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Truth
Quality
Service
Mission: to promote excellence in analysis, training and service to the community and our organization with integrity and uncompromising quality.
Lead
Character
Science
Integrity
History
Advancements
Training
Experts
Vision: to search for the truth through science and to lead and shape the advancement of forensic science.
Analysis
Competence

WSCL | Wisconsin State Crime Laboratories

Controlled Substances Board 11/11/2022 Additional Materials
Item C. Annual Hearing with Law Enforcement Leaders, Agencies, and Prosecutors
3) Discussion Regarding Drug Trends
d. Presentation from the Wisconsin State Crime Lab Bureau

Drug Trends in Wisconsin

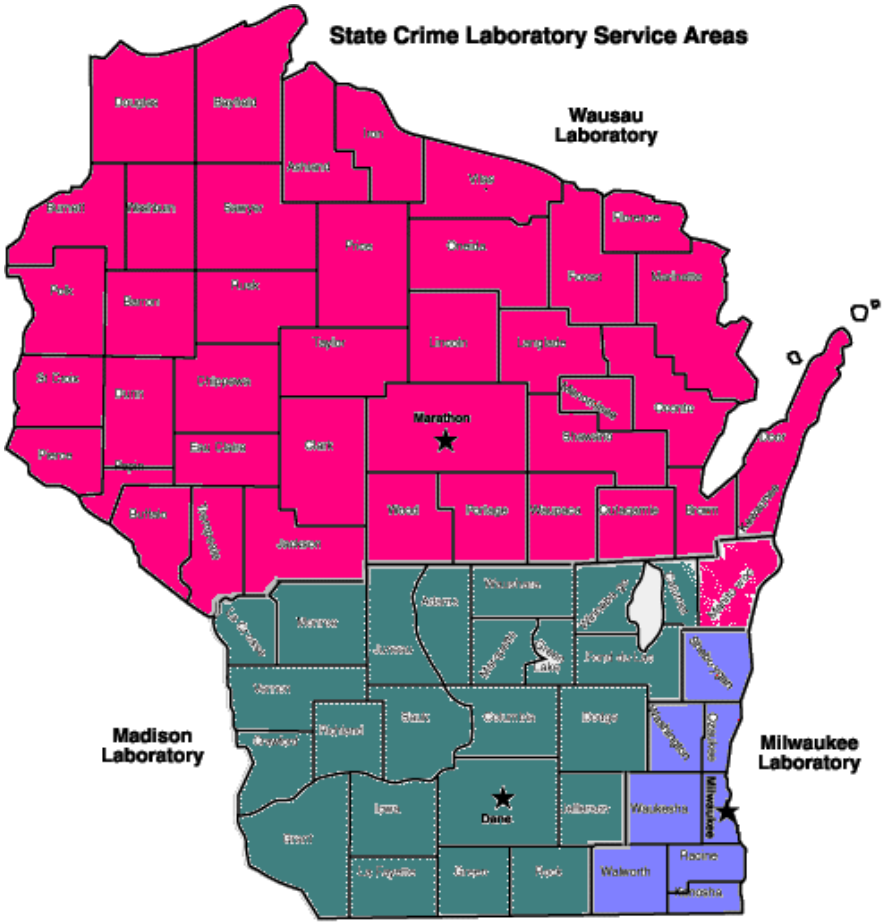
Division of Forensic Sciences

Wisconsin State Crime Laboratories

Controlled Substances Unit

Sandy Koresch

Wisconsin State Crime Laboratories



Milwaukee serves 8 Southeastern County Area
Madison serves 24 Southern County Area
Wausau serves 40 Northern County Area

Controlled Substances Unit

The examination of evidence (seized drugs) for the presence of controlled substances under Wisconsin Statute 961

Types of Evidence

Plant Materials

Powders/Chunky Substances

Liquids

Tablets/Capsules

Residues/Paraphernalia

Clandestine Laboratories

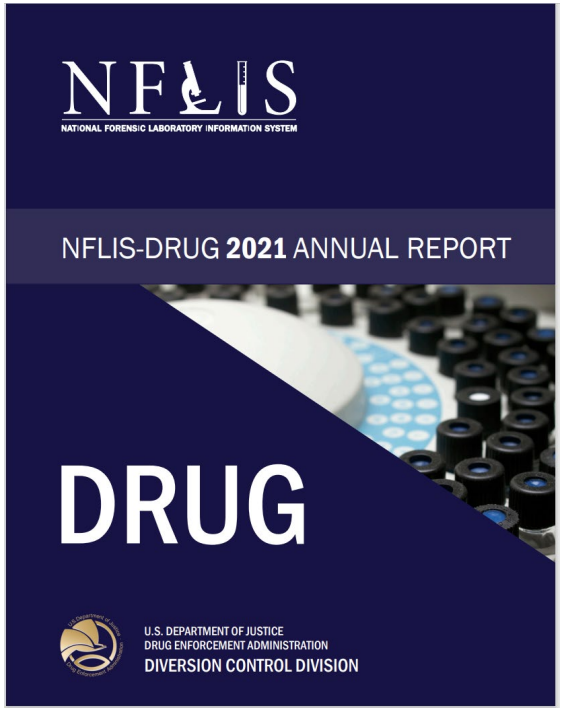
Adulterated Food Items

NFLIS DATA

National Forensic Laboratory Information System

http://www.nflis.deadiversion.usdoj.gov

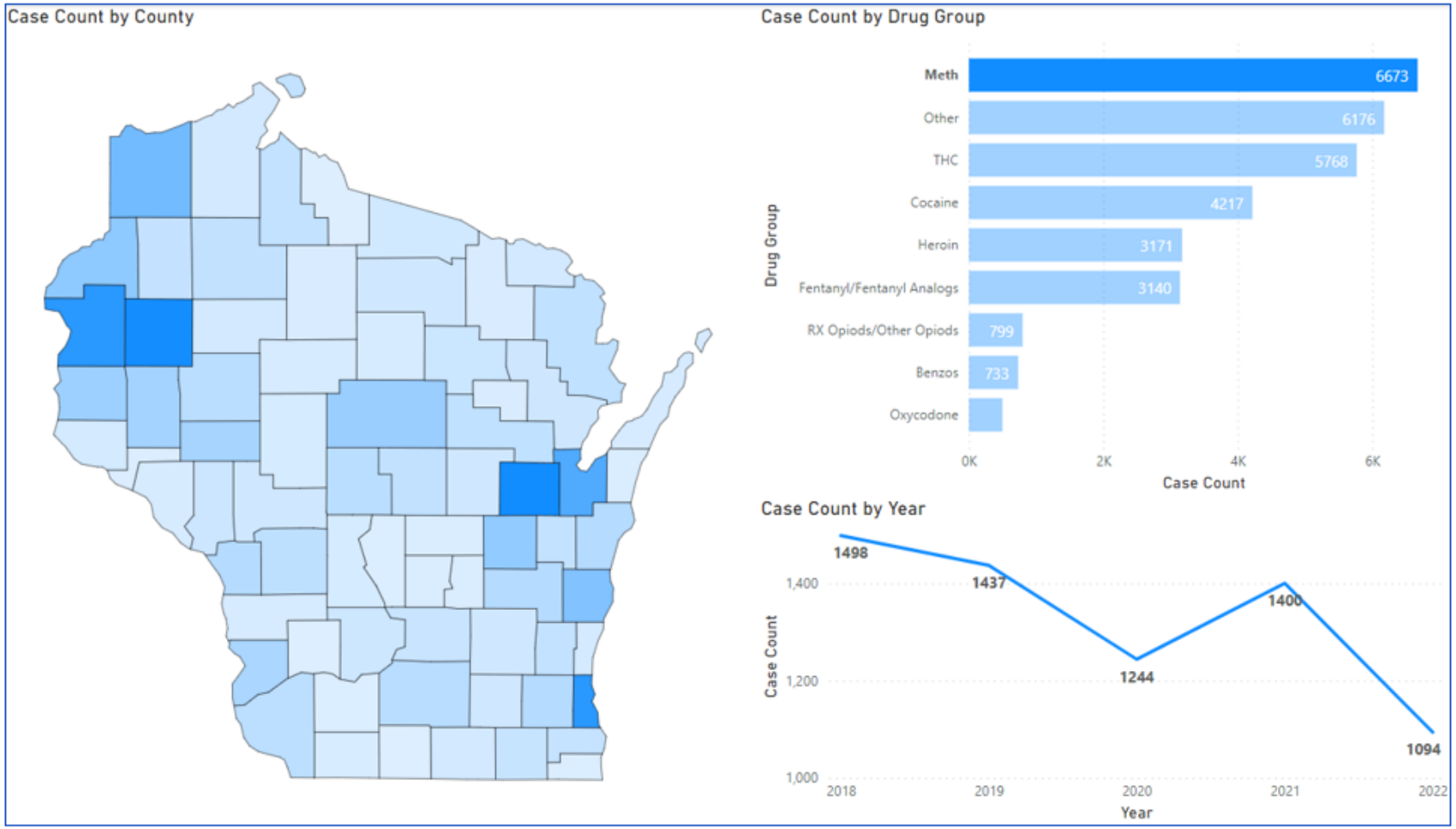
Methamphetamine:	377,787
Cannabis/THC:	188,735
Cocaine:	153,372
Fentanyl:	117,045
Heroin:	98,077



WSCL Trends

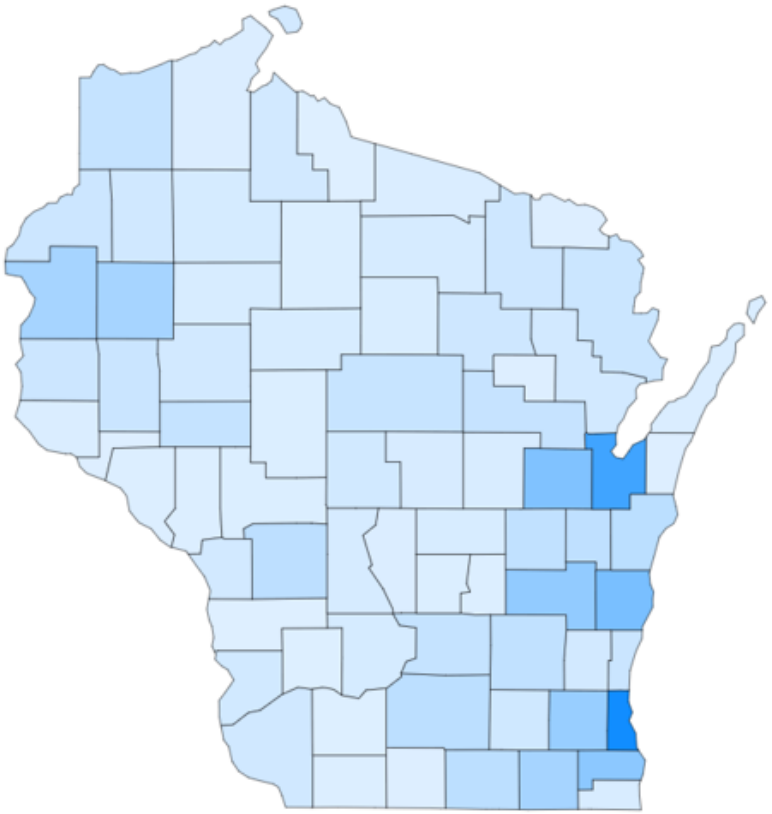
- Most Prevalent Drugs 2022
  - Methamphetamine
  - Cannabis
  - Cocaine
  - Fentanyl/Fentanyl Analogs
  - Heroin
- Fentanyl Substances
- Counterfeits/Illicit Tablets
- Novel Psychoactive Substances (NPS)
- Kratom
- THC isomers

WSCL- Methamphetamine

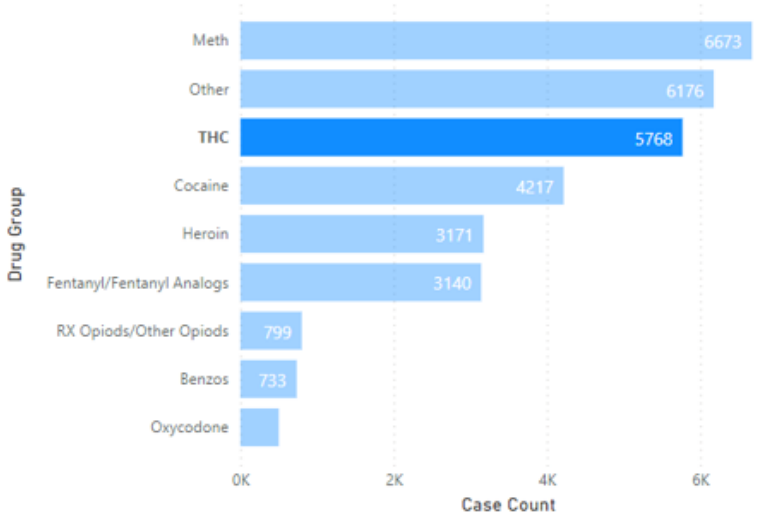


WSCL - THC

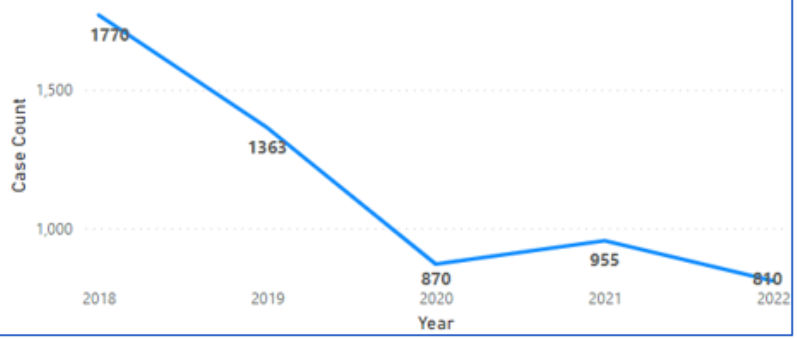
Case Count by County



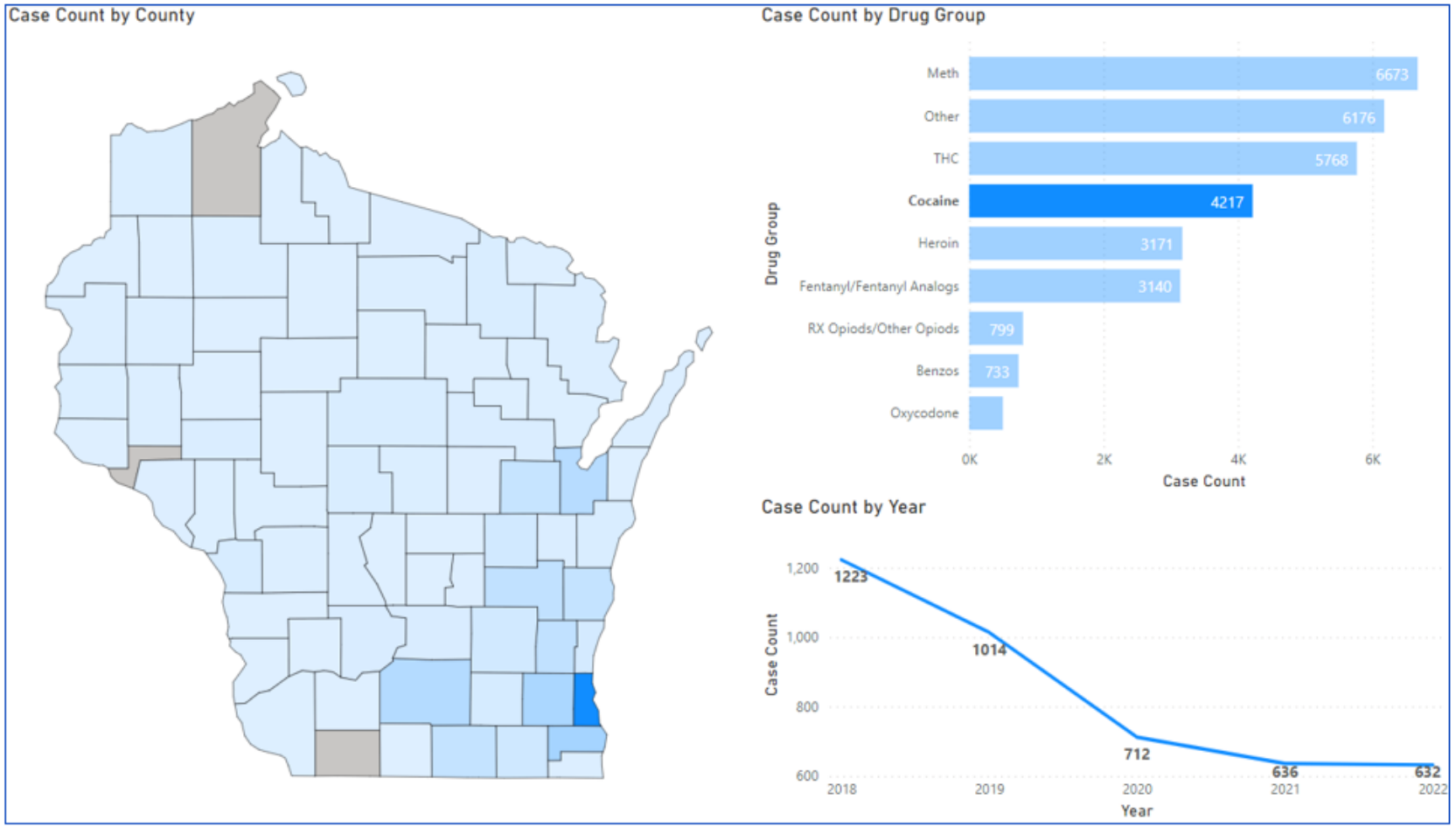
Case Count by Drug Group



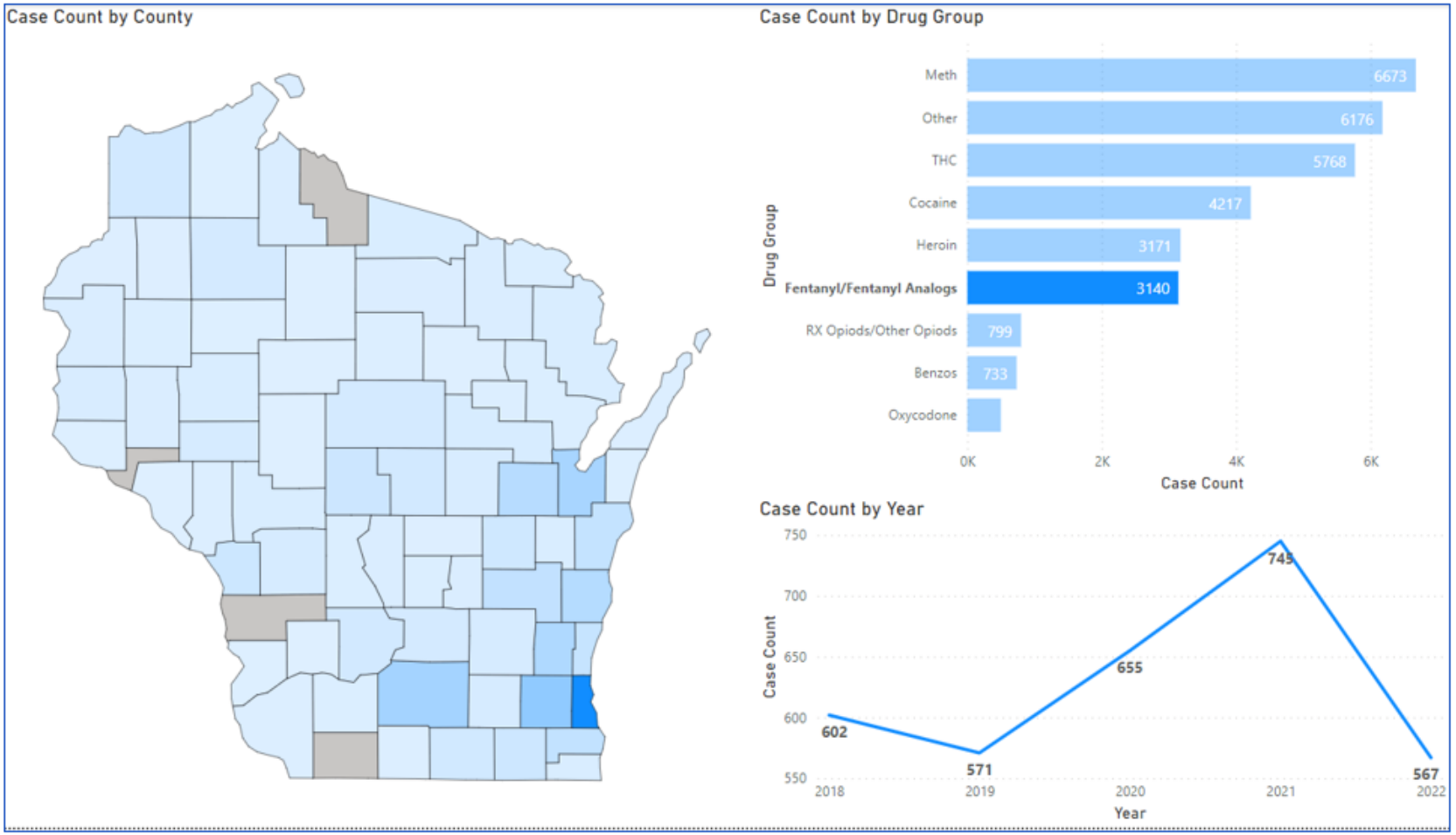
Case Count by Year



WSCL - Cocaine

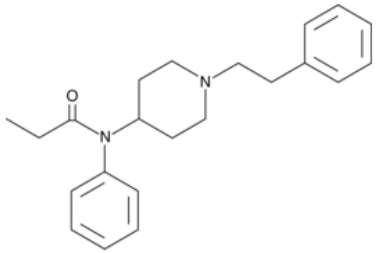


WSCL – Fentanyl Substances

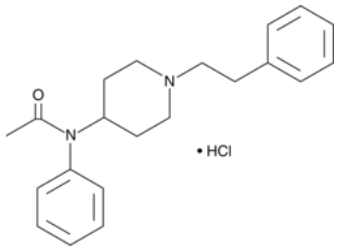


Fentanyl Substances

Fentanyl

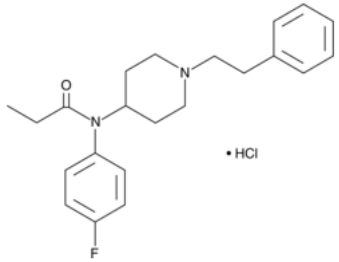


Fluorofentanyl



- Ortho, Meta, and Para isomers
- Isomer may not be determined
- When determined predominately para isomer
- Ortho and Para – specifically listed
- Meta – not listed; structurally controlled

