from hepatocellular liver injury, based on ALT and ALP. Determination of a substance's hepatotoxicity pattern by pooling R ratios is not well-described but informs classification in a standardized manner. Among 21 R ratios (Table 4) for which a RUCAM was calculated, the median was 3.4 and the mean was 4.6 (range 0.24–10.4). This result is similar to findings by the DILIN, which found a median R ratio at onset of 3.0 (range 0.9–3.2) [55]. This suggests kratom liver injury may be heterogenous or mixed, although, histologically, it seems predominantly cholestatic. Histology in animal studies was also heterogenous, including findings of both hepatocellular and cholestatic injury.

Kratom use is widespread and while kratom-induced liver injury is likely underreported, it is clear that many acute and chronic users, if not most, do not experience hepatotoxicity. It remains unclear which subgroups of users are at heightened risk and whether kratom liver injury is related to drug metabolizing enzyme polymorphisms (phase I or II) or use behaviors such as dose, frequency, or formulation. An idiosyncratic reaction should not be assumed until further pathophysiologic studies are conducted and the incidence is estimated.

16 Conclusions

Future research should focus on a more systematic investigation of the incidence of kratom-induced liver injury. Human case reports should include complete information to allow more accurate causality assessment, including hepatitis E serologies. Animal studies should utilize formulations and dosings that typical users are exposed to, rather than only methanolic extracts at often exceedingly high doses. Mechanistic underpinnings should be further explored by evaluating the effect of *M. speciosa* compounds on hepatic transporters strongly implicated in DILI, at biologically plausible concentrations.

Acknowledgments The authors would like to thank Laurie Halmo, MD, for contributions to the manuscript.

Funding This report did not receive any specific funding.

Compliance with ethical standards

Conflict of interest Jonathan Schimmel and Richard C. Dart declare no conflicts of interest.

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Int J Legal Med (2016) 130:127–138
DOI 10.1007/s00414-015-1279-y

REVIEW

The pharmacology and toxicology of kratom: from traditional herb to drug of abuse

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Received: 28 July 2015 / Accepted: 13 October 2015 / Published online: 28 October 2015

Abstract *Mitragyna speciosa* (Rubiaceae), commonly known as kratom, is a tropical tree with a long history of traditional use in parts of Africa and Southeast Asia. In recent years, kratom has gained popularity for use as a recreational drug across the globe. Relatively new to the illicit market and used in a manner different from its traditional applications, preparations of kratom are touted by many as a safe and legal psychoactive product that improves mood, relieves pain, and may provide benefits in opiate addiction. Available literature was reviewed for *M. speciosa* via PubMed, Google Scholar, CINAHL, and EBSCO to summarize its traditional uses, phytochemical composition, pharmacology and toxicology of proposed active constituents, and potential for misuse and abuse. Research has demonstrated that both stimulant and sedative dose-dependent effects do exist, but a growing concern for the drug's effects and safety of use has resulted in national and international attention primarily due to an increase in hospital visits and deaths in several countries that are said to have been caused by extracts of the plant. The main active alkaloid substances in kratom, mitragynine and 7-hydroxymitragynine, present with a range of CNS stimulant and depressant effects mediated primarily through monoaminergic and opioid receptors. Recently, Palm Beach County, located in the southeastern corridor of Florida, has considered regulating kratom due to public safety concerns following the death of a young adult. At the local, state, and even federal levels, governments are now being confronted with the task of determining the safety and the possible regulation of kratom extracts. There are currently no standard analytical screening techniques for mitragynine and its metabolites following ingestion limiting its detection to more sophisticated techniques like liquid chromatography-mass spectrometry to determine kratom use. The growing concern of the abuse potential of kratom requires careful evaluation of its benefits and potential toxicities.

Keywords Kratom · Stimulant · *Mitragyna speciosa* · Psychoactive · Drug abuse

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Introduction

At a time where new synthetic drugs such as cannabinoids and bath salts are increasingly observed in both the clinical and medicolegal setting [1–3], the natural products of *Mitragyna speciosa*, otherwise known as kratom, have also seen increased reports of misuse and abuse. Since the regulation of numerous spice and bath salt compounds, attention has seemingly shifted toward this "new" drug. Historically, kratom has been used by civilizations for many centuries. Cultures located in areas of Southeast Asia have been cultivating and using kratom for several thousand years [4, 5].

Although not new, the drug is, however, novel to the majority of the USA, Europe, and South America and its popularity is on the rise [6]. Its growing misuse and abuse has caused public concern illustrated by recent media attention focusing on its physical effects and implications to society. Moreover, governmental entities are expressing concerns, and local, state, and federal lawmakers are facing challenges in determining the severity of an emerging drug and enacting reasonable regulation.

This review will provide an overview of the appearance and traditional use of kratom, its current use and prevalence, chemistry and pharmacology of the proposed active ingredients, and analysis of the plant material and biological specimens such as blood and urine, as well as discuss some of the issues that are being experienced in local communities. Finally, discussion of legal concerns and where society is headed concerning regulation will be considered.

Methods for literature search

All authors evaluated literature via the available databases PubMed, Google Scholar, CINAHL, and EBSCO to gather the current state and development of the composition, ethnopharmacology, analysis, and abuse potential for *M. speciosa*. Search terms used were "*Mitragyna speciosa*" or "kratom" in combination with "pharmacology," "botany," "history," "analysis," "detection," "regulation," and "abuse". Essential literature as well as recent reports of abuse were included in this review.

Appearance and traditional use

Kratom (*M. speciosa* Korth.) is a tropical tree that is a member of the Rubiaceae or coffee family [4–8]. Dutch botanist Korthals named the genus, *Mitragyna*, due to similarities between the plant's leaves and stigmas compared with a bishop's miter [8]. In Thailand, kratom is sometimes referred as krathom, kakuam, ithang, or thom, while biak-biak or ketum and mambog are street names that respectively descend from Malaysia and the Philippines [6, 8]. The tree is indigenous to tropical and subtropical regions of Southeast Asia including countries such as Thailand, Malaysia, Philippines, Myanmar (Burma), and New Guinea, as well as parts of Africa [4–6]. Growing approximately 15 m tall, the kratom tree possesses relatively large, broad, glossy leaves that are oval shaped and dark green in color (Fig. 1) [4, 5]. The leaves typically grow to lengths of approximately 18 cm and widths of 10 cm [6, 8]. The plant's flowers, nearly 120 florets each, are observed as deep yellow spherical clusters. Wet and humid soil provides optimal growing conditions for kratom. Medium to full sunlight is also ideal. Harvested from the kratom tree, dried leaves and small stems are primarily used for consumption [7].

Historically, kratom was taken to ease opioid withdrawal with use dating back to the 1940s in Thailand [4]. Opium costs soared in 1942 as a result of the Greater East Asia War and drops in opium revenue were experienced. With the increase in cost, users sought out the lower cost kratom to help with withdrawal symptoms. This in turn caused Thai officials to begin controlling kratom in 1943 under the Kratom Act, an effort to gain control in the opium market [4].

Controlled in regions of Southeast Asia, kratom serves as a core component of culture and tradition, particularly in the southern peninsula of Thailand [4, 9]. Similar to that of coca and khat leaves, kratom leaves are traditionally chewed or prepared as a powder. Historically, its stimulant effects have been sought out to help reduce fatigue, in particular for those individuals carrying out manual labor on rubber plantations and seafaring. Known as "chewers," these individuals typically start chewing kratom from the age of about 25 years. Nearly 70 % of "chewers" are males and their day-to-day consumption averages from 10 to 60 leaves. In addition to the workforce, kratom is sometimes used in cultural performances and teashops or as a drink alternative by individuals whom are restricted from alcohol consumption due to their religious beliefs [4].

Dried kratom leaves (Fig. 1) are often crushed and the resulting powder may be inserted into gel capsules or prepared as a hot tea [7]. Plant ashes or baking soda is frequently added to help extract plant alkaloids prior to consumption. One resource states that the addition of lemon juice has also been used to enhance absorption of alkaloids from the small intestines in their ionized form [7] although this is contrary to the common observation that the unionized form of alkaloids is preferred for enhanced absorption. Sugar and honey are sometimes added due to the bitterness of the tea. The powder can also be cooked to yield a syrup-like consistency, which is then compressed into tablets [7].

Current use and prevalence

Kratom use is no longer limited to traditional and ceremonial uses and its recreational misuse and abuse have been increasing. Gaining popularity over the past several years across Southeast Asia, especially Thailand, is a tea-based cocktail known as 4×100 [4, 7, 8]. Consumed primarily by teenagers and young adults in their thirties, the drink is commonly found to be a concoction of kratom leaves, cough syrup, Coca-Cola, and ice [4]. Yet to gain social acceptance, community discrimination of this cocktail is relatively common, and users are sometimes compared to methamphetamine and heroin addicts. Kratom preparations were among the most commonly abused by high school students at a similar rate to cannabis (2.3–4.9 %) [10].

Public attention from local media and conservative groups have also caused an increase in community discrimination and concern since these cocktails are suspected of containing other drugs such as benzodiazepines and household consumer products including fluorescent tubes, powdered mosquito coils, road paint, and pesticides. Even ashes from the deceased have been added to these cocktails. Such additives are suggested to "enhance" the drink's effects, but there is no scientific

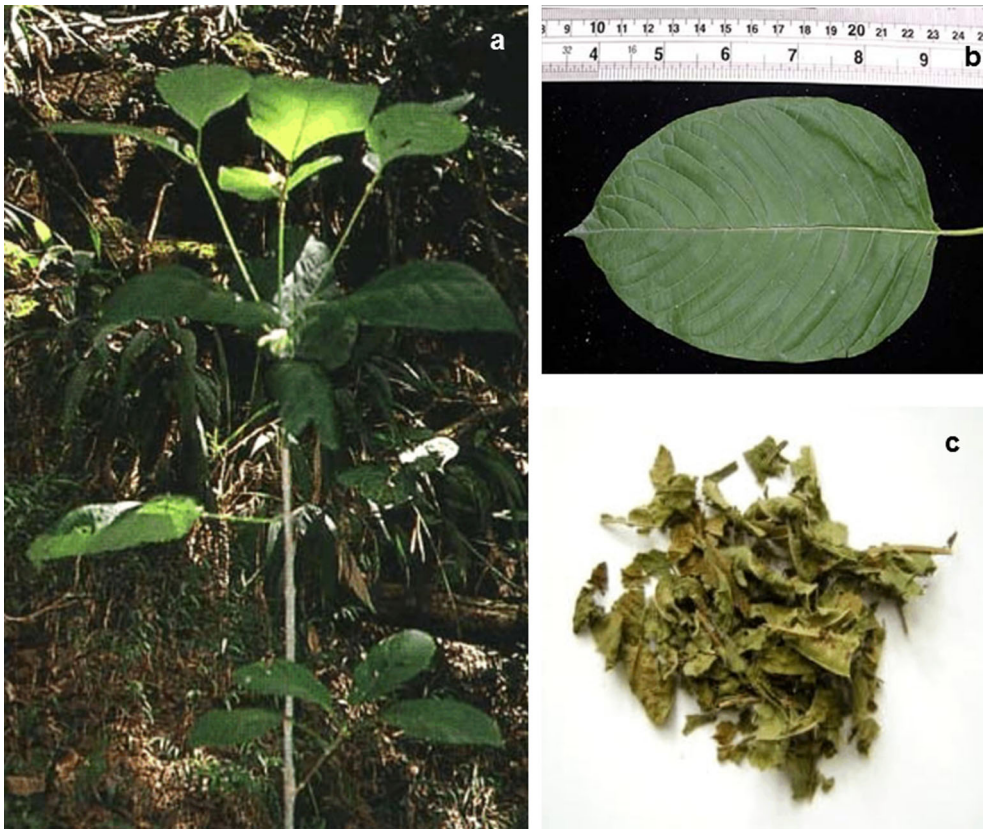

Fig. 1 Young kratom tree (**a**), fresh kratom leaf to scale (**b**), and dried kratom leaves (**c**). All images obtained from the U.S. Drug Enforcement Administration website [6]

evidence that they actually do so beyond increasing absorption of the alkaloids in their unionized state [4].

Popularity has more recently expanded overseas [6]. As a consequence of opioid addiction, especially in the USA, kratom is frequently marketed for treatment of opioid withdrawal symptoms based on its historical use for this indication in Thailand [3, 6]. A case report described the self-treatment of opioid withdrawal by a patient using kratom in conjunction with modafinil leading to a seizure which resolved after discontinuation of kratom use [11]. In addition to treatment of opioid addiction, kratom is used to help control alcohol withdrawal effects and for control of chronic pain. At variable doses, kratom has also been used to reduce appetite and control stomach cramps and diarrhea, and has been reported to have an important impact on controlling diabetes [4, 12]. Investigations have also reported that kratom extracts show antioxidant and antibacterial activity although this has not been related to traditional or current uses [13]. However, the abuse potential of kratom stems from its cocaine- and morphine-like psychoactive effects which are dose-dependent [6, 7].

Although controlled in regions of Southeast Asia [14], ease of access is not an issue in the USA due to limited legal control of kratom and its active components. Federally and statewide, kratom remains largely uncontrolled and is usually legally available [7].

The prevalence of kratom use in the USA has not been well established to date. Poison centers have reported isolated incidences of kratom use dating back to 2008 [15, 16]. Based on its traditional use and ban in Thailand, the prevalence of kratom has been reported to be in the range of 0.9 % among the general population but reaches up to 59 % of those suffering from a mental disorder or substance use disorder [17, 18].

Purchase remains relatively easy in the USA via head shops, kava bars, and especially the Internet [6, 19]. Marketing and advertising has added to kratom's presence dramatically making it widely accessible both inside and outside the country. In addition, sales of a wide variety of kratom preparations varying from the traditional use of leaves for chewing and brewing, powders, gums, and extracts for users to smoke have become prevalent via Internet distributors [6, 19]. In some instances, kratom has been marketed in similar attractive packaging as many synthetic drugs potentially contributing to its sales success [3].

Adding to kratom's popularity is the fact that it is touted as a legal, psychoactive alternative to other sedative and stimulant-type drugs [20]. As a consequence of its current legal status, kratom preparations are economically obtainable for users compared to opioids and other drugs with an ounce selling for US$10–40 [21].

Chemistry, pharmacodynamics, and pharmacokinetics

Kratom leaves have been found to contain over 25 alkaloids [4, 7]. The alkaloids mitragynine and 7-hydroxymitragynine (7-HMG) are believed to be the primary active alkaloids in the plant (Fig. 2) [4]. The total alkaloid content in kratom leaves ranges from 0.5 to 1.5 % [7]. Mitragynine makes up approximately 60 % of this extract with 7-HMG accounting for only up to 2 % [21–23]. The alkaloid paynantheine is the second most abundant compound at approximately 10 % of the total alkaloid content (Fig. 2). Other notable analogs are speciociliatine and speciogynine, which comprise about 9 and 7 %, respectively, of the total alkaloid content. The remaining alkaloids (mitraphylline, rhynchophylline, mitralactonal, raubasine, and mitragynaline) each comprise less than 1 % of the total alkaloid content in kratom (Fig. 2).

Mitragynine is an indole-containing alkaloid, structurally similar to yohimbine and voacangine (Fig. 3) [7, 21]. Structural identification occurred in 1965 and its synthesis was achieved 30 years thereafter [7, 9]. Mitragynine is suggested as having approximately 13 times the potency of morphine in regards to its opioid-like effects [3]. It was originally thought that mitragynine was the most active morphine-like chemical component in kratom [7]. Current research suggests that 7-HMG is 4 times more potent in its CNS stimulant and depressant effects than mitragynine [3, 24].

