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Tony Evers, Governor
Dan Hereth, Secretary

VIRTUAL/TELECONFERENCE
BOARD OF NURSING
Virtual, 4822 Madison Yards Way, Madison
Contact: Brad Wojciechowski (608) 266-2112
September 8, 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 record of the actions of the Board.

AGENDA

8:00 A.M.

OPEN SESSION – CALL TO ORDER – ROLL CALL

A. Adoption of Agenda (1-5)

B. Approval of Minutes of August 11, 2022 (6-19)

C. Reminders: Conflicts of Interests, Scheduling Concerns

D. Introductions, Announcements and Recognition – Discussion and Consideration
1) Introduction: John Anderson, Public Member (Succeeds: Hinkfuss)

E. Administrative Matters – Discussion and Consideration
1) Department, Staff and Board Updates
2) Board Members – Term Expiration Dates
   a. Edelstein, Janice A. – 7/1/2024
   b. Guyton, Vera L. – 7/1/2025
   c. McFarland, Rosalyn L. – 7/1/2026
   d. Saldivar Frias, Christian – 7/1/2023
   e. Scott, Linda D. – 7/1/2023
   f. Weinman, Robert W. – 7/1/2023
   g. Zentz, Emily – 7/1/2023

F. Education and Examination Matters – Discussion and Consideration

G. Board of Nursing Report on Opioid Abuse – Discussion and Consideration (20-22)

H. Report of the Quarterly Chair Connection – Discussion and Consideration

I. Legislative and Policy Matters – Discussion and Consideration
1) 2021 Wisconsin Act 158, Relating to Practice of Certain Skilled Health Services by Military Medical Personnel and Granting Rule Making Authority

J. Administrative Rule Matters – Discussion and Consideration (23)

1) Scope Statement: N 2, Relating to Board Approval to Take the NCLEX **(24-25)**
2) Pending and Possible Rulemaking Projects **(26-27)**

K. Credentialing Matters – Discussion and Consideration

1) Credentialing Statistics and License Counts **(28-31)**

L. Newsletter Matters – Discussion and Consideration (32)

M. Speaking Engagements, Travel, Public Relation Requests, and Reports – Discussion and Consideration

1) Travel Report: Conference Travel: NCSBN Annual Meeting – August 17-19, 2022 – Chicago, IL
2) NCLEX Item Review Subcommittee – September 14-16, 2022

N. Legislature Agenda Request: Status of Kratom – Discussion and Consideration (33-161)

O. COVID-19 – Discussion and Consideration

P. Nurse Licensure Compact (NLC) Update – Discussion and Consideration

Q. Board of Nursing Liaison Reports – Discussion and Consideration

R. Discussion and Consideration of Items Added After Preparation of Agenda:

1) Introductions, Announcements and Recognition
2) Administrative Matters
3) Election of Officers
4) Appointment of Liaisons and Alternates
5) Delegation of Authorities
6) Education and Examination Matters
7) Credentialing Matters
8) Practice Matters
9) Legislative and Policy Matters
10) Administrative Rule Matters
11) Liaison Reports
12) Board Liaison Training and Appointment of Mentors
13) Informational Items
14) Division of Legal Services and Compliance (DLSC) Matters
15) Presentations of Petitions for Summary Suspension
16) Petitions for Designation of Hearing Examiner
17) Presentation of Stipulations, Final Decisions and Orders
18) Presentation of Proposed Final Decisions and Orders
19) Presentation of Interim Orders
20) Petitions for Re-Hearing
21) Petitions for Assessments
22) Petitions to Vacate Orders
23) Requests for Disciplinary Proceeding Presentations
24) Motions
25) Petitions
26) Appearances from Requests Received or Renewed
27) Speaking Engagements, Travel, Public Relation Requests, and Reports

S. 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 closing disciplinary investigations with administrative warnings (ss. 19.85(1)(b), and 440.205, 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.).

T. Deliberation on Division of Legal Services and Compliance Matters

1) **Case Closings**
   a. 21 NUR 122 – V.A.P. **(162-171)**
   b. 21 NUR 287, 21 NUR 415 – A.R.P. **(172-182)**
   c. 21 NUR 401 – J.S.K. **(183-187)**
   d. 21 NUR 445 – T.C.H., C.M.O., A.L.B., S.A.L., L.A.W., A.R.S., C.A.K. **(188-196)**
   e. 21 NUR 609 – J.L.L. **(197-202)**
   f. 21 NUR 658 – M.L.M. **(203-220)**
   g. 21 NUR 668 – R.S. **(221-229)**
   h. 21 NUR 731 – C.L.M. **(230-235)**
   i. 22 NUR 147 – J.A.M. **(236-242)**
   j. 22 NUR 320 – L.S.R. **(243-247)**
   k. 22 NUR 374 – E.C.P. **(248-251)**
   l. 22 NUR 377 – Y.L. **(252-256)**
   m. 22 NUR 425 – P.A.Z. **(257-262)**

2) **Proposed Stipulations, Final Decisions, and Orders**
   a. 21 NUR 252 – Marchellie C. Sheldon, R.N. **(263-268)**
   b. 21 NUR 494, 21 NUR 625 – Carrie E. Boerema, L.P.N. **(269-275)**
   c. 21 NUR 590 – Angela D. Ramos, R.N. **(276-288)**
   d. 21 NUR 623 – Ian F. Conradt, R.N. **(289-295)**
   e. 21 NUR 656 – Lindsay L. Felda, R.N. **(296-303)**
   f. 21 NUR 724 – Amy M. Leffler, R.N. **(304-315)**
   g. 21 NUR 727 – Sherri L. Konzal, R.N. **(316-323)**
   h. 22 NUR 105 – Terry R. Dulle, R.N. **(324-330)**
   i. 22 NUR 132 – Lisa K. O'Farrell, R.N. **(331-342)**
   j. 22 NUR 166 – Cindy M. Park, R.N. **(343-348)**
   k. 22 NUR 209 – Rachel M. Kansier, L.P.N., R.N. **(349-354)**
   l. 22 NUR 264 – Ariel M. Pierringer, R.N. **(355-362)**
   m. 22 NUR 286 – Kelly K. Passo-Fasel, R.N. **(363-369)**

3) **Proposed Stipulations and Interim Orders**
   a. 20 NUR 003, 22 NUR 417, 22 NUR 504 – Alyssa M. Gates, R.N. **(370-374)**

4) **Monitoring Matters (375-376)**
   a. **Monitor Heller**
      1. Carrie Buhr, R.N. – Requesting Full Licensure **(377-390)**
      2. Michelle Chadwick, L.P.N. – Requesting Full Licensure and/or Reduction in Drug Screens **(391-404)**

3. Katie Fischer, R.N. – Requesting Termination of C.8., Termination of Work Setting Restrictions, Access to Controlled Substances with Direct Supervisor and/or Termination of Drug Screens or Reduction in Drug Screens or Treater Drug Testing in Lieu of the Approved Program **(405-430)**
4. Cheire Jess, R.N. - Requesting Full Licensure **(431-477)**
5. Amy Nelson, R.N. – Requesting Monitoring Duties to MN-HPSP Program **(478-528)**
6. Karla Price, L.P.N. - Requesting Full Licensure and/or Reduction in Drug Screens **(529-542)**
7. Jason Schuckert, R.N. – Requesting Reduction in Drug Screens **(543-556)**
8. Ashleigh A. Suhajda, R.N. - Requesting Full Licensure **(557-576)**

b. **Monitor Kane**

1. Andrea K. Olson, R.N. – Requesting a Reduction in Drug Test Frequency, Change from Direct to General Supervision, and/or a Reduction in AA/NA Meetings from 2x Per Week to 1x Per Week **(577-601)**
2. Clayton Reimer, R.N. – Requesting a Reduction in Drug Test Frequency from 36 Per Year to 28 Per Year and/or Reduction of AA/NA Meetings from 2x Per Week to 1x Per Week **(602-262)**

c. **Monitor Schramm**

1. Terry Hensel, R.N. – Requesting Full Licensure **(627-661)**
2. Leah Morgan, R.N. – Requesting a Reduction in Drug Test Frequency, Change from Direct to Indirect (General) Supervision, and/or Access to Controlled Substances **(662-687)**
3. Allyson Rossi, R.N. – Requesting Access to Controlled Substances, Decrease in AODA Treatment from Twice Per Month to Oncer Per Quarter, and/or a Reduction in Drug Test Frequency **(688-723)**

U. Deliberation on Proposed Final Decision and Orders

1) Clifton W. Davison, R.N., Respondent – DHA Case Number SPS-22-0028/DLSC Case Number 19 NUR 504 **(724-734)**