Increased Precursors/Byproducts



- 4-ANPP
- Phenethyl 4-ANPP

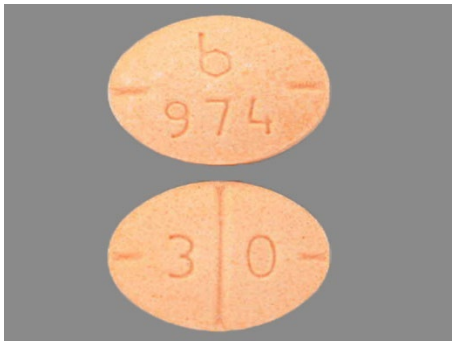
Structures from www.caymanchemical.com

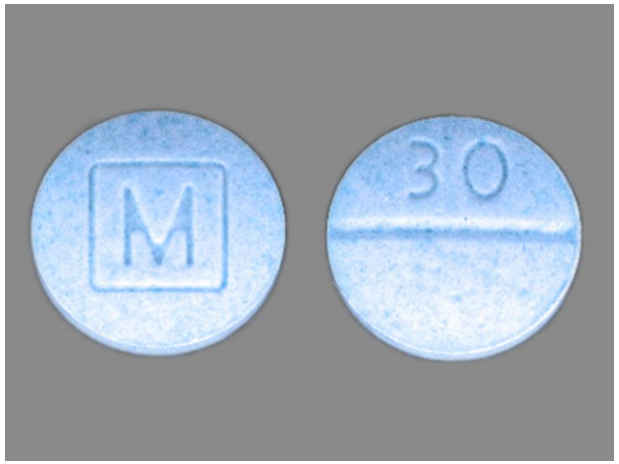
Counterfeits

- Lots of counterfeits!
- Some counterfeits very difficult to visually distinguish
- Most common counterfeits are oxycodone preparations (blue M30)

-Often contain fentanyl

- Alprazolam 2nd most common counterfeit; designer benzodiazepines
- Also now seeing amphetamine counterfeit; methamphetamine





Illicit Preparations

- Many different shapes, colors, and designs
- May contain multiple controlled substances
- Most common components currently include Methamphetamine, substituted cathinones, synthetic cannabinoids, and MDMA

Novel Psychoactive Substances (NPS)

- Substances developed to mimic the affects of a variety of drugs
- Referred to as "legal highs" or "research chemicals"
- Often small modifications to currently controlled substances which make them legal
- Readily available on the internet

FLUALPRAZOLAM 1MG

BRAND: BLUE MAN CHEMICALS
PRODUCT CODE: FLUALPRAZOLAM
AVAILABILITY: IN STOCK

AVAILABLE OPTIONS

* Select Number of Pellets:

- 10 Pellets (+10.00€)
- 25 Pellets (+20.00€)
- 50 Pellets (+35.00€)

PIPERIDYLTHIAMBUTENE .HCL

Piperidylthiambutene (Piperidinohton) is an opioid analgesic drug from the thiambutene family, which has around the same potency as morphine. If sold / was obtained for the purpose of human consumption it could be considered a controlled substance in some

Item Code: LF-0061

(1) Write a review

USD $105.00 ~~$300.00~~ You Save: 65%

Formal Name : **1-[4,4-DI(2-thienyl)-3-buten-2-yl]piperidine**

Chemical Formula: **C17H21NS2**

Molecular Weight: **303.485 g/mol**

CAS NO: **54160-31-5**

WEIGHT	1g	5g	10g	25g	50g
PRICE	$105.00 (per gram)	$40.00 (per gram)	$28.00 (per gram)	$19.20 (per gram)	$15.00 (per gram)

Designer Benzodiazepines

- Often mixed with opiates or components of counterfeit tablets
- Increase potential for overdose with opiates

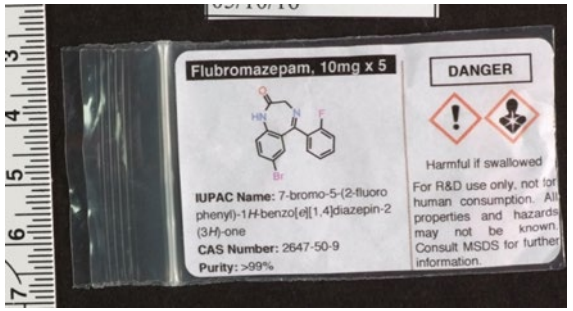
Flualprazolam*

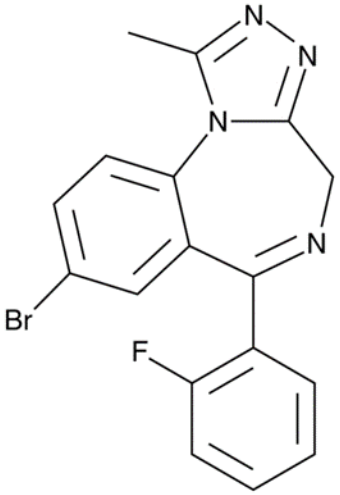
Etizolam

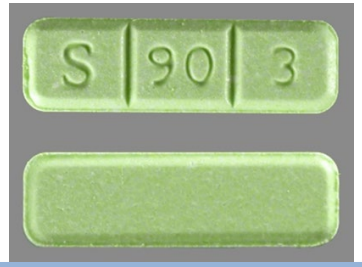
Flubromazolam

Bromazolam

Clonazolam







*Emergency scheduled 10/27/20

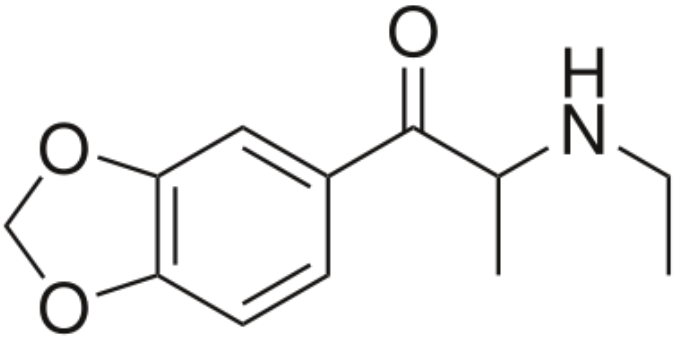
Synthetic Cathinones

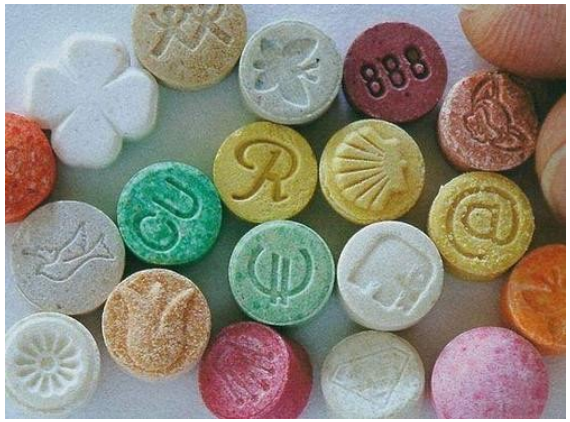
- Often seen in illicit tablets & in combination w/ methamphetamine

N-Butyl pentylone*

Ethyl heptedrone*

Benzylone* – 3,4-methylenedioxy-N-benzyl cathinone

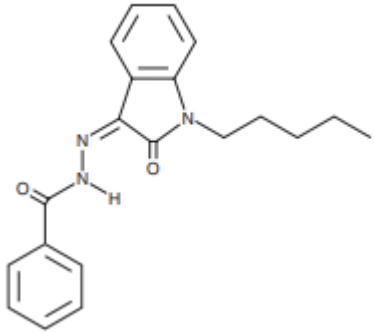




Not specifically listed but controlled by structural language

Synthetic Cannabinoids

- Decrease in cases
- A few new substances
- **BZO-POXIZID**
- **ADB-5Br-INACA** (paper sent to jail)
- Illicit Tablets
- **MMB-FUBINACA*** (combination w/ Eutylone)



*Controlled

Other Substances

Xylazine

-Veterinary anesthesia/tranquilizer

-Component in heroin/fentanyl samples

Tiletamine

-Veterinary anesthesia/ tranquilizer

- Schedule III in combination w/ zolazepam

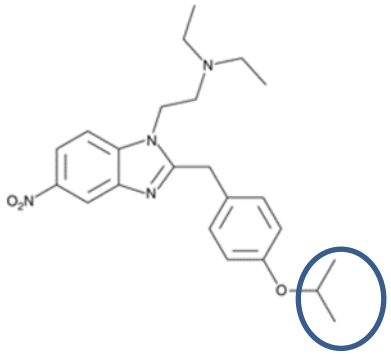
The Nitazenes

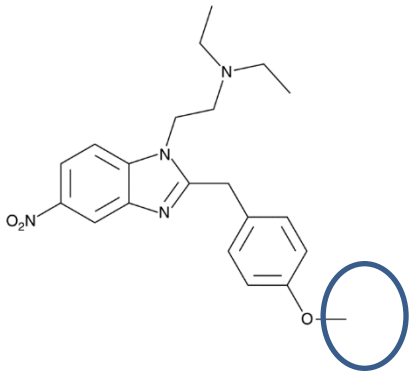
- Often mixed with other opiates or designer benzodiazepines
- Similar potency to fentanyl
- Schedule I – 9 synthetic benzimidazole-opioid substances

Isotonitazene*

Metonitazene**

Flunitazene**





*Emergency scheduled 6/5/20

**Scheduled 7/25/22 by Administrative Rule

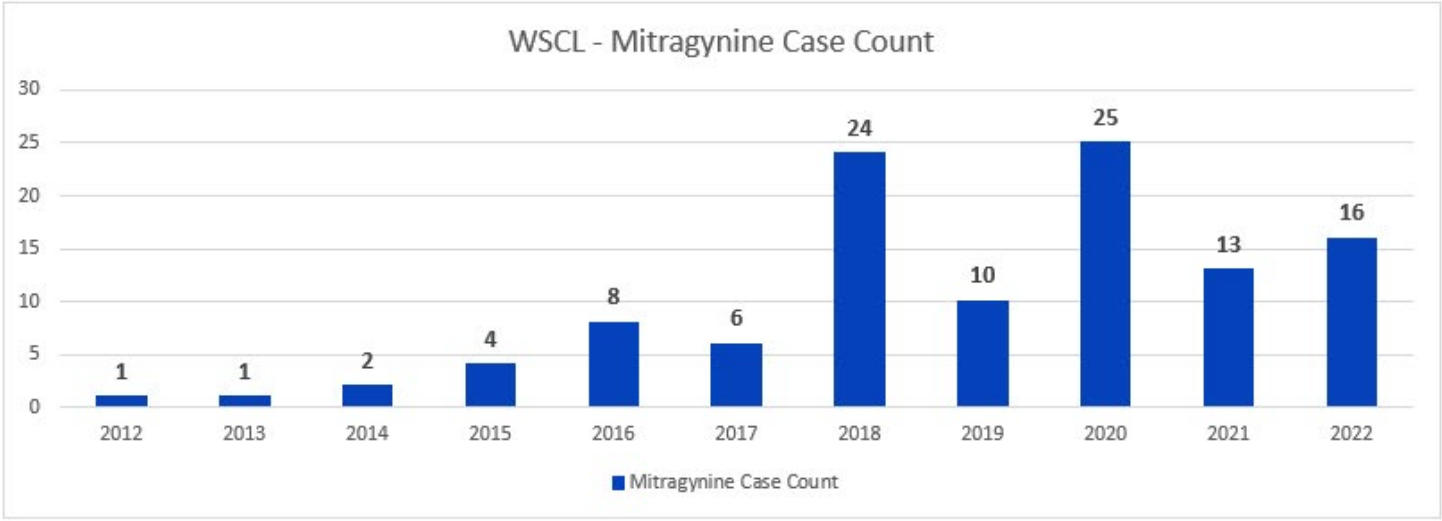
Kratom

- Major psychoactive compounds are mitragynine and 7-hydroxymitragynine (currently schedule I)
- Stimulant effects at low doses
- Sedative effects at higher doses
- CSB currently evaluating kratom with 8 factor analysis defined in 961.11(1m) to consider descheduling psychoactive compounds

WSCL Kratom Cases

WISCONSIN STATE CRIME LABORATORIES

Madison ▪ Milwaukee ▪ Wausau



THC isomers

- WSCL cases of delta-8-THC
- Occurs naturally in Cannabis in trace levels
- Most likely produced by conversion from CBD (hemp)
- Less psychoactive than delta-9-THC
- Other isomers and products being marketed
  - delta-10-THC; delta-6a,10-THC
  - THC acetate
- Legality?

  "Delta-8 Tetrahydrocannabinol (THC)" *Wisconsin Legislative Council Issue Brief,* July 2021

NPS Discovery

Center for Forensic Research and Education (CFRE)

Includes seized drug samples and biological samples

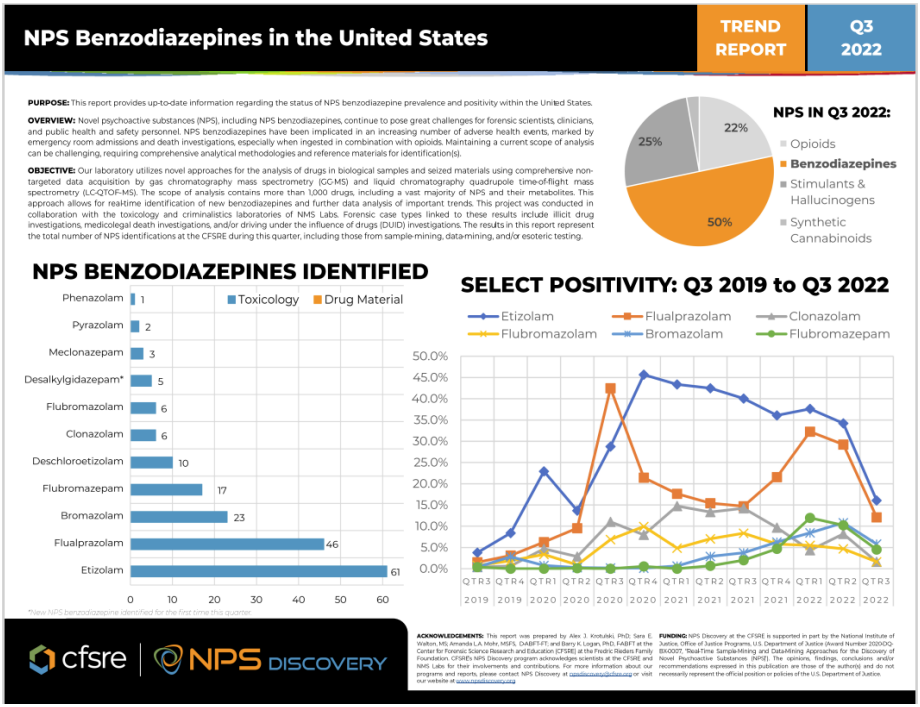
https://www.npsdiscovery.org/

NPS Discovery Dashboard →

Monographs →

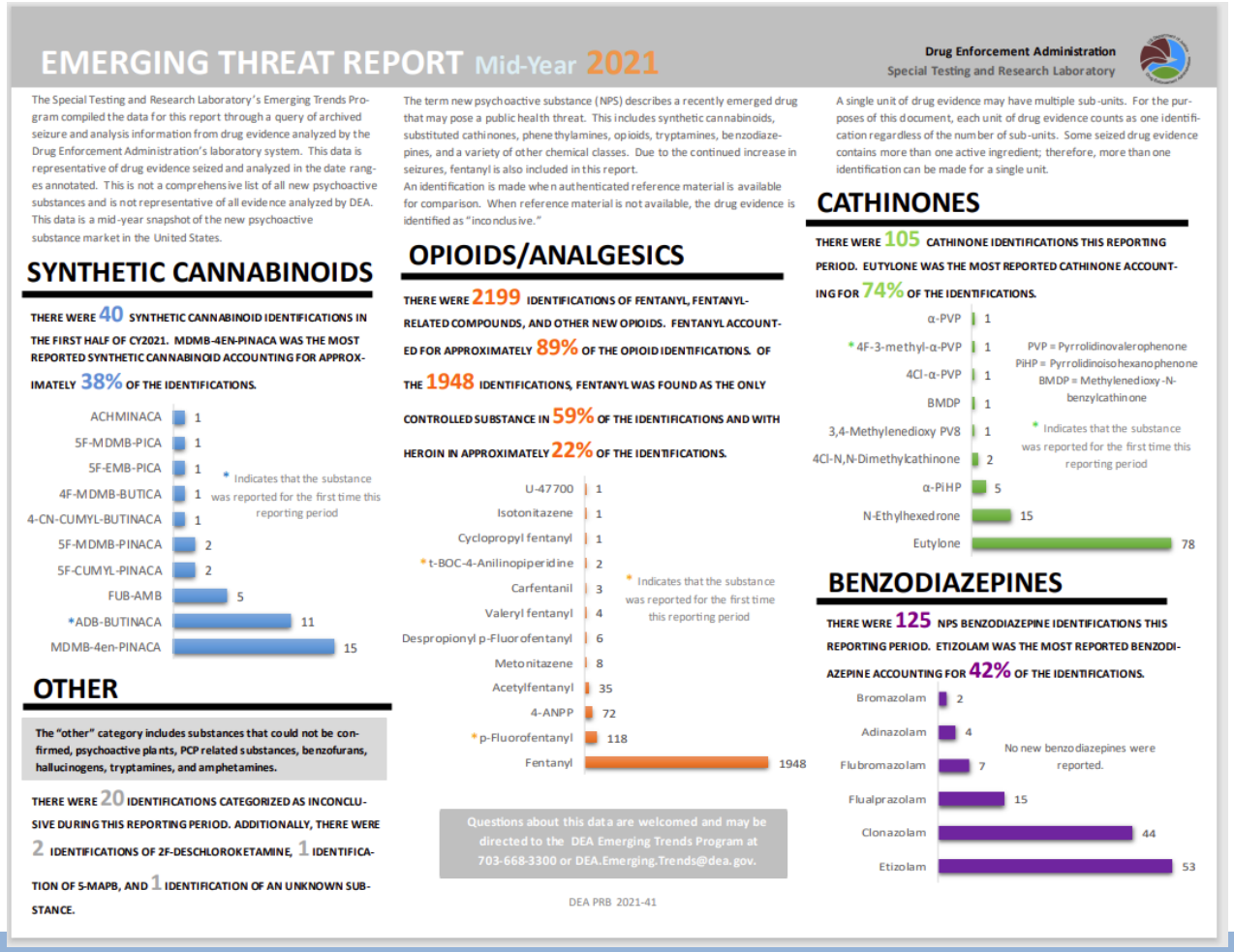
Trend Reports →

Public Alerts →



Emerging Threat Report - DEA

DEA Emerging Threat Reports | CESAR | Center for Substance Abuse Research | University of Maryland (umd.edu)



EMERGING THREAT REPORT Mid-Year 2021

Drug Enforcement Administration
Special Testing and Research Laboratory

The Special Testing and Research Laboratory's Emerging Trends Program compiled the data for this report through a query of archived seizure and analysis information from drug evidence analyzed by the Drug Enforcement Administration's laboratory system. This data is representative of drug evidence seized and analyzed in the date ranges annotated. This is not a comprehensive list of all new psychoactive substances and is not representative of all evidence analyzed by DEA. This data is a mid-year snapshot of the new psychoactive substance market in the United States.

The term new psychoactive substance (NPS) describes a recently emerged drug that may pose a public health threat. This includes synthetic cannabinoids, substituted cathinones, phenethylamines, opioids, tryptamines, benzodiazepines, and a variety of other chemical classes. Due to the continued increase in seizures, fentanyl is also included in this report.
An identification is made when authenticated reference material is available for comparison. When reference material is not available, the drug evidence is identified as "inconclusive."

A single unit of drug evidence may have multiple sub-units. For the purposes of this document, each unit of drug evidence counts as one identification regardless of the number of sub-units. Some seized drug evidence contains more than one active ingredient; therefore, more than one identification can be made for a single unit.

SYNTHETIC CANNABINOIDS

THERE WERE 40 SYNTHETIC CANNABINOID IDENTIFICATIONS IN THE FIRST HALF OF CY2021. MDMB-4EN-PINACA WAS THE MOST REPORTED SYNTHETIC CANNABINOID ACCOUNTING FOR APPROXIMATELY 38% OF THE IDENTIFICATIONS.

OTHER

The "other" category includes substances that could not be confirmed, psychoactive plants, PCP related substances, benzofurans, hallucinogens, tryptamines, and amphetamines.

THERE WERE 20 IDENTIFICATIONS CATEGORIZED AS INCONCLUSIVE DURING THIS REPORTING PERIOD. ADDITIONALLY, THERE WERE 2 IDENTIFICATIONS OF 2F-DESCHLOROKETAMINE, 1 IDENTIFICATION OF 5-MAPB, AND 1 IDENTIFICATION OF AN UNKNOWN SUBSTANCE.