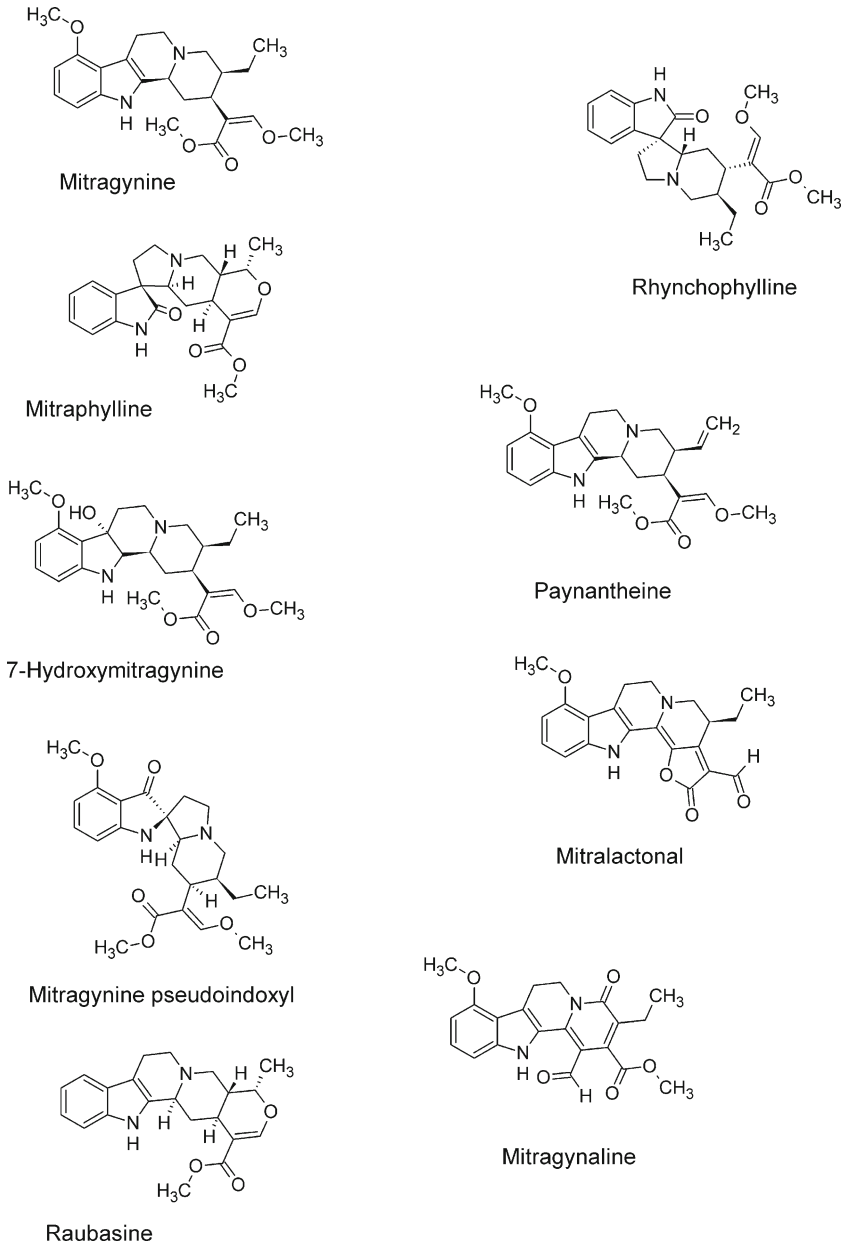

Fig. 2 Structures of *Mitragyna* compounds

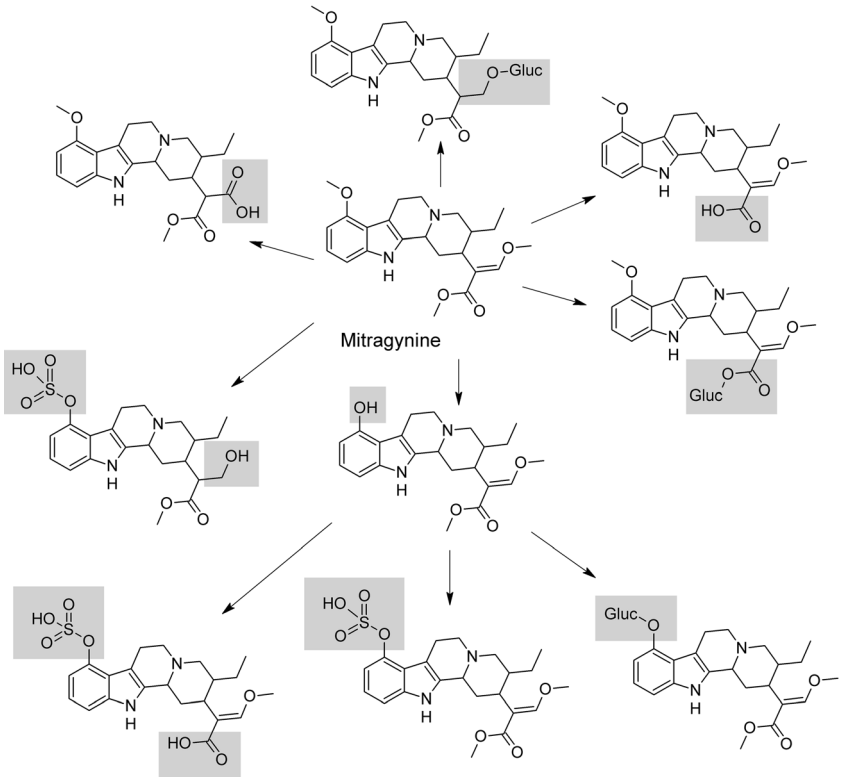

Fig. 3 Reported metabolites of mitragynine in humans. *Highlighted sections* indicate changes in the molecule through nonenzymatic and enzymatic processes

Kratom effects are complex as it may produce either stimulant or opioid-like effects [7, 21]. Depending on particular needs, the relative levels of stimulation/mood enhancement and sedation/analgesia can be controlled by both the strain of kratom chosen as well as the dosage ingested. With regard to the strain, the red vein variety indigenous to Bali tends to be a more powerful pain reliever, while the white or green vein varieties from Malaysia more often exhibit stimulating and mood-enhancing effects. The white vein tends to provide somewhat more energy than the green vein variety [4, 21]. The relative strength of stimulant and opioid-like sedative effects in each strain is most likely directly related to the varying proportions of different alkaloids present in the leaves of each strain.

Approximately 1–5 g of raw leaves, which is defined as a low to moderate dose, will yield mild stimulant effects (Table 1) [8, 21]. The onset of euphoric effects is experienced in about 10 min after using a few grams of dried leaves [8]. This dosage amount is often related to the stimulant effects commonly used by labor workers to fight fatigue [21]. Not only has increased work capacity been reported by users, but alertness, sociability, and increased sexual desire are said to occur [8]. At this dose, the user may also possess normal to slightly contracted pupils and blushing. Unwanted side effects are generally minimal; however, anxiety and internal agitation have been described [21].

Individuals using from 5 to 15 g of leaves are said to exhibit opioid-type effects (Table 1) [8, 21]. At this dosage, kratom may provide the user with pain and opioid withdrawal symptom relief, with diarrhea being a possible side effect. Both mitragynine and 7-HMG yield analgesic and antinociceptive effects. Euphoria is more often achieved at this higher level, but these effects tend to be less intense as compared with opioid drugs [21].

When exceeding 15 g of kratom leaves, one would expect to experience stupor, mimicking the effects associated with opioids [8, 21]. Initially, sweating, dizziness, nausea, and

Table 1 Pharmacological effects of kratom

	Low dose (1–5 g)	High dose (5–15 g)
Stimulant effects	Increased alertness Physical energy Talkativeness Sociable behavior	Tachycardia
Sedative/opioid-like effects	Loss of muscle coordination	Constipation Dizziness Hypotension
Adverse effects	Itching Nausea Loss of appetite Increased urination	Dry mouth Sweating

dysphoria will often result. These effects quickly subside and are followed by calmness and a dreamlike state [8].

Frequent users of kratom have displayed instances of tremor, anorexia, weight loss, seizures, and psychosis [7, 21]. Such individuals are likely using high doses of kratom for a prolonged period of time [7, 21].

Mitragynine and 7-HMG are selective and full agonists of μ-opioid subtype receptors [3, 7, 8, 21]. Mitragynine exhibits activity on supraspinal μ- and δ-opioid receptors causing its characteristic analgesic effects [3, 7, 8, 21]. With consideration to the interactions at the cellular level, studies suggest that neurotransmitter release from the nerve endings at the vas deferens is inhibited [21]. This inhibition is suggested to occur through the obstruction of neuronal calcium (Ca^{2+}) channels [7, 22]. Blocked stimulation of serotonergic 5-HT_{2A} receptors and stimulation of postsynaptic alpha-2 adrenergic receptors are thought to contribute to stimulant activity [3, 8]. Additional psychoactivity is said to exist as a consequence of binding affinities exceeding that of morphine at the δ- and κ- opioid central receptors [21]. Moreover, 7-HMG provides high opioid receptor affinity with full agonist properties [8, 21]. While polarity is increased due to the additional hydroxyl group on 7-HMG as compared to mitragynine, increased activity of 7-HMG is otherwise not well understood [21].

Mitragynine is metabolized in humans via phase I and II mechanisms. The parent undergoes hydrolysis at the side-chain methylester in position 16 [7, 8, 21]. *O*-demethylation then takes place at the 9- and 17-methoxy groups. Oxidative and reductive transformations proceed to the intermediate aldehydes, which yield carboxylic acids and alcohols, respectively. A final step involves glucuronide and sulfate conjugate formation as a result of phase II metabolism which is excreted with the urine [7, 8, 21]. In vitro experiments using isolated CYP450 enzymes indicate that kratom extracts inhibit various CYP enzymes, notably CYP 3A4, 2D6, and 1A2. This may lead to clinically significant interactions with other drugs given that a wide range of prescription and OTC medication are substrates for these CYP enzymes [25].

Kratom users can expect to experience full effects in about 30–60 min after ingestion, although onset can be noticeable within about 10–20 min. The half-lives of mitragynine and 7-HMG are about 3.5 and 2.5 h, respectively. Both are eliminated from the body primarily with the urine [21, 26, 27]. The pharmacokinetics following oral administration of mitragynine in humans has been proposed as a two-compartment model based on the observed kinetics in ten healthy human male volunteers [28]. Certain conditions such as prior food consumption or taking kratom in capsule form can delay the initial response. The effects of kratom typically last about 5–7 h, with the strongest effects at about 2–4 h after ingestion, although weak aftereffects can be felt as late as the next day [3, 21, 29, 30]. Current pharmacokinetic data in both animals and humans is limited, and there appear to be a significant variability within each species and differences between species in terms of mitragynine pharmacokinetics (Table 2).

Side effects, particularly for regular heavy users, can include nausea, weight loss, fatigue, constipation, insomnia, dry mouth, frequent urination, and hyperpigmentation of the cheeks [3, 6]. Despite being opiate-like, withdrawal symptoms are generally nonexistent to mild, even for heavy users.

Kratom is considered minimally toxic, but it is important to note that research evaluating its toxic effects on humans is limited, with the vast majority of studies involving animals [7]. The results of such animal studies have been somewhat confusing and contradictory. In one study on dogs in 1972, doses of mitragynine as high as 920 mg/kg produced no evidence of toxicity as measured by tremors and convulsions, while a more recent 2010 study in rats reported that an oral dose of 200 mg of mitragynine had lethal effects [32]. A separate study in rodents reported hypertension and nephro- and hepatotoxicity in higher doses up to 1000 mg [33]. This may point to a species-specific response which remains unexplained as of yet. It is worth mentioning that in order to ingest 200 mg mitragynine, approximately 22–67 g of kratom leaves would theoretically have to be ingested [7, 20–23]. Established dosage amounts are unavailable; however, an individual would have to consume anywhere from 6–10 up to 19–29 spoons full of kratom powder. Careful examination of animal and other studies is therefore warranted [23]. Interestingly, kratom preparations have also been shown to protect against castor oil-induced diarrhea in rats in oral doses of 400 mg/kg comparable to the effect of morphine pointing to at least partial involvement of opioid receptors in its mechanism of action [34].

There are, however, rare documented reports involving kratom toxicity in humans [21, 23]. Seizures and addiction are predominantly experienced by individuals following long-term kratom consumption or an acute overdose. Liver toxicity is also linked to significant kratom overdose [21, 23]. Specifically, intrahepatic cholestasis has been reported [23]. Studies suggest that glutathione-S-transferase is elevated in individuals consuming large doses although this has only been demonstrated in animal studies [23].

The use of kratom in conjunction with other drugs can be problematic [7, 8, 21]. Adverse effects and even death may result. Literature indicates that kratom is sometimes fatally mixed with carisoprodol, modafinil, propylhexedrine, *Datura stramonium*, fentanyl, diphenhydramine, caffeine, morphine, and/or O-desmethyltramadol (“Krypton”) [7, 8, 21, 35].

Some reports indicate that users may become addicted to kratom. However, contradictory data exists concerning the degree of addiction that is experienced due to kratom use [21]. In some instances, it is thought that kratom is less addictive as compared with traditional opioids. In contrast, some

Table 2 Noncompartmental pharmacokinetic parameters of mitragynine in humans and rats

Mitragynine All data is mean±standard deviation		
Number of data points, species, reference	N=10, human, [28]	N=6, rat, [31]
Terminal half-life ($t_{1/2}$, h)	23.24±16.07	9.43±1.74
Apparent volume of distribution (V_d, L/kg)	38.04±24.32	89.50±30.30
Time point of maximum concentration (t_{max}, h)	0.83±0.35	1.83±1.25
Clearance (CL, L/h)	1.40±0.73	1.60±0.58

case studies suggest kratom addiction to be a significant issue, especially for chronic users [7, 21]. As a consequence, tolerance and cross-tolerance with both CNS stimulant and depressant drugs may result. Withdrawal symptoms consistent with opioids such as morphine are experienced: irritability, dysphoria, nausea, hypertension, insomnia, yawning, rhinorrhea, myalgia, diarrhea, and arthralgias. Agonist and antagonist drugs have been successfully administered to manage withdrawal effects; dihydrocodeine and lofexidine have been found to curb such symptoms in one case report [7, 21, 36].

Analysis

Mitragynine and 7-HMG are not routinely detected in most drug testing or screening procedures in the clinical and forensic toxicology setting [21]. Since kratom remains licit to purchase and possess in most of the USA and other countries, crime laboratories have not expended resources for purchasing drug standards and validating methods for its analysis [21].

Based on the rise in suspected kratom exposures in recent years, a range of methods have been developed for the analysis of the plant material and other kratom-containing substances including numerous chromatographic techniques, which are most frequently used [37] (Table 3). High-performance liquid chromatography (HPLC), the most common of chromatographic techniques, and other LC techniques coupled with either ultraviolet (UV) or mass spectrometer (MS) detectors (e.g., electrospray) may be used to detect the active alkaloids in kratom leaves [3, 22, 37]. Diode array detection (DAD) is fast and simple but lacks specificity [38]. Linear ion trap, quadrupole, and triple quadrupole mass-specific detection are also suitable for detection of kratom alkaloids.

An objective comparison of chromatographic analyses was performed on a prepared solution containing extracted oxindole and indole alkaloids commonly found in kratom samples, some of which are diastereoisomers to each other. Three techniques were studied: ultra-performance liquid chromatography-mass spectrometry-diode array detection (UHPLC-MS-DAD), supercritical fluid chromatography-diode array detection (SFC-DAD), and gas chromatography-mass spectrometry (GC-MS) (Table 3). Resolution of the alkaloids was accomplished for each of the methods except GC-MS. Separation was limited by diastereoisomers mitragynine and speciociliatine, which is a cause for concern in the effective separation of mitragynine where analysis is conducted by GC. Diastereoisomer separation was not accomplished via GC-MS without derivatization. Both UHPLC and SFC were able to separate the diastereoisomers without the use of a chiral column.

Another study involved purchase of online commercial products suspected of containing kratom [29]. The samples were tested by GC-MS, which is frequently utilized for the

Table 3 Analytical techniques used in the identification of kratom plants and its constituents

Analytical technique	Analyte(s)	Matrix	Reference
HPLC-UV/HPLC-DAD	Corynoxine, paynantheine, 3-isopaynantheine, 7-hydroxymitragynine, mitragynine, speciogynine, speciociliatine	Plant	[13, 38]
HPLC-MS/UHPLC-MS	Mitragynine, 7-hydroxymitragynine, paynantheine, speciogynine, speciociliatine	Plant, urine, blood	[3, 22, 37, 38]
GC-MS	Mitragynine, paynantheine, speciogynine, speciociliatine, corynoxine, 16-carboxymitragynine, 9-O-demethylmitragynine	Plant, urine	[38, 39]
icELISA	Mitragynine	Plant	[37]
DART-MS	Mitragynine, mitraphylline, paynantheine, 7-hydroxymitragynine, rhynchophylline, epicatechin, ajmalicine, corynoxine	Plant	[40]
PCR	rDNA	Plant	[30]

HPLC high-pressure liquid chromatography, *UV* ultraviolet, *DAD* diode array detection, *UHPLC* ultrahigh-pressure liquid chromatography, *MS* mass spectrometry, *GC* gas chromatography, *PCR* polymerase chain reaction, *DART* direct analysis in real time, *icELISA* indirect competitive enzyme-linked immunosorbent assay

analysis and identification of commercial kratom preparations for the presence of active ingredients mitragynine and 7-HMG [3, 22, 29, 39]. The recent study utilized techniques for the identification of kratom that met standards recommended by the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) [29]. Due to kratom preparations yielding nonspecific color reactions, chemical spot tests were not useful in presumptive identification. However, the study determined that thin layer chromatography (TLC) followed by GC-MS was suitable in both screening and confirming mitragynine with limited sample preparation [29].

In addition to chromatographic analyses of kratom plant material and extracts, research exists for the analysis of metabolites found in biological specimens. As an example, LC-MS using a linear ion trap is suitable to identify metabolites of kratom in rat and human urine [3, 22]. High-resolution mass spectrometry (HRMS) with an Orbitrap (OT) analyzer was also successful in detecting the alkaloids in a research setting. Additional LC techniques may detect mitragynine such as UHPLC-MS and LC-MS/MS. In separate experimental procedures, both techniques were performed for the quantitation of mitragynine in rat plasma in order to evaluate pharmacokinetic parameters such as distribution and elimination [3]. Phase I and II metabolites can also be differentiated in human samples [22]. Using rats that were administered certain doses of mitragynine, metabolites of mitragynine, paynantheine, speciogynine, and speciociliatine were all detected by GC-MS [39].

Though less common, there is additional research involving nonchromatographic techniques [38]. Specifically for the analysis of plant-based products, polymerase chain reaction (PCR) and direct analysis in real-time mass spectrometry (DART-MS) were helpful for confirmatory analysis of samples. PCR using restriction fragment length polymorphism (RFLP) was utilized for the analysis of various plant products for the presence of kratom [3, 30]. Kratom could be distinguished from similar and related psychoactive plants. The technique proved useful due to its wide range of application, high accuracy, and ease of use [30]. The latter technique, DART-MS, also has the ability of differentiating between other plants and *Mitragyna* plant varieties [40]. This method provided both rapid analysis and minimal sample preparation [40].

In contrast, rapid preliminary detection of drugs in biological matrices is often desired in forensic toxicology [37]. Immunoassay is frequently used for its sensitivity and ease of use, especially for various drug preparations and biological specimens. For the detection of mitragynine in kratom leaves, indirect competitive enzyme-linked immunosorbent assay (icELISA) was carried out for the detection of mitragynine. This method proved effective as a screening technique for mitragynine in kratom leaves; however, improvements to sensitivity and potentially specificity are desired for applications involving biological fluids [37].

Present legal situation concerning kratom in the USA

In the past couple of years, kratom use has grown nationally. Internet marketing and retail accessibility have contributed to increased popularity throughout the USA. In fact, kratom's emergence correlates with trends noted in current national drug databases. In one of these drug databases, the System to Retrieve Information from Drug Evidence (STRIDE), drugs seized by DEA forensic laboratories are monitored [6]. The other primary database is the National Forensic Laboratory Information System (NFLIS) which collects analysis data from state and local laboratories. Both databases include data specific to cases of kratom; the data is compiled and quantified concerning mitragynine analysis. Since 2010, cases involving mitragynine have increased. In 2010, only a single instance of mitragynine use was reported. In 2011, there were 44 reports documented. Within only 6 months, this number had increased over 80 % to 81 in 2012 [6]. In 2013 NFLIS reported 181 total cases [32].