V. Deliberation of Items Added After Preparation of the Agenda

1) Education and Examination Matters
2) Credentialing Matters
3) DLSC Matters
4) Monitoring Matters
5) Professional Assistance Procedure (PAP) Matters
6) Petitions for Summary Suspensions
7) Petitions for Designation of Hearing Examiner
8) Proposed Stipulations, Final Decisions and Order
9) Proposed Interim Orders
10) Administrative Warnings
11) Review of Administrative Warnings
12) Proposed Final Decisions and Orders
13) Matters Relating to Costs/Orders Fixing Costs
14) Case Closings

15) Board Liaison Training
16) Petitions for Assessments and Evaluations
17) Petitions to Vacate Orders
18) Remedial Education Cases
19) Motions
20) Petitions for Re-Hearing
21) Appearances from Requests Received or Renewed

W. Consulting with Legal Counsel

1) **Report of Cases Delegated to Chief Legal Counsel (735)**
   a. **Interim Orders**
      1. 22 NUR 022 – Nicole M. Riesterer, R.N. **(736-740)**
      2. 22 NUR 058, 22 NUR 059 – Kandise L. Sporer, R.N. **(741-744)**
      3. 22 NUR 242 – Ashely M. Dietrich, R.N. **(745-748)**
   b. **Proposed Final Decisions and Orders**
      1. 21 NUR 253 – Brian D. Borowski, R.N. **(749-758)**
2) Planned Parenthood of Wisconsin, Inc. v. Wisconsin Board of Nursing, Et Al; USDC, Western District of Wisconsin

RECONVENE TO OPEN SESSION IMMEDIATELY FOLLOWING CLOSED SESSION

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

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

Z. Board Meeting Process (Time Allocation, Agenda Items) – Discussion and Consideration

AA. Board Strategic Planning and its Mission, Vision and Values – Discussion and Consideration

ADJOURNMENT

NEXT MEETING: OCTOBER 13, 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
BOARD OF NURSING
MEETING MINUTES
AUGUST 11, 2022

PRESENT: Janice Edelstein, Vera Guyton *(excused at 11:28 a.m., reconnected at 12:37 p.m.),* Rosalyn McFarland, Linda Scott, Robert Weinman *(arrived at 8:26 a.m.),* Emily Zentz *(disconnected at 12:25 p.m., reconnected at 12:43 p.m.)*

EXCUSED: Christian Saldivar Frias

STAFF: Brad Wojciechowski, Executive Director; Jameson Whitney, Legal Counsel; Sofia Anderson, Administrative Rules Coordinator; Katlin Schwartz, Bureau Assistant; Kimberly Wood, Program Assistant Supervisor-Adv.; and other Department Staff

CALL TO ORDER

Janice Edelstein, Secretary, called the meeting to order at 8:13 a.m. A quorum was confirmed with five (5) members present.

ADOPTION OF THE AGENDA

MOTION: Linda Scott moved, seconded by Rosalyn McFarland, to adopt the Agenda as published. Motion carried unanimously.

APPROVAL OF MINUTES

Approval of Minutes of June 9, 2022

MOTION: Emily Zentz moved, seconded by Linda Scott, to approve the Minutes of June 9, 2022 as published. Motion carried unanimously.

Approval of Minutes of July 25, 2022

MOTION: Linda Scott moved, seconded by Vera Guyton, to approve the Minutes of July 25, 2022 as published. Motion carried unanimously.

(Robert Weinman arrived at 8:26 a.m.)

APPEARANCE: SECRETARY DAN HERETH, STATEMENTS OF GRADUATION

MOTION: Rosalyn McFarland moved, seconded by Robert Weinman, to acknowledge and thank Dan Hereth, Secretary-Department of Safety and Professional Services, for his appearance and presentation to the Board. Motion carried unanimously.

MOTION: Rosalyn McFarland moved, seconded by Vera Guyton, to designate Rosalyn McFarland to work with Department staff to analyze and implement policies and make recommendations to improve the Nursing application process. Motion carried unanimously.

ADMINISTRATIVE MATTERS

Election of Officers

Vice Chairperson

NOMINATION: Robert Weinman nominated Emily Zentz for the Office of Vice Chairperson. Emily Zentz accepted the nomination.

Brad Wojciechowski, Executive Director, called for nominations three (3) times.

Emily Zentz was elected as Vice Chairperson by unanimous voice vote.

ELECTION RESULTS	
Chairperson	Robert Weinman
Vice Chairperson	Emily Zentz
Secretary	Janice Edelstein

Review of Liaison Appointments

LIAISON APPOINTMENTS	
Credentialing	Rosalyn McFarland *Alternate:* Vera Guyton
Newsletter Liaison	Janice Edelstein
Board Education Liaison	Linda Scott *Alternate:* Janice Edelstein
Controlled Substances Board as per Wis. Stats. §15.405(5g)	Robert Weinman *Alternate:* Rosalyn McFarland (Primary), Emily Zentz (Secondary)
Wisconsin Coalition for Prescription Drug Abuse Reduction	Rosalyn McFarland

Travel Authorization Liaison	Robert Weinman (Chair) *Alternate:* Emily Zentz (Vice Chair)
COMMITTEE MEMBER APPOINTMENTS	
Legislation and Rules Committee	Rosalyn McFarland, Janice Edelstein, Robert Weinman (Chair)

SCREENING PANEL APPOINTMENTS	
Alternates	Robert Weinman

ADMINISTRATIVE RULE MATTERS

Pending and Possible Rulemaking Projects

Discussion Possible Rule Project: N1 and N2, Relating to Approval of Out of State Schools

MOTION: Janice Edelstein moved, seconded by Linda Scott, to request that the Department draft a scope as requested by Secretary Dan Hereth to revise the requirement in Wis. Admin. Code N 2 regarding Board approval for students to take the NCLEX. Motion carried unanimously.

DIVISION OF LEGAL SERVICES AND COMPLIANCE (DLSC) MATTERS

Work Settings for Nurses on Stipulations

MOTION: Janice Edelstein moved, seconded by Robert Weinman, to request that the Division of Legal Services and Compliance modify their order template to include board or board designee approval for work positions in addition to work settings in a standard five-year impairment. Motion carried unanimously.

MOTION: Emily Zentz moved, seconded by Robert Weinman, to acknowledge and thank Gretchen Mrozinski for her appearance before the Board. Motion carried unanimously.

CLOSED SESSION

MOTION: Rosalyn McFarland moved, seconded by Linda Scott, to 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 closing disciplinary investigation with administrative warnings (ss. 19.85(1)(b), Stats. and 440.205, 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.). Robert Weinman, Chairperson, read the language of the motion. The vote of each member was ascertained by voice vote. Roll Call Vote: Janice Edelstein-yes; Vera Guyton-yes; Rosalyn McFarland-yes; Linda Scott-yes; Robert Weinman-yes; and Emily Zentz-yes. Motion carried unanimously.

The Board convened into Closed Session at 9:53 a.m.

REVIEW OF ADMINISTRATIVE WARNING

MOTION: Robert Weinman moved, seconded by Linda Scott, to affirm the issuance of the administrative warning in the matter of C.V.K, DLSC Case Number 21 NUR 556. Motion carried unanimously.

DIVISION OF LEGAL SERVICES AND COMPLIANCE MATTERS

Proposed Stipulations and Final Decisions and Orders

MOTION: Robert Weinman moved, seconded by Janice Edelstein, to adopt the Findings of Fact, Conclusions of Law and Order in the matter of disciplinary proceedings of the following cases:

1. 20 NUR 061 – Lori Cluck, L.P.N.
2. 20 NUR 174 – Paige J. O'Connor, R.N.
3. 20 NUR 295 – Abigail J. Miller, R.N.
4. 20 NUR 329 – Theresa A. Minikel, L.P.N.
5. 20 NUR 616, 21 NUR 342 – Sasha L. Leikip, R.N.
6. 21 NUR 002 – Francisco J. Solis, R.N.
7. 21 NUR 103 – Diane F. White, R.N.
8. 21 NUR 141 – Susan E. Barbee, L.P.N.
9. 21 NUR 154 – Kim M. Johnson, R.N.
10. 21 NUR 308 – Ashley R. Tobin, R.N.
11. 21 NUR 383 – Christie E. Sims, R.N.
12. 21 NUR 393 – Devon W. Deloy, R.N.
13. 21 NUR 412 – Kimberly A. Wing, R.N.
14. 21 NUR 588 – Kathryn H. Hazell, R.N.
15. 21 NUR 668 – Rebecca L. Schmidt, R.N.
16. 21 NUR 696, 22 NUR 150 – Julie A. Kaczor, R.N.
17. 21 NUR 791 – Stephanie A. Annala-Hakes, R.N.
18. 21 NUR 809, 22 NUR 172 – Amelia K. Fay, R.N.