OPIOIDS/ANALGESICS

THERE WERE 2199 IDENTIFICATIONS OF FENTANYL, FENTANYL-RELATED COMPOUNDS, AND OTHER NEW OPIOIDS. FENTANYL ACCOUNTED FOR APPROXIMATELY 89% OF THE OPIOID IDENTIFICATIONS. OF THE 1948 IDENTIFICATIONS, FENTANYL WAS FOUND AS THE ONLY CONTROLLED SUBSTANCE IN 59% OF THE IDENTIFICATIONS AND WITH HEROIN IN APPROXIMATELY 22% OF THE IDENTIFICATIONS.

Questions about this data are welcomed and may be directed to the DEA Emerging Trends Program at 703-668-3300 or DEA.Emerging.Trends@dea.gov.

DEA PRB 2021-41

CATHINONES

THERE WERE 105 CATHINONE IDENTIFICATIONS THIS REPORTING PERIOD. EUTYLONE WAS THE MOST REPORTED CATHINONE ACCOUNTING FOR 74% OF THE IDENTIFICATIONS.

BENZODIAZEPINES

THERE WERE 125 NPS BENZODIAZEPINE IDENTIFICATIONS THIS REPORTING PERIOD. ETIZOLAM WAS THE MOST REPORTED BENZODIAZEPINE ACCOUNTING FOR 42% OF THE IDENTIFICATIONS.

References

"WHO Expert Committee on Drug Dependence Critical Review -Isomers of THC", *World Health Organization,* 2018

"Delta-8 Tetrahydrocannabinol (THC)" *Wisconsin Legislative Council Issue Brief,* July 2021

Sandy Koresch
Contact Information:
Koreschsm@doj.state.wi.us
414-382-7500

Does Kratom Meet Wisconsin's 8-Factor Criteria for Scheduling?

November 11, 2022

AMERICAN KRATOM ASSOCIATION

1

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AMERICAN KRATOM ASSOCIATION

8-Factor Analysis for Scheduling

WI Code § 961 - CONTROLLED SUBSTANCES ACT

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

Section 201 (c), [21 U.S.C. § 811 (c)]

(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.

2

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Regulatory Status of Kratom in the United States

STATE	DATE OF BAN
WISCONSIN*	2014
INDIANA	2014
ARKANSAS*	2015
ALABAMA	2016
VERMONT*	2016
RHODE ISLAND*	2017

* Under Review

STATE	KCPA
UTAH	2019
GEORGIA	2019
ARIZONA	2019
NEVADA	2019
OKLAHOMA	2020
OREGON	2022
COLORADO	2022

3

3

AMERICAN KRATOM ASSOCIATION

State of Rhode Island

HOUSE OF REPRESENTATIVES

REPRESENTATIVE BRIAN PATRICK KENNEDY, *District 38*
Speaker Pro Tempore
Committee on Corporations
Committee on Rules
Committee on Innovation, Internet and Technology
Committee on State Government and Elections

November 1, 2022

Utpala Bandy, MD, MPH
Interim Director
Rhode Island Department of Health
3 Capitol Hill
Providence, Rhode Island 02908

Dear Dr. Bandy:

Representative Edwards and I have several recommendations flowing from our discussion that will inform our planning for the upcoming legislative session where we will propose a regulatory framework that will fill the gap to provide appropriate protections for consumers. We appreciated greatly the acknowledgment of the Department that emerging science confirms that kratom does not meet scheduling requirements in Rhode Island's P.L. 1974, ch. 183, §2; P.L. 1979, ch. 168, § 1.

4

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AMERICAN KRATOM ASSOCIATION

REVIEWS OF KRATOM'S SAFETY AND ADDICTION LIABILITY

OCTOBER 13, 2016: WITHDRAWAL OF EMERGENCY SCHEDULING RECOMMENDATION

DEA is withdrawing the August 31, 2016, notice of intent; and soliciting comments from the public regarding the scheduling of mitragynine and 7-hydroxymitragynine under the Controlled Substances Act.

U.S. Department of Health & Human Services

AUGUST 16, 2018: WITHDRAWAL OF KRATOM SCHEDULING RECOMMENDATION

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.

Assistant Secretary of Health, Brett Giroir, MD

World Health Organization

December 1, 2021: INSUFFICENT EVIDENCE TO RECOMMEND SCHEDULING

Expert Committee on Drug Dependence (ECDD): The Committee concluded that there is insufficient evidence to recommend a critical review of kratom.

5

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U.S. Department of Health & Human Services

Dr. Brett Girior
Assistant Secretary of Health

AUGUST 16, 2018, WITHDRAWAL OF KRATOM SCHEDULING RECOMMENDATION

FDA's recommendation [to ban kratom] was rejected because of embarrassingly poor evidence and data, and a failure to consider overall public health.

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6

U.S. Department of Health & Human Services

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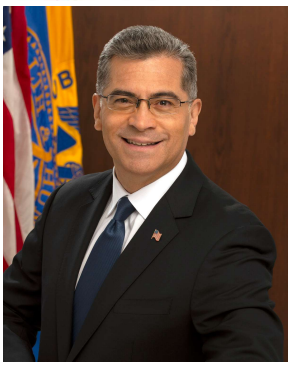

Xavier Becerra
Secretary of HHS

March 16, 2022, response to Congressional inquiry from Sen. Mike Lee and Cong. Mark Pocan on HHS position on kratom:

"To that end, HHS and its component agencies are working to address knowledge gaps through research."

"Many kratom-involved overdose deaths have occurred after use of adulterated kratom products or taking kratom with other substances."

7

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IS KRATOM DANGEROUSLY ADDICTIVE?

NIH National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

Published in 2018

Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine

Scott E Hemby [1], Scot McIntosh [1], Francisco Leon [2], Stephen J Cutler [3], Christopher R McCurdy [2]

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

Abuse liability of mitragynine assessed with a self-administration procedure in rats

Kai Yue [1], Theresa A Kopajtic [2], Jonathan L Katz [3]

These results suggest a limited abuse liability of mitragynine and potential for mitragynine treatment to specifically reduce opioid abuse . . .

8

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KRATOM OR ADULTERATED KRATOM?

> J Anal Toxicol. 2011 May;35(4):242-7. doi: 10.1093/anatox/35.4.242.

Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend Krypton

Robert Kronstrand [1], Markus Roman, Gunilla Thelander, Anders Eriksson

We believe that the **addition of the potent mu-receptor agonist O-desmethyltramadol** to powdered leaves from kratom **contributed to the unintentional death of the nine cases presented . . .**

9

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UF UNIVERSITY of FLORIDA

Christopher McCurdy, PhD
Leading scientist on kratom safety and addiction -- NIDA
University of Florida

"We know that very few deaths are attributable to a kratom product alone, and for those that are, there could be extreme circumstances, in terms of overdosing, or it could be adulterated with synthetic compounds," such as fentanyl derivatives or other novel psychoactive substances that are unknown or undetected."

NIH Record, June 24, 2022

10

10

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KRATOM AS A TOOL FOR HARM REDUCTION

NIH National Institute on Drug Abuse

Dr. Nora Volkow
NIDA Director

CONGRESSIONAL TESTIMONY ON MAY 17, 2022, ON WHAT HHS IS DOING TO ADDRESS DRUG OVERDOSE CRISIS:

". . . 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 [a safe and effective treatment for opiate use disorder] but could be utilized also for decreasing withdrawal or depression. . ."

11

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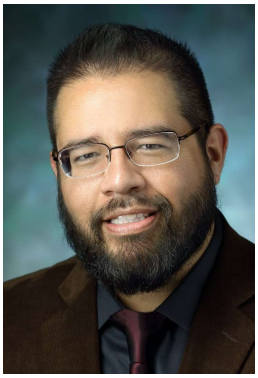
AMERICAN KRATOM ASSOCIATION

JOHNS HOPKINS UNIVERSITY



Albert Garcia-Romeu, PhD
Johns Hopkins University

"Kratom is used among white, middle-aged Americans for symptoms of pain, anxiety, depression, and opioid withdrawal. Although regular use was typical, kratom-related SUD and serious adverse effects were uncommon."

Among those treating opioid dependence:

- **87% reported relief from withdrawal symptoms**
- **35% were free from opioids >1 year**

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AMERICAN KRATOM ASSOCIATION

FISCAL YEAR 2023 APPROPRIATIONS, Page 218"

"Kratom.—Combating Opioid Overdoses.—The Committee commends NIDA for funding studies on kratom based on promising results that unadulterated kratom may provide help for some Americans struggling with addictions, given its analgesic and less addictive properties as compared to opioids."

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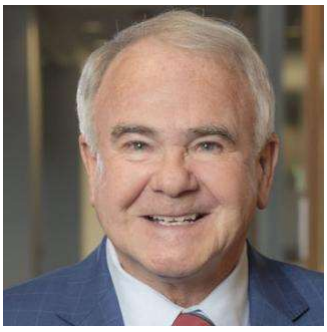
AMERICAN KRATOM ASSOCIATION

AMA



Gerald E. Harmon, MD
Immediate Past President, AMA

Letter responding to inquiry from state legislators, June 11, 2022:

"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."

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AMERICAN KRATOM ASSOCIATION

The Solution: Kratom Consumer Protection Act (KCPA)

The KCPA regulations on the sale of kratom products in Wisconsin:

- Meet GMP standards for dietary supplements
- No adulterated kratom products can be sold in Wisconsin
- No synthetic kratom alkaloids
- No kratom extract with residual solvents higher than allowed by USP 467 for food products
- No kratom containing a 7-Hyroxymitragynine in the alkaloid fraction greater than 2% of the overall alkaloid composition of the product
- No kratom product that is not labeled with ingredients and directions for use – and no illegal therapeutic claims
- No sales to minors

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Albert Garcia-Romeu, PhD
Johns Hopkins University

Oliver Grundmann, PhD
University of Florida

Jack Henningfield, PhD
Johns Hopkins University

Marilyn Huestis, PhD
Huestis & Smith Toxicology

Kratom Science Update: Evidence-Based Facts

October 2022

"What is clearly needed is balanced regulation to ensure that kratom products purchased by consumers are pure and unadulterated, in other words meeting the same types of standards that apply to other food products, and even bottled water. Steps toward such standards were taken in states that passed their own versions of kratom consumer protection act laws. Ultimately, the Food and Drug Administration (FDA) needs to develop national performance standards for kratom as it does for other products. Such standards will help ensure access to kratom products that are appropriately marketed and are without contaminants and adulterants that might pose safety risks."

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State of Rhode Island

HOUSE OF REPRESENTATIVES

REPRESENTATIVE BRIAN PATRICK KENNEDY, *District 38*
Speaker Pro Tempore
Committee on Corporations
Committee on Rules
Committee on Innovation, Internet and Technology
Committee on State Government and Elections

November 1, 2022

Utpala Bandy, MD, MPH
Interim Director
Rhode Island Department of Health
3 Capitol Hill
Providence, Rhode Island 02908

Dear Dr. Bandy:

Thank you for hosting the meeting at your offices on October 25, 2022, with Utah State Senator Curt Bramble; Mac Haddow, Senior Fellow on Public Policy with the American Kratom Association (AKA); Representative John G. Edwards, and myself. The discussion on the current ban on kratom's alkaloids, mitragynine and 7-hydroxymitragynine, that were designated as a Schedule I substances on May 31, 2017, was very productive.

Representative Edwards and I have several recommendations flowing from our discussion that will inform our planning for the upcoming legislative session where we will propose a regulatory framework that will fill the gap to provide appropriate protections for consumers. We appreciated greatly the acknowledgment of the Department that emerging science confirms that kratom does not meet scheduling requirements in Rhode Island's P.L. 1974, ch. 183, §2; P.L. 1979, ch. 168, § 1.

We would welcome your plan on the timing of withdrawing the current scheduling of kratom. We are committed to the passage of the Rhode Island Kratom Consumer Protection Act (KCPA) that will be filed in the upcoming Legislative session that will provide the protections for consumers from dangerously adulterated kratom products.

We are sensitive to the concerns raised by your staff in our meeting about resources required to properly regulate the sale of kratom products that would be compliant with the requirements of the proposed KCPA without creating an unfunded Department mandate. We offer the following recommendations to address this issue:

Product Registration:

A kratom processor (registrant) shall register annually any kratom product intended to be offered for sale to an end consumer in Rhode Island that is in an approved kratom delivery form pay a fee (adjusted annually) to cover all administrative costs

P.O. BOX 1001, ASHAWAY, RHODE ISLAND, 02804-0018
ROOM 201, STATE HOUSE, PROVIDENCE, RHODE ISLAND 02903
RES: 401.377.8818 BUS: 401.222.6580
EMAIL: rep-kennedy@rilegislature.gov

for processing and administering such registrations. The registration shall include a certificate of analysis (COA) from a certified independent third-party laboratory showing compliance with the KCPA requirements for safe kratom products.

Product Compliance Violation Report:

Upon receipt of a violation report on any kratom product offered for sale, the Department shall require the registrant to produce an updated and current COA in a reasonable time frame from a certified independent third-party laboratory showing compliance with the KCPA requirements for safe kratom products. If the registrant does not provide the COA in the specified time frame, the registration for that product is revoked.

Adverse Event Reports:

Upon receipt of any adverse event (AE) related to a registered kratom product, the registrant shall be required to submit a copy via certified mail to the Department of their AE report that is required to be submitted to the U.S. Food and Drug Administration (FDA) under Section 761 of the Federal Food Drug & Cosmetic Act. Any documented failure to report an AE to the Department shall authorize the Department to revoke the product's registration.

Third Party Verification:

If the Department has a reasonable basis to require an independent third-party test of a registered kratom product by a laboratory of the Department's choice, the registrant shall be required to submit payment for the test within 30 days of receipt of the invoice from the Department for the testing. If the registrant does not tender payment to the Department, the Department shall revoke the registration for that product.

We offer these recommendations to start discussions with the Department and interested stakeholders on how to balance protecting Rhode Island kratom consumers with a safe pure kratom product and not a potentially dangerous adulterated product. It would assure the Department's regulatory costs are funded from kratom processors rather than taxpayers. We believe it would be useful to convene a stakeholder's work session prior to finalizing legislative language for the planned KCPA as a follow-up to our meeting on October 25.

We recognize that the withdrawal of the current kratom scheduling is an administrative procedure that will be addressed internally by the Department, so we would request you provide a timeline for that process by November 14, 2022. That will allow us time to then provide the input to Legislative Counsel for bill drafting of the KCPA based on the regulatory framework that we can agree on to ensure the Department has adequate resources to implement the proposed KCPA upon its enactment.

We would also ask that you provide some options on dates convenient to your schedule when we could convene a proposed stakeholder's work session to resolve any outstanding issues that should be included in the proposed KCPA that we will then submit to Legislative Counsel for final drafting.

Respectfully submitted,

Brian Patrick Kennedy
Speaker Pro Tempore
Rhode Island House of Representatives

cc: Speaker K. Joseph Shekarchi
Representative John G. Edwards
Senator Curt Bramble, Utah State Senate
Seema Dixit, Deputy Director RIDOH
Neil Hytinen, Chief Public Affairs Officer/Legislative Liaison RIDOH
Mac Haddow, Senior Fellow on Public Policy AKA

as a result of this proposed rule would be less than two percent, or an estimated $37,151.00, of the estimated total $1,857,560.00 cost to all steel importers to process the on-line automatic licenses. These calculations were based on an hourly pay rate of $20.00 multiplied by the estimated 92,878 total annual burden hours. Based on the current patterns of license applications, the vast majority of the licenses are applied for by large companies. The approximate cost of a single license is less than 10 minutes of the applicant's time and this is reduced if applicants use templates or the electronic data interface for multiple licenses. This amounts to an average cost per license of $3.33.

This proposed rule contains collection-of-information requirements subject to review and approval by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA).

These requirements have been approved by OMB (OMB No.: 0625–0245; Expiration Date: 1/31/2018). Public reporting for this collection of information is estimated to be less than 10 minutes per response, including the time for reviewing instructions, and completing and reviewing the collection of information.

Paperwork Reduction Act Data

OMB Number: 0625–0245.

ITA Number: ITA–4141P.

Type of Review: Regular Submission.

Affected Public: Business or other for-profit.

Estimated Number of Registered Users: 3,500.

Estimated Time per Response: Less than 10 minutes.

Estimated Total Annual Burden Hours: 92,878 hours.

Estimated Total Annual Costs: $0.00.

Notwithstanding any other provision of law, no person is required to respond to nor shall a person be subject to a penalty for failure to comply with a collection of information subject to the requirements of the Paperwork Reduction Act unless that collection of information displays a current valid OMB Control Number.

Executive Order 12866

This rule has been determined to be not significant for purposes of Executive Order 12866.

Executive Order 13132

This rule does not contain policies with federalism implications as that term is defined in EO 13132.

List of Subjects in 19 CFR Part 360

Administrative practice and procedure, Business and industry, Imports, Reporting and recordkeeping requirements, Steel.

Dated: October 4, 2016.

Ken Hyatt,

Acting Under Secretary for International Trade.

For the reasons discussed above, we propose amending 19 CFR part 360 as follows:

PART 360—STEEL IMPORT MONITORING AND ANALYSIS SYSTEM

■ 1. The authority citation for part 360 continues to read as follows:

Authority: 13 U.S.C. 301(a) and 302.

■ 2. Section 360.105 is revised to read as follows.

§ 360.105 Duration of the steel import licensing requirement.

The licensing program will be in effect through March 21, 2022, but may be extended upon review and notification in the **Federal Register** prior to this expiration date. Licenses will be required for all subject imports entered during this period, even if the entry summary documents are not filed until after the expiration of this program. The licenses will be valid for 10 business days after the expiration of this program to allow for the final filing of required Customs documentation.

[FR Doc. 2016–24649 Filed 10–12–16; 8:45 am]

BILLING CODE 3510–DS–P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–442W]

Withdrawal of Notice of Intent to Temporarily Place Mitragynine and 7-Hydroxymitragynine Into Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Withdrawal of Notice of Intent; Solicitation of Comments.

SUMMARY: On August 31, 2016, the Drug Enforcement Administration (DEA) published in the **Federal Register** a notice of intent to temporarily place mitragynine and 7-hydroxymitragynine, which are the main psychoactive constituents of the plant Mitragyna speciosa, also referred to as kratom, into schedule I pursuant to the temporary scheduling provisions of the Controlled Substances Act. Since publishing that notice, DEA has received numerous comments from members of the public challenging the scheduling action and requesting that the agency consider those comments and accompanying information before taking further action. In addition, DEA will receive from the Food and Drug Administration (FDA) a scientific and medical evaluation and scheduling recommendation for these substances, which DEA previously requested.

DEA is therefore taking the following actions: DEA is withdrawing the August 31, 2016 notice of intent; and soliciting comments from the public regarding the scheduling of mitragynine and 7-hydroxymitragynine under the Controlled Substances Act.

DATES: The notice of intent that was published on August 31, 2016 (81 FR 59929) is withdrawn as of October 13, 2016. The comment period will be open until December 1, 2016. All comments for the public record must be submitted electronically or in writing in accordance with the procedures outlined below. Electronic comments must be submitted, and written comments must be postmarked, on or before December 1, 2016. Commenters should be aware that the electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. Please note that if you previously submitted a comment via email or regular mail following the August 31, 2016 notice, that comment is being considered by DEA—it is not necessary to resubmit the same comment *unless* you wish to provide additional information, or you wish to have your comment posted for public view in accordance with the instructions provided below.

ADDRESSES: To ensure proper handling of comments, please reference ''Docket No. DEA–442W'' on all correspondence, including any attachments.

• *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the Web page or attach a file for lengthier comments. Please go to *http://www.regulations.gov* and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on *Regulations.gov*. If you have

received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.

• *Paper comments:* Paper comments that duplicate the electronic submission are not necessary and are discouraged. Should you wish to mail a paper comment *in lieu of* an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/ODW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Michael J. Lewis, Diversion Control Division, Drug Enforcement Administration; Mailing Address: 8701 Morrissette Drive, Springfield, Virginia 22152; Telephone: (202) 598–6812.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received in response to this notice are considered part of the public record. If you previously submitted a comment via email or regular mail following the August 31, 2016 notice, that comment is being considered by DEA—it is not necessary to resubmit the same comment unless you wish to provide additional information, or you wish to have your comment posted for public view in accordance with the instructions provided below.

All comments received in response to this notice of opportunity to comment will, unless reasonable cause is given, be made available by DEA for public inspection online at *http://www.regulations.gov.* Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act (FOIA) applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase ''PERSONAL IDENTIFYING INFORMATION'' in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase ''CONFIDENTIAL BUSINESS INFORMATION'' in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information and confidential business information identified as directed above will generally be made publicly available in redacted form. If a comment has so much personal identifying information or confidential business information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to *http://www.regulations.gov* may include any personal identifying information (such as name, address, and phone number) or confidential business information included in the text of your electronic submission that is not identified as directed above as personal or confidential.

Background

Withdrawal of Notice of Intent

The Controlled Substances Act (CSA) contains a temporary scheduling provision, 21 U.S.C. 811(h), pursuant to which the DEA Administrator [1] may temporarily place a substance in schedule I where he finds that doing so is necessary to avoid an imminent hazard to the public safety. This provision of the CSA requires DEA to publish a notice in the **Federal Register** of its intent to issue a temporary scheduling order at least 30 days before issuing any such order. DEA published such a notice of intent on August 31, 2016, with respect to mitragynine and 7-hydroxymitragynine, which are the main psychoactive constituents of the plant commonly known as kratom. 81 FR 59929.

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).[2]

Accordingly, the August 31, 2016, notice of intent to temporarily place mitragynine and 7-hydroxymitragynine in schedule I is withdrawn. Mitragynine and 7-hydroxymitragynine therefore remain—as has been the case—noncontrolled substances under federal law.[3]

Consideration of Public Comments and FDA's Analysis

With respect to mitragynine and 7-hydroxymitragynine, DEA will consider all public comments received under the above procedures, as well as FDA's scientific and medical evaluation and scheduling recommendation for these substances. Once DEA has received and considered all of this information, DEA will decide whether to proceed with permanent scheduling of mitragynine and 7-hydroxymitragynine, or both permanent and temporary scheduling of these substances.