The increased use of kratom has contributed to an increase in reports of individuals becoming dependent on kratom [21]. The majority of these instances are case reports involving individuals compulsively using the substance [21]. Emergency room visits have increased with patients becoming ill, especially teenagers using the substance to achieve its euphoric effects [26]. Figures concerning emergency room visits by users of kratom are currently not well documented. Of the data available, there were two instances of emergency visits in 2005 throughout the nation as reported by poison centers. In Phoenix, Arizona, just one of the many metropolitan areas throughout the USA, there were six emergency visits documented in 2011 [26]. Relatively consistent with the observed increase in Arizona, the state of Texas did not have any reported incidents from 1998 to 2008 [15]. From 2009 to 2013, there were 14 incidents of kratom exposure documented by state poison centers [15].

A more recent publication from NMS Labs indicated that 12 % of the postmortem and human performance blood samples submitted for testing from agencies and labs throughout the USA in 2014 contained mitragynine [41]. That is, 55 of the 459 samples contained this component. This is over double the previous year where of the 472 blood samples submitted, 4.7 % or 22 samples were positive for mitragynine [41].

Although death has been attributed to kratom use, there is no solid evidence that kratom was the sole contributor to an individual's death [42]. In most documented instances, mitragynine was detected in combination with other drugs. As an example, death resulted in an individual with high blood concentrations of propylhexedrine and mitragynine—1.7 and 0.39 mg/L, respectively [43]. Propylhexedrine was determined to be the cause of death with mitragynine possibly also contributing to the death. Urine analysis further detected

acetaminophen, morphine, and promethazine [43]. In another event, a fatality was recorded involving multiple drugs, notably mitragynine [27]. Unlike the previous case, a mitragynine blood concentration of 0.60 mg/L was determined. Therapeutic levels of temazepam, diphenhydramine, and dextromethorphan were also detected. Kratom toxicity was declared as the possible cause of death. Interestingly, the autopsy report findings were consistent with opioid toxicity. Pulmonary congestion and edema, as well as urinary bladder distention, were indicated, though nonspecific. Unlike other case studies, the concentration of mitragynine surpassed other drug levels whose effects were determined minimal [27]. A similar fatal report presented with the same postmortem findings of pulmonary edema and urinary retention at a mitragynine peripheral blood concentration of 0.23 mg/L [44]. From these isolated fatalities, it appears that no threshold concentration for lethal mitragynine or kratom exposure can be determined at this point, especially since many cases involve multidrug exposures.

Concerns with kratom in the USA resulting from such case reports caused federal agencies to disseminate information regarding the substance. The DEA Drug and Chemical Evaluation Section published an informational bulletin [6] (Srihari Tella, 2014, personal communication) and listed kratom on its "Drugs and Chemicals of Concern," which include substances monitored by the DEA that are considered to pose a risk to individuals who abuse such substances [45]. However, more reliable research and data is necessary regarding potential health hazards and addictive properties. The drug remains under evaluation and the likelihood of future federal control is currently unknown (Srihari Tella, 2014, personal communication).

The Federal government has taken some steps to reduce its presence in the USA. The DEA officially declared that there is no legitimate medical use for kratom in the USA. As a result, kratom cannot be advertised in this country as a remedy for any medical condition [21]. Early November of 2014, the Food and Drug Administration (FDA) issued an alert due to the increase in the number of shipments of kratom-containing dietary supplements [46]. The FDA concluded that kratom has a limited history of use and insufficient evidence with respect to safety. Therefore, in order to control shipments of the potentially hazardous substance, the FDA may detain products sent from listed vendors without physical examination. Additional vendors may be added to this list based on whether they meet specified criteria [46].

Kratom has followed a slightly different path internationally. United Nation (UN) Member States are not required to follow international drug conventions [4]. Some of these countries are shifting toward the control of kratom and mitragynine due to adverse health effects. *Kratom acetate* and *mitragynine acetate* started coming to light in the early 2000s, a few years ahead of the USA [47]. Surprisingly, mitragynine was not a component of these substances, also known as *krypton*, which contained caffeine and O-desmethyltramadol. It was not until more recently that products referred to as "incense" started containing kratom's active alkaloids. Surveys administered by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2008 and 2001 discovered that kratom ranked near the top of new psychoactive substances most widely offered among khat and *Salvia divinorum*. In 2011, kratom was listed as being the most frequently identified new psychoactive substance for sale in 220 total shops [48].

Thailand initially regulated kratom under the Kratom Act in 1943, which was loosely enforced [4, 49]. The penalty was later reduced by listing the drug as a Schedule 5 substance on the Thai Narcotics Act in 1979. Myanmar (Burma) and Malaysia moved to control kratom in 1993 and 2003, respectively. In 2004, under the Australian National Drugs and Poisons Schedule, Australia listed mitragynine and kratom under Schedule 9. Neighboring New Zealand added kratom and mitragynine under the prescription drug schedule (I) of the Medicines Amendment Regulations Act of 2009 [50]. Meanwhile, six European Union (EU) Member States have moved to control kratom or some of its chemical constituents: Denmark, Latvia, Lithuania, Poland, Romania, and Sweden. South Korea, Israel, and Germany have also enacted controls of either kratom or its alkaloids [50].

On a notably smaller scale, kratom concerns are also being addressed. Several states and cities throughout the USA plan to ban or have banned the substance [51–53]. As was observed with the emergence of bath salts and synthetic cannabinoids, state and local governments have taken interest and action regarding kratom regulation. More precisely, they are faced with whether or not to control the sale and possession of the substance.

In the state of Florida, Sarasota banned the substance in early 2014 [53]. Other Florida counties and even its state legislatures are currently challenged with determining where kratom regulation should stand. Interest has particularly increased in Florida due to the death of a young adult male which was believed to be caused by kratom [54]. The 20-year old plunged to his death after jumping from an overpass [54–56]. His death captured local and statewide attention as the deceased's mother announced and asserted that addiction to kratom contributed to her son's death [54, 57, 58]. The medical examiner's report revealed that kratom was present (not quantitated). Antidepressants citalopram and trazodone, in addition to the analgesic gabapentin, were found at therapeutic levels in the individual's system [54]. As was observed with other case studies, the cause and manner of death could not be contributed to kratom alone.

In Palm Beach County, kratom use appears on the rise as exhibited by the number of medical examiner cases from 2013 to 2014 that contained mitragynine (not quantitated) in blood

samples [43]. In 2013, it was reported that a single deceased individual's blood contained mitragynine. In 2014, there were five cases of positively identified mitragynine. So far this year, two deaths were reported of individuals where mitragynine was identified.

In February 2015, several months since the 20-year-old's death, the Florida Senate introduced a bill in an effort to control kratom or *M. speciosa* as a schedule I substance. The bill was amended to list mitragynine and 7-HMG instead. In April, the proposed senate bill was adopted by the Florida House of Representatives without objection; however, before becoming law, Florida's Office of the Attorney General (AG) must work in collaboration with the Department of Children and Families' Substance Abuse and Mental Health Program Office and the Florida Department of Law Enforcement (FDLE) in order to determine whether the substance fits placement into a controlled substance schedule by December 31, 2015 [53, 59].

It is interesting to note that while some governments are immersed with the idea of whether the substance warrants the need for regulation, some states in the USA are revoking laws originally enacted in order to ban kratom. In the instance of Illinois, mitragynine and 7-HMG were originally Schedule I controlled substances [60]. They were eventually moved to become regulated under the Kratom Control Act which allows legal purchase or possession by those 18 years of age or older [60]. In Arizona, mitragynine and 7-HMG were initially proposed for addition as a controlled substance [61]. The bill was later amended since kratom is not synthetic allowing it to remain legal [61].

Conclusion

At a time when public awareness is increasing, additional kratom research is necessary. Meanwhile, lawmakers and scientists around the world should continue to monitor kratom use and continue to take efforts focusing on research in order to attain a global view of its current use and abuse potential.

Since the recent death in Florida, counties have considered banning kratom but, as of yet, taken no action [56]. Both Palm Beach and Broward counties have deemed kratom not ready for regulation due to the lack of information demonstrating the substance as being unsafe or hazardous [56]. The position of these counties appears to be consistent with other state and federal legislators throughout the country.

As with any drug of concern, there are many aspects that must be considered in order to help protect society without taking unjustified steps toward regulation whenever there appear to be real advantages. Yet, potential side effects, especially when improperly used, and real health hazards must not go unnoticed. Research of kratom should move forward with close monitoring of any incidents that should arise. As of yet, research has not determined if the medicinal benefits of kratom may prove to outweigh the acute and chronic dangers of its recreational use.

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Pharmacologic and clinical assessment of kratom: An update

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Purpose. This article presents updated information on kratom (*Mitragyna speciosa*), a natural opioid with stimulant properties that is currently sold in the United States without a prescription.

Summary. Kratom exerts opioid and alpha-2 agonistic effects, as well as anti-inflammatory and mild stimulant effects. Respiratory depression has not been commonly reported, but kratom does cause a host of adverse effects. While kratom may have a role in patients who are in chronic pain or dependent on opioid painkillers or heroin, this needs to be established in clinical trials. Kratom may have drug interactions as both a cytochrome P-450 system substrate and inhibitor. Kratom does not appear in normal drug screens and, especially when ingested with other substances of abuse, may not be recognized as an agent of harm. There are numerous cases of death in kratom users, but many involved polypharmaceutical ingestions. There are assessments where people have been unable to stop using kratom therapy and withdrawal signs/symptoms occurred in patients or their newborn babies after kratom cessation. Both banning and failure to ban kratom places people at risk; a middle-ground alternative, placing it behind the pharmacy counter, might be useful.

Conclusion. Kratom has a unique pharmacologic profile that might offer advantages over other opioids, but its high abuse liability, potential for drug interactions and adverse events, and inadequate research into the balance of benefits to harm are concerning. There is mounting information on the adverse events associated with kratom use and potential treatments that can be useful to clinicians.

Keywords: herb, kratom, *Mitragyna speciosa*, opioid, withdrawal

Am J Health-Syst Pharm. 2019; 76:1915-1925

Since 2017, when *AJHP* published a review of kratom (*Mitragyna speciosa*),[1] continued interest and new information on usage patterns, risks, and potential treatments of adverse events have warranted an update.[2-4]

The Drug Enforcement Administration (DEA) designated kratom a drug of concern but has not yet scheduled it.[5-8] It is illegal to possess or use kratom in Alabama, Arkansas, Indiana, Rhode Island, Tennessee, Vermont, and Wisconsin.[5] In other states where kratom use is permitted, use of the drug is banned in some cities, including Denver, Colorado; Jerseyville, Florida; San Diego, California; and Sarasota, Florida (kratom use is also banned in Washington, D.C.).[9] New York and New Jersey have pending legislation that would make kratom illegal as well. Kratom is banned in Thailand and Malaysia and is controlled in Denmark, Finland, Latvia, Lithuania, Poland, Romania, Sweden, and the United Kingdom but is not listed as a controlled substance by the United Nations Drug Convention.[7,10,11]

Kratom is available as compressed tablets and liquids for oral administration, loose leaves for steeping or smoking, and whole leaves for chewing.[1] The products can be adulterated, contaminated, or used with other drugs in an attempt to accentuate their effects.[12-15]

The American Kratom Association estimates that 4–5 million Americans

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DOI 10.1093/ajhp/zxz221

may have used kratom.[5] Kratom users' demographics were assessed in an online Internet survey (n = 8,049).[16] Users were predominantly 21–50 years old (80%), Caucasian (89%), and male (57%). Over 71% of kratom users were employed, 61% had private insurance, 82% had at least some college education, and 63% made between $35,000 and $75,000 yearly. Fifty-four percent heard about kratom from the Internet or social media, 27% from an acquaintance/friend, and only 3% from a healthcare provider. Only 40% of kratom users told their healthcare providers about their use. Among patients using kratom to control or reduce withdrawal from opioids or illicit drugs, participants were more likely to be 21–30 years of age (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.02–3.51) and have no insurance (OR, 1.97; 05% CI, 1.51–2.59). Kratom use is not assessed in National Institute on Drug Abuse surveys of eighth, 10th, and 12th graders in the United States, and kratom's main constituents are not a part of standard drug screens.[13,17]

Over a million people reported using kratom in a 2008 Thailand national survey.[14] The most common reasons for use in Southeast Asia are to feel better or enhance physical performance, coping (use to forget problems), and social interaction. However, in a survey of 116 regular kratom users in Malaysia, those using more than 3 glasses of kratom daily were more likely to use it for coping (p = 0.001) and enhancement (p = 0.031) than those with lesser consumption.[11]

Any subsequent DEA ruling, or continued lack of ruling, will have major implications for recreational users, people substituting kratom for other drugs of abuse, clinicians caring for kratom users, and researchers.

Pharmacologic and pharmacokinetic effects

There are many biologically active alkaloids of kratom, but mitragynine and 7-hydroxymitragynine are 2 of the most significant, constituting 66% and 2% of the total alkaloid content, respectively.[13,18] Other alkaloids include paynantheine, speciogynine, and speciophylline, accounting for 1%–9% of the total alkaloid content.

KEY POINTS

- Kratom is a naturally derived opioid analgesic associated with a low risk of respiratory depression and is currently legal to sell, possess, and use in the United States without a prescription.
- Kratom has important adverse events that could result in death, so using it without any clinical oversight is risky.
- Kratom can cause tolerance and withdrawal symptoms, making it difficult to attain and maintain abstinence once people use it chronically.

Twenty kratom leaves have approximately 17 mg of mitragynine, with an average leaf weighing 1.7 g before drying and 0.43 g afterwards.[19] However, in an assessment of several kratom products that are commercially sold, the concentrations of 7-hydroxymitragynine was higher than could be achieved without adulteration.[20]

The Food and Drug Administration (FDA) applied mitragynine and 7-hydroxymitragynine to a 3-dimensional computer simulation called the Public Health Assessment via Structural Evaluation and is confident that both mitragynine and 7-hydroxymitraginine bind and stimulate the mu opioid receptor.[21] However, in vitro studies suggest that mitragynine and 7-hydroxymitragynine are partial agonists at the mu receptor and interact in a unique way that shunts away from beta-arrestin 2 pathways and more towards G protein–coupled pathways.[22] Beta-arrestin 2 activity may be a cofactor in the development of opioid-induced respiratory depression.[23] The data on how mitragynine and 7-hydroxymitragynine impact delta receptors conflict, and both constituents appear to antagonize kappa receptors.[13] While found in a much lower concentration in kratom leaves than mitragynine, 7-hydroxymitragyinine is 46 times more potent as an antinociceptive compound.[18,22]

In animal studies, naloxone partially reversed kratom's pain-relieving effects, while caffeine and acetaminophen enhanced them.[1,18] Importantly, oral kratom doses of 807 and 920 mg/kg did not induce respiratory depression, the most common life-threatening adverse effect of traditional opioids.[24]

Mitragynine stimulates postsynaptic alpha-2 adrenoceptors and inhibits cyclooxygenase-2 messenger RNA (mRNA) and protein expression, suggesting nonopioid receptor pain-relieving effects.[13,18,25] The alpha-2 adrenergic agonist effect can also lessen withdrawal symptoms. It is possible that mitragynine in lower doses induces a methylxanthine sympathomimetic effect, owing to its coffee family relationship.[3,26]

An extract of kratom reduced diarrhea, and both kratom and subcutaneous 7-hydroxymitragynine slowed intestinal transit in rodents, an effect only partially blocked by naloxone.[18] Speciociliatine, speciogynine, and paynatheine inhibit intestinal smooth muscle function independent of opioid receptors.[13,18]

In human-induced pluripotent stem cell–derived cardiomyocytes, mitragynine and several other components of kratom (paynatheine, speciociliatine, and speciogynine) significantly inhibited the rapid component of the delayed rectifier potassium channel (IKr).[27] IKr tail current inhibition was similarly reduced by each constituent in the range of 39% to 84% in a concentration-dependent fashion, ranging from 1 to 100 μM (p < 0.001 for all baseline comparisons). Mitragynine was then tested at 10 μM and significantly prolonged the action potential duration at 50% repolarization from the normal range of 439.0 ± 11.6 msec to 585.2 ± 45.5 msec (p < 0.001), a level that if seen in humans would dramatically increase the risk of torsades de pointes.

Even more disconcerting, mitragynine induced early afterdepolarizations, an intermediate surrogate endpoint for arrhythmogenesis. It is unclear whether combining kratom constituents, as occurs with normal ingestion, would produce additive effects on IKr blockade, thus compounding the arrhythmogenic risk. Figure 1 delineates the pharmacologic effects of kratom and how they are related to potential adverse events associated with its use.[1,13,18,21,25,27]

Nine subjects were given kratom at differing doses, and the pharmacokinetic parameters of mitragynine were determined.[28] Kratom pharmacokinetics fit a 2-compartment model, and as the dose on the day of testing increased from 6 to 23 mg, the maximum concentration went up linearly (R^2 = 0.68). The time to reach the maximum plasma concentration was 0.83 ± 0.35 hours, the terminal half-life is 23.24 ± 16.07 hours, and the apparent volume of distribution was 38.04 ± 24.32 L/kg. Only 0.14% of mitragynine was eliminated unchanged in the urine.