19. 21 NUR 811 – Nicole L. Luke, R.N.
20. 21 NUR 825 – Rose E. Solem, R.N.
21. 22 NUR 013 – Nichole E. Madison, L.P.N.
22. 22 NUR 027 – David W. Erickson, R.N., A.P.N.P.
23. 22 NUR 046 – Amanda L. Ocacio, L.P.N.
24. 22 NUR 113 – Susan E. Ziebert, L.P.N.
25. 22 NUR 122 – Kristina C. Turner, R.N.
26. 22 NUR 130 – April R. Simmons, R.N.
27. 22 NUR 175 – Angela K. Pettis, R.N.
28. 22 NUR 206 – Pamela J. Masteller, L.P.N.
29. 22 NUR 240 – Jason J. Diaz, R.N.
30. 22 NUR 303 – Kurtis Stoddard, R.N.
31. 22 NUR 400 – April I. Smith, L.P.N., R.N.

Motion carried unanimously.

Proposed Stipulations and Interim Orders

22 NUR 022 – Nicole M. Riesterer, R.N.

MOTION: Linda Scott moved, seconded by Janice Edelstein, to delegate to DSPS Chief Legal Counsel the Board's authority to preside over and resolve the matter of the Interim Order against Nicole M. Riesterer, R.N., DLSC Case Number 22 NUR 022. Motion carried unanimously.

(Robert Weinman recused himself and left the room for deliberation and voting in the matter concerning Nicole M. Riesterer, R.N., DLSC Case Number 22 NUR 022. Emily Zentz, Vice Chairperson presided for the duration of the Chairperson's recusal.)

22 NUR 242 – Ashley M. Dietrich, R.N.

MOTION: Rosalyn McFarland moved, seconded by Vera Guyton, to delegate to DSPS Chief Legal Counsel the Board's authority to preside over and resolve the matter of the Interim Order against Ashley M. Dietrich, R.N., DLSC Case Number 22 NUR 242. Motion carried unanimously.

(Robert Weinman recused himself and left the room for deliberation and voting in the matter concerning Ashley M. Dietrich, R.N., DLSC Case Number 22 NUR 242. Emily Zentz, Vice Chairperson presided for the duration of the Chairperson's recusal.)

DELIBERATION ON PROPOSED FINAL DECISIONS AND ORDERS

Brian D. Borowski, R.N., Respondent – DHA Case Number SPS-22-0017/DLSC Case Number 21 NUR 253

MOTION: Emily Zentz moved, seconded by Rosalyn McFarland, to delegate to DSPS Chief Legal Counsel the Board's authority to preside over and resolve the matter of disciplinary proceedings against Brian D. Borowski, R.N., Respondent – DHA Case Number SPS-22-0017/DLSC Case Number 21 NUR 253. Motion carried unanimously.

(Janice Edelstein recused herself and left the room for deliberation and voting in the matter concerning Brian D. Borowski, R.N., Respondent – DHA Case Number SPS-22-0017/DLSC Case Number 21 NUR 253.)

DELIBERATION ON MATTERS RELATING TO COSTS/ORDERS FIXING COSTS

Ernest W. Colburn, R.N., Respondent – DHA Case Number SPS-21-0052/DLSC Case Number 19 NUR 525

MOTION: Linda Scott moved, seconded by Rosalyn McFarland, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Ernest W. Colburn, R.N., Respondent – DHA Case Number SPS-21-0052/DLSC Case Number 19 NUR 525. Motion carried unanimously.

(Janice Edelstein recused herself and left the room for deliberation and voting in the matter concerning Ernest W. Colburn, R.N., Respondent – DHA Case Number SPS-21-0052/DLSC Case Number 19 NUR 525.)

Leora R. Taylor-Sanderson, R.N., A.P.N.P., Respondent – DHA Case Number SPS-21-0072/DLSC Case Number 21 NUR 173

MOTION: Vera Guyton moved, seconded by Robert Weinman, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Leora R. Taylor-Sanderson, R.N., Respondent – DHA Case Number SPS-21-0072/DLSC Case Number 21 NUR 173. Motion carried unanimously.

(Janice Edelstein recused herself and left the room for deliberation and voting in the matter concerning Leora R. Taylor-Sanderson, R.N., Respondent – DHA Case Number SPS-21-0072/DLSC Case Number 21 NUR 173.)

Francie A. Heaser, R.N., Respondent – DHA Case Number SPS-21-0084/DLSC Case Number 21 NUR 182

MOTION: Vera Guyton moved, seconded by Emily Zentz, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Francie A. Heaser, R.N., Respondent – DHA Case Number SPS-21-0084/DLSC Case Number 21 NUR 182. Motion carried unanimously.

(Linda Scott recused herself and left the room for deliberation and voting in the matter concerning Francie A. Heaser, R.N., Respondent – DHA Case Number SPS-21-0084/DLSC Case Number 21 NUR 182.)

Amanda G. Dryer, R.N., Respondent – DHA Case Number SPS-21-0078/DLSC Case Number 21 NUR 194

MOTION: Janice Edelstein moved, seconded by Linda Scott, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Amanda G. Dryer, R.N., Respondent – DHA Case Number SPS-21-0078/DLSC Case Number 21 NUR 194. Motion carried unanimously.

(Emily Zentz recused herself and left the room for deliberation and voting in the matter concerning Amanda G. Dryer, R.N., Respondent – DHA Case Number SPS-21-0078/DLSC Case Number 21 NUR 194.)

Tiffany Gimenez, L.P.N., Respondent – DHA Case Number SPS-21-0056/DLSC Case Number 20 NUR 529

MOTION: Vera Guyton moved, seconded by Robert Weinman, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Tiffany Gimenez, L.P.N., Respondent – DHA Case Number SPS-21-0056/DLSC Case Number 20 NUR 529. Motion carried unanimously.

(Emily Zentz recused herself and left the room for deliberation and voting in the matter concerning Tiffany Gimenez, L.P.N., Respondent – DHA Case Number SPS-21-0056/DLSC Case Number 20 NUR 529.)

Melanie J. Hunter, R.N., Respondent – DHA Case Number SPS-21-0059/DLSC Case Number 19 NUR 215

MOTION: Rosalyn McFarland moved, seconded by Janice Edelstein, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Melanie J. Hunter, R.N., Respondent – DHA Case Number SPS-21-0059/DLSC Case Number 19 NUR 215. Motion carried unanimously.

(Emily Zentz recused herself and left the room for deliberation and voting in the matter concerning Melanie J. Hunter, R.N., Respondent – DHA Case Number SPS-21-0059/DLSC Case Number 19 NUR 215.)

Andrea L. Wilke, R.N., Respondent – DHA Case Number SPS-21-0058/DLSC Case Number 20 NUR 096

MOTION: Vera Guyton moved, seconded by Linda Scott, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Andrea L. Wilke, R.N., Respondent – DHA Case Number SPS-21-0058/DLSC Case Number 20 NUR 096. Motion carried unanimously.

(Emily Zentz recused herself and left the room for deliberation and voting in the matter concerning Andrea L. Wilke, R.N., Respondent – DHA Case Number SPS-21-0058/DLSC Case Number 20 NUR 096.)

Allison G. Krawza, R.N., Respondent – DHA Case Number SPS-21-0063/DLSC Case Number 21 NUR 189

MOTION: Janice Edelstein moved, seconded by Vera Guyton, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Allison G. Krawza, R.N., Respondent – DHA Case Number SPS-21-0063/DLSC Case Number 21 NUR 189. Motion carried unanimously.

Alicia R. Krisher-Behm, R.N., Respondent – DHA Case Number SPS-20-0020/DLSC Case Number 18 NUR 076

MOTION: Linda Scott moved, seconded by Emily Zentz, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Alicia R. Krisher-Behm, R.N., Respondent – DHA Case Number SPS-20-0020/DLSC Case Number 18 NUR 076. Motion carried unanimously.

Glenda S. Walstrom, L.P.N., Respondent – DHA Case Number SPS-21-0086/DLSC Case Numbers 20 NUR 097, 20 NUR 554, 21 NUR 274

MOTION: Robert Weinman moved, seconded by Vera Guyton, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Glenda S. Walstrom, L.P.N., Respondent – DHA Case Number SPS-21-0086/DLSC Case Numbers 20 NUR 097, 20 NUR 554, 21 NUR 274. Motion carried unanimously.