Permanent Scheduling Process: As the CSA provides, if DEA determines that the medical and scientific facts contained in the FDA scheduling evaluation, along with all other relevant data and information, constitute substantial evidence of potential for abuse to support permanent scheduling of mitragynine and 7-hydroxymitragynine, DEA will publish in the **Federal Register** a notice of proposed rulemaking, which will give interested members of the public an additional opportunity to submit comments and request a hearing.[4] As provided in 21 U.S.C. 811(a), permanent scheduling rules shall be made on the record after opportunity for a hearing pursuant to the rulemaking procedures prescribed by 5 U.S.C. 553, 556, and 557.

Temporary Scheduling Process: The pendency of permanent scheduling proceedings for a substance does not preclude a simultaneous or subsequent order to temporarily control that substance. If DEA finds in light of FDA's scientific and medical evaluation and after consideration of all public

[1] The Attorney General has delegated her functions under the CSA to the DEA Administrator.

[2] Section 811(b) provides that the scientific and medical evaluation and scheduling recommendation shall be conducted by the Secretary of Health and Human Services (HHS). This function has been delegated to the Assistant Secretary for Health. 58 FR 35460 (1993). Within HHS, the FDA has primary responsibility for conducting the evaluation and making the recommendation.

[3] Under some state and local laws, kratom and/or its constituents mitragynine and 7-hydroxymitragynine are currently listed as controlled substances or otherwise subject to control. Nothing in this publication alters the validity of such laws, or any pending state efforts to implement those laws or enact new laws controlling these substances.

[4] In permanent scheduling actions, when DEA reviews the FDA evaluation and scheduling recommendation, the FDA determinations as to scientific and medical matters are binding on DEA. 21 U.S.C. 811(b).

comments and other relevant information that, based on the criteria of section 811(h), temporary placement of mitragynine and 7-hydroxymitragynine in schedule I is necessary to avoid an imminent hazard to the public safety, DEA will follow the statutory procedures for issuing such a temporary scheduling order. As indicated above, before issuing such a temporary scheduling order, DEA would be required to publish in the **Federal Register** a new notice of intent.

Dated: October 6, 2016.

Chuck Rosenberg,

Acting Administrator.

[FR Doc. 2016–24659 Filed 10–12–16; 8:45 am]

BILLING CODE 4410–09–P

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 300

[REG–108934–16]

RIN 1545–BN38

User Fees for Offers in Compromise

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Notice of proposed rulemaking and notice of public hearing.

SUMMARY: This document contains proposed amendments to the regulations that provide user fees for offers in compromise. The proposed amendments affect taxpayers who wish to pay their liabilities through offers in compromise. The proposed effective date for these proposed amendments to the regulations is for offers in compromise submitted on or after February 27, 2017. This document also provides a notice of public hearing on these proposed amendments to the regulations.

DATES: Written or electronic comments must be received by November 28, 2016. Outlines of topics to be discussed at the public hearing scheduled for December 16, 2016 at 10:00 a.m. must be received by November 28, 2016.

ADDRESSES: Send submissions to: Internal Revenue Service, CC:PA:LPD:PR (REG–108934–16), Room 5203, Post Office Box 7604, Ben Franklin Station, Washington, DC 20044. Submissions may be hand-delivered Monday through Friday between the hours of 8 a.m. and 4 p.m. to CC:PA:LPD:PR (REG–108934–16), Courier's Desk, Internal Revenue Service, 1111 Constitution Avenue NW., Washington, DC 20224 or sent electronically via the Federal eRulemaking Portal at *http://www.regulations.gov* (indicate IRS and REG–108934–16). The public hearing will be held in the Main IR Auditorium beginning at 10:00 a.m. in the Internal Revenue Service Building, 1111 Constitution Avenue NW., Washington, DC 20224.

FOR FURTHER INFORMATION CONTACT: Concerning the proposed amendments to the regulations, Maria Del Pilar Austin at (202) 317–5437; concerning submissions of comments, the hearing, or to be placed on the building access list to attend the hearing, Regina Johnson, at (202) 317–6901; concerning cost methodology, Eva Williams, at (202) 803–9728 (not toll-free numbers).

SUPPLEMENTARY INFORMATION:

Background

This document contains proposed regulations that would amend § 300.3 of the User Fee Regulations (26 CFR part 300), which provides for a user fee applicable to offers in compromise under section 7122 of the Internal Revenue Code (Code).

Section 7122(a) provides the Secretary the authority to compromise any civil or criminal case arising under the internal revenue laws, prior to the referral of that case to the Department of Justice. Section 7122(d)(1) requires the IRS to prescribe guidelines for officers and employees of the IRS to determine whether an offer in compromise is adequate and should be accepted to resolve a dispute. Those guidelines can generally be found in § 301.7122–1. Under those guidelines, an offer in compromise may be accepted if there is doubt as to liability, if there is doubt as to collectability, or if acceptance will promote effective tax administration. See § 301.7122–1(b).

When the IRS receives an offer in compromise, it initially determines whether the taxpayer submitting the offer is eligible for the offer in compromise program and, if the taxpayer is eligible, whether the offer submitted is otherwise processable. Currently, a taxpayer may be ineligible for the offer in compromise program for a number of reasons, including if the taxpayer is in bankruptcy or has not filed all required tax returns. The IRS will return an offer as nonprocessable if the taxpayer is ineligible or if the offer has not been properly submitted.

If the IRS determines the offer in compromise is processable, then except where the offer is made under section 7122(d)(3)(B) relating only to issues of liability and the case is processed without a financial investigation, the IRS investigates and verifies the taxpayer's financial information submitted with the offer to determine whether such a compromise is appropriate before accepting the terms of the offer in compromise. If the IRS initially rejects a processable offer in compromise based on an investigation of the taxpayer's financial position, section 7122(e)(1) provides that the IRS must conduct an independent administrative review of that decision before communicating the rejection to the taxpayer. If the independent administrative review upholds the IRS's initial decision to reject a processable offer in compromise, section 7122(e)(2) provides that the taxpayer is notified of the rejection and has the right to appeal the rejection to the IRS's Appeals Office. When the IRS accepts an offer in compromise, the IRS processes the payments and monitors the taxpayer's compliance with the terms of the offer.

Under § 300.3, the IRS currently charges $186 for processing an offer in compromise, which includes reviewing and monitoring the offer. Under § 300.3(b)(2)(i) and (ii), if a fee is charged and the offer is accepted to promote effective tax administration or accepted based on doubt as to collectability where the IRS has determined that collection of an amount greater than the amount offered would create economic hardship, then the user fee is applied against the amount to be paid under the offer unless the taxpayer requests that it be refunded. Section 300.3(b)(1)(i) and (ii) provide that no fee is charged if an offer is based solely on doubt as to liability, or made by a low-income taxpayer.

Explanation of Provisions

A. Overview

To bring the user fee rate for offers in compromise closer to the full cost to the IRS of providing this taxpayer specific service, the proposed regulations under § 300.3 would increase the user fee for an offer in compromise to $300. The proposed regulations do not modify other portions of the User Fee Regulations regarding offers in compromise, such as § 300.3(b)(1)(i) and (ii) which waive the user fee for offers in compromise submitted by low-income taxpayers and offers in compromise based solely on doubt as to liability. The increased user fee for offers in compromise is proposed to be effective for offers submitted on or after February 27, 2017.

B. User Fee Authority

The Independent Offices Appropriations Act (IOAA) (31 U.S.C.

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

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1038

WHO Expert Committee on Drug Dependence

Forty-fourth report

World Health Organization

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WHO Expert Committee on Drug Dependence

Forty-fourth report

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

World Health Organization

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Contents

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Abbreviations and acronyms

4-ANPP	4-anilino-*N*-phenethyl piperidine
CB_1	cannabinoid
CFSRE	Center for Forensic Science Research and Education (USA)
CND	Commission on Narcotic Drugs
CYP	cytochrome P450
DAMGO	[D-Ala2, *N*-mePhe4, Gly-ol]-enkephalin
DART	direct analysis in real time
DAT	dopamine receptor transporter
DEA	Drug Enforcement Administration (USA)
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DUID	driving under the influence of drugs
EC_{50}	half maximal effective concentration
ECDD	Expert Committee on Drug Dependence
ED_{50}	median effective dose
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GABA	γ-aminobutyric acid
GC	gas chromatography
GC–MS	gas chromatography–mass spectrometry
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
5-HT	5-hydroxytryptamine

IC_{50}	half maximal inhibitory concentration
INCB	International Narcotics Control Board
ip	intraperitoneal
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
K_i	inhibitory constant
LC	liquid chromatography
MDMA	±-3,4-methylenedioxymethamphetamine
MDMB	methyl 2,3-dimethyl butanoate
MDMB-4en-PINACA	methyl (*S*)-3,3-dimethyl-2-(1-(pent-4-en-1-yl)-1H-indazole-3 carboxamido)butanoate
MOR	μ-opioid receptor
MS	mass spectrometry
NET	norepinephrine receptor transporter
NFLIS	National Forensic Laboratory Information System (USA)
NMR	nuclear magnetic resonance
NPS	new psychoactive substance
SERT	serotonin receptor transporter
THC	Δ^9-tetrahydrocannabinol
TLC	thin-later chromatography
TOF	time of flight
UHPLC	ultra-high-performance liquid chromatography
UNODC	United Nations Office on Drugs and Crime
UV	ultraviolet

Executive summary

The International Drug Control Conventions of 1961 and 1971 mandate WHO to make recommendations to the United Nations Secretary-General on the need for and level of international control of psychoactive substances according to the advice of its independent scientific advisory body, the ECDD.

At its forty-fourth meeting, the ECDD critically reviewed five new psychoactive substances, comprising one synthetic cannabinoid receptor agonist (4F-MDMB-BICA), two novel synthetic opioids (brorphine and metonitazene) and two cathinones/stimulants (eutylone and benzylone). These substances had not previously been reviewed formally by WHO and are currently not under international control. A critical review of the use of each substance and its effects was undertaken so that the Expert Committee could determine whether the information available on these substances justified scheduling or a change in scheduling from that in the 1961 or 1971 Convention. In addition, the meeting pre-reviewed kratom, mitragynine and 7-hydroxymitragynine and phenibut to determine whether the current information justified a critical review.

After the Forty-fourth Meeting of the ECDD, WHO endorsed and submitted the following recommendations to the United Nations Secretary General for further consideration by the Commission on Narcotic Drugs.

	Substance name	Alternative name	International Union of Pure and Applied Chemistry (IUPAC) name
To be added to Schedule I of the Single Convention on Narcotic Drugs (1961)	Brorphine		3- {1- [1- (4-bromophenyl) ethyl] piperidin-4-yl} -1H-benzimidazol-2-one
	Metonitazene		*N,N*-Diethyl-2-(2-(4-methoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazol-1- yl) ethan-1-amine
To be added to Schedule II of the Convention on Psychotropic Substances (1971)	Eutylone	3,4-Methylenedioxy-*a*-ethylamino butiophenone	1-(Benzo[d][1,3]dioxol-5-yl)-2-(ethylamino)butan-1-one 1-(1,3-Benzodioxol-5-yl)-2-(ethylamino)butan-1- one
To be kept under surveillance	4F-MDMB-BICA	4F-MDMB-BUTICA	Methyl 2-({[1-(4-fluorobutyl)-1*H*-indol-3- yl] carbonyl}amino)-3,3-dimethylbutanoate Methyl 2-(1-(4-fluorobutyl)-1*H*-indole-3- carbaxamido)-3,3-dimethylbutanoate
	Benzylone	3,4-Methylenedioxy-*N*-benzylcathinone	1-(Benzo[d][1,3]dioxol-5-yl)-2- (benzylamino) propan-1-one
	Kratom, mitragynine, 7-hydroxymitragynine		
	Phenibut	4-Amino-3-phenyl-butyric acid	4-Amino-3-phenylbutanoic acid

1. Information session

On 11 October 2021, before the Expert Committee convened, an information session was held so that the Committee could hear presentations and question representatives of interested parties about data that had been provided on the substances under review.

The session was opened and chaired by Gilles Forte, Secretary of the ECDD.

Dilkushi Poovendran, Technical Officer, described the role and mandate of the ECDD with respect to the international drug control conventions. WHO has the mandate to assess the risks of abuse, dependence and harm to health of psychoactive substances and make recommendations to the Commission on Narcotic Drugs (CND) about the appropriate level of international control. When relevant, the ECDD also considers whether a substance has a medical or scientific application. This mandate is reinforced by several resolutions of the United Nations General Assembly and the CND. WHO fulfils its mandate through the ECDD in accordance with WHO guidance on the review of psychoactive substances for international control. The processes and procedures were developed by the World Health Assembly, and revisions were approved by the WHO Executive Board in 2010.

The 44th ECDD heard oral presentations by the following individuals: Don Land, Wat Ku Daeng Wat Yang Temple, Thailand; Greg Fryett, Fryett, Thailand; Ekkasit Kumarnsit, Prince of Songkla University, Thailand; Evgeny Kruptisky, V.M. Bekhterev National Medical Center for Psychiatry and Neurology, Russian Federation; Fabian Pitter Steinmetz, European Coalition for Just and Effective Drug Policies, Germany; Christopher McCurdy, University of Florida, USA; David Heldreth, Panacea Plant Sciences, USA; Jack Henningfield, USA; Mac Haddow, American Kratom Association, USA; Marilyn Huestis, USA; and Walter Prozialeck, Midwestern University, USA.

Additionally, the secretariat received written statements from the following individuals, which were presented to the 44th ECDD: Fabian Pitter Steinmetz, European Coalition for Just and Effective Drug Policies, Germany; Christopher McCurdy, University of Florida, USA; David Heldreth Jr, Panacea Plant Sciences, USA; Marilyn Huestis, USA; Walter Prozialeck, Midwestern University, USA; Mac Haddow, American Kratom Association, USA; Jakub Zientala, Zientala, Netherlands; Evgeny Krupitsky, V.M. Bekhterev National Medical Center for Psychiatry and Neurology, Russian Federation; Daniel Wang, Pinney Associates, Inc., USA; Lora Romney, International Plant and Herbal Alliance, USA; Peter Candland, American Kratom Association, USA; Christopher Deaney, Christopher's Organic Botanicals, USA; Marek Chawarski, USA; Denise Sigelkow, USA; Mohammad Farris Iman Leong Bin Abdullah, Malaysia; Martin Jelsma, Transnational Institute, Netherlands; Konstantin Kunts, Smart Solutions Integration Agency, Russian Federation; Gloria Lai, International Drug Policy Consortium, Thailand; and Lukáš Vlasák, Czech Republic.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Detections of benzylone may be under-reported if there is no routine screening for this substance in all laboratories that receive samples for analysis.

3.2 Pre-review reports

3.2.1 Kratom (Mitragyna speciosa), mitragynine and 7-hydroxymitragynine

1. Substance identification

A. International Nonproprietary Name (INN)

Kratom: No information was available.
Mitragynine: No information was available.
7-Hydroxymitragynine: No information was available.

B. Chemical Abstracts Services Registry Number

Kratom: Not applicable.
Mitragynine:

4098-40-2 (-)-Mitragynine free base
1908497-94-8 (+)-Mitragynine free base
36455-45-5 Mitragynine hydrochloride
58375-35-2 Mitragynine hydriodide
11047-38-4 Mitragynine hydrobromide
11047-42-0 Mitragynine perchlorate
11047-41-9 Mitragynine oxalate
11047-35-1 Mitragynine cinnamate
11047-36-2 Mitragynine trichloroacetate
36455-46-6 Mitragynine ethanedisulfonate
11047-37-3 Mitragynine, compd. with 1,3,5-trinitrobenzene (1:1)
7-Hydroxymitragynine:
174418-82-7 7-Hydroxymitragynine

C. Other chemical names

Kratom: Not applicable
Mitragynine:

Corynan-16-carboxylic acid, 16,17-didehydro-9,17-dimethoxy-, methyl ester, (16E,20β)- (ZCI)
Corynantheidine, 9-methoxy- (7CI)
Mitragynine (6CI)
(–)-Mitragynine

9-Methoxycorynantheidine

Indolo[2,3-a]quinolizine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy-α-(methoxymethylene)-, methyl ester, [2S-[2α(E),3α,12bβ]]-

Mitragynin

7-Hydroxymitragynine:

Corynan-16-carboxylic acid, 1,2,16,17-tetradehydro-2,7-dihydro-7-hydroxy-9,17-dimethoxy-, methyl ester, (7α,16E,20β)- (ZCI)

7-Hydroxymitragynine

7α-Hydroxy-7*H*-mitragynine

9-Methoxycorynantheidine hydroxyindolenine

Mitragynine hydroxyindolenine

D. Trade names

Kratom:

M. speciosa is available online and in shops that sell equipment for smoking cannabis and tobacco ("head shops"). The derived products are often distinguished according to vein colour, "provenance" (origin) and potency. Three types of kratom with different leaves and potency have been described, such as red-veined (*kan daeng* in Thai), white-veined (tang gua) and yak yai, which has two small teeth-like formations near the apex of the leaf *(225, 226)*.

Several other types of kratom are available online with the following names *(227)*:

Premium kratom
Commercial grade kratom
Bali kratom
Enhanced Bali kratom
Ultra enhanced Indo (U.E.I.) kratom
Indo red vein, Malaysian kratom
Red-vein Thai kratom
Green- or white-vein Thai kratom
Maeng Da kratom
White-veined Borneo kratom
New Guinea kratom
Java kratom
Sumatra red
The Rifat strain
The bumblebee strain
Red Riau
Green Riau.

The "strain" of kratom designated by the vein colour actually corresponds to the leaf age *(228)*. For example, the red-vein "strain" is younger and more potent than the mature green vein "strain", grows more abundantly in South-East Asia and is slightly more persistent than other *M. speciosa* trees. The red-vein "strain" is

marketed with several names including (Kratomgardens):

Borneo Red
Red Vein Sumatra
Pontianak Red Horn
Red Thai.

White-vein kratom is known as (Kratomgardens):

White Vein Sumatra
Borneo White
Pontianak White Horn.

The green vein is described as a mix of the red and the white types and is called Malaysian Green or Pontianak Green Horn (Kratomgardens).

Todd et al. *(229)* investigated the chemical composition of over 50 commercial kratom products with different names.

E. Street names

Kratom is the common term used for the *M. speciosa* leaf and derived products. Street names in South-East Asia include *krathom, kakuam, ithang* and *thom* (Thailand), *biak-biak* and *ketum* (Malaysia) and *mambog* (Philippines). Kratom "cocktail" refers to a decoction of kratom leaves mixed with another beverage. In Germany, "krypton" refers to a mixture of kratom and *O*-demethyltramadol *(230).*

F. Physical appearance

Kratom

Marketed kratom products usually consist of light to dark-green crushed or powdered dried leaves *(231)*. Vendors also offer powdered, greenish or beige–brown preparations fortified with extracts of other leaves. An aqueous decoction of kratom leaves can be used to make paste-like extracts and dark-brown kratom resin by partially or fully boiling down the water. Tinctures and capsules filled with powdered kratom are also available.

Botanical description: Kratom, *Mitragyna speciosa* (Korth.) Havil., is a tropical tree that grows in Thailand, Myanmar, Malaysia, Borneo, Sumatra, the Philippines and New Guinea *(227). Mitragyna* Korth. is a small genus of the Rubiaceae family. The genus *Mitragyna* belongs to the tribe Naucleeae of the subfamily Cinchonoideae *(232).*

The genus *Mitragyna* comprises 10 species, of which four occur in Africa (*M. inermis, M. ledermannii, M. rubrostipulata and M. stipulosa*) and six in South and South-East Asia, between India and New Guinea (*M. speciosa, M. tubulosa, M. rotundifolia, M. parvifolia, M. hirsuta and M. diversifolia*). The nomenclature of M. speciosa has been changed over the years. First described by the Dutch botanist Pieter Willem Korthals (1807–1892) *(233),* the genus was reclassified several times, until George Darby Haviland gave the final name and classification in 1897 *(234).*

M. speciosa is an evergreen tree that reaches 25 m in height and 0.6–0.9 m in diameter. It generally has a straight trunk, a smooth, grey outer bark and a pinkish inner bark *(227).* The petiolate leaves are generally dark glossy green and elliptical and can reach 14–20 cm in length and 7–12 cm in width. They typically present 12–17 pairs of veins. The flowers are arranged in groups of three heads, one with a short peduncle between two heads with a longer peduncle. The heads are 1.5–2.5 cm in diameter with light, hairy interfloral bracts 4–6 mm long. The flower calyx is about 2 mm long, with five lobes. The corolla is funnel-shaped, with an intense yellow colour. The corolla tube measures 3.5–5 mm, while the corolla lobes are 2.5–3 mm long and hairless with a revolute margin and a distinct ring of hairs within the base of the lobes. The fruiting heads are 2–3 cm wide, with 10 ribbed fruits of 7–9 mm length and 4–5 mm width. They contain numerous flat seeds, which are about 1 mm long with a 1–2-mm paper wing at each end *(227, 233, 234).*

Synonyms for *M. speciosa* Korth. (Havil.) *(227):*
Nauclea korthalsii Steud.; *Nauclea luzoniensis* Blanco; *Nauclea speciosa* (Korth.) Miq.; *Stephegyne speciosa* Korth.