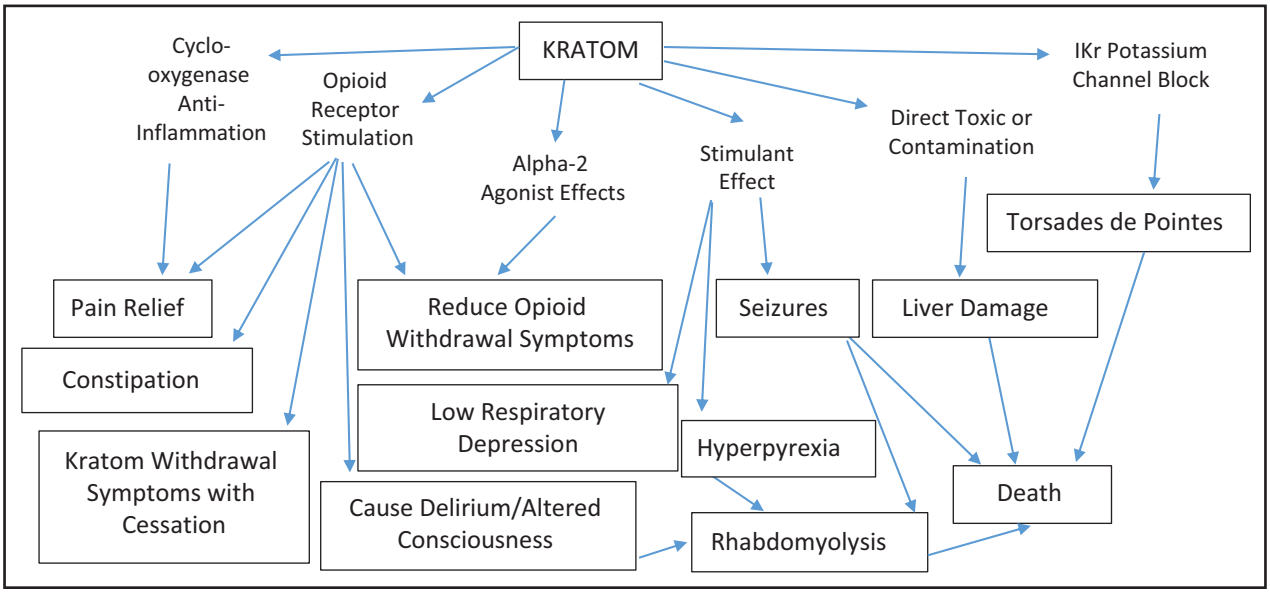
In vitro, mitragynine is converted to 7-hydroxymitragynine via cytochrome P-450 (CYP) isozyme 3A4 but is also metabolized by CYP2C9 and CYP2D6.[29] However, kratom potently inhibits CYP2D6 but also inhibits CYP2C9, CYP2D6, CYP1A2, and CYP3A4.[4,18] Many opioids and other drugs of abuse are CYP2D6 or CYP3A4 substrates.[30–32] In addition, mitragynine was found to be a P-glycoprotein inhibitor and downregulated mRNA and protein expression of P-glycoprotein in vitro.[33,34] Morphine and loperamide are known substrates of P-glycoprotein.[35] However, a methanolic extract of kratom was found to triple the activation of pregnane X receptor, a transcription factor that when activated increases the expression of CYP isozymes and P-glycoprotein.[36] Human drug interaction data are desperately needed to reconcile these conflicting findings.[33,34,36]

Role in pain or opioid abstinence

Anecdotal reports of kratom use for pain or opioid addiction suggest that kratom produces mild stimulant effects at lower doses, but when 5–15 g of raw leaves is ingested, the sedative effects predominate.[13,37] The euphoric effects of kratom are less pronounced than those arising from traditional opioid agonists.[13,37]

There are no published clinical trials assessing the impact of kratom or mitragynine on pain relief or opioid abstinence.[1,4,18] There is only 1 trial reported in ClinicalTrials.gov with the index terms *kratom*, *ketchum*, or *mytragyna* that is currently underway.[38] This is a randomized, double-blind, placebo-controlled trial of 20 participants using a cold pressor pain stimuli. While kratom was identified as a potential opium addiction treatment in Southeast Asia in the 1800s, use for that purpose in the United States was not promoted until discussion threads for opioid addiction surged in 2005.[18,39] In animal models ranging from zebrafish to rodents, kratom has been found to ameliorate opioid withdrawal symptoms but also induce withdrawal after chronic kratom therapy was stopped.[18,40,41] In a survey of 136

Figure 1. Analytical framework of the pharmacology of kratom. The properties of kratom's alkaloid constituents are linked with the reported beneficial and harmful effects. Understanding kratom's complex pharmacology is useful in anticipating issues and potential treatments when they arrive. All of kratom's effects need verification in adequately powered clinical trials or larger registries where confounding can be controlled. The information is based on previous studies.[1,13,18,21,25,27] IKr = delayed rectifier potassium channel.



kratom users in Malaysia, 90% of people were using kratom to treat addiction, with self-reported benefits including reduced withdrawal symptoms, increase in work capacity, and increased energy.[42] There are 2 case reports of people treating heroin addiction with kratom, and both subjects found it a suitable maintenance medication.[14] One of the patients felt methadone would have been better, but it was unavailable.

Potential averse effects

Common but not serious adverse events associated with kratom therapy include hyperpigmentation of the skin on the cheeks, constipation, weight loss, insomnia, xerostomia, and limited sexual desire.[20,42] There are a growing number of cases of acute toxicity reported in the Western literature, but many of the most severe cases are confounded by the concomitant consumption of other drugs. The acceleration in the number of adverse events associated with kratom use since 2015 could be due to increased use of the product over time or because of increased awareness of kratom as a potential product of use and abuse among first responders and the medical community.

In an assessment of U.S. poison control center calls from 2011 to 2017, there were 1,807 reports of kratom exposure.[43] Sixty-five percent of calls occurred from 2016 to 2017, and the rates of exposure for persons 20 years and older, 13–19 years, and 12 years or younger increased 58.1-fold, 41.7-fold, and 20.1-fold, respectively, from 2011 to 2017. Kratom was the only substance used in 65% of cases, 71% of patients were male, and the users' median age was 29 years. The routes of administration were oral in 83% of cases, with other routes (including smoking and nasal insufflation) being used with, or instead of, oral administration in 8.6% of cases. Overall, 32% of exposures resulted in admission to a healthcare facility, and 52% had a serious outcome. Multiple substance exposure was associated with greater odds of admission to a healthcare facility (OR, 2.8; 95% CI, 2.2–3.6) and serious medical outcome (OR, 2.3; 95% CI, 1.8–2.9) and accounted for 9 of 11 deaths. The major adverse effects among the 1,174 patients using kratom alone at the time of the incident precipitating the poison control center call included agitation or irritability (23%), tachycardia (21%), nausea (15%), drowsiness/lethargy (14%), vomiting (13.2%), confusion (11%), hypertension (10%), and seizures (10%). Other serious outcomes of note included deaths (n = 2), respiratory issues (respiratory depression [n = 42], dyspnea [n = 28], respiratory arrest [n = 6], or cyanosis [n = 4]), cardiac issues (conduction disturbances [n = 33], chest pain [n = 31], cardiac arrest/asystole [n = 5]), neurological issues (tremor [n = 79], dizziness/vertigo [n = 62], hallucinations [n = 61], coma [n = 37], syncope [n = 23], and slurred speech [n = 19]), liver issues (aspartate transamine [AST] or alanine transaminase [ALT] concentration of >100 units/L [n = 59], increased bilirubin [n = 30]), renal failure (n = 6), fever/hyperthermia (n = 27), and rhabdomyolysis (n = 10). Therapy for adverse events included benzodiazepines (n = 368), naloxone (n = 147), intubation (n = 101), antiemetics (n = 89), vasopressors (n = 17), cardiopulmonary resuscitation (n = 12), antihypertensives (n = 11), anticonvulsants (n = 10), antiarrhythmics (n = 8), and hemodialysis (n = 5). In children <12 years of age, most of the use was unintentional (81%), and 69% occurred in children <2 years old. There were 7 cases of neonatal exposure, including 1 exposure from breastfeeding and 1 exposure that also included tramadol. Five of the cases of in utero kratom exposure are described below.[43] These findings are generally similar to those from a U.S. Poison Control Center assessment from 2010 to 2015.[8] In an update of U.S. Poison Control Center data, in the first 7 months of 2018, there were 357 new kratom cases versus 18 in all of 2011 and 300 in all of 2017.[44]

In an assessment from a regional poison control center in Virginia over the years 2002 to 2016, 3 patients had an electrocardiogram taken, and the median QRS and corrected QT (QTc) intervals were 114 msec (normal, 80–100 msec) and 476 msec (normal, 360–440 msec), respectively.[45] While no arrhythmias occurred, these data suggest that the in vitro increases in action potential duration result in QTc interval prolongation in humans and can explain the cardiac conduction issues associated with kratom.

As of February 2018, FDA was aware of 44 deaths associated with the use of kratom-containing products.[46] Many of these occurred after the use of several drugs, including other opioids, tramadol, high-dose loperamide, benzodiazepines, antidepressants, diphenhydramine, and antiseizure medication. Pulmonary causes (edema, aspiration, and arrest), sudden cardiac or cardiopulmonary arrest, and seizures were elucidated as causes of death.[46–48] The lack of detail in most cases and the ingestion of several drugs simultaneously make it very difficult to determine to what extent kratom was a cause of death or a contributor to death (due to direct additive effects or drug interactions) in these cases. In addition, the total number of kratom-associated deaths that have occurred is likely higher than 44, because kratom was not recognized as a potential cause of death prior to 2016 by many users, families, first responders, and healthcare personnel.[1–4] Since it is not a part of standard drug screens, it would not be detected if not specifically assessed for. In the absence of reliable use data, it is impossible to establish if the number of deaths would create a signal for harm, as per FDA's standard practice for assessing prescription drug safety.

Nine of the deaths occurred after concomitant ingestion of kratom and O-desmethyltramadol.[4] Blood levels of mitragynine (0.02–0.18 μg/g) and O-desmethyltramadol (0.4–4.3 μg/g) were identified in these cases.[4] Individual cases of patient death have been reported in the literature, but again, it is difficult to determine causality in many cases given the use of other drugs or herbs or underlying health issues.[4,49–52] In 1 case, a 27-year-old man died from apparent seizures

and malignant hyperthermia after having taken quetiapine, kratom, and valproic acid.[52] The quetiapine serum concentration was 12 mg/L, much higher than would be anticipated given a pill count that did not suggest an intentional overdose. The authors suggested that the kratom enzyme inhibition coinciding with quetiapine caused this toxic concentration.

In Colorado, death certificates mentioned kratom or mitragynine as a cause of 15 deaths from 1999 to 2017, but 14 involved the use of other drugs that could have caused or exacerbated the adverse impact of kratom, and in the remaining case, no residual blood was available for comprehensive testing.[53] In a recent review of deaths from the County Medical Examiners Office in New York State, 4 cases were identified where kratom had been used.[44] Kratom was identified as the sole cause of death in 2 decedents (blood mitragynine concentrations of 260 and 1,400 ng/mL). Kratom (blood mitragynine concentration of 200 ng/mL) plus ethanol or kratom (blood mitragynine concentration of 540 ng/mL) plus clonazepam and cocaine were identified as the cause of death in the other 2 decedents.

A total of 5 individual cases of seizures linked to kratom use were reported.[54–56] One case had concomitant use of modinafil. Another had concomitant use of *Datura stramonium* (jimsonweed), a plant with analgesic, antispasmotic, and hallucinogenic effects.[54] Thirty minutes after drinking kratom/*Datura stramonium* tea (mitragynine urine concentration, 167 ng/mL), the patient began seizing until lorazepam and phenytoin were administered. There is a recent case of recurrent seizures with prolonged kratom use.[55] A 19-year-old man with attention deficit disorder treated with chronic lisdexamphetamine experienced a generalized tonic–clonic seizure. The patient was deemed to be at low risk for seizures, and no cause could be found after a metabolic profile, electroencephalogram, and urine drug screen (that did not include kratom) were conducted. One year later, the patient had a recurrent seizure and at that point admitted to kratom use starting before both seizure episodes. The patient continued to use kratom and had 4 other seizures over time, even with the prescription of levetiracetam. The last seizure resulted in an automobile accident and was associated with frequent use of kratom and weekly use of cannabis. Cannabis is an unlikely cause of the seizures and may possess anticonvulsant properties. When he stopped kratom and initiated lamotrigine, he was seizure free until breakthrough seizures occurred secondary to kratom relapse.

A case was reported of a 24-year-old patient with massive ingestion of kratom (about 600 mg) but no use of other drugs (urine screen was free of alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, or traditional opiates).[56] The patient was found minimally responsive and hypothermic and had a seizure witnessed by emergency response personnel. His QTc interval was 492 msec, with a heart rate of 58 beats/min, and the patient had an initial total creatine kinase concentration of 1,342 units/L peaking at 8,099 units/L. The patient had persistent severe delirium and was not discharged until day 28 of hospitalization.

Kratom has been reported to cause hypothyroidism in a single case report.[4] In addition, kratom was found in another case to be associated with poor libido and lethargy that was linked to elevated prolactin and suppressed testosterone levels.[57] The symptoms and laboratory abnormalities were absent after 2 months of kratom abstinence. The extent or duration of his kratom use was not elucidated in the case. However, in a cross-sectional study of 19 regular kratom users (average mitragynine dose, 76–94 mg), no impairment of free thyroxine, testosterone, follicular stimulating hormone, or luteinizing hormone occurred.[58]

Normal serum concentrations of the hepatic enzymes AST, ALT, and bilirubin are approximately 4–37 units/L, 4–40 units/L, and <1 mg/dL, respectively. Before 2017, only a single case of kratom-associated liver toxicity (intrahepatic cholestasis) was reported.[4] Since 2017, 7 additional cases of elevated liver function tests or liver damage have been reported.[59–65] In all cases except 2, AST concentrations ranged from 129 to 294 units/L, ALT concentrations ranged from 210 to 578 units/L, and bilirubin concentrations ranged from 2.2 to 6.3 mg/dL. In one of the 2 cases involving liver transaminase elevations above those ranges, the maximum AST and ALT values were 1,347 and 3,717 units/L, respectively, with no reported bilirubin concentration. In the other case, the AST and ALT concentrations were only modestly elevated, at 53 and 59 units/L, but the bilirubin concentration was 33.7 mg/dL. In all cases, the ALT concentration was higher than the AST concentration on presentation. The AST and ALT concentrations went down continuously over time after kratom was stopped in all cases but 1, in which it rose for another day before trending downward. In 4 cases where repeat bilirubin concentrations were taken, the levels rose slightly the next day or 2 before starting to resolve in 2 cases, remained the same in another case, and went down in the final case. There are basic animal data to support kratom's ability to damage the liver.[4,42] Symptoms in humans, such as upper gastrointestinal quadrant pain and light-colored stools, were reported.[39,42]

There is a case report of posterior leukoencephalopathy after abuse of kratom and dextroamphetamine.[66] Leukoencephalopathy is a syndrome that can be caused by excessive increases in blood pressure, but it is unclear to what extent dextroamphetamine, kratom, or the combination contributed to its occurrence.

In 1 case report, a person was pulled over by a police officer for reckless driving after almost striking an oncoming car.[67] The officer suspected the use of a stimulant and cannabis, but after drug screening, the driver tested positive for amphetamine and mitragynine. In a simulated environment, 70 regular kratom users and 25 controls underwent the Cambridge

Neuropsychological Test Automated Battery to assess the cognitive impact of long-term kratom use.[68] Relative to control subjects, long-term kratom users had impaired performance on the Paired Associates Learning Task (total errors, $p = 0.001$; total errors with 6-shape adjustment, $p = 0.005$) reflecting deficits in visual episodic memory and new learning. There were also reductions in the simple accuracy score ($p = 0.005$) and a trend towards a reduction in the 5-choice reaction time ($p = 0.057$) under the reaction time field. No deficits were detected in the motor screening tasks, delayed matching to sample tasks, or attention-switching tasks.

It is not only the kratom constituents that can cause harm but also how kratom is cultivated, manufactured, and packaged. FDA is aware of kratom being laced with other opioids like hydrocodone and being contaminated with *Salmonella*.[69] From January 11, 2017, to May 18, 2018, the Centers for Disease Control and Prevention reported 199 cases of infection with outbreak strains of *Salmonella* from 41 states that were subsequently linked to contamination from kratom products. Thirty-eight percent of infected persons were hospitalized, and widescale product recalls were instituted. On June 27, 2018, FDA declared an end to this outbreak and ceased investigation. However, in June 2019, FDA urged Kratom NC to recall several of its kratom products secondary to *Klebsiella*, *Enterobacter*, and *Escherichia* species contamination.[70] Similarly, FDA conducted laboratory testing of 30 different kratom products from a variety of sources and found levels of lead and nickel that were significantly above the recommended levels.[71]

Kratom-induced addiction and withdrawal

In the U.S. Poison Control Center assessment from 2011 to 2017, there were 5 neonates exposed to kratom in utero who experienced withdrawal symptoms such as agitation/irritability, diarrhea, and hyperventilation/tachypnea after birth.[43] Most of the details from these cases were not presented. In the literature, the first case of neonatal withdrawal was reported in 2017, but by 2018, various authors reported 5 additional cases.[72–76] These cases suggest that kratom withdrawal in neonates with in utero exposure begins about 24–36 hours after delivery and is a serious and increasingly common event. Symptoms included runny nose/sneezing, watery eyes, jitteriness, irritability, hypertonia, difficulty breathing, and facial excoriations. An extension of these cases of neonatal abstinence syndrome is the use of kratom in pregnant women.[75,77] There are 3 cases in which women became pregnant and attempted to discontinue kratom use by themselves but were unsuccessful.

In 30 kratom-addicted people from Thailand in 1975, the dose initially was about 3 leaves daily but over time escalated to 10–20 and 21–30 leaves daily in 40% and 37% of people, respectively.[20] Withdrawal symptoms included hostility, tearfulness, rhinorrhea, inability to work, arthralgias, myalgias, and "jerky motions" of the limbs.