Crystal A. Zimmerman, R.N., Respondent – DHA Case Number SPS-21-0027/DLSC Case Number 19 NUR 452, 20 NUR 346

MOTION: Emily Zentz moved, seconded by Janice Edelstein, to adopt the Order Fixing Costs in the matter of disciplinary proceedings against Crystal A. Zimmerman, R.N., Respondent – DHA Case Number SPS-21-0027/DLSC Case Number 19 NUR 452, 20 NUR 346. Motion carried unanimously.

CREDENTIALING MATTERS

Application Reviews

Kelly M. Crowder, L.P.N. – Licensed Practical Nurse Renewal Applicant

MOTION: Rosalyn McFarland moved, seconded by Vera Guyton, to issue an intent to deny the Licensed Practical Nurse Renewal application of Kelly M. Crowder, L.P.N., and offer her a limited license with the following conditions: submit order to employer, quarterly work reports, provide proof of attendance at NA/AA Meetings at least once per week for one year. **Reason for Denial**: N7.03 (8) (e) and (6) (e) and (f). Motion carried unanimously.

DIVISION OF LEGAL SERVICES AND COMPLIANCE MATTERS

Administrative Warnings

MOTION: Robert Weinman moved, seconded by Emily Zentz, to issue an Administrative Warning in the following DLSC Cases:

1. 21 NUR 707 – A.M.M.
2. 21 NUR 823 – J.B.C.
3. 22 NUR 040 – L.L.K.
4. 22 NUR 065 – M.E.K.
5. 22 NUR 142 – H.M.J.
6. 22 NUR 356 – H.A.O.
7. 22 NUR 371 – A.A.K.

Motion carried unanimously.

Case Closings

MOTION: Robert Weinman moved, seconded by Emily Zentz, to close the following DLSC Cases for the reasons outlined below:

1. 20 NUR 220 – T.C.G. – Prosecutorial Discretion (P5)
2. 20 NUR 505 – E.H.H. – No Violation
3. 20 NUR 575 – A.G. – Insufficient Evidence
4. 21 NUR 080 – C.L.K. – No Violation
5. 21 NUR 154 – K.S.A. – No Violation
6. 21 NUR 216 – T.S.B., B.A.H. – Prosecutorial Discretion (P1)
7. 21 NUR 247 – L.M.G. – Prosecutorial Discretion (P1)
8. 21 NUR 308 – M.T.S. – Insufficient Evidence
9. 21 NUR 426 – W.D.W. – No Violation
10. 21 NUR 469 – D.D., N.M., M.C. – Insufficient Evidence
11. 21 NUR 508 – C.S.L. – Prosecutorial Discretion (P2)
12. 21 NUR 653 – J.R.M. – Prosecutorial Discretion (P7)
13. 21 NUR 672 – T.L.T. – Prosecutorial Discretion (P1)
14. 21 NUR 767 – N.L.L. – No Violation
15. 21 NUR 771 – S.L.R. – No Violation

16. 21 NUR 774 – J.M.R. – No Violation
17. 21 NUR 780 – M.J.L. – Prosecutorial Discretion (P2)
18. 22 NUR 015 – A.R. – Insufficient Evidence
19. 22 NUR 060 – A.M.M. – Prosecutorial Discretion (P2)
20. 22 NUR 063 – I.M.L – Prosecutorial Discretion (P1)
21. 22 NUR 065 – M.E.K. – Lack of Jurisdiction (L2)
22. 22 NUR 086 – E.C.P. – No Violation
23. 22 NUR 095 – M.A.F. – No Violation
24. 22 NUR 115 – K.A.S. – No Violation
25. 22 NUR 139 – Unknown – Lack of Jurisdiction (L2)
26. 22 NUR 156 – S.B. – No Violation
27. 22 NUR 162 – T.M. – Insufficient Evidence
28. 22 NUR 178 – L.A.T. – Prosecutorial Discretion (P7)
29. 22 NUR 214 – T.S.S. – No Violation
30. 22 NUR 248 – R.R.R. – Insufficient Evidence
31. 22 NUR 257 – D.M.W. – Prosecutorial Discretion (P5)
32. 22 NUR 263 – M.E.N. – Prosecutorial Discretion (P1)
33. 22 NUR 267 – A.M.H. – No Violation
34. 22 NUR 280 – A.A.W. – Prosecutorial Discretion (P7)
35. 22 NUR 324 – L.A.S. – Lack of Jurisdiction (L1)
36. 22 NUR 325 – B.N.T. – No Violation
37. 22 NUR 364 – K.M. – Prosecutorial Discretion (P2)

Motion carried unanimously.

(Vera Guyton was excused at 11:28 a.m.)

Monitoring Matters

Mitchell W. Babcock, R.N.
Requesting Full Licensure

MOTION: Janice Edelstein moved, seconded by Linda Scott, to grant the request of Mitchell W. Babcock, R.N., for full licensure. Motion carried unanimously.

Cheyanne Cochran (CYR), R.N.
Requesting Virginia as Primary Monitoring State

MOTION: Rosalyn McFarland moved, seconded by Robert Weinman, to grant the request of Cheyanne Cochran (CYR), R.N., for Virginia to serve as the primary monitoring State. Motion carried unanimously.

Sara Elflein, R.N.
Requesting Full Licensure

MOTION: Linda Scott moved, seconded by Rosalyn McFarland, to deny the request of Sara Elflein, R.N., for full licensure. **Reason for Denial**: Failure to demonstrate continuous and successful compliance (poor testing history). Respondent needs to fully comply with the complete terms and conditions of the original Board Order (7/15/2020). Motion carried unanimously.

Travis Floyd, R.N.
Requesting Full Licensure

MOTION: Emily Zentz moved, seconded by Janice Edelstein, to grant the request of Travis Floyd, R.N., for full licensure. Motion carried unanimously.

Robert J. Fox, R.N., A.P.N.P.
Requesting Full Licensure for Both Credentials

MOTION: Janice Edelstein moved, seconded by Robert Weinman, to grant the request of Robert J. Fox, R.N., A.P.N.P., for full licensure for his Registered Nurse license and Advanced Practice Nurse Prescriber certification. Motion carried unanimously.

Erica Koerner, R.N.
Review of Fitness to Practice Evaluation

MOTION: Janice Edelstein moved, seconded by Emily Zentz, to impose additional limitations on the license of Erica Koerner, R.N., requiring quarterly work reports and requiring her to show her disciplinary order to her employer for a period of at least one year, based on the report of the evaluator and the terms of the August 2021 order. Motion carried unanimously.

Brook Morrison, R.N.
Requesting Full Licensure

MOTION: Robert Weinman moved, seconded by Janice Edelstein, to grant the request of Brook Morrison, R.N., for full licensure. Motion carried unanimously.

Lobsang Phintso, R.N.
Requesting a Reduction in Drug Testing Frequency

MOTION: Linda Scott moved, seconded by Emily Zentz, to grant the request of Lobsang Phintso, R.N., for a reduction in drug testing frequency to 36 screens per year. Motion carried unanimously.

Kimberly Reilly, R.N.
Requesting Full Licensure and/or Reduction in Drug Test Frequency

MOTION: Robert Weinman moved, seconded by Janice Edelstein, to deny the request of Kimberly Reilly, R.N. for full licensure, but to grant a reduction in drug testing frequency to 36 screens per year. **Reason for Denial**: Failure to demonstrate continuous and successful compliance. Respondent needs to fully comply with the complete terms and conditions of the original Board Order (11/5/2019). Motion carried unanimously.

(Emily Zentz disconnected at 12:25 p.m.)

(Vera Guyton reconnected at 12:37 p.m.)

Lacie Borde, R.N.
Requesting to Use OWI Treatment Court Drug and Alcohol Testing in Place of Approved Program

MOTION: Janice Edelstein moved, seconded by Robert Weinman, to grant the request of Lacie Borde, R.N., for a request to use OWI Treatment Court Drug and Alcohol Testing in place of approved program, until such time as she completes the program. Ms. Borde shall revert to the approved program as specified in the July 11 limited license order at the rate of no less than 48 drug and alcohol screens per year pending further order from the Board. Motion carried unanimously.

Jennifer Busche, R.N.
Requesting Full Licensure

MOTION: Linda Scott moved, seconded by Janice Edelstein, to grant the request of Jennifer Busche, R.N., for full licensure. Motion carried unanimously.

Jennifer Kosmicki, R.N.
Requesting Full Licensure

MOTION: Robert Weinman moved, seconded by Janice Edelstein, to grant the request of Jennifer Kosmicki, R.N., for full licensure. Motion carried unanimously.

(Emily Zentz reconnected at 12:43 p.m.)