Common names used for *Mitragyna speciosa* Korth. (Havil.) (227):

Indonesia: *kadamba* (Kelantan), *puri* (Batak Toba, Sumatra), *keton*

Malaysia: *biak, biak-biak, ketum, kutum, pokok biak, pokok ketum, sepat* (Sabah)

Myanmar: *beinsa, bein-sa-ywat*

Philippines: *mambog* (Tagalog), *lugub* (Mandaya), *polapupot* (Ibanag)

Thailand: *ithang* (central), *thom* (peninsular), *bai krathom, gratom, kakaum, katawn, krathawm, kratom, kraton*

Viet Nam: *giam d[ef]p, giam l[as] nh[or].*

Marketed kratom products:

A mix of kratom extract combined with codeine or diphenhydramine containing cough syrup, soda, ice and potentially other pharmaceuticals, drugs or chemicals is referred to as "4x100" *(235–237).*

Kratom is sold for recreational use either whole or as crushed leaves, leaf powder, encapsulated powder, concentrated extracts (5–100x times), solid resin or tinctures. Kratom extracts or raw material are also used in dietary supplements *(238).* Live plants and seeds are available online *(227).*

Mitragynine

White, amorphous crystals *(231)*

7-Hydroxymitragynine

Amorphous powder *(239)*

G. WHO review history

Kratom has not been formally reviewed by WHO and is not currently under international control. Kratom has been under ECDD surveillance since national reports of the abuse liability of its main psychoactive ingredient, mitragynine, and reports from international organizations on fatalities. A pre-review was initiated after a proposal from an international organization that provided information about fatalities due to kratom use.

2. Chemistry

A. Chemical Name

IUPAC name:

Kratom: Not applicable

Mitragynine: Methyl (E)-2-[(2S,3S,12bS)-3-ethyl-8-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate

7-Hydroxymitragynine: Methyl (2E)-2-[(2S,3S,7aS,12bS)-3-ethyl-7a-hydroxy-8-methoxy-1,2,3,4,6,7,7a,12b-octahydroindolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate

Chemical Abstratcs Index Name:

Kratom: Not applicable

Mitragynine: Indolo[2,3-a]quinolizine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy-α-(methoxymethylene)-, methyl ester, (αE,2S,3S,12bS)-(9CI, ACI)

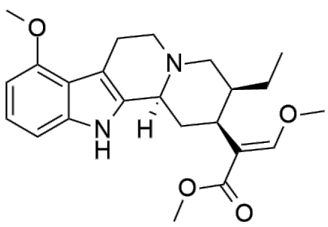
7-Hydroxymitragynine: Indolo[2,3-a]quinolizine-2-acetic acid, 3-ethyl-1,2,3,4,6,7,7a,12b-octahydro-7a-hydroxy-8-methoxy-α-(methoxymethylene)-, methyl ester, (αE,2S,3S,7aS,12bS)- (9CI, ACI)

B. Chemical structure

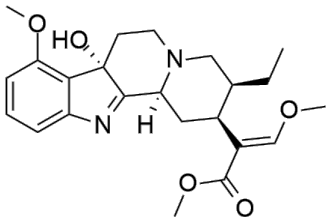
Free base:

Kratom: Not applicable

Mitragynine:



7-Hydroxymitragynine:

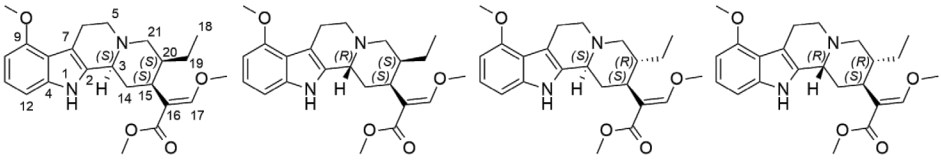


Molecular formula:
Kratom: Not applicable
Mitragynine: $C_{23}H_{30}N_2O_4$
7-Hydroxymitragynine: $C_{23}H_{30}N_2O_5$
Molecular weight:
Kratom: Not applicable
Mitragynine: 398.50 g/mol
7-Hydroxymitragynine: 414.50 g/mol

C. Stereoisomers

Kratom: Not applicable
Mitragynine: The presence of three stereogenic centres and an *E-Z* isomerism in the double bond on the methoxy acrylate group indicate the possibility of 16 stereoisomers; however, only four stereoisomers occur naturally in M. speciosa: mitragynine, which has the 3S,15S,20S configuration (1); speciociliatine 3R,15S,20S (2), speciogynine 3S,15S,20R (3) and mitraciliatine 3*R*,15S,20R (4) (Fig. 4). The *E*- stereochemistry is always present in the double bond on the C-15 methoxy acrylate group in mitragynine stereoisomers isolated from *M. speciosa (240).* Of the four stereoisomers, mitragynine (1) is the most abundant, accounting for up to 66% of the total alkaloid content in kratom leaves, while speciociliatine (2) and speciogynine (3) combined account for an average of 8–9%. Mitraciliatine (4) is the least abundant, accounting for < 1% of the total alkaloid content *(240).*

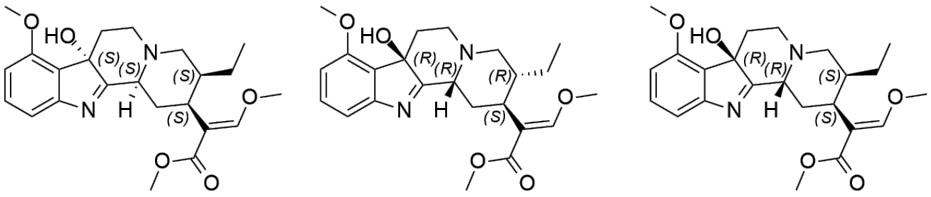
Fig. 4. Naturally occurring stereoisomers of mitragynine



Atom numbering is shown in the main component (1). Absolute configurations are indicated.

7-Hydroxymitragynine: The presence of four stereogenic centres and an *E–Z* isomerism in the double bond on the methoxy acrylate group generate 32 potential stereoisomers, but only three are found in *M. speciosa*: 7-hydroxymitragynine, which has the configuration 3*S*,7*S*,15*S*,20*S* (5), 7-hydroxyspeciociliatine 3*R*,7*R*,15*S*,20*S* (6) and 7-hydroxymitraciliatine 3*R*,7*R*,15*S*,20*R* (7), all presenting the *S*- configuration and *E*- stereochemistry in the double bond on the C-15 methoxy acrylate group (Fig. 5) *(240)*.

Fig. 5. Naturally occurring stereoisomers of 7-hydroxymitragynine



Absolute configurations are indicated.

D. Methods and ease of illicit manufacture

Kratom

Chemical composition

Most studies of the chemical composition of kratom have addressed the alkaloids, resulting in isolation of at least 54 alkaloids from the plant *(241)*. Secondary metabolites, like flavonoids, terpenoid saponins, polyphenols and glycosides, have also been isolated or identified. The main psychoactive components, which are exclusive to *M. speciosa*, are mitragynine and 7-hydroxymitragynine and are found in the leaves. The total alkaloid content in dried leaves is 0.5–1.5%. The most abundant compounds are indoles, mainly of the corynanthe type, which are found in tetra- or penta-cyclic rings. A hydroxy or methoxy group at C-9, unsaturation at C-3, C-5 or C-18, hydroxylation at C-7 and various configurations at C-3, C-7 and/or C-20 are found in indole and oxindole alkaloids *(241)*.

Mitragynine is the major alkaloid in the kratom plant, representing up to 66% of the total alkaloid content. It was initially isolated by Field in 1921 *(242)*, but its structure was definitely elucidated only in 1965 *(240, 243)* and the absolute stereochemistry confirmed by X-ray crystallographic analysis. Its concentration depends on the plant organ and origin and also to genetic and morphogenetic factors, the plant defence system against pathogenic attacks, light, ultraviolet (UV) light, moisture, temperature, soil microorganisms, soil fertility, salinity and storage conditions *(244, 245)*.

Mitragynine has a corynanthe-type skeleton, with a tetracyclic tetrahydro-β-carboline, four cycles with a methoxyl substitution at C-9, an ethyl group at C-20 and a β-methoxy acrylate moiety at C-15 *(246)*. Paynantheine is described as the second major alkaloid, accounting for 10% of the total alkaloid content. On average, 7α-hydroxymitragynine (5) (Fig. 5) accounts for < 2% of the alkaloid content *(247)*. Oxindole alkaloids are biosynthesized from indole alkaloids through an oxidative rearrangement *(248)* and are found in *Mitragyna* and other Rubiaceae species, such as *Uncaria (249)*.

The presence of fungi or bacteria can affect the presence and concentration of alkaloids in the plant. For example, *M. speciosa* root cultures infected with *Agrobacterium rhizogenes* generated more mitragynine than uninfected plants *(250)*. Another reported spirocyclic oxindole is mitragynine pseudoindoxyl, which is a major transformation product when fungal *Helminthosporium* spp. feed on mitragynine *(251)*.

Flavonoids and flavonols have been identified in *M. speciosa* leaves, including apigenin and its 7-glycosides, with quercetin and its glycosides (quercitrin, rutin, isoquercitrin, hyperoside and quercetin-3-galactoside-7-rhamnoside, kaempferol and its 3-glucoside derivative and epicatechin). Other phenolic compounds include caffeic acid and chlorogenic acid, 1-*O*-feruloyl-β-D-glucopyranoside and benzyl-β-D-glucopyranoside *(227, 252)*. The phytosterols sitosterol, stigmasterol and daucosterol have been reported in *M. speciosa (250)*. The leaves of *M. speciosa* also contain the monoterpenes 3-oxo-α-ionyl-*O*-β-D-glucopyranoside and roseoside and secoiridoid glycosides such as vogeloside and epivogeloside *(227)*.

Adulteration

Preparation of kratom products intended for sale can involve adulteration of the original material. In 2011, it was reported that products sold in Germany and Sweden under the name "Krypton" were "enhanced" kratom preparations containing caffeine and synthetic *O*-desmethyltramadol *(231, 253, 245)*. In 2016, concentrations of 7-hydroxymitragynine suspiciously higher than those found in raw *M. speciosa* leaves were reported in several commercial kratom products, suggesting artificial addition *(255)*.

Alkaloid extraction

Alkaloids from Mitragyna are generally extracted from raw material with methanol, ethanol (or 2-propanol), an alcohol–chloroform or an alcohol–water mixture by maceration, sonication or the Soxhlet technique. The crude extract is subjected to acid–base purification to yield the alkaloid fraction *(227, 256)*. Other techniques used are ultrasound-assisted extraction, microwave-assisted extraction and supercritical carbon-dioxide extraction, which increase the yield of alkaloids over that of other techniques *(257)*.

Mitragynine

Several methods for total synthesis of mitragynine (1) (Fig. 4) have been developed *(258–262),* but they are too complex, with too many steps, for economic production of this alkaloid *(231)* and provide the final product in very low yields. Moreover, they can be performed only in well-equipped chemical laboratories by well-trained personnel. Extraction of the compound appears to be more convenient.

7-Hydroxymitragynine

7-Hydroxymitragynine can be obtained from mitragynine by a single-step chemical reaction. Takayama et al. *(263)* reported in 2002 that treatment of mitragynine with lead tetraacetate and subsequent alkaline hydrolysis led to 7-hydroxy-7*H*-mitragynine in good yield.

In 2016, Kruegel et al. *(262)* reported that mitragynine was easily oxidized to 7-hydroxymitragynine with the hypervalent iodine species [bis(trifluoroacetoxy) iodo]benzene or by irradiation with visible light in the presence of rose bengal under air or pure oxygen. Interestingly, they also found that room temperature and sunlight alone cause conversion of mitragynine into its 7-hydroxy derivative, albeit in low yield (8% by NMR). A similar process may occur naturally or, more likely, in dry leaf material exposed to air for a long time, with strongly coloured phytochemicals (e.g., porphyrins) playing the role of rose bengal. This phenomenon may account for the observation of 7-hydroxymitragynine in some samples of *M. speciosa.* In 2019, Kruegel et al. *(249)* reported that singlet oxygen and potassium peroxymonosulfate (oxone) were also effective oxidants for the conversion of mitragynine into 7-hydroxymitragynine.

E. Chemical properties

Melting-point:

Kratom: Not applicable.

Mitragynine: Forms white, amorphous crystals that melt at 102–106 °C. The melting-point of mitragynine hydrochloric acid salt is 243 °C; the picrate melts at 223–224 °C and the acetate at 142 °C *(253).*

Amorphous crystals of mitragynine show optical rotation [α]D = −126 (c. 0.66, CHCl3) (or −128 (c. 1.2, CHCl3)) *(261).*

7-Hydroxymitragynine: No information was available.

An amorphous powder of 7-hydroxymitragynine showed optical rotation [α]D = +47.9 (c. 0.55, CHCl3) *(239).*

Boiling-point:

Kratom: Not applicable.

Mitragynine: Mitragynine distils at 230-240 °C at 5 mm Hg *(231).*

7-Hydroxymitragynine: No information was available.

Solubility:
Kratom: Not applicable.
Mitragynine: Mitragynine is insoluble in water; it is soluble in conventional organic solvents such as acetone, acetic acid, alcohols, chloroform and diethyl ether, forming fluorescent solutions. The solubility limit of mitragynine was measured in aqueous solution at pH 4 and pH 7 to be 130 and 83 μM, respectively *(264)*. Mitragynine has a logP (partition coefficient) of 1.73 and a pKa of 8.11 ± 0.11 *(265)*.

7-Hydroxymitragynine: No information was available.

Stability of kratom alkaloids
Basiliere and Kerrigan *(266)* reported the short-term stability of mitragynine, 7-hydroxymitragynine, speciociliatine, speciogynine and paynantheine over pH 2–10 and temperatures of 4–80 °C over 8 h. All the Mitragyna alkaloids studied were acid labile. The methyl ester is hydrolysed under alkaline conditions to produce 16-carboxymitragynine. 7-Hydroxymitragynine is reported to be the most unstable alkaloid, with significant drug loss after 8 h at ≥ 40 °C. No significant drug losses were observed in aqueous solution (pH 2–10) at 4, 20 or 40 °C. Diastereoisomers of mitragynine (speciociliatine and speciogynine) were even more stable *(267, 268)*.

F. Identification and analysis

Kratom
Botanical identification
M. speciosa can be identified macroscopically by examining the leaf, which is elliptic to ovate, with the apex shortly pointed and the base rounded to cordate *(240)*. Macroscopic identification can, however, be misleading, as the leaves from plants of the same tribe or genus such as *Uncaria homomalla* and M. diversifolia are similar *(240, 244, 267)*, and chemical analysis can be resolutive.

Microscopic identification of eight Mitragyna species (but not *M. speciosa*) was reported by examination of calcium oxalate crystal concretions, but the studies were based on limited samples *(268)*.

Sukrong et al. *(226)* showed that sequences from the nuclear internal transcribed spacer region can be used to differentiate *M. speciosa* from related species by the polymerase chain reaction–restriction fragment length polymorphism method.

A highly specific, selective assay based on DNA bar-coding was reported for the detection of kratom products, in which the matK nucleotide signature site is used as a marker to discriminate *M. speciosa* from other Mitragyna species *(269)*. DNA bar-coding with high-resolution melting analysis was proposed as a simple method for use in routine forensic analysis *(270)*.

Chemical analysis

Numerous analytical methods have been reported for the identification and quantification of kratom alkaloids, particularly mitragynine, in a wide range of samples, including commercial samples, raw plant material and biological specimens. Commercial standards are available for mitragynine and its stereoisomers speciogynine, mitraciliatine and speciociliatine, its hydroxylate derivative 7-hydroxymitragynine and deuterated mitragynine and 7-hydroxymitragynine. Other indole and oxindole kratom alkaloids are sold as analytical standards, although Flores-Bocanegra et al. *(241)* reported that some "pure" commercial standards were either mixtures or even completely different compounds.

Chromatographic methods, and particularly LC, are most commonly used for analysis of M. speciosa alkaloids.

- Thin-layer chromatography (TLC)

Kratom alkaloids can be separated by TLC on silica gel plates and detected under a UV lamp (254 nm). A mobile phase composed of hexane:ethyl acetate:25% ammonia solution (30:15:1, v/v/v) provides an Rf value of mitragynine of 0.49 *(271)*. After spraying with either modified Ehrlich's reagent or ferric chloride–perchloric acid reagent, mitragynine can be detected as purple or grey-to-brown spots, respectively *(255)*.

- Gas chromatography (GC)

The first GC method for the analysis of mitragynine in kratom was published in 2005 *(257)*, but identification of mitragynine was given only by comparison of experimental mass spectra with library spectra. Philipp et al. *(272)* developed a GC–MS method for the analysis of kratom and/or krypton in urine by trimethylsilylation to increase the volatility of the alkaloids. Cornara et al.*(273)* described a GC–MS method for the analysis of underivatized mitragynine and other alkaloids in kratom.

Wang et al. *(274)* compared three chromatographic methods coupled to two detection systems, GC with MS, supercritical fluid chromatography with diode array detection (DAD) and HPLC with MS and DAD, for the analysis of mitragynine and structurally related alkaloids in M. speciosa plants. They concluded that the GC method could not resolve the two diasteroisomers mitragynine and speciociliatine, which also give identical electron impact mass spectra. This could be overcome only by derivatization. Moreover, the temperature range available for method optimization is limited.

A GC–MS method for the determination of mitragynine in three Malaysian M. speciosa samples includes ultrasonic-assisted extraction *(275)*. Basiliere et al. *(276)* suggested that GC methods lack overall sensitivity (limit of detection, about 50 ng/mL) and therefore cannot be used to quantify the alkaloids in biological specimens.

- Liquid chromatography (LC)

  – LC–UV

HPLC and UHPLC (ultrahigh) methods provide the most accurate discrimination of structurally similar kratom alkaloids *(240)*.

An HPLC-DAD method was developed to identify and quantify mitragynine, caffeine, codeine, chlorpheniramine and phenylephrine in a "kratom cocktail" prepared by mixing boiled kratom leaves, carbonated cola beverages, antitussive syrup, coffee and codeine *(277)*. Parthasarathy et al. *(278)* reported a HPLC-DAD method for quantifying mitragynine from raw material. Mudge and Brown *(279)* reported a validated HPLC-UV method for qualitative and quantitative analysis of mitragynine and 7α-hydroxymitragynine in solid and liquid commercial kratom products.

Parthasarathy et al. *(280)* reported a solid-phase extraction method for HPLC-UV determination of mitragynine in rat plasma, with a limit of quantification of 50 ng/mL. Neng et al. *(281)* developed a method for extraction of mitragynine from human urine by bar adsorptive microextraction, consisting of a modified N-vinylpyrrolidone polymer sorbent phase combined with liquid desorption, followed by analysis by HPLC-DAD.

  – LC–MS

LC-based methods are the most widely used for determination of kratom alkaloids, as they allow good resolution of mitragynine isomers and are highly sensitive, a key factor for qualitative and quantitative determination of trace amounts in biological specimens. As metabolites of mitragynine are not yet commercially available, kratom in forensic toxicology specimens is currently evaluated by analysis for the parent drug and related alkaloids. The mitragynine concentrations in urine from 50 people who use kratom recreationally covered a broad dynamic range (1–50 000 ng/mL) *(282)*.

LC–MS methods were developed for simultaneous determination of mitragynine, 7-hydroxymitragynine, speciogynine, speciociliatine and paynantheine in both raw material and commercial kratom products (*283)*. Some methods are highly sensitive, with limits of detection and quantification of mitragynine of 0.02 ng/mL and 0.1 ng/mL, respectively *(284)*.

LC has also been coupled to low- and high-resolution MS to identify phase-I and -II metabolites of speciogynine in rat urine after administration of a high dose of the pure alkaloid and in human urine after kratom use *(285)*. The same method was used to determine paynantheine *(286)*, speciociliatine *(287),* mitraciliatine and isopaynantheine *(288)* and their metabolites in rat urine after administration of the pure alkaloids, which showed that they matched the metabolites detected in the urine of people who use kratom.

An LC-MS/MS method was used to detect *O*-desmethyltramadol and kratom alkaloids in the urine of a woman who consumed "krypton", a mixture of kratom and *O*-desmethyltramadol *(253)*. Mitragynine was also detected in post-mortem urine and blood samples by LC-MS/MS *(289)* after hydrolysis with glucuronidase and sulfatase and extraction with n-butyl chloride before analysis. The method was also used for other specimens, including liver, vitreous humour, kidney, spleen, lung, bile and heart, the last being the only specimen in which mitragynine was not detected. Solid phase extraction and LC-MS/MS were used to detect and quantify mitragynine, 16-carboxy mitragynine and 9-O-demethyl mitragynine in human urine *(290)*.

Simultaneous quantification in marketed products of 10 kratom alkaloids (corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine, mitragynine, mitraphylline, paynantheine, speciociliatine and speciogynine) in a UHPLC tandem MS method has been reported (291). The limit of quantification was 1 ng/ml. The method was used to quantify kratom alkaloids in alkaloid-rich fractions, ethanolic extracts, lyophilized teas and commercial products. The most abundant alkaloids were mitragynine (0.7–38.7% w/w), paynantheine (0.3–12.8%), speciociliatine (0.4–12.3%) and speciogynine (0.1–5.3%). Minor kratom alkaloids like corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine and isocorynantheidine were found at 0.01–2.8% (w/w). Mitraphylline was below the limit of quantification in all analyses. An HPLC method for quantification of mitragynine in kratom leaf extracts and a multiple reaction mode ultra-performance LC–MS/MS method for the quantification of the same alkaloid in rat plasma have also been reported *(292)*.

Speciociliatine and speciogynine were investigated as alternative biomarkers of kratom use in urine, as their levels often exceeded the concentration of mitragynine in unhydrolysed urine *(293)*.

A method for the detection of mitragynine and 7-hydroxymitragynine by LC-MS/MS in hair samples has been reported, with limits of quantification of 4 pg/mg and 30 pg/mg, respectively *(294)*.

- Supercritical fluid chromatography (SFC)

Three chromatographic techniques, GC–MS, SFC-DAD and LC, were compared for the analysis of the indole alkaloids paynantheine, 3-isopaynantheine, mitragynine, speciogynine and speciociliatine and the oxindole alkaloids corynoxine and corynoxine B in M. speciosa plants *(274)*. LC and SFC resolved the major components with slightly different elution orders, but the GC method failed to resolve the diasteroisomers mitragynine and speciociliatine.