In 2014, a study was conducted in Malaysia among 293 male kratom users, of whom 36% were former illicit drug users.[78] Eighty-nine percent of subjects had tried to abstain from kratom in the past, but due to physical withdrawal symptoms, reported as insomnia, anorexia, nausea, vomiting, diarrhea, myalgia, muscle spasms/tremor, shakiness, lacrimation, rhinorrhea, and hot flashes, as well as psychological symptoms of withdrawal, including anxiousness, anhedonia, restlessness, anger, and tension, none were successful. Only 18% of people went more than 3 months from quitting to relapsing.[79] Those reporting consuming greater amounts (OR, 7.05; 95% CI, 4.09–12.13) or more frequent use (OR, 5.19; 95% CI, 3.02–8.92) were 7 and 5 times more likely to report severe dependence, respectively.[78] Urine toxicologic screening confirmed that kratom was the only illicit substance consumed in the previous 30 days.[79] While 13% of people reported depressive symptoms, 14% reported anxiety, 17% reported trouble concentrating or remembering, 6% reported violent behavior, and less than 1% reported hallucinations or attempted suicide in the past 30 days, subjects and researchers believed that kratom maintenance was not as destructive socially and financially as heroin/opium addiction but was indeed an addictive substance.[79]

In 2018, 2 observational studies on kratom withdrawal symptoms were published from the same authors.[80,81] The inclusion criteria for both studies included patients who were regular users of kratom for a prolonged period of time but were not taking other drugs of abuse. The participants were not currently abstinent but were asked to report on the severity of adverse effects from their last abstinence attempt. In the first study, 170 regular users reported on pain using the brief pain inventory and sleep issues using the Pittsburgh Sleep Quality Index. During abstinence, 845 of participants reported moderate-intensity pain, and 70% reported pain that moderately interfered with their normal activities, while 46% reported more severe sleep issues. In the second study, 150 regular users reported on depression and anxiety during abstinence using the Beck Depression Inventory and the Beck Anxiety Inventory. Overall, 81% experienced mild depression, and 70% reported mild anxiety. In both studies, people consuming 4 or more glasses daily experienced greater risk and/or severity of these adverse effects than did those with smaller ingestion amounts.

Treatment of kratom's adverse events and withdrawal

Kratom has opioid- and nonopioid-related adverse events. The opioid adverse events, including pulmonary and gastrointestinal issues, could be amenable to naloxone but could also bring about withdrawal symptoms and acute pain. Constipation, seizures, and arrhythmias can be induced by nonopioid mechanisms, suggesting that other therapies would be adjunctively needed or even superior to naloxone. Seizures

induced by the stimulant effect of kratom would not be amenable to treatment with naloxone, so benzodiazepines and anticonvulsant therapy have been used most commonly.[32,33,54–56,82]

Kratom-induced torsades de pointes would be due to the direct effects of its constituents on blocking IKr potassium channels and not to opioid receptors.[28] As such, naloxone would not be helpful in this regard. Megadose loperamide and methadone are opioids that have been shown to block IKr potassium channels and induce torsades de pointes and might be used together with kratom.[83,84] Magnesium and cardiac pacing are frequently needed to treat torsades de pointes in these patients. Haloperidol or other antipsychotics could help with kratom-induced agitation and hallucinations but could prolong the QTc interval, an effect that could exacerbate the risk of torsades de pointes.[85]

In a case of possible kratom-induced cardiorespiratory arrest (primarily pulseless electrical activity alternating with ventricular arrhythmia), standard advanced cardiac life-support drugs augmented with sodium bicarbonate for metabolic acidosis and naloxone were given, resulting in the return of spontaneous circulation.[86] While maintaining a perfusing rhythm, the patient needed escalating doses of inotropic agents, so intravenous (i.v.) lipid emulsion was given. To maintain the mean arterial pressure at 90 mm Hg, the norepinephrine and epinephrine requirements fell 30% and 28%, respectively, and the alveolar to arterial oxygenation gap fell by 16% within a few minutes of lipid emulsion administration. These positive effects were maintained for an hour, but then care was withdrawn and the patient died. Anecdotal reports suggest that lipid emulsion may be used successfully in the treatment of cardiac effects from lipophilic local anesthetics, typical and atypical antipsychotics, and tricyclic antipsychotics or from lipophilic constituents of drug formulations.

In most cases, liver toxicity with kratom has been treated with i.v. fluid and supportive measures.[59–65] In 1 case, acetylcysteine (140 mg/kg followed by 70 mg/kg every 4 hours) was used over 4 days, but it is not clear whether this changed the natural course.[62] After rising the day after admission, AST and ALT concentrations were at or above baseline values by day 4 of acetylcysteine treatment, but AST concentration was within normal limits by 2 weeks after the admission and ALT concentration was normalized by 2 months after admission. To treat rhabdomyolysis in 1 case, i.v. fluids were given to prevent renal damage.[56]

Kratom withdrawal symptoms necessitating pharmacologic therapy usually begin 12 to 16 hours after receiving the last dose.[87] In adults, the most commonly employed regimen is to give a fixed dose of hydroxyzine or gabapentin with clonidine doses adjusted for the Clinical Opioid Withdrawal Scale score or to give fixed-dose and/or fixed-interval buprenorphine along with adjunctive drugs such as hydroxyzine and gabapentin.[56,87–90] The initial withdrawal symptoms abate within 4 to 7 days of kratom abstinence, but there can be an ongoing desire to use kratom which could require ongoing psychological and pharmacologic treatment. In most cases, there was no long-term follow-up reported, while in 3 cases, patients were continued on buprenorphine/naltrexone.[56,87–90] In a single case, the use of dihydrocodeine and lofexidine (an alpha-2 agonist) was used to attenuate the subjective and objective withdrawal phenomenon.[91] In another case, the combination of doxepine and diazepam was used to treat a patient with both alcohol and kratom dependence.[92] For selective symptoms, such as anxiety and limb muscle spasms, benzodiazepines can be used sparingly, while diarrhea can be treated with nonopioid antidiarrheals and joint or muscle pain can be treated with nonopioid pain relievers.[56]

In the aforementioned cases of neonatal abstinence syndrome from kratom, the babies were treated with their hospital-approved regimens that included several days of morphine before it was slowly tapered off, and 1 baby required supplemental clonidine that was effective but caused sinus bradycardia.[73–76] In the pregnant women who were addicted to kratom, 2 were switched to buprenorphine (1 with naloxone and 1 without) but were unable to wean off that drug, while in a third case, the patient began morphine and halved the dose of kratom and over 4 weeks tapered both drugs and stopped their use. There was no long-term follow-up to gauge the long-term success of this approach.[75,77] Table 1 summarizes potential treatments for the kratom's reported adverse events.[1,4,8,13,18,27,43,54–56,59–65,86]

Discussion

FDA's position statement about kratom states:

Table 1. Pharmacologic Effects of Kratom Observed in Human Trials[1,4,8,13,18,27,43,54-56,59-65,87]

Adverse Event	Therapy for Adverse Events[a]
Sedation	Naloxone
Constipation	Laxative, stool softener
Tachycardia and hypertension	Benzodiazepines, negative chronotropic drugs
Seizures	Benzodiazepines, anticonvulsants, and naloxone
Delirium	Benzodiazepines, naloxone
Torsades de pointes	Magnesium, cardiac pacing
Liver toxicity	Intravenous fluids
Rhabdomyolysis	Intravenous fluids

[a]These general treatment suggestions are extrapolated from pharmacologic causes or anecdotal experiences.

> It's very troubling to the FDA that patients believe they can use kratom to treat opioid withdrawal symptoms. The FDA is devoted to expanding the development and use of medical therapy to assist in the treatment of opioid use disorder. However, an important part of our commitment to this effort means making sure patients have access to treatments that are proven to be safe and effective. There is no reliable evidence to support the use of kratom as a treatment for opioid use disorder. Patients addicted to opioids are using kratom without dependable instructions for use and, more importantly, without consultation with a licensed health care provider about the product's dangers, potential side effects or interactions with other drugs.[93]

FDA is rightfully concerned about having people with opioid addiction trying to self-manage a serious opioid addiction with kratom and then having to self-limit their kratom ingestion. People tend to increase their ingested amount of kratom over time, increasing the risk associated with use and inducing significant withdrawal symptoms when stopping therapy. The ability for children to purchase kratom is a scary proposition, as is the creation of neonatal opioid withdrawal when kratom is used among pregnant mothers. Kratom does not appear in normal drug screens and when taken with other substances of abuse may not be recognized but could accentuate the harm caused by these other illicit drugs via pharmacokinetic and pharmacodynamic means. Drug interactions could cause kratom to be more dangerous or could make prescription drugs or drugs of abuse more dangerous. In addition, the kratom supply may include products that are adulterated or contaminated, raising the risks for patients. There are many reported adverse events from kratom use, and the incidence of reports is increasing over time. However, without reliable data on use, it is impossible to know the balance of benefits to harm for this product. Kratom may be found to be effective for opioid withdrawal and to treat chronic pain in the future, but those trials are currently lacking.

Currently, people addicted to opioids could use standard therapy with psychotherapy and drugs such as methadone or suboxone instead of kratom. These therapies are FDA approved and have an acceptable balance of benefits to harm. However, many people are unwilling to confront their opioid addiction, have concomitant chronic pain that is not otherwise alleviated, lack access to healthcare services, or do not want their addiction to be known. For these people, there are 3 common options, kratom, illicit opioids (heroin, fentanyl, and others), or megadose loperamide. While it may seem intuitive that kratom just be banned, such a move may cause kratom users to move to illicit fentanyl or heroin. As such, health professionals need to appreciate the comparative risks among the 3 options.

In 2017, more than 47,000 Americans died as a result of an opioid overdose, mostly secondary to respiratory depression.[94] Over 652,000 people currently suffer from heroin use disorder. Illicit opioids are prone to impurities, undisclosed dosing variability, contamination, and adulteration. Their procurement from drug dealers can place patients at risk, and their possession can result in arrest and incarceration.[94]

Megadose loperamide is increasingly being used as a self-medication alternative or bridge therapy to other opioids.[95] Nonprescription loperamide is free of contamination or adulteration and has standard predictable doses. However, its use is also associated with a host of adverse effects, including cardiac arrhythmias. Since it is not possible to estimate a prevalence of usage for megadose loperamide, the comparative risks between loperamde and kratom are not known. Proposed changes in packaging for loperamide to impede patients from using megadoses, such as blister packs, will make it harder for patients to use this alternative to illicit opioids or kratom in the future.

Kratom might be a candidate for behind-the-counter status.[2] In that scenario, kratom would still be widely accessible but only from a licensed pharmacist. Only high-quality kratom products, certified by outside laboratories, could be sold. Requiring identification to purchase kratom can prevent underage acquisition or recreational use. Drug interactions with kratom could be assessed for and prevented. Pregnant women could be discouraged from using kratom. Patients could be counseled about alternative options for pain relief or opioid addiction during pharmacist interactions. Adverse events could be elucidated and referred to FDA, and the prevalence of use could be determined so the adverse events could be better placed in context. This could be the middle ground between the current unfettered access that people have and a complete ban. Making kratom a prescription product would be untenable given the lack of quality trials establishing benefits and risks.

Conclusion

Kratom has a unique pharmacologic profile that might offer advantages over other opioids, but its high abuse liability, potential for drug interactions and adverse events, and inadequate research into the balance of benefits to harm in patients makes it difficult to justify its use. There is mounting information on the adverse events associated with kratom use and potential treatments that can be useful to clinicians.

Disclosures

The author has declared no potential conflicts of interest.

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92. Havemann-Reincke. P01-50-Kratom and alcohol dependence: clinical symptoms, withdrawal treatment and pharmacological mechanism–a case report. *Eur Psychiatry.* 2011;26(Suppl 1):50.
93. FDA. Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom. Silver Spring, MD: Food and Drug Administration; 2017 Nov 14. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm (accessed 2019 Jul 4).
94. National Institute of Drug Abuse. Opioid overdose crisis. https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis. (accessed 2019 Jul 24).
95. White CM. Loperamide: a readily available but dangerous opioid substitute. *J Clin Pharmacol.* 2019; 59:1165-9.

Dear Dr. Ferguson,

By way of introduction, my name is Jack Henningfield and I have been involved in kratom research for the past decade and, along with my colleague Marilyn Huestis, PhD, we have collaborated on several kratom research projects that are relevant to the current scheduling of kratom in Wisconsin. Through PinneyAssociates I consult on the development of new medicines and dietary supplements. Prior to PinneyAssociates, I was a pharmacologist at the National Institute on Drug Abuse, Intramural Research Program (1980-1996), serving as Chief of the Clinical Pharmacology Research Branch, and Chief of the Behavioral Biology and Abuse Potential Assessment Section. My responsibilities included working with NIDA, FDA and DEA on drug abuse potential assessment and Controlled Substances Act drug scheduling, and those are my primary activities at PinneyAssociates. Dr. Huestis retired from NIDA a few years ago, where she served as Chief of the Chief of the Chemistry and Drug Metabolism, section also providing expertise in abuse potential assessment, drug testing and analytics, and forensic toxicology.

I have been following the actions of the Wisconsin Controlled Substances Board (CSB) regarding their decision to review and provide guidance to the state legislature about whether kratom meets the statutory criteria to be scheduled. I understand that you have been tasked with leading the review of the available scientific data on behalf of the Wisconsin Medical Examining Board (MEB). Included in the information that was provided by the CSB to the MEB is written testimony that I provided to a legislative committee on AB 599 and the 8-Factor Analysis that we submitted to FDA and DEA in 2016, after the DEA withdrew its August 2016 proposal to schedule kratom in September of 2016 with a request for additional comment and information. In 2018 we published a peer-reviewed 8-Factor Analysis in Psychopharmacology, again concluding that kratom didn't meet the criteria of the 8 factors for scheduling. In fact, we found, as did Assistance Secretary of Health Dr. Brett Giroir, following a 2018 Department of Health and Human Services review, that scheduling kratom carries foreseeable serious public health risks including opioid overdose deaths in people using kratom to stay off opioids, in discouraging pregnant women and others from talking to their health care providers about their kratom use, discouraging research, and more. See Dr. Giroir's formal 2018 scheduling rescission letter to the DEA at https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/60145eab6df59e7e36a7cfc1/1611947693695/dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf

As you are aware, the actions of the Legislature to originally classify kratom's alkaloids as Schedule I substances in 2014 was predicated on, in addition to now outdated information, the assurances by the US Food and Drug Administration (FDA) that federal scheduling was imminent. The FDA did make the scheduling recommendation in 2016 and that was proposed and then withdrawn by the Drug Enforcement Administration (DEA) for lack of evidence, concern about public health risks, and thousands of comments in opposition by consumers as well as scientists, and bipartisan concerns from members of the US House of Representatives and Senate.

In 2017 the FDA initiated a second scheduling recommendation effort that was formally

submitted to the DEA. That recommendation was officially withdrawn on August 16 2018 by then Assistant Secretary of Health Dr. Brett Giroir for what he characterized as FDA's "poor evidence and data" and ignoring the public safety impact that kratom scheduling would have. See Dr. Giroir's letter at https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/60145eab6df59e7e36a7cfc1/1611947693695/dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf

Then, in 2021, the World Health Organization Expert Committee on Drug Dependence (WHO ECDD) voted unanimously to reject a petition to the UN Commission on Narcotic Drugs to schedule kratom under the 1961 and 1971 Treaty Conventions. Specifically, the WHO ECDD conducted extensive Pré review and public meeting hearing from public health experts and kratom researchers around the world on the topic. Dr Huestis and I were among those who provided both oral and written comments. The WHO ECDD addressed that evidence and public health considerations including the fact that many people use kratom therapeutically, for a variety of reasons including management of opioid withdrawal. The Committee concluded that there is insufficient evidence to recommend a critical review [that is the formal WHO scheduling pathway] of kratom, mitragynine or 7-hydroxymitragynine. Consistent with Dr. Giroir and other experts, the committee concluded that "Although mitragynine has been analytically confirmed in a number of deaths, almost all involve use of other substances". See the ECDD summary report at https://cdn.who.int/media/docs/default-source/controlled-substances/44ecdd_unsg_annex1.pdf?sfvrsn=9c380ac2_5.

In early 2022, Dr Huestis and I also published an extensive peer-reviewed update of kratom abuse potential and safety related research drawing on more than 100 studies published since FDA's 2017 scheduling recommendation. There has been additional research published and presented since the February publication of our 2022 review and this includes recent studies of the respiratory effects of mitragynine in animals, and of kratom safety and pharmacokinetics in humans that we would be pleased to discuss with you. This extensive research has been primarily funded by NIDA through grants to universities, though there continues to be considerable research in Southeast Asia that had been largely ignored by FDA, but which has been highlighted in NIDA supported conferences, and which currently involves collaborations with NIDA funded researchers. Our 2022 abuse potential update article includes many of these studies. It can be viewed and downloaded at https://www.frontiersin.org/articles/10.3389/fphar.2021.775073/full

Dr. Huestis and I would be pleased to discuss this research with you and provide our perspective on why the FDA's recommendations to schedule kratom, that was accepted by the Wisconsin Legislature, does not meet the required scientific standards including public health considerations required under the federal and Wisconsin controlled substances legislation.

Please let me know a convenient time in your schedule where we could schedule a Zoom call on this important issue.

Thank you,

Jack E. Henningfield, PhD
Vice President, Research, Health Policy, and Abuse Liability
PinneyAssociates | pinneyassociates.com

State of Wisconsin
Department of Safety & Professional Services
AGENDA REQUEST FORM

1) Name and title of person submitting the request:	2) Date when request submitted:
Nilajah Hardin, Administrative Rules Coordinator	**08/26/22** Items will be considered late if submitted after 12:00 p.m. on the deadline date which is 8 business days before the meeting

3) Name of Board, Committee, Council, Sections:

Controlled Substances Board

4) Meeting Date:	5) Attachments:	6) How should the item be titled on the agenda page?
09/09/22	☒ Yes ☐ No	**Administrative Rule Matters – Discussion and Consideration** 1. Final Rule Draft and Legislative Report a. CSB 2.91, Relating to Scheduling 4,4'-Dimethylaminorex 2. Scope Statements a. CSB 2.92, Relating to Scheduling 38 Anabolic Steroids b. CSB 2.93, Relating to Scheduling Daridorexant c. CSB 2.94, Relating to Scheduling 7 Synthetic Benzimidazole-Opioids d. CSB 2.95, Relating to Scheduling Ganaxolone e. CSB 4, Relating to National Provider Identifier Requirement 3. Pending or Possible Rulemaking Projects

2.	8) Is an appearance before the Board being scheduled? *(If yes, please complete Appearance Request for Non-DSPS Staff)*	9) Name of Case Advisor(s), if required:
	☐ Yes ☒ No	**N/A**

10) Describe the issue and action that should be addressed:

Take Action on CSB 2.91-2.95 and 4

Copies of all current Board Rule Projects Can be Viewed Here:
https://dsps.wi.gov/Pages/RulesStatutes/PendingRules.aspx

11) Authorization

Nilajah D. Hardin — 08/26/22

Signature of person making this request — **Date**

Supervisor (if required) — **Date**

Executive Director signature (indicates approval to add post agenda deadline item to agenda) **Date**

Directions for including supporting documents:
1. This form should be attached to any documents submitted to the agenda.
2. Post Agenda Deadline items must be authorized by a Supervisor and the Policy Development Executive Director.
3. If necessary, provide original documents needing Board Chairperson signature to the Bureau Assistant prior to the start of a meeting.