Scott Moscoso (Woik), R.N.
Requesting Full Licensure

MOTION: Janice Edelstein moved, seconded by Linda Scott, to deny the request of Scott Moscoso (Woik), R.N., for full licensure. **Reason for Denial**: Insufficient time under the Board Order (12/2/2020) to demonstrate adequate compliance. Motion carried unanimously.

Mackenzie Campbell, R.N.
Requesting Termination of Drug and Alcohol Testing and a Reduction in the Frequency of AA/NA Meetings to Once Per Week

MOTION: Emily Zentz moved, seconded by Vera Guyton, to deny the request of Mackenzie Campbell, R.N., for a termination of drug and alcohol testing and grant a reduction in the frequency of AA/NA meetings to once per week, but to grant a reduction to 14 tests per year, plus one annual hair test **Reason for Denial**: Insufficient time under the Board Order (6/2/2021) to demonstrate adequate compliance. Motion carried unanimously.

James Hansen, R.N.
Requesting Reduction in Drug and Alcohol Screens to 25 per year and that Drug and Alcohol Screens be Scheduled Every Other Week

MOTION: Linda Scott moved, seconded by Janice Edelstein, to deny the request of James Hansen, R.N., for a reduction in drug and alcohol screens to twenty-five (25) per year and that drug and alcohol screens be scheduled every other week, but to grant a reduction to 36 screens per year. **Reason for Denial**: Insufficient time under the Board Order (5/13/2021). to demonstrate adequate compliance. Motion carried unanimously.

Amanda J. Kaufman, R.N.
Requesting Decrease in Drug Test Frequency, Termination of Direct Supervision Requirement, and Termination or Decrease in Frequency of AA/NA Meetings

MOTION: Robert Weinman moved, seconded by Janice Edelstein, to grant the request of Amanda J. Kaufman, R.N., for a reduction in drug test frequency to 36 screens per year, plus one annual hair test and decrease in frequency of AA/NA meetings to once per week, but to deny the request for decrease or termination of supervision requirement. **Reason for Denial**: Insufficient time under the Board Order (3/11/2021) to demonstrate adequate compliance. Motion carried unanimously.

Deborah Le Sieur, L.P.N.
Requesting Reduction in Work Reports to Bi-annually

MOTION: Robert Weinman moved, seconded by Linda Scott, to grant the request of Deborah Le Sieur, L.P.N., for a reduction in frequency of work reports to Bi-annually. Motion carried unanimously.

Stacy Rutsch, R.N.
Requesting Termination of Direct Supervision and Practice Limitations

MOTION: Robert Weinman moved, seconded by Janice Edelstein, to deny the request of Stacy Rutsch, R.N., for termination of direct supervision and practice limitations. **Reason for Denial**: Failure to demonstrate continuous and successful compliance. Respondent needs to fully comply with the complete terms and conditions of the original Board Order (8/10/2018). Motion carried unanimously.

RECONVENE TO OPEN SESSION

MOTION: Emily Zentz moved, seconded by Robert Weinman, to reconvene into Open Session. Motion carried unanimously.

The Board reconvened into Open Session at 12:58 p.m.

VOTING ON ITEMS CONSIDERED OR DELIBERATED UPON IN CLOSED SESSION

MOTION: Robert Weinman moved, seconded by Janice Edelstein, to affirm all motions made and votes taken in Closed Session. Motion carried unanimously.

(Be advised that any recusals or abstentions reflected in the Closed Session motions stand for the purposes of the affirmation vote.)

ADJOURNMENT

MOTION: Linda Scott moved, seconded by Janice Edelstein, to adjourn the meeting. Motion carried unanimously.

The meeting adjourned at 12:59 p.m.

State of Wisconsin
Department of Safety & Professional Services

AGENDA REQUEST FORM

1) Name and title of person submitting the request: Brad Wojciechowski, Executive Director		**2) Date when request submitted:** 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: Board of Nursing			
4) Meeting Date: 09/08/2022	**5) Attachments:** ☒ Yes ☐ No	**6) How should the item be titled on the agenda page?** Board of Nursing Report on Opioid Abuse – Discussion and Consideration	
7) Place Item in: ☐ Open Session ☐ Closed Session	**8) Is an appearance before the Board being scheduled?** *(If yes, please complete Appearance Request for Non-DSPS Staff)* ☐ Yes <Appearance Name(s)> ☐ No	**9) Name of Case Advisor(s), if applicable:** <Click Here to Add Case Advisor Name or N/A>	
10) Describe the issue and action that should be addressed: 1) Review of 2021 Report 2) Proposals for 2022 Report			
11) **Authorization**  **08/29/2022** **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**			
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 BOARD OF NURSING

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REPORT ON OPIOID ABUSE

Proactive Efforts Taken by the Board of Nursing to Address Opioid Abuse

1. **Controlled Substances Prescribing Guidelines –** The Board of Nursing adopted Best Practices for Prescribing Controlled Substances Guidelines (Guidelines) on January 12, 2017. The Guidelines were developed using the following:
   - Centers for Disease Control's *Guideline for Prescribing Opioids for Chronic Pain.*
   - American Association of Nurse Anesthetists' *Chronic Pain Management Guidelines*.
   - American Nurses Association's *Nursing's Role in Addressing Nation's Opioid Crisis.*
   - Federal Drug Administration's *Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*.
   - Wisconsin Medical Examining Board's *Opioid Prescribing Guideline.*
   - Michigan's *Guidelines for the Use of Controlled Substances for the Treatment of Pain*.
   - The Joint Commission's *Statement on Pain Management.*
   - National Transportation Safety Board recommendations for advising patients of the effect-controlled substances may have on their ability to safely operate a vehicle.

   The Board of Nursing published the Guidelines in their newsletter and provided a copy of the Guidelines to every advanced practice nurse prescriber with an active license and an email on file with the Department of Safety and Professional Services. The Guidelines are available at https://dsps.wi.gov/Documents/BoardCouncils/NUR/BONGuidelinesV1.pdf.

2. **Controlled Substances Continuing Education –** The Board of Nursing requires each advanced practice nurse prescriber to complete 2 hours of the required 16 hours of continuing education in the topic of responsible prescribing of controlled substances.

3. **Prescription Drug Monitoring Program (PDMP) Information in Newsletter –** The Board of Nursing has highlighted information regarding the Prescription Drug Monitoring Program in their newsletter.

4. **PDMP Prescribing Metrics for Prescribing Practice Complaints –** The Board of Nursing Screening Panel reviews the PDMP Prescribing Metrics Summary for any advanced practice nurse prescriber who has a complaint relating to the advance practice nurse prescriber's prescribing practices.

5. **Membership on the Controlled Substances Board –** A member of the Board of Nursing is designated as a standing member of the Controlled Substances Board (CSB). The CSB is instrumental in the efforts to combat opioid abuse, primarily through its involvement with the PDMP and the scheduling of controlled substances under Wisconsin's Controlled Substances Act.

Goals for Addressing the Issue of Opioid Abuse as it Relates to the Practice of Nursing

1. **Compliance with the PDMP Provider Review Requirement –**The Board of Nursing will continue its effort to increase compliance by raising awareness of the PDMP provider review requirement.

2. **Education –** The Board of Nursing will continue to explore opportunities to expand on its educational outreach in the areas of safe opioid prescribing and opioid abuse.

3. **PDMP Outreach –** The Board of Nursing will continue to work with PDMP staff to provide information concerning the PDMP to its licensees.

4. **PDMP Prescribing Outliers –** The Board of Nursing will continue to review referrals of advanced practice nurse prescribers from the Controlled Substances Board to identify those advance practice nurse prescribers whose prescribing practices are outliers. In addition, the Board of Nursing Screening Panel will continue to review the PDMP Prescribing Metrics Summary for any advanced practice nurse prescriber who has a complaint relating to the advance practice nurse prescriber's prescribing practices.

Actions Taken by the Board of Nursing to Achieve the Goals Identified in Previous Reports

1. **Compliance with Provider Review Requirement –** The Board of Nursing's goal was to continue its effort to increase compliance by raising awareness of the PDMP provider review requirement. As a means of facilitating this effort, the Board has requested PDMP staff to provide data on waivers for advanced practice nurse prescribers.

2. **Education –** The Board of Nursing's goal was to explore opportunities to expand on its educational outreach in the areas of safe opioid prescribing and opioid abuse. The Board has requested PDMP staff to provide opioid abuse statistics coming out of the COVID-19 public health emergency, as the Board anticipates this information will produce opportunities to expand on its educational outreach.

3. **PDMP Outreach –** The Board of Nursing's goal was to continue to work with PDMP staff to provide information concerning the PDMP to its licensees. As a member of the Controlled Substances Board, an appointed member of the Board of Nursing, regularly meets with and receives updates from PDMP staff. During the current reporting period, licensees received an update informing them that Gabapentin is not a monitored drug.