- Capillary electrophoresis (CE)

Non-aqueous capillary electrophoresis (NACE) interfaced to an MS detector was used to separate a large number of diastereomeric compounds in alkaloid mixtures from a plant extract of M. speciosa *(295)*. In this technique, background electrolytes often consist of a mixture of methanol and acetonitrile, with soluble ammonium salts added as electrolyte. A mixture of glacial acetic acid and and acetonitrile was used, creating an acidic background electrolyte with a very low dielectric constant. The addition of ammonium formate as electrolyte and variation of the solvent ratio significantly changed the selectivity and resolution necessary for separation of structurally closely related indole alkaloids, including diastereomers.

- DART

A direct analysis in real time (DART)–MS method was developed for rapid identification of M. speciosa plant material and discrimination from other plants *(296)* and also for analysis and classification of M. speciosa plant varieties according to their chemical profile. A DART-HRMS method for quantification of mitragynine and 7-hydroxymitragynine in 16 kratom products available commercially online was reported *(297)*. The linear range was 5–100 μg/mL, the limit of quantification was 5 μg/mL, and the mitragynine concentrations in these samples were 2.76–20.05 mg/g dried plant material. The advantage of a DART system is that it allows straightforward analysis of raw plant material with no sample preparation (296, 297).

- Ion mobility spectrometry

An ion mobility spectrometry method was used for quantification of mitragynine in 15 commercial samples, and the results were compared with those obtained by an LC-MS/MS method *(298)*. The limit of detection was 0.5 ng. Mitragynine was detected in 14 of 15 samples by LC-MS/MS and 13 of 15 samples by ion mobility spectrometry, as the compound was below the limit of detection in one sample.

- Raman and portable devices

Surface-enhanced Raman spectroscopy was used to detect mitragynine in M. speciosa samples *(299)*. The advantage of the method is that it can be used by non-experts. Over 100 samples and blanks were examined in duplicate with five identical handheld Raman spectrometers, with a false-positive rate of 2.1% and a false-negative rate of 0.7%. The limit of detection for mitragynine was 342 ng/mL. The method is ideal for preliminary screening for mitragynine, which can be confirmed by more time-consuming laboratory techniques.

DART with thermal desorption MS, hand-held MS, portable ion mobility spectrometry and portable Fourier-transform IR spectroscopy were all tested as

field screening techniques for detection of mitragynine in food and drug products, and the results were compared with those obtained with laboratory techniques such as LC-MS, HPLC-UV and GC–MS *(300)*. The methods were applied to 96 kratom products, including capsules, bulk powder and bulk plant material. The portable devices allowed rapid detection of mitragynine in chloroform extracts and in solid kratom matrices. DART-TD-MS and ion mobility spectrometry are useful for initial screening because of short analysis time and absence of sample preparation. Hand-held MS gace the highest false-negative rate (6%). Both FT-IR and the hand-held MS require extraction of samples.

Immunological methods

Although chromatographic techniques have the advantage of good sensitivity, the separation step limits their routine use, and other screening and detection methods have been developed. For example, immunoassays are used worldwide for rapid screening or detection drugs in kratom preparations and biological fluids, with the advantages of good sensitivity, simplicity and convenience *(301)*. The antibody to a specific kratom alkaloid prepared for an immunological assay may, however, cross-react with other alkaloids present in a sample *(302, 303)*.

An electrochemical immunosensor for sensitive, rapid detection of mitragynine has been reported, with a modifier for the sensor based on multiwalled carbon nanotubes or chitosan nanocomposite *(304)*. Mitragynine was detected in an indirect competitive assay with 3,3',5,5'-tetramethylbenzidine, which is the substrate in the enzymatic reaction of horseradish peroxidase-modified secondary antibody. The electrochemical immunosensor was 10 times more sensitive than conventional ELISA, with a limit of detection of 0.018 μg/mL and a limit of quantification of 0.06 μg/mL.

Mitragynine

The pure synthetic compound was obtained and characterized by NMR *(258–262)*, HRMS *(260)*, [α]D (*258, 262)* and elemental analysis *(259)*.

7-Hydroxymitragynine

The pure synthetic compound was obtained and analysed by NMR *(258, 262)* and both EI-MS and HRMS *(258)*.

3. Ease of convertibility into controlled substances

Kratom: No information was available.

Mitragynine: No information was available. As reported above (section 2D), mitragynine can be converted into the bioactive 7-hydroxymitragynine in only one step *(247, 258, 262);* however, 7-hydroxymitragynine is not listed as a controlled substance.

7-Hydroxymitragynine: No information was available.

4. General pharmacology

Kratom is the common term for M. speciosa, a tree native to South-East Asia. The indigenous population has used kratom leaves and derived products for centuries as a herbal medicine to treat pain, cough, diabetes, diarrhoea and fever and as a wound poultice, to enhance sociability and sexual desire and to increase energy and decrease fatigue *(304)*. More recently, kratom has been used as an opioid substitute and to treat opioid withdrawal. Lower doses (1–5 g of plant material orally) reportedly have stimulant effects, while higher doses (concentrated products such as kratom extracts or > 5 g of plant material) have opioid-like effects *(305)*. Use of kratom has spread to western Europe and the USA during the past two decades, chiefly to self-medicate pain and opioid withdrawal and as a substitute for opioids *(304)*.

Kratom contains more than 50 alkaloids, but only two indole alkaloids, mitragynine and its active metabolite 7-hydroxymitragynine *(247)*, have been well characterized pharmacologically *(229, 306)*. A third alkaloid, mitragynine pseudoindoxyl, is not found in the plant but is a metabolite of 7-hydroxymitragynine and is active in vitro at the MOR *(307)*. Mitragynine represents up to two thirds of the total alkaloid content of kratom and is considered to be primarily responsible for its pharmacological actions. 7-Hydroxymitragynine comprises ≤ 1% of kratom alkaloids in the leaf but is often present at a higher concentration in processed kratom products sold commercially *(255)*. Kratom grown experimentally in the USA may have a lower mitragynine content than kratom grown in Thailand *(308)*.

A. Routes of administration and dosage

Kratom in several forms is almost always taken orally. In South-East Asia, typical usage includes chewing raw leaves, ingesting powdered leaves, brewing leaves or leaf extract in tea or boiling the leaves for several hours to make a decoction (304, 309). A kratom decoction is often mixed with another beverage (e.g., cola, cough syrup) to create a kratom "cocktail", in part to hide its bitter taste *(304, 309)*. In western Europe and the USA, kratom is commonly taken as a powder dissolved in a beverage or in a capsule or tablet (304, 310, 311). Mitragynine and 7-hydroxymitragynine have been found in resins and liquids sold online for use in electronic drug delivery devices (so-called "e-cigarettes") *(312)*.

If kratom products are not accurately labelled, the actual doses of kratom alkaloids ingested by people who use kratom are not known. Surveys of convenience samples of people who use kratom in South-East Asia suggest that a typical daily dose of liquid formulation (tea, decoction) is three to six glasses per day, containing an estimated 200–400 mg of mitragynine *(236, 313)*. In the USA, surveys of people who use kratom suggest that a typical daily dose of powder formulations is 2–6 g/day, although people with heavy use may ingest up to 20 g/day *(310, 311)*.

B. Pharmacokinetics

a. Animal studies

Orally administered mitragynine (20–50 mg/kg) in rats had a mean T_{max} of 1.3–4.5 h, a mean C_{max} of 400–700 ng/mL and a mean half-life of 3.3–9.4 h *(280, 314, 315)*. The mean oral bioavailability was 17% and 3% (280, 292). Oral dosing of rats with lyophilized kratom tea or an organic extract of kratom tea (equivalent to 20 mg/kg mitragynine) showed T_{max} of 0.3 and 1.0 h, C_{max} of 0.55 and 0.66 ng/mL and oral bioavailability of 25.1% and 31.2%, respectively (as compared with 17.0% for pure mitragynine) *(292)*.

Mitragynine administered orally (5 mg/kg) to beagle dogs had a T_{max} of 0.3 (± 0.1) h, C_{max} of 278 (± 47.4) ng/mL, a half-life of 8.7 (± 0.2) h and bioavailability of 69.6% (316).

In rats, iv mitragynine readily crossed the blood–brain barrier, with a T_{max} and half-life comparable to those in plasma *(317)*.

b. Human studies

Two published studies of the pharmacokinetics of oral kratom were conducted in young men in South-East Asia who had used kratom daily for at least 6 months at the time of the study. In a study in Thailand, 10 men (mean [SD] body weight 77.3 [14.8] kg) drank kratom tea (60 mL, containing 6.25–11.5 mg mitragynine) daily for 7 days (318). Blood and urine samples were collected for 24 h after a loading dose (equivalent to 6.25–23 mg mitragynine) given on the 8th day. The mean (SD) T_{max} of mitragynine was 0.83 (0.35) h, and the elimination half-life was 23.24 (16.07) h. The C_{max} varied linearly (R2 = 0.677) with the loading dose, from 18–30 ng/mL after 6.25 mg to 50–100 ng/mL after 20–23 mg. In a study in Malaysia, 26 men were given a single dose of 1.6 mg/kg of mitragynine in a kratom decoction containing 0.4–0.5 mg/mL mitragynine. The mean (SD) T_{max} was 2.0 (0.8) h (range, 1–3 h), and the C_{max} was 1884 (1056) ng/mL (range, 829–5034 ng/mL) *(319)*.[2]

No data were available on the oral bioavailability of mitragynine or 7-OH-mitragynine, either alone or in a kratom product. In view of the variation in oral bioavailability between rodents and dogs (see above), an accurate extrapolation canot be made to humans.

The effect of mitragynine on human liver cytochrome P450 activity is unclear. Mitragynine inhibited three P450 enzymes (CYP2C9, CYP2D6, CYP3A) in human liver cells in vitro at 1 μM concentration (229) and 7-hydroxymitrigynine more weakly. Mitragynine (1–25 μM) produced concentration-dependent increases in mRNA and protein expression and the activity of CYP1A2, CYP2D6 and CYP3A4 in human liver cells in vitro (320). These findings suggest the possibility of clinically significant interactions of kratom–drug pharmacokinetics with

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commonly used medications that are metabolized by these liver cytochromes, such as warfarin (CYP2C9), desipramine and dextromethorphan (CYP2D6) and benzodiazepines (CYP3A) *(321)*.

C. Pharmacodynamics

a. Animal studies

Mitragynine, 7-hydroxymitragynine, and mitragynine pseudoindoxyl are partial agonists at the human MOR, activating the G-protein-coupled intracellular signalling pathway but with little or no effect on the β-arrestin pathway *(229, 262, 306, 322, 323)*. This so-called MOR agonist bias has been proposed to confer differential efficacy on MOR ligands. Ligands that preferentially activate the G-protein-coupled intracellular signalling pathway should be more effective in producing analgesia and less effective in producing respiratory depression and physical dependence than ligands that preferentially activate the β-arrestin pathway *(324, 325)*. In mice, mitragynine pseudoindoxyl at subcutaneous doses equipotent with morphine for analgesia was significantly less potent than morphine in generating tolerance or withdrawal, slowing gastrointestinal transit, causing respiratory depression or rewarding behaviour *(323)*.

7-Hydroxymitragynine has 5–23 times greater affinity than mitragynine at the MOR (depending on the binding assay used) *(229, 323, 326, 327)*, and morphine has 8–10 times greater affinity than 7-OH-mitragynine *(229, 323, 327)*. MOR activation is considered to be responsible for most of the pharmacodynamics of kratom and its alkaloids observed in rodents and humans. Mitragynine and 7-hydroxmitragynine are also competitive antagonists at the human κ- and δ-opioid receptors *(262)*, with less affinity than at the MOR *(327, 328)*.

7-Hydroxymitragynine is 5–20 times more effective than mitragynine in activating the β-arrestin pathway (i.e., intrinsic activity) at the MOR *(229, 323, 327)*. Morphine has three times more intrinsic activity at the MOR than 7-hydroxymitragynine *(229, 327)*.

Mitragynine, but not 7-hydroxymitragynine, binds to α1- and α2-adrenergic receptors and serotonin-1A and -2A receptors *(326, 329)*. Mitragynine binds with low affinity to dopamine-D1 receptors on rat striatal membranes and not at all to dopamine-D2 receptors *(330)*. The functional significance of this binding pattern remains unclear.

Kratom extracts, mitragynine and 7-hydroxymitragynine have various effects on the behaviour of rodents. Some are observed inconsistently among studies, perhaps because of differences in dose, type of kratom extract, route of administration and timing of data collection (e.g., on motor activity, see below). Few studies included a broad range of doses and might therefore have missed some effects or non-linear dose–response relations. The most consistently observed effects are opioid-like *(331)*: analgesia *(332)*, suppression of opioid withdrawal *(333)* and inhibition of gastrointestinal transit *(292)*.

Kratom extracts, mitragynine, 7-hydroxymitragynine and mitragynine pseudoindoxyl significantly reduced acute mechanical or thermal pain in rats and mice when given by the intracerebroventricular, ip, subcutaneous or oral route *(332, 334)*. The analgesic effect was blocked by pretreatment with MOR antagonists *(332)* and did not occur in knock-out mice lacking the MOR *(330, 334, 335)*, suggesting a MOR mechanism of action. Repeated dosing generated tolerance to the analgesic effect, with cross-tolerance among mitragynine, 7-hydroxymitragynine and morphine *(332)*. The relative analgesic potency of kratom alkaloids and conventional opioids is uncertain, as few studies have been conducted in which the two were compared after administration by the same route of a range of doses to establish equipotent doses. In rats, 100 mg/kg of mitragynine given orally had the same analgesic effect as 6 mg/kg oral oxycodone *(336)*.

Kratom extracts, mitragynine and 7-hydroxymitragynine suppressed naloxone-precipitated opioid withdrawal in rodents when given ip or orally *(333, 334, 337, 338)*.

Kratom extracts and mitragynine have inconsistent effects on motor activity in rodents. In mice, kratom extract decreased (mitragynine 0.5 mg/kg ip or orally) *(330)*, increased (mitragynine 7.4 mg/kg orally) *(334)* or had no effect (50–200 mg/kg methanolic extract or 5–20 mg/kg alkaloid extract orally) *(339)* on motor activity. In another study, mitragynine (30 mg/kg ip) had no effect *(340)*. In three studies of motor activity in rats, kratom alkaloid extract (60 mg/kg orally) had no effect *(341)*, and mitragynine had no effect (1–10 mg/kg ip) *(342)* or increased (30 mg/kg ip) motor activity *(343)*. 7-Hydroxymitragynine (3 mg/kg ip) increased motor activity in male and female mice *(322)*.

Kratom extracts and migragynine have various non-opioid-like behavioural effects in rodents *(331)*. They reduce immobility in the forced swim test and tail suspension test, which are considered models of anti-depressant action *(344, 345)*. Kratom extract significantly influenced behaviour in several mouse models of anti-psychotic action, including apomorphine-induced climbing, haloperidol-induced catalepsy and ketamine-induced social withdrawal *(346)*. Kratom extracts reduced alcohol self-administration, alcohol reinforcement (conditioned place preference), alcohol-induced increase in dopamine concentration in the nucleus accumbens and alcohol withdrawal in mice and rats *(322, 347, 348)*. In rats, mitrogynine (10–30 mg/kg ip) attenuated the acquisition and expression of morphine-conditioned place preference *(349)* and reduced self-administration of heroin but not of methamphetamine (0.1-3.0 mg/kg ip) *(328)*.

b. Human studies

In an observational study in the United Kingdom in the early 1930s, five men given mitragynine acetate orally (50 mg once or twice separated by 2 h) or kratom (0.65 g or 1.3 g of powdered leaves) showed reduced heat sensitivity, dermal electrical

Twitter Exchange Between Former FDA Commissioner Scott Gottlieb and Former HHS Assistant Secretary for Health Brett Giroir May 21, 2021

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

Addiction Biology

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Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine

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ABSTRACT

Kratom, derived from the plant *Mitragyna speciosa,* is receiving increased attention as an alternative to traditional opiates and as a replacement therapy for opiate dependence. Mitragynine (MG) and 7-hydroxymitragynine (7-HMG) are major psychoactive constituents of kratom. While MG and 7-HMG share behavioral and analgesic properties with morphine, their reinforcing effects have not been examined to date. 7-HMG, but not MG, substituted for morphine self-administration in a dose-dependent manner in the rat self-administration paradigm. Following the substitution procedure, re-assessment of morphine self-administration revealed a significant increase following 7-HMG and a significant decrease following MG substitution. In a separate cohort, 7-HMG, but not MG, engendered and maintained intravenous self-administration in a dose-dependent manner. The effects of pretreatment with nalxonaxine (NLXZ), a μ1 opiate receptor antagonist, and naltrindole (NTI), a δ opiate receptor antagonist, on 7-HMG and morphine self-administration were also examined. Both NLXZ and NTI reduced 7-HMG self-administration, whereas only NLXZ decreased morphine intake. The present results are the first to demonstrate that 7-HMG is readily self-administered, and the reinforcing effects of 7-HMG are mediated in part by μ and δ opiate receptors. In addition, prior exposure to 7-HMG increased subsequent morphine intake whereas prior exposure to MG decreased morphine intake. The present findings indicate that MG does not have abuse potential and reduces morphine intake, desired characteristics of candidate pharmacotherapies for opiate 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.

Keywords 7-hydroxymitragynine, addiction, mitragynine, opiate, reinforcement, self-administration.

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INTRODUCTION

The increasing use of kratom (*Mitragyna speciosa korth*; aka *thang, kakuam, thom, ketum, biak biak*), a plant indigenous to Southeast Asia, has emerged as a public health concern in the US. Kratom has been used traditionally to combat fatigue and increase work productivity amongst farm populations in Southeast Asia. Kratom leaves are chewed or made into an extract and brewed (Hassan *et al.* 2013; Warner, Kaufman, & Grundmann 2016), and consumption is reported to produce stimulation (at low doses) and opiate-like effects (at higher doses) including analgesia, antitussive, antidiarrheal, and anti-inflammatory effects. Historically, kratom has also been used to reduce the intensity and duration of opiate withdrawal symptoms (Boyer *et al.* 2008; Ward *et al.* 2011; Cinosi *et al.* 2015; Warner *et al.* 2016); however, studies assessing the clinical efficacy of kratom are limited. In Southeast Asia, regular kratom use has been associated with physical dependence and withdrawal symptoms (Suwanlert 1975; Saingam *et al.* 2013; Singh, Muller, & Vicknasingam 2014), effects attributed in large part to mitragynine (MG). In the United States, there is growing concern regarding the safe use of kratom based on reports of addiction (Sheleg & Collins 2011; Galbis-Reig 2016) and toxicity and fatalities associated with use

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(McWhirter & Morris 2010; Neerman, Frost, & Deking 2013; Singh, Narayanan, & Vicknasingam 2016; Drago *et al.* 2017; Fluyau & Revadigar 2017).

Various strains of kratom are widely available over the internet as well as in various locations throughout the country. Forecasting models indicate kratom use will continue to increase in the United States (Stogner 2015). Currently, kratom consumption remains legal in the majority of states in the US. FDA's associate commissioner for regulatory affairs has stated that the FDA has 'identified Kratom as a botanical substance that poses a risk to public health and has the potential for abuse' (Food and Drug Administration, 2016). Concerns about Kratom have led the FDA to issue an import alert and public health advisory and the DEA to include kratom on the list of Drugs and Chemicals of Concern.

Kratom leaves contain more than 25 identified alkaloids (Hassan *et al.* 2013). Mitragynine (MG) and 7-hydroxymitrgynine (7-HMG), the main psychoactive alkaloids of kratom, constitute approximately 60 and 2 percent of the plant's alkaloids, respectively (Prozialeck, Jivan, & Andurkar 2012). MG and 7-HMG are partial agonists at the μ opiate receptor and weak antagonists at δ and κ opiate receptors (Kruegel *et al.* 2016; Varadi *et al.* 2016), with 7-HMG exhibiting approximately 5-fold greater affinity at the μ opiate receptor compared to MG. Assays of opiate receptor-mediated G-protein function reveal similar potencies for MG and 7-HMG (Kruegel *et al.* 2016; Varadi *et al.* 2016). While both compounds exhibit naloxone-sensitive antinociceptive activity, 7-HMG exhibits 40-fold greater potency than MG and 10-fold greater potency than morphine in these assays (Takayama *et al.* 2002; Matsumoto *et al.* 2004). Repeated administration of 7-HMG produces tolerance to the compound's analgesic effects as well as cross-tolerance to morphine's antinociceptive action (Matsumoto *et al.* 2005). Chronic consumption of kratom as well as repeated administration of 7-HMG induces physical dependence as determined by naloxone-precipitated withdrawal (Matsumoto *et al.* 2005).

Few studies have examined the abuse/addiction potential of MG and 7-HMG. The absence of controlled studies in humans creates space for basic science studies to provide critical information to help guide use and policy decisions. The abuse liability of compounds is generally assessed in animal models using drug discrimination, place conditioning and/or self-administration paradigms —all of which address different aspects of abuse. Studies in animal models have provided considerable insight into the behavioral effects of MG and 7-HMG as well as the potential neurobiological mechanisms underlying those effects. Acute administration of MG increases locomotor activity, induces anxiolytic effects and induces conditioned place preference (Yusoff *et al.* 2016), while repeated MG administration induces locomotor sensitization but impairs performance on a variety of cognitive tasks (Yusoff *et al.* 2016; Ismail *et al.* 2017). Moreover, MG and 7-HMG fully generalize to the discriminative stimulus effects of morphine, suggesting the potential for abuse (Harun et al., 2015).

The reinforcing effects of drugs are an important indicator of abuse liability which is typically evaluated using drug self-administration procedures. Inherent in the operational definition of reinforcement is the contingency between behavior and drug administration, an important differentiation between self-administration and place conditioning and drug discrimination. Drug self-administration is widely accepted as the gold standard of measurements for abuse liability (Katz 1989; Hemby 1999; Lynch & Hemby 2011). In spite of the concern of the potential abuse liability of MG and 7-HMG in humans, no published studies to date have examined the ability of these compounds to maintain self-administration in experimental subjects. To that end, we assessed that ability of MG and 7- HMG to substitute for morphine self-administration and to engender and maintain self-administration in drug naïve animals. Additionally, the contribution of μ and δ opiate receptors on the reinforcing effects of 7-HMG was examined. Results of these studies provide an objective assessment of the abuse potential of MG and 7-HMG in a rodent model that recapitulates key features of human drug taking.