STATE OF WISCONSIN
CONTROLLED SUBSTANCES BOARD

IN THE MATTER OF RULE-MAKING PROCEEDINGS BEFORE THE CONTROLLED SUBSTANCES BOARD	:	PROPOSED ORDER OF THE CONTROLLED SUBSTANCES BOARD ADOPTING RULES (CLEARINGHOUSE RULE 22-054)

PROPOSED ORDER

An order of the Controlled Substances Board to create CSB 2.91 relating to 4,4'-Dimethylaminorex.

Analysis prepared by the Department of Safety and Professional Services.

ANALYSIS

Statutes interpreted: s. 961.16, Stats.

Statutory authority: s. 961.11 (1) and (4), Stats.

Explanation of agency authority:
Section 961.11 (1), Stats. provides that "[t]he controlled substances board shall administer this subchapter and may add substances to or delete or reschedule all substances listed in the schedules in ss. 961.14, 961.16, 961.18, 961.20 and 961.22 pursuant to the rule-making procedures of ch. 227."

Section 961.11(4), Stats. provides that "[i]f a substance is designated, rescheduled or deleted as a controlled substance under federal law and notice thereof is given to the controlled substances board, the board by affirmative action shall similarly treat the substance under this chapter after the expiration of 30 days from the date of publication in the federal register of a final order designating the substance as a controlled substance or rescheduling or deleting the substance or from the date of issuance of an order of temporary scheduling under 21 USC 811 (h), unless within that 30−day period, the board or an interested party objects to the treatment of the substance. If no objection is made, the board shall promulgate, without making the determinations or findings required by subs. (1), (1m), (1r) and (2) or s. 961.13, 961.15, 961.17, 961.19 or 961.21, a final rule, for which notice of proposed rulemaking is omitted, designating, rescheduling, temporarily scheduling or deleting the substance. If an objection is made the board shall publish notice of receipt of the objection and the reasons for objection and afford all interested parties an opportunity to be heard. At the conclusion of the hearing, the board shall make a determination with respect to the treatment of the substance as provided in subs. (1), (1m), (1r) and (2) and shall publish its decision, which shall be final unless altered by statute. Upon publication of an objection to the treatment by the board, action by the board under this chapter is stayed until the board promulgates a rule under sub. (2)."

Related statute or rule: s. 961.14, Stats.

Summary of, and comparison with, existing or proposed federal regulation:
On August 12, 2021, the Department of Justice, Drug Enforcement Administration published its final rule in the Federal Register listing 4,4'-Dimethylaminorex into schedule I of the federal Controlled Substances Act. The scheduling action is effective September 13, 2021.

Plain language analysis:
This rule schedules 4,4'-Dimethylaminorex as a schedule I controlled substance.

The Controlled Substances Board did not receive an objection to similarly listing Perampanel as a schedule III under ch. 961, Stats. within 30 days of the date of publication in the federal register of the final order listing 4,4'-Dimethylaminorex as a schedule I controlled substance.

Pursuant to s. 961.11(4), Stats., the Controlled Substances Board by affirmative action similarly treats 4,4'-Dimethylaminorex under chapter 961, Stats. by creating the following:

CSB 2.91 Addition of 4,4'-Dimethylaminorex to schedule I. Section 961.14 (7) (cm), Stats., is created to read: 961.14 (7) (cm) *4,4'-Dimethylaminorex.*

The Affirmative Action order, dated September 16, 2021, took effect on September 27, 2021, when it was published in the Administrative Register and expires upon promulgation of a final rule.

Summary of public comments received on statement of scope and a description of how and to what extent those comments and feedback were taken into account in drafting the proposed rule: N/A

Comparison with rules in adjacent states:
Illinois: Illinois has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

Iowa: Iowa has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

Michigan: Michigan has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

Minnesota: Minnesota has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

Summary of factual data and analytical methodologies:
The methodology was to schedule 4,4'-Dimethylaminorex to conform with the federal Controlled Substances Act.

Analysis and supporting documents used to determine effect on small business or in preparation of economic impact analysis:
The proposed rules were posted for a period of 14 days to solicit public comment on economic impact, including how the proposed rules may affect businesses, local government units, and individuals. No comments were received.

Fiscal Estimate:
The Fiscal Estimate and Economic Impact Analysis is attached.

Effect on small business:
These proposed rules do not have an economic impact on small businesses, as defined in s. 227.114 (1), Stats. The Department's Regulatory Review Coordinator may be contacted by email at Daniel.Hereth@wisconsin.gov, or by calling (608) 267-2435.

Agency contact person:
Nilajah Hardin, Administrative Rules Coordinator, Department of Safety and Professional Services, Division of Policy Development, 4822 Madison Yards Way, P.O. Box 8366, Madison, Wisconsin 53708; telephone 608-267-7139; email at DSPSAdminRules@wisconsin.gov.

Place where comments are to be submitted and deadline for submission:
Comments may be submitted to Nilajah Hardin, Administrative Rules Coordinator, Department of Safety and Professional Services, Division of Policy Development, 4822 Madison Yards Way, Madison, WI 53708-8366, or by email to DSPSAdminRules@wisconsin.gov. Comments must be received by September 9, 2022 to be included in the record of rulemaking proceedings.

TEXT OF RULE

SECTION 1. CSB 2.91 is created to read:

CSB 2.91 Addition of 4,4'-Dimethylaminorex to schedule I. Section 961.14 (7) (cm), Stats., is created to read:

961.14 (7) (cm) 4,4'-Dimethylaminorex.

SECTION 2. EFFECTIVE DATE. The rules adopted in this order shall take effect on the first day of the month following publication in the Wisconsin Administrative Register, pursuant to s. 227.22 (2) (intro.), Stats.

(END OF TEXT OF RULE)

This Proposed Order of the Controlled Substances Board is approved for submission to the Governor and Legislature.

Dated _____ Agency _____

Chairperson
Controlled Substances Board

STATE OF WISCONSIN
CONTROLLED SUBSTANCES BOARD

IN THE MATTER OF RULEMAKING PROCEEDINGS BEFORE THE CONTROLLED SUBSTANCES BOARD	**:**	**REPORT TO THE LEGISLATURE CR 22-054**

I. THE PROPOSED RULE:
The proposed rule, including the analysis and text, is attached.

II. REFERENCE TO APPLICABLE FORMS: N/A

III. FISCAL ESTIMATE AND EIA: The Fiscal Estimate and EIA is attached.

IV. DETAILED STATEMENT EXPLAINING THE BASIS AND PURPOSE OF THE PROPOSED RULE, INCLUDING HOW THE PROPOSED RULE ADVANCES RELEVANT STATUTORY GOALS OR PURPOSES:
On August 12, 2021, the Department of Justice, Drug Enforcement Administration published its final rule in the Federal Register listing 4,4'-Dimethylaminorex into schedule I of the federal Controlled Substances Act. The scheduling action is effective September 13, 2021. The Controlled Substances Board did not receive an objection to similarly listing 4,4'-Dimethylaminorex as a schedule I under ch. 961, Stats. within 30 days of the date of publication in the federal register of the final order listing 4,4'-Dimethylaminorex as a schedule I controlled substance. Pursuant to s. 961.11(4), Stats., the Controlled Substances Board by affirmative action similarly treats 4,4'-Dimethylaminorex under chapter 961, Stats. by creating the following:

> **CSB 2.91 Addition of 4,4'-Dimethylaminorex to schedule I**. Section 961.14 (7) (cm), Stats., is created to read: 961.14 (7) (cm) *4,4'-Dimethylaminorex.*

The Affirmative Action order, dated September 16, 2021, took effect on September 27, 2021, when it was published in the Administrative Register and expires upon promulgation of a final rule.

V. SUMMARY OF PUBLIC COMMENTS AND THE BOARD'S RESPONSES, EXPLANATION OF MODIFICATIONS TO PROPOSED RULES PROMPTED BY PUBLIC COMMENTS:
Per s. 961.11(4), Stats., if no objection is made, the board shall promulgate a final rule for which notice of proposed rulemaking is omitted. Therefore, the Board did not hold a public hearing.

VI. RESPONSE TO LEGISLATIVE COUNCIL STAFF RECOMMENDATIONS:
All of the recommendations suggested in the Clearinghouse Report have been accepted in whole.

VII. REPORT FROM THE SBRRB AND FINAL REGULATORY FLEXIBILITY ANALYSIS: N/A

STATE OF WISCONSIN
DEPARTMENT OF ADMINISTRATION
DOA-2049 (R09/2016)

DIVISION OF EXECUTIVE BUDGET AND FINANCE
101 EAST WILSON STREET, 10TH FLOOR
P.O. BOX 7864
MADISON, WI 53707-7864
FAX: (608) 267-0372

ADMINISTRATIVE RULES
Fiscal Estimate & Economic Impact Analysis

1. Type of Estimate and Analysis
☒ Original ☐ Updated ☐ Corrected

2. Date
06/29/22

3. Administrative Rule Chapter, Title and Number (and Clearinghouse Number if applicable)
CSB 2.91

4. Subject
Scheduling 4,4'-Dimethylaminorex

5. Fund Sources Affected
☐ GPR ☐ FED ☐ PRO ☐ PRS ☐ SEG ☐ SEG-S

6. Chapter 20, Stats. Appropriations Affected

7. Fiscal Effect of Implementing the Rule
☒ No Fiscal Effect ☐ Increase Existing Revenues ☐ Increase Costs ☐ Decrease Costs
☐ Indeterminate ☐ Decrease Existing Revenues ☐ Could Absorb Within Agency's Budget

8. The Rule Will Impact the Following (Check All That Apply)
☐ State's Economy
☐ Local Government Units
☐ Specific Businesses/Sectors
☐ Public Utility Rate Payers
☐ Small Businesses **(if checked, complete Attachment A)**

9. Estimate of Implementation and Compliance to Businesses, Local Governmental Units and Individuals, per s. 227.137(3)(b)(1).
$0

10. Would Implementation and Compliance Costs Businesses, Local Governmental Units and Individuals Be $10 Million or more Over Any 2-year Period, per s. 227.137(3)(b)(2)?
☐ Yes ☒ No

11. Policy Problem Addressed by the Rule
On August 12, 2021, the Department of Justice, Drug Enforcement Administration published its final rule in the Federal Register listing 4,4'-Dimethylaminorex into schedule I of the federal Controlled Substances Act.

12. Summary of the Businesses, Business Sectors, Associations Representing Business, Local Governmental Units, and Individuals that may be Affected by the Proposed Rule that were Contacted for Comments.
The rule was posted on the Department's website for 14 days to solicit public comment on economic impact, including how the proposed rules may affect businesses, local government units, and individuals. No comments were received.

13. Identify the Local Governmental Units that Participated in the Development of this EIA.
None

14. Summary of Rule's Economic and Fiscal Impact on Specific Businesses, Business Sectors, Public Utility Rate Payers, Local Governmental Units and the State's Economy as a Whole (Include Implementation and Compliance Costs Expected to be Incurred)
None

15. Benefits of Implementing the Rule and Alternative(s) to Implementing the Rule
The benefit is that the federal and state controlled substances acts will be uniform to avoid confusion. In addition it is in the best interest of Wisconsin citizens to schedule 4,4'-Dimethylaminorex as a controlled substance.

16. Long Range Implications of Implementing the Rule
The long range implications of implementing the rule will be to schedule 4,4'-Dimethylaminorex as a schedule I controlled substance.

17. Compare With Approaches Being Used by Federal Government
The federal government has scheduled 4,4'-Dimethylaminorex as a schedule I controlled substance.

18. Compare With Approaches Being Used by Neighboring States (Illinois, Iowa, Michigan and Minnesota)
Illinois: Illinois has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

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MADISON, WI 53707-7864
FAX: (608) 267-0372

ADMINISTRATIVE RULES
Fiscal Estimate & Economic Impact Analysis

Iowa: Iowa has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

Michigan: Michigan has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

Minnesota: Minnesota has not scheduled 4,4'-Dimethylaminorex as a controlled substance.

19. Contact Name	20. Contact Phone Number
Nilajah Hardin, Administrative Rules Coordinator	608-267-7139

This document can be made available in alternate formats to individuals with disabilities upon request.

STATE OF WISCONSIN
DEPARTMENT OF ADMINISTRATION
DOA-2049 (R09/2016)

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ADMINISTRATIVE RULES
Fiscal Estimate & Economic Impact Analysis

ATTACHMENT A

1. Summary of Rule's Economic and Fiscal Impact on Small Businesses (Separately for each Small Business Sector, Include Implementation and Compliance Costs Expected to be Incurred)

2. Summary of the data sources used to measure the Rule's impact on Small Businesses

3. Did the agency consider the following methods to reduce the impact of the Rule on Small Businesses?
☐ Less Stringent Compliance or Reporting Requirements
☐ Less Stringent Schedules or Deadlines for Compliance or Reporting
☐ Consolidation or Simplification of Reporting Requirements
☐ Establishment of performance standards in lieu of Design or Operational Standards
☐ Exemption of Small Businesses from some or all requirements
☐ Other, describe:

4. Describe the methods incorporated into the Rule that will reduce its impact on Small Businesses

5. Describe the Rule's Enforcement Provisions

6. Did the Agency prepare a Cost Benefit Analysis (if Yes, attach to form)
☐ Yes ☐ No

LCRC
FORM 2

Wisconsin Legislative Council

RULES CLEARINGHOUSE

Scott Grosz
Clearinghouse Director

Anne Sappenfield
Legislative Council Director

Margit Kelley
Clearinghouse Assistant Director

CLEARINGHOUSE REPORT TO AGENCY

[THIS REPORT HAS BEEN PREPARED PURSUANT TO S. 227.15, STATS. THIS IS A REPORT ON A RULE AS ORIGINALLY PROPOSED BY THE AGENCY; THE REPORT MAY NOT REFLECT THE FINAL CONTENT OF THE RULE IN FINAL DRAFT FORM AS IT WILL BE SUBMITTED TO THE LEGISLATURE. THIS REPORT CONSTITUTES A REVIEW OF, BUT NOT APPROVAL OR DISAPPROVAL OF, THE SUBSTANTIVE CONTENT AND TECHNICAL ACCURACY OF THE RULE.]

CLEARINGHOUSE RULE **22-054**

AN ORDER to create CSB 2.91, relating to 4,4'-Dimethylaminorex.

Submitted by **CONTROLLED SUBSTANCES BOARD**

06-29-2022 RECEIVED BY LEGISLATIVE COUNCIL.
07-22-2022 REPORT SENT TO AGENCY.

MSK:BL

LEGISLATIVE COUNCIL RULES CLEARINGHOUSE REPORT

This rule has been reviewed by the Rules Clearinghouse. Based on that review, comments are reported as noted below:

1. STATUTORY AUTHORITY [s. 227.15 (2) (a)]

   Comment Attached YES ☐ NO ☑

2. FORM, STYLE AND PLACEMENT IN ADMINISTRATIVE CODE [s. 227.15 (2) (c)]

   Comment Attached YES ☐ NO ☑

3. CONFLICT WITH OR DUPLICATION OF EXISTING RULES [s. 227.15 (2) (d)]

   Comment Attached YES ☐ NO ☑

4. ADEQUACY OF REFERENCES TO RELATED STATUTES, RULES AND FORMS [s. 227.15 (2) (e)]

   Comment Attached YES ☑ NO ☐

5. CLARITY, GRAMMAR, PUNCTUATION AND USE OF PLAIN LANGUAGE [s. 227.15 (2) (f)]

   Comment Attached YES ☐ NO ☑

6. POTENTIAL CONFLICTS WITH, AND COMPARABILITY TO, RELATED FEDERAL REGULATIONS [s. 227.15 (2) (g)]

   Comment Attached YES ☐ NO ☑

7. COMPLIANCE WITH PERMIT ACTION DEADLINE REQUIREMENTS [s. 227.15 (2) (h)]

   Comment Attached YES ☐ NO ☑

Wisconsin Legislative Council
RULES CLEARINGHOUSE

Scott Grosz
Clearinghouse Director

Margit Kelley
Clearinghouse Assistant Director

Anne Sappenfield
Legislative Council Director

CLEARINGHOUSE RULE 22-054

Comments

[NOTE: All citations to "Manual" in the comments below are to the Administrative Rules Procedures Manual, prepared by the Legislative Council Staff and the Legislative Reference Bureau, dated November 2020.]

4. Adequacy of References to Related Statutes, Rules and Forms

In the agency's analysis for the proposed rule, under the headings for both "statutes interpreted" and "related statute or rule", each citation is provided for s. 961.16, Stats. However, both instances should be changed to s. 961.14, Stats., because the proposed rule relates to a schedule I controlled substance.

STATEMENT OF SCOPE

CONTROLLED SUBSTANCES BOARD

Rule No.: CSB 2.92

Relating to: Scheduling thirty-eight (38) anabolic steroids

Rule Type: Permanent

1. Finding/nature of emergency:

N/A

2. Detailed description of the objective of the proposed rule:

The objective of the proposed rule is to schedule thirty-eight (38) anabolic steroids as a schedule III controlled substance under s. 961.11 (4), Stats.