4. **PDMP prescribing outliers –** The Board of Nursing's goal was to continue to review referrals of advanced practice nurse prescribers from the Controlled Substances Board (CSB) to identify those advance practice nurse prescribers whose prescribing practices are outliers.

   The Controlled Substances Board referred a total of eight providers to the Board of Nursing for the current reviewing period. (Status: DLSC intake)

   Another goal was for the Board of Nursing Screening Panel to continue to review the PDMP Prescribing Metrics Summary for any advanced practice nurse prescriber who has a complaint relating to the advance practice nurse prescriber's prescribing practices. The Screening Panel continues this practice as part of its review of a complaint. The Board requested the PDMP prescribing monitoring reports of two providers in April and June respectively as part of this process.

State of Wisconsin
Department of Safety & Professional Services

AGENDA REQUEST FORM

1) Name and title of person submitting the request: Sofia Anderson, Administrative Rules Coordinator			**2) Date when request submitted:** 8/26/2022 **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: Board of Nursing			
4) Meeting Date: September 8, 2022	**5) Attachments:** ☒ **Yes** ☐ **No**	**6) How should the item be titled on the agenda page?** Administrative Rules Matters – Discussion and Consideration 1. Scope Statement: N 2, relating to Board approval to take the NCLEX 2. Pending and Possible rulemaking projects	
7) Place Item in: ☒ **Open Session** ☐ **Closed Session**	**8) Is an appearance before the Board being scheduled?** *(If yes, please complete **Appearance Request** for Non-DSPS Staff)* ☐ **Yes** ☒ **No**	**9) Name of Case Advisor(s), if required:** N/A	

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

Attachments:

1. Scope Statement: N 2, relating to Board approval to take the NCLEX.
2. Nursing rule projects chart.

11) Authorization

SAnderson

8/26/2022

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.

STATEMENT OF SCOPE

BOARD OF NURSING

Rule No.: N 2

Relating to: Board approval to take the NCLEX

Rule Type: Emergency and Permanent

1. Finding/nature of emergency (Emergency Rule only):

This rule is necessary for the public by increasing health care access by allowing nurse applicants to take the National Council Licensure Examination (NCLEX) without Board approval. An expeditious promulgation of the proposed rule is in the best interest of Wisconsin's economy and public welfare, as it will help ensure the opportunity for nurses to start practicing faster in Wisconsin by meeting one of the many licensure requirements without having to wait for approval.

2. Detailed description of the objective of the proposed rule:

The Board's primary objective is to promulgate an emergency and permanent rule that will revise the requirement that the Board needs to make applicants for licensure eligible to take the NCLEX, which has created delays in licensure due to the extended application processing times.

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:

Section N 2 contains the application procedures for single state and multistate licenses, which includes the provision that the Board of Nursing will make the applicants eligible to take the NCLEX upon receiving the required education verifications. The Board of Nursing would like to remove this requirement in an effort to make nurse applications go through the licensure process much faster than in the past, which will benefit the state of Wisconsin by having more nurses join the workforce.

The alternative is to not remove this requirement, which will maintain the current delays in the application process and delay the entrance of nurses into the workforce.

4. Detailed explanation of statutory authority for the rule (including the statutory citation and language):

Section 15.08 (5) (b), Stats., provides an examining board "[s]hall promulgate rules for its own guidance and for the guidance of the trade or profession to which it pertains. . ."

Section 227.24 (1) (a), Stats., provides "[a]n agency may, except as provided in s. 227.136 (1), promulgate a rule as an emergency rule without complying with the notice, hearing, and publication requirements under this chapter if preservation of the public peace, health, safety, or welfare necessitates putting the rule into effect prior to the time it would take effect if the agency complied with the procedures."

Section 441.01 (3), Stats., provides "[t]he board may establish minimum standards for schools for professional nurses and schools for licensed practical nurses, including all related clinical units and facilities, and make and provide periodic surveys and consultations to such schools. It may also establish rules to prevent unauthorized persons from practicing professional nursing. It shall approve all rules for the administration of this chapter in accordance with ch. 227."

5. Estimate of amount of time that state employees will spend developing the rule and of other resources necessary to develop the rule:

80 hours

6. List with description of all entities that may be affected by the proposed rule:

Nursing students, nursing school graduates, entities that hire or may hire nursing students and nursing school graduates, and individuals accessing health care services.

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):

The proposed rule will have minimal to no economic impact on small businesses and the state's economy as a whole.

Contact Person: Sofia Anderson, Administrative Rules Coordinator, DSPSAdminRules@wisconsin.gov, (608) 261-4463.

Approved for publication:

Authorized Signature

Date Approved

Approved for implementation:

Authorized Signature

Date Approved

Board of Nursing
Rule Projects (Updated 8/26/2022)

Clearinghouse Rule Number	Scope #	Scope Expiration	Date Scope Requested by Board	Rules Affected	Relating Clause	Synopsis	Stage of Rule Process	Next step
	044-22	11/23/2024	N/A	Med 26	Military Medical Personnel	Medical Board rule project would create provisions in order to implement 2021 WI Act 158.	Drafting rule	EIA Comment Period

Permanent Rules

Clearinghouse Rule Number	Scope #	Scope Expiration	Date Scope Requested by Board	Rules Affected	Relating Clause	Synopsis	Stage of Rule Process	Next step
20-069	014-20	9/30/2022	3/25/2020	N 1 to 8	Requirements in emergency situations	Comprehensive review of the Board's rules with the objective of establishing waivers and alternate requirements that the Board may utilize to respond to emergency situations.	Final rule and legislative report submitted to Governor's Office, 1/12/21.	Once Governor approves, it can be sent for Legislative review.

Scope Statements

Clearinghouse Rule Number	Scope #	Scope Expiration	Date Scope Requested by Board	Rules Affected	Relating Clause	Synopsis	Stage of Rule Process	Next step

			8/11/2022	N 2	Board approval to take the NCLEX	The Board would like to revise the requirement that the Board needs to make applicants for licensure eligible to take the NCLEX in order to speed up the application process. **This is for an emergency and permanent rule.**	Scope ready for review at the September meeting.	If scope is approved, it will be submitted to Governor's Office for review.
			10/8/2020	N 8	APNP prescribing limitations	Review of limitations in N8 regarding APNPs prescribing certain drugs.	Scope submitted to Governor's Office, 11/24/20.	
			7/30/2020	N 8	Collaboration with other health care providers	Review of the collaboration requirements in N8 and other changes throughout the chapter.	Scope submitted to Governor's Office, 10/15/20.	
			6/11/2020	N 2	Temporary permits	Requirements for temporary permits to respond to a future emergency and may promulgate a permanent rule to allow the Board to grant a waiver of or variance to the requirements in emergency situations.	Scope submitted to Governor's Office on 10/15/20	

Emergency Rules

EMR Number	Rules Affected	Rule	Stage of Rule Process	Brief Synopsis of Rule	Stage Details	Next step

State of Wisconsin
Department of Safety & Professional Services

AGENDA REQUEST FORM

1) Name and title of person submitting the request: Kathy Gagas, LPPA Lead			2) Date when request submitted: 08/31/2022 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: Board of Nursing			
4) Meeting Date: 09/08/2022	5) Attachments: ☒ Yes ☐ No	6) How should the item be titled on the agenda page? Credentialing license counts	
7) Place Item in: ☒ Open Session ☐ Closed Session	8) Is an appearance before the Board being scheduled?) ☐ Yes ☒ No	9) Name of Case Advisor(s), if applicable: N/A	

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

Act 10 for August 2022:

LPN: 4

RN: 43

APNP: 8

11) Authorization

Kathy Gagas 08/31/22

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

Directions for including supporting documents:
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APPLICATION COUNTS by MONTH

FROM: 1/1/2022 TO: 8/31/2022

PROFESSION NAME	YEAR	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	YEAR TOTAL
Advanced Practice Nurse Prescriber(33)	**2022**	84	103	122	109	34	3	0	0	0	0	0	0	**455**
Licensed Practical Nurse(31)	**2022**	91	60	99	191	11	0	1	1	0	0	0	0	**454**
Nurse - Midwife(32)	**2022**	0	0	0	2	1	0	0	0	0	0	0	0	**3**
Registered Nurse(30)	**2022**	559	471	908	1275	97	2	6	10	0	0	0	0	**3328**