MATERIALS AND METHODS

Subjects

Male Fischer 344 rats (100–130 days; Charles River, Wilmington, MA) were housed in a temperature-controlled vivarium on a 12-hour reversed light/dark cycle (lights on at 6:00 PM). Rats were group-housed two per cage with water available *ad libitum*. Food was restricted such that rats were maintained at 90 percent of their free feeding weight throughout the experiment. Experimental sessions were conducted during the dark phase of the light/dark cycle. All procedures were performed in accordance with the High Point University Institutional Animal Care and Use Committee and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23) revised in 1996.

Chemicals

Mitragynine was isolated according to published procedures (Ponglux *et al.* 1994). 7-HMG was synthesized from mitragynine by McCurdy's research group, Department of BioMolecular Sciences, University of Mississippi, as previously published (Ponglux *et al.* 1994; Takayama *et al.* 2002). Mitragynine and 7-HMG were analyzed by ^{1}H NMR, ^{13}C NMR, elemental analysis, HPLC and HR-MS,

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and were found to be >99 percent pure. Morphine SO_4 was purchased from Gallipot, Inc. (St. Paul, MN), penicillin G procaine from Butler Company (Columbus, OH), propofol, ketamine HCl (Ketaset), xylazine (Xylamed) from Patterson Veterinary Supply, Inc. (Greely, CO), naltrindole and naloxonazine from Tocris Bioscience/Biotechne (Minneapolis, MN). Drugs were dissolved in heparinized saline. Morphine, MG and 7-HMG were infused in a volume of 200 µl.

Behavioral apparatus and training

Operant apparatus

Experiments were conducted in operant conditioning chambers (ENV-008CT; Med Associates, St. Albans, VT) enclosed in sound-attenuating cubicles (ENV-018; Med Associates). The front panel of the operant chambers contained a response lever (4 cm above the floor and 3 cm from the side wall), a cue light (3 cm above the lever) and a food chute centered on the front wall (2 cm above the floor) that was connected to a food pellet dispenser (ENV-023; Med Associates) located behind the front wall and a tone generator to mask extraneous noise. A syringe pump (PHM-100; Med Associates) holding a 20-ml syringe delivered infusions. A counterbalanced arm containing the single channel liquid swivel was located 8–8.5 cm above the chamber and attached to the outside of the front panel. An IBM compatible computer was used for session programming and data collection (Med Associates Inc., East Fairfield, VT).

Lever training

Subjects were transferred to the operant chambers for daily experimental sessions, and responding was engendered and maintained by delivery of food pellets (45-mg pellets; Noyes, Lancaster, NH) under an FR 1 schedule of reinforcement that was gradually increased to FR3 (every third response produced a food pellet). The lever light was illuminated when the schedule was in effect. Completion of the response requirement extinguished lights, delivered food and was followed by a 20-second timeout (TO) period during which all lights were extinguished, and responses had no scheduled consequences. After the TO, the lights were illuminated, and the FR schedule was again in effect. Sessions lasted 20 minutes or until 30 food pellets were delivered. Responding was considered stable when there was less than 10 percent variation in the number of reinforcers for three consecutive sessions.

Intravenous jugular surgery

After operant responding was acquired and maintained by food, subjects surgically implanted with an intravenous jugular catheter. Venous catheters were inserted into the right jugular vein following administration of ketamine (90 mg/kg; IP) and xylazine (5 mg/kg; IP) for anesthesia as described previously (Pattison *et al.* 2012; Pattison *et al.* 2014; McIntosh *et al.* 2015). Catheters were anchored to muscle near the point of entry into the vein. The distal end of the catheter was guided subcutaneously to exit above the scapulae through a Teflon shoulder harness. The harness provided a point of attachment for a spring leash connected to a single-channel fluid swivel at the opposing end. The catheter was threaded through the leash and attached to the swivel. The other end of the swivel was connected to a syringe (for saline and drug delivery) mounted on a syringe pump. Rats were administered penicillin G procaine (75 000 units in 0.25 ml, i.m.) and allowed a minimum of 5 days to recover before self-administration studies were initiated. Hourly infusions of heparinized saline were administered through the catheter to maintain functional catheters. The health of the rats was monitored daily by the experimenters and weekly by institutional veterinarians per the guidelines issued by the Institutional Animal Care and Use Committee and the National Institutes of Health. Infusions of propofol (6 mg/kg; i.v.) were manually administered as needed to assess catheter patency.

Rats were transferred to the operant chambers for daily two-hour self-administration sessions. Before each session, the swivel and catheter were flushed with 500 µl of heparinized saline before connecting the catheter to the syringe via a 20 ga luer hub and 28 ga male connector. The start of each session was indicated by the illumination of the house light, stimulus light above the lever and the extension of the lever. Completion of the response requirement was followed by a 20-second time out (FR3:TO 20 seconds) during which time the subject received a 200-µl intravenous infusion over the first 6 seconds, retraction of the lever, extinguishing of lever light, generation of a tone and illumination of the house light. At the end of the TO, the lever was extended, lever light illuminated, tone silenced and the house light extinguished (Hemby, Smith, & Dworkin 1996; Hemby *et al.* 1999; McIntosh *et al.* 2015).

Experiment 1: Substitution for morphine self-administration

Self-administration was engendered using 100 µg/inf of morphine sulfate. When responding was stable (two consecutive sessions in which the number of reinforcers did not vary by more than 20 percent), the dose was changed to 50 µg/inf. Following stable responding at this dose, saline was substituted for morphine until responding stabilized. Following the conclusion of extinction testing, rats were assigned to one of two groups to

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receive MG (n = 9; 25, 50, 100 and 150 μg/inf) or 7-HMG (n = 8; 2.5, 5, 10 and 20 μg/inf)—doses were randomized. The dose range for MG self-administration was based on the finding that equivalent doses of morphine and MG induced place conditioning in rats (Yusoff *et al*. 2016). The dose range for 7-HMG was based on the finding that 7-HMG substitutes for morphine in the drug discrimination procedure at a dose five-fold lower than the training dose of morphine. Once responding stabilized for a particular dose, the next dose was made available the following session until all doses mentioned above were assessed. After all doses had been assessed for a subject within a group, the rat was allowed to self-administer morphine (50 and 100 μg/inf) to determine the effect of prior drug history on subsequent morphine intake.

Experiment 2: Acquisition of self-administration

Whereas substitution procedures may be more sensitive for determining the reinforcing effects of a compound, acquisition procedures assess only the reinforcing effects of a single compound, without the potential confound of prior drug associations. The ability of MG and 7-HMG to engender and maintain responding without prior drug history was determined in a separate cohort of rats. Rats were assigned to one of three groups to self-administer MG (n = 8; 100 μg/infusion), 7-HMG (n = 8; 10 μg/infusion) or morphine (n = 6; 100 μg/infusion). Following stable responding at the initial dose, rats in the MG group were given access to 25 and 50 μg/infusion MG, 7-HMG group was allowed to self-administer 5.0 and 2.5 μg/infusion 7-HMG, while rats in the morphine group were allowed to self-administer 50 μg/infusion morphine. The presentation of doses for MG and 7-HMG was randomized following the initial dose.

Experiment 3: Selective opiate receptor antagonism of morphine and 7-HMG self-administration

To determine the contribution of μ and δ opiate receptors on the reinforcing effects of 7-HMG, rats that had previously acquired morphine and 7-MHG self-administration were administered naloxonazine (NLXZ), a selective μ1 receptor antagonist or the δ receptor antagonist naltrindole (NTI). NLXZ (5 and 15 mg/kg, i.p.) and NTI (0.5 and 5 mg/kg, i.p.) were administered 30 minutes before the session. The effects of saline pretreatment and saline extinction on responding were also assessed.

Data analysis

Experiment 1

Morphine self-administration as well as MG and 7-HMG substitution was analyzed using a one-factor ANOVA (Dose). Morphine self-administration before and after MG and 7-HMG substitution was analyzed using a two-way ANOVA (Dose × Pre/Post). Analysis of three days following MG and 7-HMG substitution was conducted using a two-way repeated measures ANOVA (Dose × Pre/Post) with Sessions as the repeated measure. **Experiment 2.** Acquisition of self-administration was analyzed using one-factor ANOVA (Dose) ANOVA and number of infusions as the dependent measure. **Experiment 3.** Comparisons between baseline intake and intake following saline pretreatment were conducted using two-tailed paired t-test for both the morphine and 7-HMG groups. The effects of NLXZ and NTI on morphine and 7-HMG were analyzed independently using a one-factor ANOVA (Antagonist Dose). Analysis of the session in which the antagonists or saline were administered, and the following session was conducted using a two-way repeated measures ANOVA (Dose × Day) with Sessions as the repeated measure. The number of infusions was the dependent variable for analyses. Where appropriate, post hoc analyses were conducted using Tukey's test.

RESULTS

Substitution and reintroduction of morphine

Responding was engendered and maintained by morphine at the doses tested [$F(2,17) = 24.4$, $P < 0.0001$]. Morphine self-administration was dose-dependent with both morphine doses significantly greater than saline and 50 μg greater than 100 μg/infusion ($P < 0.05$) (Fig. 1a). MG was not reliably self-administered when substituted for morphine [$F(4,38) = 0.51$, $P = 0.73$]. MG intake was not significantly different from vehicle, suggesting that MG does not function as a reinforcer at the doses tested (Fig. 1b). In contrast, 7-HMG substituted for morphine with intake dependent on the dose available [$F(4,32) = 6.3$, $P = 0.0009$]. The number of infusions obtained for 5 and 10 μg/inf were significantly greater than vehicle ($P < 0.05$), confirming that these doses of 7-HMG functioned as reinforcing stimuli. 7-HMG resulted in an inverted 'U'-shaped dose-effect function with maximal intake observed at 5 and 10 μg/inf (Fig. 1c).

Following completion of the substitution protocol, morphine self-administration was re-assessed. Morphine intake was significantly altered by both MG [$F(1,32) = 5.5$, $P = 0.025$] and 7-HMG [$F(1,24) = 12.92$, $P = 0.0015$], albeit in opposite directions. MG exposure significantly reduced morphine self-administration of 50 μg ($P < 0.01$), but not 100 μg [Fig. 1d (top panel)]. The decrease in morphine self-administration (50 μg) was not observed on the first day following MG exposure but was significantly decreased on days two and three Fig. 1c (middle panel)].

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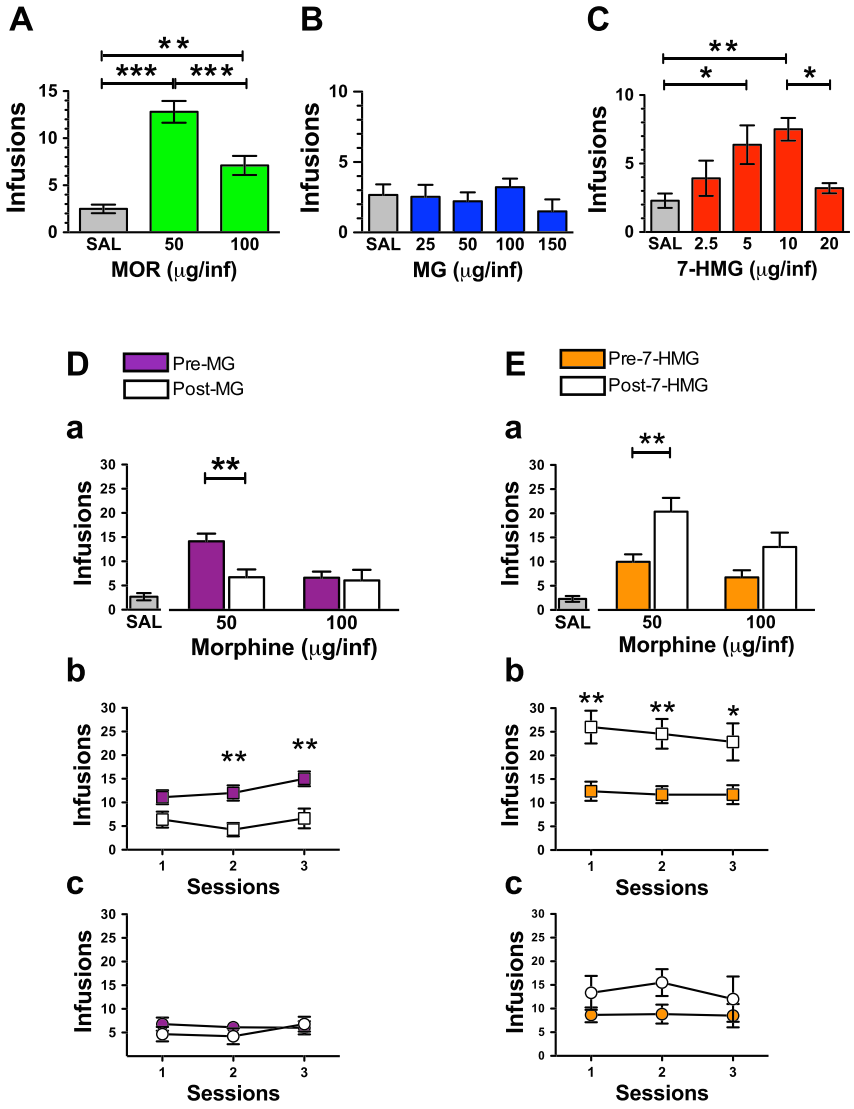

Figure 1 Substitution of MG and 7-HMG following morphine self-administration and the impact on subsequent morphine self-administration. (a) Morphine was reliably self-administered in a dose-dependent manner (***$P < 0.001$ saline versus 50 μg/inf and 50 versus 100 μg/inf, **$P < 0.01$ saline versus 100 μg/inf). (b) MG did not substitute for morphine (100 μg/inf) at any of the doses tested. (c) 7-HMG substituted for morphine (100 μg/inf) in a dose-dependent manner (*$P < 0.05$ saline versus 5 μg/inf, 10 versus 20 μg/inf, $P < 0.01$ saline versus 10 μg/inf). (d, e) Comparisons were made between morphine self-administration pre-exposure and post-exposure to MG ($n = 9$), and 7-HMG ($n = 7$) substitution. (d) Top panel: Comparison of morphine intake pre-MG exposure versus post-MG exposure revealed a significant difference in self-administration (**$P < 0.01$, pre-MG exposure versus post-MG exposure for 50 μg/inf). (d) Middle panel: Assessment of morphine self-administration for 3 days following MG exposure revealed a decrease in intake of 50 μg/inf morphine compared to pre-MG exposure levels (**$P < 0.01$ sessions 2 and 3 pre-exposure versus post-exposure to MG). (d) Bottom panel but had no change in morphine self-administration of 100 μg/inf across the 3 days. (e) Top panel, Comparison of morphine intake pre-7-HMG exposure versus post-7-HMG exposure revealed a significant difference in self-administration (**$P < 0.01$, pre-7-HMG exposure versus post-7-HMG exposure for 50 μg/inf morphine). (e) Middle panel: Substitution of 7-HMG resulted in a significant increase in morphine self-administration (50 μg/inf) for the 3 days following 7-HMG exposure (**$P < 0.01$ sessions 1 and 2, *$P < 0.05$ session 3 pre-exposure versus post-exposure to 7-HMG). (e) Bottom panel whereas self-administration of 100 μg/inf of morphine was not altered by 7-HMG exposure. Data are expressed as mean ± s.e.m.

Intake of 100-μg morphine did not differ from saline before or following exposure to MG [Fig. 1d (bottom panel)].

In contrast, 7-HMG administration significantly increased self-administration of 50-μg morphine ($P < 0.01$), and there was a trend towards increased intake of 100-μg morphine ($P = 0.054$) [Fig. 1e (top panel)]. Morphine self-administration (50 μg) was significantly elevated for the three days following 7-HMG exposure by 109, 110 and 95 percent, respectively

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[Fig. 1e (middle panel)]. Self-administration of 100-μg morphine was also increased for the 3 days following 7-HMG exposure by 53, 75 and 41 percent, respectively [Fig. 1e (bottom panel)]. We also determined whether morphine self-administration was altered by forced abstinence for an equivalent number of days to the substitution procedure. Morphine intake was not altered by the forced abstinence period [$F(1,20) = 8$, $P = 0.1523$], suggesting that the amount of time between morphine self-administration availability did not influence intake (*data not shown*).

Acquisition of self-administration

Following the assessment of the ability of MG and 7-HMG to substitute for morphine self-administration, we assessed the ability of MG and 7-HMG to engender and maintain responding in a separate cohort of rats. Morphine was readily self-administered at the doses tested [$F(2,17) = 24$, $P < 0.0001$]. Self-administration of 50 and 100 μg was greater than saline and the number of infusions obtained for the 50 μg/inf was significantly greater than 100 μg/inf (Fig. 2a). In contrast, access to MG did not reliably engender or maintain self-administration at any of the doses tested [$F(3,31) = 2.255$, $P = 0.1038$] as intake was not significantly different from vehicle, indicating that MG does not function as a reinforcer in this procedure at the doses tested (Fig. 2b). Similar to morphine, rats self-administered 2.5, 5 and 10 μg/infusion of 7-HMG [$F(3,31) = 6.2$, $P = 0.0024$]—the same doses that substituted for morphine self-administration (Fig. 2c). The number of infusions obtained 5 and 10 μg/inf was significantly greater than vehicle ($P < 0.05$), demonstrating that these doses served as reinforcing stimuli. Intake for 2.5 and 20 μg/inf 7-HMG did not significantly differ from vehicle. Comparison of saline intake for all groups revealed there was no statistically significant difference between the groups [$F(2,22) = 2.99$, $P = 0.0731$]. Tukey's post hoc test revealed there was no statistically significant difference between any of the group pairs.

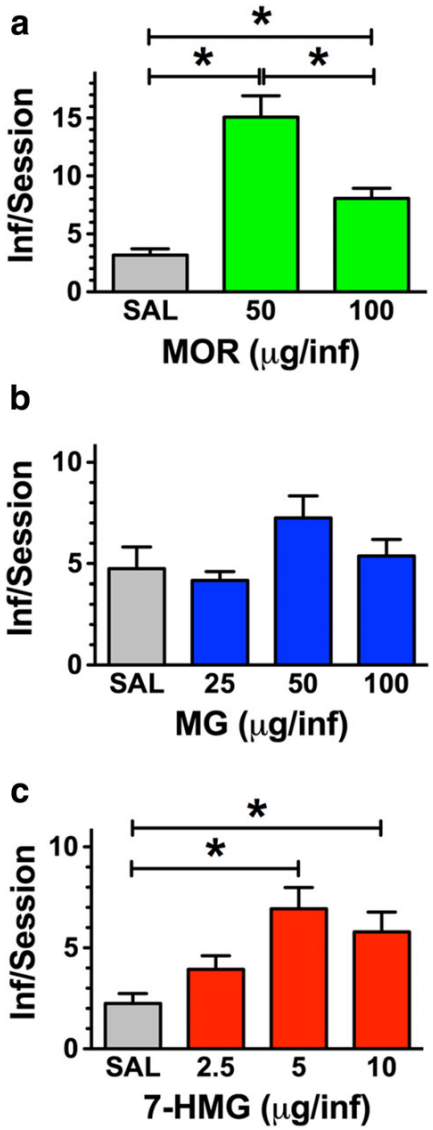

Figure 2 Acquisition of intravenous self-administration with 7-HMG but not MG. (a) Rats acquired morphine self-administration, and intake was dose dependent. (b) Rats did not acquire self-administration of MG at any of the doses tested. (c) However, a separate cohort of rats acquired self-administration of 7-HMG. $n = 8$ rats. Data are expressed as mean ± s.e.m. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{\#}P < 0.0001$

Antagonist effects on 7-HMG and morphine self-administration

The effects of the selective μ opiate receptor antagonist NLXZ and the δ receptor antagonist NTI on morphine (50 μg/inf) and 7-HMG (5 μg/inf) self-administration were examined. The selection was based on doses that maintained the highest intake for morphine and 7-HMG self-administration, respectively. NLXZ pretreatment attenuated morphine self-administration [$F(2,15) = 76$, $P < 0.0001$] [Fig. 3a (left panel)]. Both 5 and 15 mg/kg NLXZ produced a significant decrease in the number of infusions for morphine ($P < 0.05$); however, there was no significant difference in the number of infusions between the doses. Morphine intake was significantly decreased the day of NLXZ pretreatment for both doses ($P < 0.001$) and returned to control levels the following session [Fig. 3a (right panel)]. Pretreatment with NLXZ also significantly reduced 7-HMG self-administration [$F(2,22) = 39$, $P < 0.0001$] [Fig. 3b (left panel)]. Both NLXZ doses significantly reduced 7-HMG

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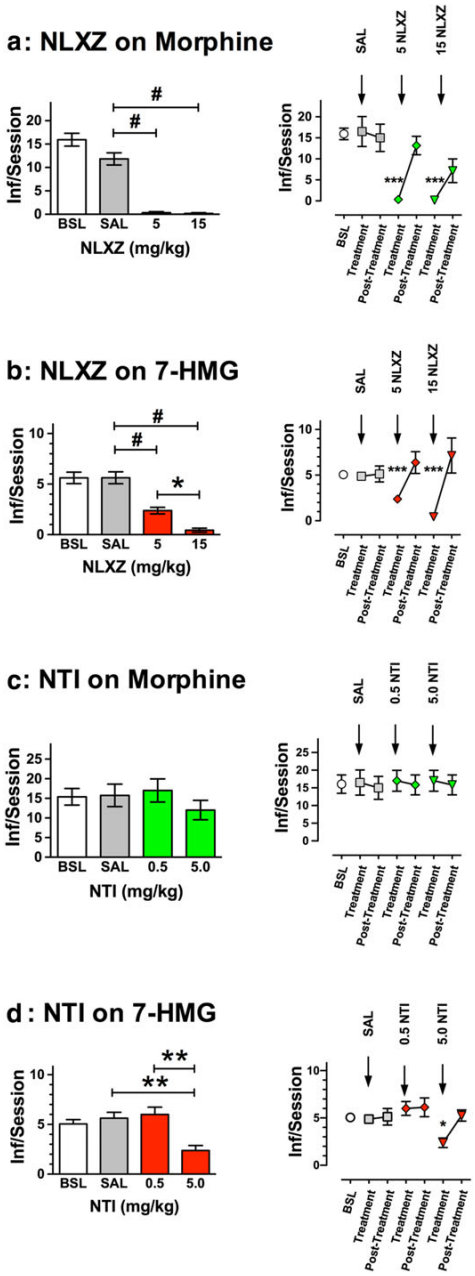

Figure 3 Selective μ and δ opiate receptor antagonist pretreatment alters 7-HMG self-administration. Effects of NLXZ on morphine (50 μg/inf) and 7-HMG (5 μg/inf) self-administration. Baseline drug intake was not significantly different than intake following saline pretreatment for morphine analysis or 7HMG analysis. (a) Left panel NLXZ significantly reduced the number of morphine infusions compared to saline pretreatment ($^{\#}P < 0.0001$, saline versus 5 and 15 mg/kg NLXZ). (a) Right panel There was a significant interaction between NLXZ doses and sessions with infusions on the day of pretreatment significantly less than following saline pretreatment for the 15 mg/kg NLXZ dose ($^{***}P < 0.001$). (b) Left panel NLXZ decreased 7-HMG self-administration, the effect was dose dependent ($^{\#}P < 0.0001$, $^{*}P < 0.05$) and (b) right panel There was a significant interaction between NLXZ doses and sessions with infusions on day of pretreatment significantly less than following saline pretreatment for both NLXZ doses. We also examined the effects of NTI on morphine (50 μg/inf) and 7-HMG (5 μg/inf) self-administration. Baseline drug intake was not significantly different than intake following saline pretreatment for morphine analysis and 7HMG analysis. (c) Left panel NTI did not significantly alter morphine self-administration at either dose tested. (c) Right panel No significant interaction of NTI dose and session was observed. (d) Left panel Pretreatment with NTI decreased 7-HMG self-administration in a dose-dependent manner ($^{**}P < 0.01$, saline versus 5.0 mg/kg NTI, 0.5 versus 5.0 mg/kg NTI) and (d) right panel There was a significant interaction between NTI doses and sessions although Bonferroni's post hoc analysis did not reveal any significant differences between saline and NTI pretreatment for either day. Data are expressed as mean ± s.e.m.