3. Description of the existing policies relevant to the rule, new policies proposed to be included in the rule, and an analysis of policy alternatives:

On December 16, 2005, and July 30, 2012, the Department of Justice, Drug Enforcement Administration published its final rules in the Federal Register listing thirty-eight (38) anabolic steroids into schedule III of the federal Controlled Substances Act. The scheduling action were effective January 20, 2005, and August 29, 2012.

The Controlled Substances Board did not receive an objection to similarly treating thirty-eight (38) anabolic steroids as a Schedule III controlled substance under ch. 961, Stats within 30 days of the date of publication in the Federal Register of the final order designating thirty-eight (38) anabolic steroids as a controlled substance.

Pursuant to s. 961.11 (4), Stats., the Controlled Substances Board took affirmative action to similarly treat thirty-eight (38) anabolic steroids under ch. 961, Stats. by repealing and recreating the following:

961.18 (7) ANABOLIC STEROIDS. Unless specifically excepted or listed in another schedule, any material, compound, mixture, or preparation containing any quantity of any of the following anabolic steroids, including any of their esters, ethers, isomers, esters or ethers of isomers, salts and salts of esters or ethers, isomers and esters or ethers of isomers that are theoretically possible within the specific chemical designation, except that such terms do not include an anabolic steroid that is expressly intended for administration through implants to cattle or other nonhuman species and that has been approved by the secretary of health and human services for such administration; and if any person prescribes, dispenses, or distributes such steroid for human use, the person shall be considered to have prescribed, dispensed, or distributed an anabolic steroid within the meaning of this section:

(a) 3beta,17-dihydroxy-5alpha-androstane.
(ag) 3alpha,17beta-dihydroxy-5alpha-androstane.
(ar) 5alpha-androstan-3,17-dione.
(b) 1-androstenediol (3beta,17beta-dihydroxy-5alpha-androst-1-ene; 3alpha,17beta-dihydroxy-5alpha-androst-1-ene).
(bg) 4-androstenediol.
(br) 5-androstenediol.

(c) 1-androstenedione.
(cg) 4-androstenedione.
(cr) 5-androstenedione.
(d) 13beta-ethyl-17beta-hydroxygon-4-en-3-one.
(dg) Bolasterone.
(dr) Boldenone.
(e) Boldione.
(eg) Calusterone.
(er) 4-chlorotestosterone, which is also called clostebol.
(f) Dehydrochloromethyltestosterone.
(fg) Delta1-dihydrotestosterone.
(fr) Desoxymethyltestosterone.
(g) 4-dihydrotestosterone, which is also called stanolone.
(gg) Drostanolone.
(gr) Ethylestrenol.
(h) Fluoxymesterone.
(hg) Formebulone, which is also called fromebolone.
(hr) Furazabol.
(i) 4-hydroxytestosterone.
(ig) 4-hydroxy-19-nortestosterone.
(ir) Mestanolone.
(j) Mesterolone.
(jg) Methandienone, which is also called methandrostenolone.
(jr) Methandriol.
(k) Methasterone.
(kg) Methenolone.
(kr) 17alpha-methyl-3beta, 17beta-dihydroxy-5alpha-androstane.
(L) 17alpha-methyl-3alpha,17beta-dihydroxy-5alpha-androstane.
(Lg) 17alpha-methyl-3beta,17beta-dihydroxyandrost-4-ene.
(Lr) 17alpha-methyl-4-hydroxynandrolone.
(m) Methyldienolone.
(mg) Methyltestosterone.
(mr) Methyltrienolone.
(n) Mibolerone.
(ng) 17alpha-methyl-delta1-dihydrotestosterone, which is also called 17-alpha-methyl-1-testosterone.
(nr) Nandrolone.
(o) 19-nor-4-androstenediol (3beta, 17beta-dihydroxyestr-4-ene; 3alpha, 17beta-dihydroxyestr-4-ene).
(og) 19-nor-5-androstenediol (3beta, 17beta-dihydroxyestr-5-ene; 3alpha, 17beta-dihydroxyestr-5-ene).
(or) 19-nor-4,9(10)-androstadienedione.
(p) 19-nor-4-androstenedione (estr-4-en-3,17-dione).
(pg) 19-nor-5-androstenedione (estr-5-en-3,17-dione).
(pr) Norbolethone.
(q) Norclostebol.
(qg) Norethandrolone.
(qr) Normethandrolone.
(r) Oxandrolone.
(rg) Oxymesterone.
(rr) Oxymetholone.
(s) Prostanozol.
(sg) Stanozolol.
(sr) Stenbolone.
(t) Testolactone.
(tg) Testosterone.
(tr) Tetrahydrogestrinone.
(u) Trenbolone.

The Affirmative Action order, dated August 3, 2022, took effect on August 15, 2022, upon publication in the Administrative Register and expires upon promulgation of a final rule.

4. Detailed explanation of statutory authority for the rule:

Section 961.11 (1), Stats. provides that "[t]he controlled substances board shall administer this subchapter and may add substances to or delete or reschedule all substances listed in the schedules in ss. 961.14, 961.16, 961.18, 961.20 and 961.22 pursuant to the rule-making procedures of ch. 227."

Section 961.11(4), Stats. provides that "[i]f a substance is designated, rescheduled or deleted as a controlled substance under federal law and notice thereof is given to the controlled substances board, the board by affirmative action shall similarly treat the substance under this chapter after the expiration of 30 days from the date of publication in the federal register of a final order designating the substance as a controlled substance or rescheduling or deleting the substance or from the date of issuance of an order of temporary scheduling under 21 USC 811 (h), unless within that 30−day period, the board or an interested party objects to the treatment of the substance. If no objection is made, the board shall promulgate, without making the determinations or findings required by subs. (1), (1m), (1r) and (2) or s. 961.13, 961.15, 961.17, 961.19 or 961.21, a final rule, for which notice of proposed rulemaking is omitted, designating, rescheduling, temporarily scheduling or deleting the substance. If an objection is made the board shall publish notice of receipt of the objection and the reasons for objection and afford all interested parties an opportunity to be heard. At the conclusion of the hearing, the board shall make a determination with respect to the treatment of the substance as provided in subs. (1), (1m), (1r) and (2) and shall publish its decision, which shall be final unless altered by statute. Upon publication of an objection to the treatment by the board, action by the board under this chapter is stayed until the board promulgates a rule under sub. (2)."

5. Estimate of amount of time that state employees will spend developing the rule and of other resources necessary to develop the rule:

Approximately 80 hours.

6. List with description of all entities that may be affected by the proposed rule:

Law enforcement, district attorney offices, Dept of Justice, state courts and the Controlled Substances Board.

7. Summary and preliminary comparison with any existing or proposed federal regulation that is intended to address the activities to be regulated by the proposed rule:

On December 16, 2005, and July 30, 2012, the Department of Justice, Drug Enforcement Administration published its final rules in the Federal Register listing thirty-eight (38) anabolic steroids into schedule III of the federal Controlled Substances Act. The scheduling action were effective January 20, 2005, and August 29, 2012.

8. Anticipated economic impact of implementing the rule:

None to minimal.

Contact Person: Nilajah Hardin, Administrative Rules Coordinator, DSPSAdminRules@wisconsin.gov

Approved for publication:

Authorized Signature

Date Submitted

Approved for implementation:

Authorized Signature

Date Submitted

STATEMENT OF SCOPE

CONTROLLED SUBSTANCES BOARD

Rule No.: CSB 2.93

Relating to: Scheduling Daridorexant

Rule Type: Permanent

1. Finding/nature of emergency:

N/A

2. Detailed description of the objective of the proposed rule:

The objective of the proposed rule is to schedule Daridorexant as a schedule IV controlled substance under s. 961.11 (4), Stats.

3. Description of the existing policies relevant to the rule, new policies proposed to be included in the rule, and an analysis of policy alternatives:

On April 7, 2022, the Department of Justice, Drug Enforcement Administration published its interim final rule in the Federal Register listing Daridorexant into schedule IV of the federal Controlled Substances Act. The scheduling action was effective April 7, 2022.

The Controlled Substances Board did not receive an objection to similarly listing Daridorexant as a Schedule IV controlled substance under ch. 961, Stats., within 30 days of the date of publication in the Federal Register of the interim final order listing Daridorexant as a schedule IV controlled substance.

Pursuant to s. 961.11 (4), Stats., the Controlled Substances Board took affirmative action to similarly treat Daridoxerant under ch. 961, Stats. creating the following:

CSB 2.93 Addition of Daridorexant to schedule IV. Section 961.20 (2) (cpm), Stats., is created to read:

961.20 (2) (cpm) Daridorexant;

The Affirmative Action order, dated July 20, 2022, took effect on July 25, 2022, upon publication in the Administrative Register and expires upon promulgation of a final rule.

4. Detailed explanation of statutory authority for the rule:

Section 961.11 (1), Stats. provides that "[t]he controlled substances board shall administer this subchapter and may add substances to or delete or reschedule all substances listed in the schedules in ss. 961.14, 961.16, 961.18, 961.20 and 961.22 pursuant to the rule-making procedures of ch. 227."

Section 961.11(4), Stats. provides that "[i]f a substance is designated, rescheduled or deleted as a controlled substance under federal law and notice thereof is given to the controlled substances board, the board by affirmative action shall similarly treat the substance under this chapter after the expiration of 30 days from the date of publication in the federal register of a final order designating the substance as a controlled substance or rescheduling or deleting the substance or from the date of issuance of an order of temporary scheduling under 21 USC 811 (h), unless within that 30−day period, the board or an interested

party objects to the treatment of the substance. If no objection is made, the board shall promulgate, without making the determinations or findings required by subs. (1), (1m), (1r) and (2) or s. 961.13, 961.15, 961.17, 961.19 or 961.21, a final rule, for which notice of proposed rulemaking is omitted, designating, rescheduling, temporarily scheduling or deleting the substance. If an objection is made the board shall publish notice of receipt of the objection and the reasons for objection and afford all interested parties an opportunity to be heard. At the conclusion of the hearing, the board shall make a determination with respect to the treatment of the substance as provided in subs. (1), (1m), (1r) and (2) and shall publish its decision, which shall be final unless altered by statute. Upon publication of an objection to the treatment by the board, action by the board under this chapter is stayed until the board promulgates a rule under sub. (2)."

5. Estimate of amount of time that state employees will spend developing the rule and of other resources necessary to develop the rule:

Approximately 80 hours.

6. List with description of all entities that may be affected by the proposed rule:

Law enforcement, district attorney offices, Dept of Justice, state courts and the Controlled Substances Board.

7. Summary and preliminary comparison with any existing or proposed federal regulation that is intended to address the activities to be regulated by the proposed rule:

On April 7, 2022, the Department of Justice, Drug Enforcement Administration published its interim final rule in the Federal Register listing Daridorexant into schedule IV of the federal Controlled Substances Act. The scheduling action was effective April 7, 2022.

8. Anticipated economic impact of implementing the rule:

None to minimal.

Contact Person: Nilajah Hardin, Administrative Rules Coordinator, DSPSAdminRules@wisconsin.gov

Approved for publication:	Approved for implementation:
_____	_____
Authorized Signature	Authorized Signature
_____	_____
Date Submitted	Date Submitted

STATEMENT OF SCOPE

CONTROLLED SUBSTANCES BOARD

Rule No.: CSB 2.94

Relating to: Scheduling seven (7) synthetic benzimidazole-opioid substances

Rule Type: Permanent

1. Finding/nature of emergency:

N/A

2. Detailed description of the objective of the proposed rule:

The objective of the proposed rule is to schedule seven (7) synthetic benzimidazole-opioid substances as a schedule I controlled substance under s. 961.11 (4), Stats.

3. Description of the existing policies relevant to the rule, new policies proposed to be included in the rule, and an analysis of policy alternatives:

On April 12, 2022, the Department of Justice, Drug Enforcement Administration published its temporary scheduling order in the Federal Register placing the following seven (7) synthetic benzimidazole-opioid substances into schedule I of the federal Controlled Substances Act. The scheduling action was effective immediately.

- 2-(2-(4-butoxybenzyl)-5-nitro-1Hbenzimidazol-1-yl)-N,N-diethylethan-1- amine (butonitazene),
- 2-(2-(4-ethoxybenzyl)-1Hbenzimidazol-1-yl)-N,N-diethylethan-1- amine (etodesnitazene; etazene),
- N,N-diethyl-2-(2-(4-fluorobenzyl)-5- nitro-1H-benzimidazol-1-yl)ethan-1- amine (flunitazene),
- N,N-diethyl-2-(2-(4- methoxybenzyl)-1H-benzimidazol-1- yl)ethan-1-amine (metodesnitazene),
- N,N-diethyl-2-(2-(4- methoxybenzyl)-5-nitro-1Hbenzimidazol-1-yl)ethan-1-amine (metonitazene),
- 2-(4-ethoxybenzyl)-5-nitro-1-(2- (pyrrolidin-1-yl)ethyl)-1Hbenzimidazole (N-pyrrolidino etonitazene; etonitazepyne), and
- N,N-diethyl-2-(5-nitro-2-(4- propoxybenzyl)-1H-benzimidazol-1- yl)ethan-1-amine (protonitazene).

The Controlled Substances Board did not receive an objection to similarly treating the seven (7) synthetic benzimidazole-opioid substances listed above in schedule I under ch. 961, Stats. within 30 days of the date of publication in the federal register of the final order designating these seven (7) synthetic benzimidazole-opioid substances as controlled substances.

Pursuant to s. 961.11(4), Stats., the Controlled Substances Board by affirmative action similarly treats the seven (7) synthetic benzimidazole-opioid substances listed above under chapter 961, Stats. by creating the following:

CSB 2.94 Addition of seven (7) synthetic benzimidazole-opioid substances to schedule I.
(1) Section 961.14 (2) (mm) and (pe), stats. are renumbered to 961.14 (2) (xm) 3. and 5. And amended to read:

961.14 (2) (xm) 3. Etonitazene (2-(2-(4-ethoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)-N,N-diethylethan-1- amine).

961.14 (2) (xm) 5. Isotonitazene (N,N -diethyl-2-(2-(4-isopropoxybenzyl)-5-nitro-1H-benizimidazol-1-yl)ethan-1-amine).

(2) Section 961.14 (2) (xm) (intro.), 1., 2., 4., and 6. to 9., Stats., are created to read:

961.14 (2) (xm) Synthetic Benzimidazole-opioid Substances, specifically including all of the following:

1. Butonitazene (2-(2-(4-butoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)-N,N-diethylethan-1- amine).
2. Etodesnitazene also known as Etazene (2-(2-(4-ethoxybenzyl)-1H-benzimidazol-1-yl)-N,N-diethylethan-1- amine).
4. Flunitazene (N,N-diethyl-2-(2-(4-fluorobenzyl)-5- nitro-1H-benzimidazol-1-yl)ethan-1- amine).
6. Metodesnitazene (N,N-diethyl-2-(2-(4- methoxybenzyl)-1H-benzimidazol-1- yl)ethan-1-amine).
7. Metonitazene (N,N-diethyl-2-(2-(4- methoxybenzyl)-5-nitro-1H-benzimidazol-1-yl)ethan-1-amine).
8. N-pyrrolidino etonitazene also known as etonitazepyne (2-(4-ethoxybenzyl)-5-nitro-1-(2- (pyrrolidin-1-yl)ethyl)-1H-benzimidazole).
9. Protonitazene (N,N-diethyl-2-(5-nitro-2-(4- propoxybenzyl)-1H-benzimidazol-1- yl)ethan-1-amine).

The Affirmative Action order, dated August 3, 2022, took effect on August 15, 2022, upon publication in the Administrative Register and expires upon promulgation of a final rule.

4. Detailed explanation of statutory authority for the rule:

Section 961.11 (1), Stats. provides that "[t]he controlled substances board shall administer this subchapter and may add substances to or delete or reschedule all substances listed in the schedules in ss. 961.14, 961.16, 961.18, 961.20 and 961.22 pursuant to the rule-making procedures of ch. 227."

Section 961.11(4), Stats. provides that "[i]f a substance is designated, rescheduled or deleted as a controlled substance under federal law and notice thereof is given to the controlled substances board, the board by affirmative action shall similarly treat the substance under this chapter after the expiration of 30 days from the date of publication in the federal register of a final order designating the substance as a controlled substance or rescheduling or deleting the substance or from the date of issuance of an order of temporary scheduling under 21 USC 811 (h), unless within that 30−day period, the board or an interested party objects to the treatment of the substance. If no objection is made, the board shall promulgate, without making the determinations or findings required by subs. (1), (1m), (1r) and (2) or s. 961.13, 961.15, 961.17, 961.19 or 961.21, a final rule, for which notice of proposed rulemaking is omitted, designating, rescheduling, temporarily scheduling or deleting the substance. If an objection is made the board shall publish notice of receipt of the objection and the reasons for objection and afford all interested parties an opportunity to be heard. At the conclusion of the hearing, the board shall make a determination with respect to the treatment of the substance as provided in subs. (1), (1m), (1r) and (2) and shall publish its decision, which shall be final unless altered by statute. Upon publication of an objection to the treatment by the board, action by the board under this chapter is stayed until the board promulgates a rule under sub. (2)."

5. Estimate of amount of time that state employees will spend developing the rule and of other resources necessary to develop the rule:

Approximately 80 hours.

6. List with description of all entities that may be affected by the proposed rule:

Law enforcement, district attorney offices, Dept of Justice, state courts and the Controlled Substances Board.

7. Summary and preliminary comparison with any existing or proposed federal regulation that is intended to address the activities to be regulated by the proposed rule:

On April 12, 2022, the Department of Justice, Drug Enforcement Administration published its temporary scheduling order in the Federal Register placing the following seven (7) synthetic benzimidazole-opioid substances into schedule I of the federal Controlled Substances Act. The scheduling action was effective immediately.

8. Anticipated economic impact of implementing the rule:

None to minimal.

Contact Person: Nilajah Hardin, Administrative Rules Coordinator, DSPSAdminRules@wisconsin.gov

Approved for publication:

Authorized Signature

Date Submitted

Approved for implementation:

Authorized Signature

Date Submitted

STATEMENT OF SCOPE

CONTROLLED SUBSTANCES BOARD

Rule No.: CSB 2.95

Relating to: Scheduling Ganaxolone

Rule Type: Permanent

1. Finding/nature of emergency:

N/A

2. Detailed description of the objective of the proposed rule:

The objective of the proposed rule is to schedule Ganaxolone as a schedule V controlled substance under s. 961.11 (4), Stats.