CREDENTIALS ISSUED BY MONTH

FROM: 1/1/2022 TO: 8/31/2022

PROFESSION NAME	YEAR	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	YR TOTALS
Advanced Practice Nurse Prescriber(33)	2022	48	80	73	64	61	93	76	104	0	0	0	0	**599**
Licensed Practical Nurse(31)	2022	97	105	105	111	58	105	101	117	0	0	0	0	**799**
Nurse - Midwife(32)	2022	1	1	1	0	1	1	1	3	0	0	0	0	**9**
Registered Nurse(30)	2022	601	912	500	347	452	786	682	505	0	0	0	0	**4785**

In LicensE apps pending totals: (unable to break down by months) from 5/16/22 to 8/31/22:

APNP = 175

LPN = 229

Nurse Midwife = 10

RN = 515

Wisconsin Department of Safety and Professional Services

License Counts

(Includes Temp. Licenses)

Active = Current License / Inactive = Licensed Expired

			In State			Out of State			Totals		
Reg.	**Profession**	**License Count Date**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**
30	Registered Nurse	8/31/2022	91,999	58,452	150,451	13,620	64,215	77,835	105,619	122,667	228,286
		8/5/2022	97,888	52,255	150,143	17,886	59,877	77,763	115,774	112,132	227,906
		5/25/2022	96,589	52,268	148,857	17,532	59,931	77,463	114,121	112,199	226,320
		4/27/2022	96,339	52,305	148,644	17,260	59,968	77,228	113,599	112,273	225,872
		4/4/2022	96,201	52,329	148,530	17,111	59,964	77,075	113,312	112,293	225,605
		3/1/2022	95,967	52,353	148,320	16,816	59,990	76,806	112,783	112,343	225,126
		2/4/2022	95,723	52,367	148,090	16,332	59,967	76,299	112,055	112,334	224,389
		12/9/2021	95,009	52,382	147,391	15,965	59,991	75,956	110,974	112,373	223,347
		11/26/2021	94,957	52,386	147,343	15,915	59,997	75,912	110,872	112,383	223,255
		11/4/2021	94,803	52,410	147,213	15,786	60,008	75,794	110,589	112,418	223,007
		9/29/2021	94,540	52,439	146,979	15,525	59,998	75,523	110,065	112,437	222,502
Reg.	**Profession**	**License Count Date**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**
31	Licensed Practical Nurse	8/31/2022	11,891	36,066	47,957	857	9,971	10,828	12,748	46,037	58,785
		8/5/2022	14,594	33,286	47,880	1,167	9,653	10,820	15,761	42,939	58,700
		5/25/2022	14,372	33,286	47,658	1,145	9,655	10,800	15,517	42,941	58,458
		4/27/2022	14,325	33,285	47,610	1,137	9,658	10,795	15,462	42,943	58,405
		4/4/2022	14,248	33,288	47,536	1,120	9,660	10,780	15,368	42,948	58,316
		3/1/2022	14,161	33,292	47,453	1,098	9,659	10,757	15,259	42,951	58,210
		2/4/2022	14,086	33,322	47,408	1,081	9,630	10,711	15,167	42,952	58,119
		12/9/2021	13,982	33,332	47,314	1,038	9,620	10,658	15,020	42,952	57,972
		11/26/2021	13,971	33,335	47,306	1,031	9,619	10,650	15,002	42,954	57,956
		11/4/2021	13,937	33,340	47,277	1,015	9,620	10,635	14,952	42,960	57,912
		9/29/2021	13,879	33,355	47,234	999	9,615	10,614	14,878	42,970	57,848

			In State			Out of State			Totals		
Reg.	**Profession**	**License Count Date**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**
32	Nurse - Midwife	8/31/2022	237	99	336	31	97	128	268	196	464
		8/5/2022	247	87	334	45	83	128	292	170	462
		5/25/2022	243	88	331	44	84	128	287	172	459
		4/27/2022	243	88	331	44	84	128	287	172	459
		4/4/2022	243	88	331	44	84	128	287	172	459
		3/1/2022	245	88	333	41	84	125	286	172	458
		2/4/2022	248	88	336	38	84	122	286	172	458
		12/9/2021	243	89	332	41	83	124	284	172	456
		11/26/2021	243	89	332	41	83	124	284	172	456
		11/4/2021	242	89	331	41	83	124	283	172	455
		9/29/2021	239	89	328	41	83	124	280	172	452
Reg.	**Profession**	**License Count Date**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**	**Active**	**Inactive**	**Total**
33	Advanced Practice Nurse Prescriber	8/31/2022	7,703	1,321	9,024	1,812	1,419	3,231	9,515	2,740	12,255
		8/5/2022	7,625	1,322	8,947	1,807	1,422	3,229	9,432	2,744	12,176
		5/25/2022	7,506	1,333	8,839	1,718	1,423	3,141	9,224	2,756	11,980
		4/27/2022	7,472	1,335	8,807	1,684	1,424	3,108	9,156	2,759	11,915
		4/4/2022	7,429	1,335	8,764	1,676	1,427	3,103	9,105	2,762	11,867
		3/1/2022	7,373	1,342	8,715	1,647	1,426	3,073	9,020	2,768	11,788
		2/4/2022	7,349	1,346	8,695	1,593	1,431	3,024	8,942	2,777	11,719
		12/9/2021	7,282	1,355	8,637	1,554	1,433	2,987	8,836	2,788	11,624
		11/26/2021	7,260	1,354	8,614	1,520	1,433	2,953	8,780	2,787	11,567
		11/4/2021	7,227	1,356	8,583	1,500	1,434	2,934	8,727	2,790	11,517
		9/29/2021	7,136	1,358	8,494	1,452	1,440	2,892	8,588	2,798	11,386

Nursing Licenses Issued Pursuant to Emergency Order 2/Act 10:

Profession	**2/2021**	**3/2021**	**4/2021**	**5/2021**	**6/2021**	**7/2021**	**8/2021**	**10/2021**	**11/2021**	**12/2021**	**1/2022**	**2/2022**	**3/2022**	**4/2022**	**5/2022**	**7/2022**	**8/2022**
Registered Nurse	27	19	20	4	10	6	10	68	91	100	40	56	32	4	15	54	43
Licensed Practical Nurse	1	-	1	3	-	2	-	6	6	7	5	2	1	1	1	9	4
Nurse Midwife	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Advanced Practice Nurse Prescriber	13	10	24	12	10	4	1	24	30	34	12	7	5	1	6	9	8

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:
Kimberly Wood, Program Assistant Supervisor	9/1/2022
	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:

Board of Nursing

4) Meeting Date:	5) Attachments:	6) How should the item be titled on the agenda page?
9/8/2022	☐ Yes ☒ No	Newsletter Matters

7) Place Item in:	8) Is an appearance before the Board being scheduled?	9) Name of Case Advisor(s), if applicable:
☒ Open Session ☐ Closed Session	☐ Yes ☒ No	N/A

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

Newsletter Future Planning:

Based on the revised distribution schedule the Board's next newsletter will be due out this month with a deadline for article submission on September 30, 2022. Given distributions delays for the July newsletter the Board should discuss if an additional newsletter will be needed this year, and if so, when it should be distributed. Review the topics below and discuss any others the Board may wish to add to the list below.

Articles/Ideas:

- Chair's Corner – By Robert Weinman
- Rotating Articles on Professional Nursing Roles – Emily Zentz (October), Linda Scott (January 2023)
- New Member Introduction Articles/Photos
  - New Members (subject to new member appointments and oath receipts)
- Rotating Articles on Administrative Code – Robert Weinman (N7)

11) Authorization

Kimberly Wood — *9/1/2022*

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

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.

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	8/2/2022
	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:

Board of Nursing

4) Meeting Date:	5) Attachments:	6) How should the item be titled on the agenda page?
9/8/2022	☒ 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.

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

11) Authorization

Adam Barr — 8/5/2022

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

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

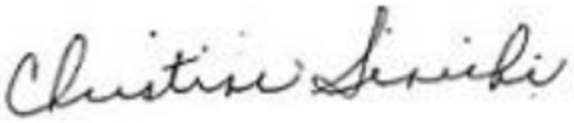
Representative Brostoff
19th Assembly District

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:

---

[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
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10 EAST DOTY STREET, SUITE 405
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1727 LONGWORTH HOUSE OFFICE BUILDING
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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

[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

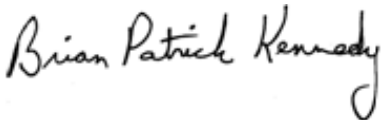
Senator Lena Taylor
Wisconsin Senate

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

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December 6, 2021

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

Dear Chair Swearingen:

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

Mark Pocan
Member of Congress

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for your efforts and the opportunity to comment.