3. Description of the existing policies relevant to the rule, new policies proposed to be included in the rule, and an analysis of policy alternatives:

On June 1, 2022, the Department of Justice, Drug Enforcement Administration published its interim final rule in the Federal Register listing Ganaxolone into schedule V of the federal Controlled Substances Act. The scheduling action was effective June 1, 2022.

The Controlled Substances Board did not receive an objection to similarly listing Ganaxolone as a schedule V under ch. 961, Stats. within 30 days of the date of publication in the federal register of the interim final order listing Ganaxolone as a schedule V controlled substance.

Pursuant to s. 961.11(4), Stats., the Controlled Substances Board by affirmative action similarly treats Ganaxolone under chapter 961, Stats. by creating the following:

CSB 2.95 Addition of Ganaxolone to schedule V. Section 961.22 (11), Stats., is created to read:

961.22 (11) GANAXOLONE. Ganaxolone.

The Affirmative Action order, dated July 20, 2022, took effect on July 25, 2022, upon publication in the Administrative Register and expires upon promulgation of a final rule.

4. Detailed explanation of statutory authority for the rule:

Section 961.11 (1), Stats. provides that "[t]he controlled substances board shall administer this subchapter and may add substances to or delete or reschedule all substances listed in the schedules in ss. 961.14, 961.16, 961.18, 961.20 and 961.22 pursuant to the rule-making procedures of ch. 227."

Section 961.11(4), Stats. provides that "[i]f a substance is designated, rescheduled or deleted as a controlled substance under federal law and notice thereof is given to the controlled substances board, the board by affirmative action shall similarly treat the substance under this chapter after the expiration of 30 days from the date of publication in the federal register of a final order designating the substance as a

controlled substance or rescheduling or deleting the substance or from the date of issuance of an order of temporary scheduling under 21 USC 811 (h), unless within that 30−day period, the board or an interested party objects to the treatment of the substance. If no objection is made, the board shall promulgate, without making the determinations or findings required by subs. (1), (1m), (1r) and (2) or s. 961.13, 961.15, 961.17, 961.19 or 961.21, a final rule, for which notice of proposed rulemaking is omitted, designating, rescheduling, temporarily scheduling or deleting the substance. If an objection is made the board shall publish notice of receipt of the objection and the reasons for objection and afford all interested parties an opportunity to be heard. At the conclusion of the hearing, the board shall make a determination with respect to the treatment of the substance as provided in subs. (1), (1m), (1r) and (2) and shall publish its decision, which shall be final unless altered by statute. Upon publication of an objection to the treatment by the board, action by the board under this chapter is stayed until the board promulgates a rule under sub. (2)."

5. Estimate of amount of time that state employees will spend developing the rule and of other resources necessary to develop the rule:

Approximately 80 hours.

6. List with description of all entities that may be affected by the proposed rule:

Law enforcement, district attorney offices, Dept of Justice, state courts and the Controlled Substances Board.

7. Summary and preliminary comparison with any existing or proposed federal regulation that is intended to address the activities to be regulated by the proposed rule:

On June 1, 2022, the Department of Justice, Drug Enforcement Administration published its interim final rule in the Federal Register listing Ganaxolone into schedule V of the federal Controlled Substances Act. The scheduling action was effective June 1, 2022.

8. Anticipated economic impact of implementing the rule:

None to minimal.

Contact Person: Nilajah Hardin, Administrative Rules Coordinator, DSPSAdminRules@wisconsin.gov

Approved for publication:

Authorized Signature

Date Submitted

Approved for implementation:

Authorized Signature

Date Submitted

STATEMENT OF SCOPE

CONTROLLED SUBSTANCES BOARD

Rule No.: CSB 4

Relating to: National Provider Identifier Requirement

Rule Type: Permanent

1. Finding/nature of emergency (Emergency Rule only):

N/A

2. Detailed description of the objective of the proposed rule:

The objective of the proposed rule is to amend CSB 4 to reflect that there will be updates made to the Prescription Drug Monitoring Program relating to requiring a National Provider Identifier to be reported for prescriber accounts and on dispensing records.

3. Description of the existing policies relevant to the rule, new policies proposed to be included in the rule, and an analysis of policy alternatives:

Wisconsin Administrative Code Chapter CSB 4 currently outlines requirements for what is to be recorded in the Prescription Drug Monitoring Program. These requirements do not currently include the provision of a National Provider Identifier. By requiring this information, the program will be able to accurately monitor non-controlled substances that the Controlled Substances Board has deemed necessary to track, such as Gabapentin. Without making this change, the program will continue to operate without the ability to accurately monitor non-controlled substances.

4. Detailed explanation of statutory authority for the rule (including the statutory citation and language):

961.385 (2) (b) states that the board shall establish by rule and have the prescription drug monitoring program “Identify specific data elements to be contained in a record documenting the dispensing of a monitored prescription drug, including the method of payment and, subject to sub. (2m), the name recorded under s. 450.44 (1b) (bm). In identifying specific data elements, the board shall consider data elements identified by similar programs in other states and shall ensure, to the extent possible, that records generated by the program are easily shared with other states.”

5. Estimate of amount of time that state employees will spend developing the rule and of other resources necessary to develop the rule:

60 hours

6. List with description of all entities that may be affected by the proposed rule:

Pharmacies, pharmacists, prescribers, and law enforcement.

7. Summary and preliminary comparison with any existing or proposed federal regulation that is intended to address the activities to be regulated by the proposed rule:

None.

8. Anticipated economic impact of implementing the rule (note if the rule is likely to have a significant economic impact on small businesses):

None to minimal. It is not likely to have a significant economic impact on small businesses.

Contact Person: Nilajah Hardin, (608) 267-7139, DSPSAdminRules@wisconsin.gov

Approved for publication:

Authorized Signature

Date Submitted

Approved for implementation:

Authorized Signature

Date Submitted

Controlled Substances Board
Rule Projects (updated 08/26/22)

CH Rule Number	Scope Number	Scope Expiration Date	Code Chapter Affected	Relating Clause	Stage of Rule Process	Next Step
22-011	070-21	02/29/2024	CSB 2.78	Scheduling Crotonyl Fentanyl	Submitted to the Legislature on 04/14/2022	Legislative Review After 01/03/2023
22-014	071-21	02/29/2024	CSB 2.79	Scheduling Remimazolam	Submitted to the Legislature on 04/14/2022	Legislative Review After 01/03/2023
21-098	061-21	12/28/2023	CSB 2.80	Scheduling Oliceridine	Rule Effective on 09/01/22	N/A
22-016	072-21	02/29/2024	CSB 2.81	Scheduling Brorphine	Submitted to the Legislature on 04/14/2022	Legislative Review After 01/03/2023
22-032	088-21	04/18/2024	CSB 2.82	Scheduling Serdexmethylphenidate	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-033	089-21	04/18/2024	CSB 2.83	Scheduling 10 Fentanyl Related Substances	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-034	090-21	04/18/2024	CSB 2.84	Scheduling Alfaxalone	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-035	091-21	04/18/2024	CSB 2.85	Excluding 6-beta-Naltrexol	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-036	092-21	04/18/2024	CSB 2.86	Scheduling Fospropofol	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-037	093-21	04/18/2024	CSB 2.87	Scheduling Embutramide	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-039	094-21	04/18/2024	CSB 2.88	Scheduling Lacosamide	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-038	095-21	04/18/2024	CSB 2.89	Scheduling Perampanel	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023

Controlled Substances Board
Rule Projects (updated 08/26/22)

CH Rule Number	Scope Number	Scope Expiration Date	Code Chapter Affected	Relating Clause	Stage of Rule Process	Next Step
22-040	096-21	04/18/2024	CSB 2.90	Transferring 1-phenylcyclohexylamine and 1-piperidinocyclohexanecarbonitrile, Immediate Precursors to Phencyclidine, Also Known as PCP	Submitted to the Legislature on 08/18/2022	Legislative Review After 01/03/2023
22-054	015-22	08/28/2024	CSB 2.91	Scheduling 4,4'-Dimethylaminorex	Board Review of Final Rule Draft and Legislative Report at 09/09/22 Meeting	Board Review of Final Rule Draft and Legislative Report at 09/09/22 Meeting
Not Assigned Yet	Not Assigned Yet	Not Assigned Yet	CSB 2.92	Scheduling 38 Anabolic Steroids	Scope Statement Submitted for Board Review at 09/09/22 Meeting	Board Approval and Submission to the Governor's Office and for Publication
Not Assigned Yet	Not Assigned Yet	Not Assigned Yet	CSB 2.93	Scheduling Daridorexant	Scope Statement Submitted for Board Review at 09/09/22 Meeting	Board Approval and Submission to the Governor's Office and for Publication
Not Assigned Yet	Not Assigned Yet	Not Assigned Yet	CSB 2.94	Scheduling 7 Synthetic Benzimidazole-Opioids	Scope Statement Submitted for Board Review at 09/09/22 Meeting	Board Approval and Submission to the Governor's Office and for Publication
Not Assigned Yet	Not Assigned Yet	Not Assigned Yet	CSB 2.95	Scheduling Ganaxolone	Scope Statement Submitted for Board Review at 09/09/22 Meeting	Board Approval and Submission to the Governor's Office and for Publication
Not Assigned Yet	Not Assigned Yet	Not Assigned Yet	CSB 4	National Provider Identifier Requirement	Scope Statement Submitted for Board Review at 09/09/22 Meeting	Board Approval and Submission to the Governor's Office and for Publication

State of Wisconsin
Department of Safety & Professional Services

AGENDA REQUEST FORM

1) Name and title of person submitting the request:	2) Date when request submitted:
Marjorie Liu **Program Lead, PDMP**	8/29/2022 Items will be considered late if submitted after 12:00 p.m. on the deadline date which is 8 business days before the meeting

3) Name of Board, Committee, Council, Sections:

Controlled Substances Board

4) Meeting Date:	5) Attachments:	6) How should the item be titled on the agenda page?
9/9/2022	☒ Yes ☐ No	Prescription Drug Monitoring Program (PDMP) Updates – Discussion and Consideration

7) Place Item in:	8) Is an appearance before the Board being scheduled? *(If yes, please complete **Appearance Request** for Non-DSPS Staff)*	9) Name of Case Advisor(s), if required:
☒ Open Session ☐ Closed Session	☐ Yes ☒ No	

10) Describe the issue and action that should be addressed:

1. WI ePDMP Operations
    a. Recent and Upcoming Releases
    b. Status of Grant Projects:
        i. FY 2020 Harold Rogers Prescription Drug Monitoring Program
        ii. FY 2021 Harold Rogers Prescription Drug Monitoring Program
    c. Interstate Data Sharing
    d. EHR Integration Status
2. WI ePDMP Outreach

11) Authorization

Marjorie Liu — 08/29/2022

Signature of person making this request — Date

Supervisor (if required) — Date

Executive Director signature (indicates approval to add post agenda deadline item to agenda) — Date

Directions for including supporting documents:
1. This form should be attached to any documents submitted to the agenda.
2. Post Agenda Deadline items must be authorized by a Supervisor and the Policy Development Executive Director.
3. If necessary, provide original documents needing Board Chairperson signature to the Bureau Assistant prior to the start of a meeting.

2020-2022 Development and Release Summary

Updated 08.25.2022

Release Date	Description
Pending	
Harold Rogers Grant 2020 Component 3 Release date TBD	Ability for users to change the order in which the sections of the patient report are presented. Adding a Buprenorphine Naïve Alert section to the patient report.
Harold Rogers Grant 2020 Component 2 Release date TBD	Infrastructure and Technology stack changes to improve performance in the following areas: • Patient Matching • Dispensing Matching • Reporting Statistics
Completed	
R28 July 2022	Adding language related to Buprenorphine Alert Override Maintenance Updates
Harold Rogers Grant 2021 Promotional Materials May 2022	Promotional Materials for free EHR Integrations Maintenance Updates
R26 April 2022	Buprenorphine Alert Override • Ability to override prescriber facing alerts, metrics, and MME calculations for certain drugs. Maintenance Updates RxCheck 3.0 Upgrades
Harold Rogers Grant 2020 Component 1 December 2021	Security Enhancements • Two-Factor Authentication • Compromised Email Address Check Patient Report and other User Experience Updates
R25 November 2021	Maintenance Updates • Adjustments to triggering Annual Terms and Conditions prompt • Enhanced EHR Integration Testing capabilities Chatbot display changes
R24 August 2021	Text Updates • Gabapentin related text changes to the Submitter Error Email. Security-Related Enhancements

R23 **July 2021**	Text Updates • Gabapentin related text changes to the Submitter Error Email.
R22 **July 2021**	Pharmacy-Related Enhancements • Missing DEA Number Error Process Updates Administrative-Related Enhancements
R21 **May 2021**	New Design Enhancements • Proactive MC/HCP linkage renewals • Search enhancements Administrative-Related Enhancements Additional administrator tools
R20 **March 2021**	WI DOJ-Medical College of Wisconsin DataShare Project • Automatically send data extracts to DOJ-MCW • Automatically receive data extracts from DOJ-MCW Administrative-Related Enhancements • Additional improvements to query process • Additional administrator tools
R19 **September 2020**	New Design Enhancements • Enhanced MME calculation process • Ability to set map display defaults Administrative-Related Enhancements • Improvements to query approval process Search Engine Optimization Updates to non-user facing parts of the PDMP to optimize search engine results
R18 **July 2020**	New Design Enhancements • Updated layout and design of Patient Report including alerts and dispensing details, based on user feedback • Opioid naïve alert Additional EHR Enhancements • Multi-state default settings Prescriber Metrics Notifications Proactive notice to prescribers to review metrics, based on time and/or prescribing thresholds
R17.1 **April 2020**	Pharmacy-Related Enhancements • Display of Date Sold, if provided in the submission • ASAP file processing improvements

R17 **March 2020**	Pharmacy-Related Enhancements • Improvements to workflow for error corrections/void • Display of Date Sold, if provided in the submission New Design Enhancements • Better access to history of recent Patient Reports for Delegates • Additional data element on overdose alerts entered by law enforcement to capture administration of Naloxone • MME calculator Additional EHR Enhancements • Expanded patient search from within EHR • Expanded navigation from within EHR

Interstate Data Sharing

RxCheck/EHR	PMPi
In Progress	
ME*	
Connected	
IL, MD, NE, PA, UT, WA,	AZ, CO, DE, FL, HI, IA, ID, IN, MI, MN, MT, NC, ND, NM, NV, NY, PR, SC, SD, TN, WV, Military Health System
*Moving from PMPi to RxCheck	

WI ePDMP Integration Services Summary

Current as of 08.25.2022

Pending Health Systems and EHR Platforms
Advent Health (In Discussion/Contracting)
Marshfield EHR System Change (In Discussion/Contracting)
Wisconsin Statewide Health Information Network (Converting to New Platform)
Bluestone Physician Services (In Discussion/Contracting)
Connected Health Systems (approx. 57% of monthly patient queries)
Ascension Wisconsin
Aspirus Health Care
Aurora Health Care
Children's Hospital of Wisconsin
Clean Slate
DrFirst **Alay Health Team, Door County Memorial Hospital,** Fort Healthcare, Heartland Hospice, **Lake Superior Community Health Center,** Lifestance Health WI, Marshfield Clinic Health System, Oak Medical, Watertown Rainbow Hospice, Regional Medical Center, Rogers Memorial Hospital, Wauwatosa Children's Clinic
Froedtert & the Medical College of Wisconsin
GHC of South Central Wisconsin
Gundersen Health System

HealthPartners
HSHS / Prevea Health
M Health Fairview
Marshfield Clinic
Mayo Clinic
Mercy Health
Monroe Clinic
NOVO Health Technology Group
ProHealth Care
SSM Health
Thedacare
UnityPoint
UW Health
Wisconsin Statewide Health Information Network

2022 WI PDMP Outreach Calendar

MONTH	EVENT	DESCRIPTION	DATES	NOTES
January	Overdose Fatality Review (OFR) State Advisory Group	DSPS Representative; inter-agency advisory board for OFR participating local sites	1/13/2022	Quarterly meeting
February				
March				
April	DOJ Law Enforcement (LE) Bulletin	Updated FAQ for LE alert reporting	WILENET April Issue	
	Overdose Fatality Review (OFR) State Advisory Group	DSPS Representative; inter-agency advisory board for OFR participating local sites	4/14/2022	Quarterly meeting
	Rx Drug Abuse & Heroin Summit	Participant; national conference led by multidisciplinary experts for stakeholders addressing the opioid crisis	4/18-4/21/2022	Atlanta, GA
May	RxCheck Governance Board Bi-Annual Meeting	Participant; bi-annual meeting for state PDMP administrators	5/12/2022	Virtual
June	Waukesha County Heroin Taskforce Community Partners Meeting	PDMP presentation and discussion	6/14/2022	Virtual
July	Overdose Fatality Review (OFR) State Advisory Group	DSPS Representative; inter-agency advisory board for OFR participating local sites	7/14/2022	Quarterly meeting
August	RxCheck Governance Board North & West Region Meeting	Participant; regional meeting for PDMP administrators Organized by PDMP Training and Technical Assistance Center	8/9-8/10/2022	Hybrid
September				
October	PMPi Steering Committee Annual Meeting	Participant; annual meeting for PDMP administrators organized by National Association of Boards of Pharmacy	10/4-10/5/2022 (Rescheduled)	Mount Prospect, IL
	Overdose Fatality Review (OFR) State Advisory Group	DSPS Representative; inter-agency advisory board for OFR participating local sites	10/13/2022	Quarterly meeting
	RxCheck Governance Board Bi-Annual Meeting	Participant; bi-annual meeting for state PDMP administrators	TBD	In-person
November				
December	RxCheck Governance Board Annual Meeting	Participant; Annual meeting for state PDMP administrators	12/7-12/9/2022	Washington, DC