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Wisconsin Medical Society

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

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

DATE: December 8, 2021

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

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

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

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

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

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

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

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

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

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

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

Continuing Research into Kratom Use Shows Troubling Effects

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

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

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

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

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

WISAM WISCONSIN SOCIETY of ADDICTION MEDICINE

07/14/2021

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

Dear Mr. Grapentine,

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

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

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

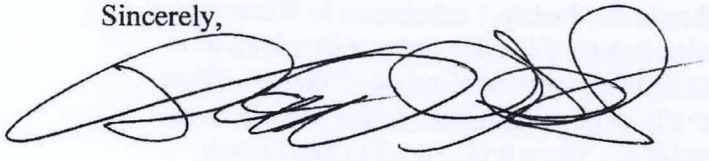
Finally, any attempt to introduce this bill as part of the HOPE legislation under the guise of treatment for OUD is anti-scientific and harmful. The FDA has issued warning letters to

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

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

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

Sincerely,



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

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A Case Report of Kratom Addiction and Withdrawal

David Galbis-Reig, MD

ABSTRACT

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

CASE PRESENTATION

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

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CME available. See page 53 for more information.

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

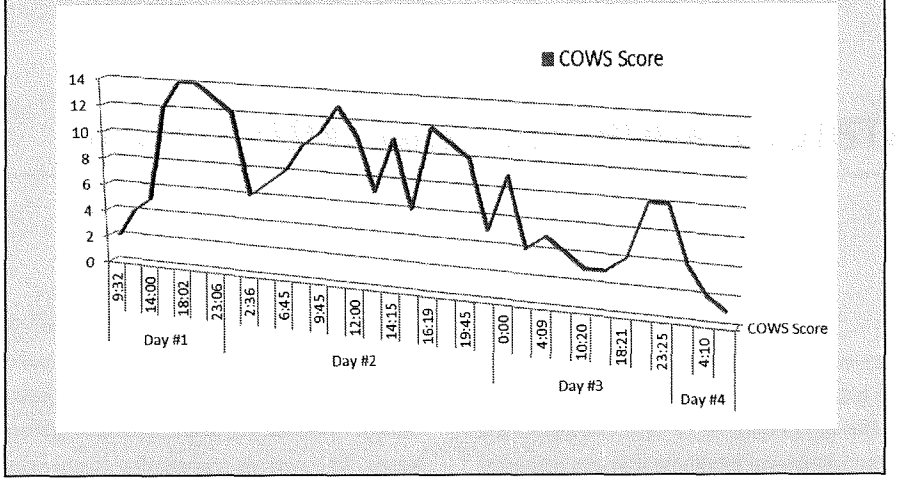
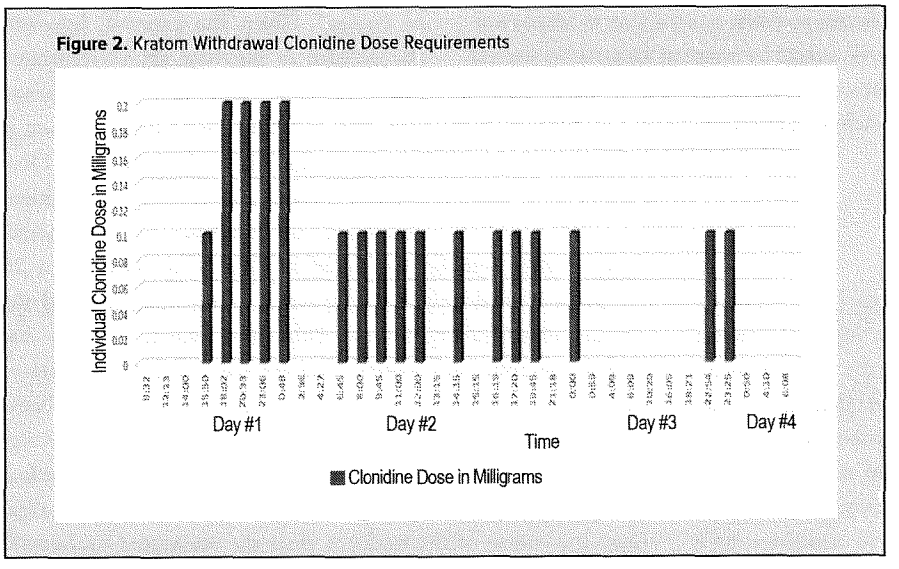


Figure 2. Kratom Withdrawal Clonidine Dose Requirements



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

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

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

DISCUSSION

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

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

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

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

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

CONCLUSION

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

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

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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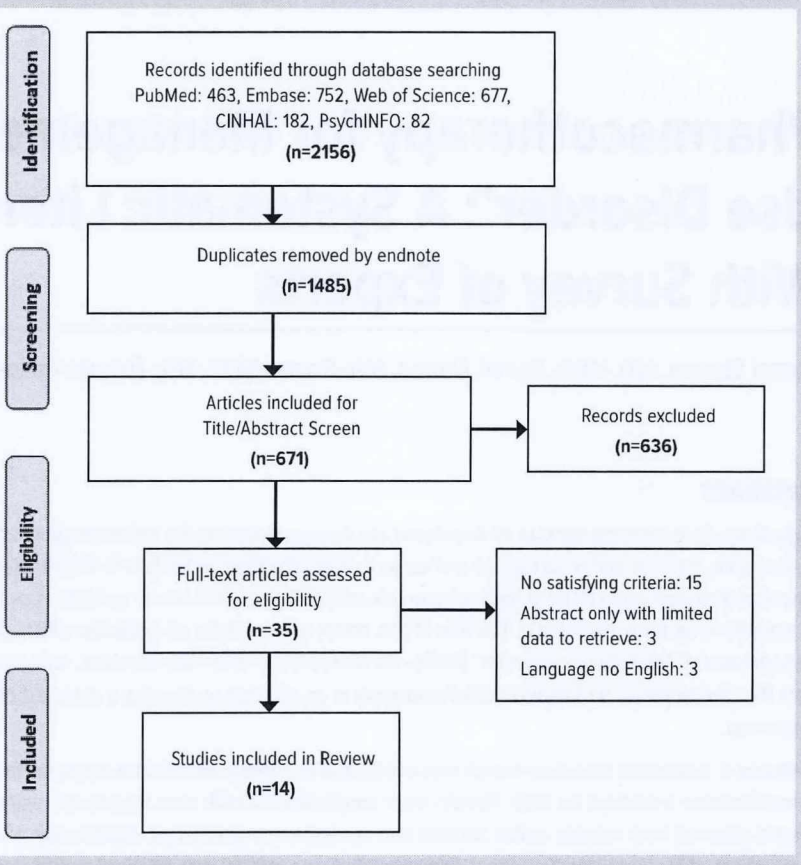
INTRODUCTION

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.

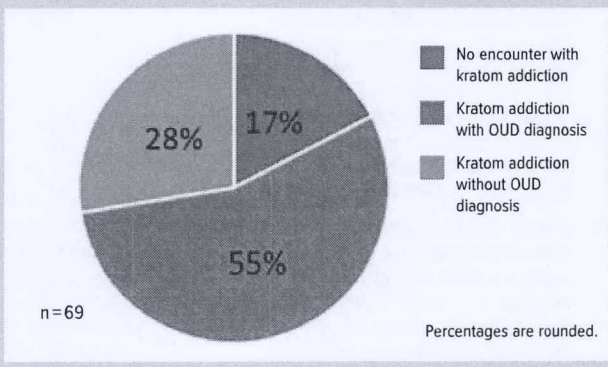
There is a clear need to establish a consensus on how to manage KUD independent of an OUD. As demonstrated in this review, there has been success with treating KUD using the same pharmacological agents as those approved for OUD. In the cases included here that did not involve a comorbid OUD diagnosis,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

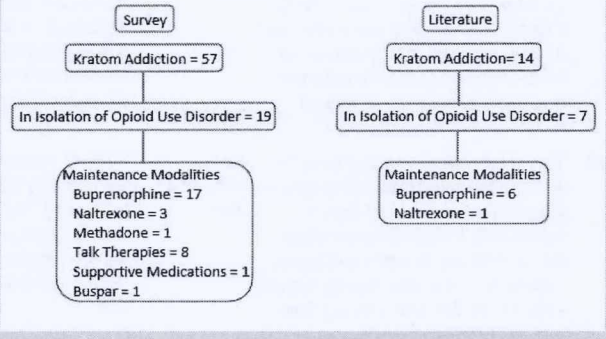
The cases resulting from the literature search and included in the analysis/comparison have a significant amount of heterogeneity in the descriptions, information provided (ie, kratom dose, route, etc), toxicology screens used for abstinence monitoring, reporting of maintenance follow-up duration, etc.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

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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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