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intake compared to saline ($P < 0.0001$), although intake following 15 mg/kg was significantly less than following 5 mg/kg ($P < 0.05$). For both doses, 7-HMG intake was significantly reduced the day of NLXZ pretreatment ($P < 0.001$) and returned to control levels the following session [Fig. 3b (right panel)]. Comparison of baseline intake was not significantly different than intake following saline pretreatment for the morphine [$t = 2.5$, df = 5, $P = 0.057$] or 7-HMG groups [$t = 0.03$, df = 7, $P = 0.98$]; therefore, the number of infusions following saline was used for comparison with NLXZ.

NTI pretreatment produced differential effects on morphine and 7-HMG self-administration. Neither 0.5 nor 5.0 mg/kg NTI significantly altered morphine self-administration [$F(2,17) = 0.88$, $P = 0.434$] [Fig. 3c (left panel)]. Morphine intake following either dose of NTI did not differ significantly from saline pretreatment the day of or the day following pretreatment [Fig. 3c (right panel)]. In contrast, 5.0 mg/kg NTI pretreatment significantly altered 7-HMG self-administration [$F(2,23) = 11$, $P < 0.0007$] [Fig. 3d (left panel)]. The effect of NTI on 7-HMG intake was dose dependent as intake following the 5 mg/kg dose was significantly lower than saline ($P < 0.05$) as well as the 0.5 g/kg dose ($P < 0.05$). 7-HMG intake was significantly reduced the day of 5.0 mg/kg NTI pretreatment ($P < 0.05$) and returned to control levels the following session [Fig. 3 (right panel)]. For naltrindole (NTI), comparison of baseline intake was not significantly different than intake following saline pretreatment for the morphine [$t = 0.13$, df = 5, $P = 0.90$] or 7-HMG groups [$t = 0.94$, df = 7, $P = 0.38$].

DISCUSSION

The present study provides the first characterization of the reinforcing effects of MG and 7-HMG in an animal model of human drug consumption. Using the intravenous self-administration procedure, the study demonstrates 7-HMG, but not MG, substitute for morphine self-administration and engender and maintain self-administration in drug-naïve rats. Under both the substitution and acquisition self-administration procedures, 7-HMG self-administration exhibited an inverted 'U' dose–effect curve, typical of other drugs of abuse under similar experimental conditions, wherein low to moderate doses increase responding and higher doses decrease responding (Wilson, Hitomi, & Schuster 1971; Pickens 1978). In both self-administration procedures, 7-HMG maintained intake above levels observed for saline, indicating the compound serves as a reinforcing stimulus within the range of the doses examined. Previous studies have shown MG induces a conditioned place preference (Sufka *et al.* 2014; Yusoff *et al.* 2016; Yusoff *et al.* 2017) and both MG and 7-HMG generalize to the discriminative stimulus effects of morphine (Harun *et al.* 2015). Both procedures provide valuable information about the abuse liability of compounds such as the motivational effects of contextual cues associated with a drug (place conditioning) and whether a compound shares subjective effects with a known drug of abuse (drug discrimination). Self-administration is used to examine the reinforcing effects of drugs, a key feature influencing the potential risk for abuse. With regard to opioids, findings from studies using rat self-administration models are highly consistent with clinical measures of abuse liability and have proven to be a reliable predictor of abuse liability in humans (O'Connor *et al.* 2011). While MG shares a similar mechanism of action with morphine, the present results demonstrate a difference in the reinforcing effects and thus the abuse potential between the two compounds. The discrepancy between the present finding and those of aforementioned place conditioning and drug discrimination studies are intriguing and warrant further assessment of routes of administration as well as non-human primate and human abuse potential studies. The self-administration of 7-HMG along with the shared subjective effects of morphine (Harun *et al.* 2015) indicate that 7-HMG has a significant potential to be abused. Additional studies are needed to examine the ability of 7-HMG self-administration to induce physical dependence and withdrawal, and the effects of 7-HMG on relapse to morphine, other opiates and other drug classes. The present findings along with the results of additional studies will provide critical information as to whether the compounds warrant control under the Controlled Substances Act.

In addition to abuse liability assessments, we also explored the impact of exposure to MG and 7-HMG to subsequent morphine intake following completion of the substitution procedure. Exposure to less than 2 mg of MG over a 2-week period (when examining the ability of MG to substitute for morphine) significantly reduced subsequent morphine self-administration up to 3 days following the last administration of MG. These findings raise the possibility that MG may contribute to the reported reduction in opiate intake in dependent individuals. Buprenorphine, a μ receptor partial agonist like MG, also reduced morphine (Harrigan & Downs 1981) as well as heroin self-administration (Mello, Bree, & Mendelson 1983) when administered continuously or intravenously twice daily but the effects on intake were acute. The effects of MG on morphine intake in the present study are intriguing but should be interpreted with caution for several reasons including the lack of morphine dose-dependent effects, the absence of a MG dose-effect determination on morphine and other commonly abused opiates, and the need to assess the effect of MG on animal

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models of opiate relapse and withdrawal. The finding that MG, in contrast to buprenorphine which has abuse liability (Jones et al., 2017), does not appear to have abuse liability and reduces morphine intake is intriguing and warrants further investigation to determine the efficacy of MG as a potential pharmacotherapy for opiate addiction. Comparison of MG with buprenorphine as well as methadone, on the self-administration of morphine as well as other opiates, is needed to determine the therapeutic potential and potency of MG. The effects of 7-HMG on morphine intake are opposite to those observed with MG. An average total intake of approximately 700 μg of 7-HMG over a 2 to 3-week period (when examining substitution for morphine) induced a significant elevation in subsequent morphine self-administration over 3 days following the last exposure to the compound, indicative of tolerance to morphine. Previous reports indicate that kratom users develop tolerance, increasing intake over time (Suwanlert 1975; Hassan *et al.* 2013). While tolerance to the analgesic effects of 7-HMG has been reported (Matsumoto *et al.* 2005; Matsumoto *et al.* 2008), no published studies to date report tolerance or cross-tolerance to morphine (or other opiates) intake. The increase in morphine intake in the present study could reflect a compensatory response to withdrawal from 7-HMG; however, this is unlikely as no overt signs of withdrawal were observed. Additional studies are warranted to determine if the observed increase in morphine intake following 7-HMG self-administration is related to a change in the reinforcing effects of morphine, a decrease in the adverse effects or a combination of the two. The demonstration that 7-HMG has significant abuse potential and increases the intake of morphine and possibly other opiates has significant potential clinical relevance.

The present study utilized two variations of the intravenous self-administration procedure to determine abuse liability of MG and 7-HMG: substitution and acquisition of self-administration. The substitution procedure assessed the ability of MG and 7-HMG to substitute for morphine in rats with a history of morphine self-administration and provided a clinically relevant evaluation given the potential for cross-generalization of opiates, the use of kratom to reduce intake of and withdrawal from other opiates, and the use of kratom as an affordable substitute for heroin (Boyer, Babu, & Macalino 2007; Boyer *et al.* 2008; Vicknasingam *et al.* 2010). The ability of 7-HMG to substitute for morphine in the present study suggests that the reinforcing effects may be mediated by similar neural mechanisms such as μ and δ opiate receptors. The effects of NLXZ on 7-HMG and morphine self-administration may reflect nonspecific effects on responding; however, we do not consider this a viable interpretation inasmuch as NLXZ doses within this range do not affect responding maintained by saccharin or food (Liu & Jernigan 2011; Peana *et al.* 2011). The present results confirm and extend previous studies of the effects of NLXZ on opiates including decreasing heroin self-administration (Negus *et al.* 1993), decreasing morphine-induced place conditioning in rats (Piepponen *et al.* 1997) and attenuating the discriminative stimulus effects of morphine (Suzuki *et al.* 1995). These results indicate that the reinforcing effects of morphine 7-HMG are mediated in part by μ opiate receptors.

NTI, the selective δ opiate receptor antagonist, attenuated 7-HMG in a dose-dependent manner. The lack of effect of NTI on morphine self-administration is supported by previous studies, which indicates that NTI does not alter morphine place conditioning (Suzuki *et al.* 1994; Piepponen *et al.* 1997) or the discriminative stimulus effects of morphine (Stevenson *et al.* 2000). In contrast, NTI and naltrindole-5′-isothiocyanate have been shown to attenuate the reinforcing effects of heroin (Negus *et al.* 1993; Martin *et al.* 2000); however, δ opiate receptors are not considered to directly mediate heroin reinforcement. The reinforcing effects of heroin are mediated via μ opiate receptors which bind the major heroin metabolites, morphine and 6-monoacetylmorphine, neither of which bind to the δ receptor with appreciable affinity. The difference in the effects of NTI between the Negus *et al.* study is likely attributable to the finding that only the 10 and 17 mg/kg doses of NTI were effective in attenuating heroin self-administration—compared with 0.5 and 5 mg/kg in the present study. Given that the 5 mg/kg NTI dose slightly decreased morphine self-administration, higher doses of NTI may have significantly attenuated intake. The significant attenuation of the reinforcing effects of 7-HMG by NTI reflects involvement of δ opiate receptors in the reinforcing effects of this compound. Given that 7-HMG is a weak δ opiate receptor antagonist, the finding that antagonism of the δ receptor partially attenuates the reinforcing effects of this compound seems counterintuitive. However, two potential mechanisms may account in part for the finding. Martin *et al.* suggested that morphine-induced activation of μ opiate receptors in the pallidum stimulates release of met-enkephalin that then binds to δ opiate receptors to exert reinforcing effects (Martin *et al.* 2000). Because 7-HMG is a partial μ opiate receptor agonist, the compound may exert effects similar to morphine via this mechanism. An alternative hypothesis suggests that chronic μ opiate receptor stimulation results in δ opiate receptor recruitment and μ opiate receptor desensitization. However, the dose-dependent effect of NLXZ on 7-HMG indicates that μ receptors were not de-sensitized. The manner in which δ opiate receptors are involved in 7-HMG reinforcement remains to be determined. Nonetheless, results from the present study indicate that both μ and δ opiate receptors contribute to the reinforcing

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effects of 7-HMG. Current pharmacotherapies for opiate addiction including methadone, buprenorphine and naloxone do not bind appreciably to δ opiate receptors and therefore may be less effective in treating kratom abuse.

The current results are the first demonstration of self-administration of MG and 7-HMG in the preclinical literature; however, several issues related to study design and methodology deserve to be addressed. First, food was restricted for all subjects in the present study in order to enhance acquisition and maintenance of self-administration in both the substitution and acquisition procedures. Previous studies have demonstrated that food restriction facilitates the acquisition of opiate self-administration and increases intake during the maintenance phase as well as enhances drug seeking (Piazza & Le Moal 1998). The absence of MG acquisition or substitution under food restriction conditions provides confidence that administration of this alkaloid is not reinforcing even under conditions that enhance the probability of intake. Nonetheless, negative results in self-administration procedures are difficult to interpret and may be due to multiple experimental variables that are not optimal for the drug being investigated including, but not limited to, the schedule of reinforcement, response contingencies, selected doses, rate of infusion, route of administration and drug availability. For example, the lack of MG self-administration may be attributed in part to the route of administration. Kratom is administered orally by humans whereas intravenous administration was used in the present study—routes which would yield different rates of onset of drug effects, drug levels, duration of effect and metabolism. The concern is mitigated to some extent by the finding that 7-HMG, a structurally similar compound from the same plant, is readily self-administered intravenously using the same procedure. Thus, the relevance of the current findings using the intravenous self-administration is not diminished, although future studies need to address the abuse liability of MG and 7-HMG using voluntary oral consumption methods (food and liquid). Another caveat to the present experimental design is the use of one versus two levers in the self-administration procedure. The determination of reinforcement is based on the statistical comparison of intake maintained by doses of a drug versus a negative control, which is vehicle in the present study. Alternatively, comparisons can be made between the rates of responding on an 'active' versus the 'inactive' lever. In either case, drugs that engender and/or maintain responding at levels that exceed responding maintained by the negative control are considered to be self-administered (function as reinforcing stimuli) (O'Connor *et al.* 2011).

In summary, the present findings from the rodent self-administration model indicate that MG, the main kratom alkaloid, does not have abuse or addiction potential and reduces morphine intake—desired characteristics of candidate pharmacotherapies for opiate addiction and withdrawal. In contrast, 7-HMG should be considered a kratom constituent with high abuse potential that may also increase the intake of other opiates. Although 7-HMG constitutes only 2 percent of the alkaloid content of kratom, purified extracts of 7-HMG are widely available on the internet and are consumed for their euphoric effects. Additional danger is posed by adulteration or the presence of high concentrations of 7-HMG in commercially available kratom products (Lydecker *et al.* 2016) which may increase the abuse liability.

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Conflict of Interest

The authors have no competing financial interests.

Authors Contribution

S.E.H., S.J.C. and C.R.M. jointly conceived the study; S.E.H. designed the experiments; J.F., S.J.C. and C.R.M. isolated, purified and prepared salts of mitragynine and 7-hydroxymitragynine; S.M. and S.E.H. performed the experiments, collected the data and analyzed the data; S.E.H. wrote and revised the manuscript and S.M., S.J.C. and C.R.M. edited the manuscript.

References

Boyer EW, Babu KM, Adkins JE, McCurdy CR, Halpern JH (2008) Self-treatment of opioid withdrawal using kratom (Mitragynia speciosa korth). Addiction 103:1048–1050.

Boyer EW, Babu KM, Macalino GE (2007) Self-treatment of opioid withdrawal with a dietary supplement, Kratom. Am J Addict 16:352–356.

Cinosi E, Martinotti G, Simonato P, Singh D, Demetrovics Z, Roman-Urrestarazu A, Bersani FS, Vicknasingam B, Piazzon G, Li JH, Yu WJ, Kapitany-Foveny M, Farkas J, Di Giannantonio M, Corazza O (2015) Following "the Roots" of kratom (Mitragyna speciosa): the evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in western countries. Biomed Res Int 2015:968786.

Drago JZ, Lane B, Kochav J, Chabner B (2017) The harm in kratom. Oncologist 22:1010–1011.

Fluyau D, Revadigar N (2017) Biochemical benefits, diagnosis, and clinical risks evaluation of kratom. Front Psychiatry 8:62.

Food and Drug Administration (2016) Marshals seize dietary supplements containing kratom [Press release].

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Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm480344.htm

Galbis-Reig D (2016) A case report of kratom addiction and withdrawal. WMJ 115:49–52. quiz 53.

Harrigan SE, Downs DA (1981) Pharmacological evaluation of narcotic antagonist delivery systems in rhesus monkeys. NIDA Res Monogr 28:77–92.

Harun N, Hassan Z, Navaratnam V, Mansor SM, Shoaib M (2015) Discriminative stimulus properties of mitragynine (kratom) in rats. Psychopharmacology (Berl) 232:2227–2238.

Hassan Z, Muzaimi M, Navaratnam V, Yusoff NH, Suhaimi FW, Vadivelu R, Vicknasingam BK, Amato D, von Horsten S, Ismail NI, Jayabalan N, Hazim AI, Mansor SM, Muller CP (2013) From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. Neurosci Biobehav Rev 37:138–151.

Hemby SE (1999) Recent advances in the biology of addiction. Curr Psychiatry Rep 1:159–165.

Hemby SE, Co C, Dworkin SI, Smith JE (1999) Synergistic elevations in nucleus accumbens extracellular dopamine concentrations during self-administration of cocaine/heroin combinations (Speedball) in rats. J Pharmacol Exp Ther 288:274–280.

Hemby SE, Smith JE, Dworkin SI (1996) The effects of eticlopride and naltrexone on responding maintained by food, cocaine, heroin and cocaine/heroin combinations in rats. J Pharmacol Exp Ther 277:1247–1258.

Ismail NIW, Jayabalan N, Mansor SM, Muller CP, Muzaimi M (2017) Chronic mitragynine (kratom) enhances punishment resistance in natural reward seeking and impairs place learning in mice. Addict Biol 22:967–976.

Jones JD, Manubay JM, Mogali S, Metz VE, Madera G, Martinez S, Mumtaz M, Comer SD (2017) Abuse liability if intravenous buprenorphine vs. buprenorphine/naloxone: Importance of absolute naloxone amount. Drug Alcohol Depend 179:362–369.

Katz JL (1989) Drugs as reinforcers: pharmacological and behavioural factors. In: Liebman JM, Cooper SJ eds. The Neuropharmacological Basis of Reward, pp. 164–213. Oxford University Press: New York.

Kruegel AC, Gassaway MM, Kapoor A, Varadi A, Majumdar S, Filizola M, Javitch JA, Sames D (2016) Synthetic and receptor signaling explorations of the mitragyna alkaloids: Mitragynine as an atypical molecular framework for opioid receptor modulators. J Am Chem Soc 138:6754–6764.

Liu X, Jernigan C (2011) Activation of the opioid mu1, but not delta or kappa, receptors is required for nicotine reinforcement in a rat model of drug self-administration. Prog Neuropsychopharmacol Biol Psychiatry 35:146–153.

Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW (2016) Suspected adulteration of commercial kratom products with 7-hydroxymitragynine. J Med Toxicol 12:341–349.

Lynch WJ, Hemby SE (2011) Drug reinforcement in animals. In: Johnson BA ed. Addiction Medicine: Science and Practice, pp. 117–128. Springer: New York.

Martin TJ, Kim SA, Cannon DG, Sizemore GM, Bian D, Porreca F, Smith JE (2000) Antagonism of delta(2)-opioid receptors by naltrindole-5′-isothiocyanate attenuates heroin self-administration but not antinociception in rats. J Pharmacol Exp Ther 294:975–982.

Matsumoto K, Horie S, Ishikawa H, Takayama H, Aimi N, Ponglux D, Watanabe K (2004) Antinociceptive effect of 7-hydroxymitragynine in mice: discovery of an orally active opioid analgesic from the Thai medicinal herb Mitragyna speciosa. Life Sci 74:2143–2155.

Matsumoto K, Horie S, Takayama H, Ishikawa H, Aimi N, Ponglux D, Murayama T, Watanabe K (2005) Antinociception, tolerance and withdrawal symptoms induced by 7-hydroxymitragynine, an alkaloid from the Thai medicinal herb Mitragyna speciosa. Life Sci 78:2–7.

Matsumoto K, Takayama H, Narita M, Nakamura A, Suzuki M, Suzuki T, Murayama T, Wongseripipatana S, Misawa K, Kitajima M, Tashima K, Horie S (2008) MGM-9 [(E)-methyl 2-(3-ethyl-7a,12a-(epoxyethanoxy)-9-fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxy indolo[2,3-a] quinolizin-2-yl)-3-methoxyacrylate], a derivative of the indole alkaloid mitragynine: a novel dual-acting mu- and kappa-opioid agonist with potent antinociceptive and weak rewarding effects in mice. Neuropharmacology 55:154–165.

McIntosh S, Sexton T, Pattison LP, Childers SR, Hemby SE (2015) Increased sensitivity to cocaine self-administration in HIV-1 transgenic rats is associated with changes in striatal dopamine transporter binding. J Neuroimmune Pharmacol 10: 493–505.

McWhirter L, Morris S (2010) A case report of inpatient detoxification after kratom (Mitragyna speciosa) dependence. Eur Addict Res 16:229–231.

Mello NK, Bree MP, Mendelson JH (1983) Comparison of buprenorphine and methadone effects on opiate self-administration in primates. J Pharmacol Exp Ther 225:378–386.

Neerman MF, Frost RE, Deking J (2013) A drug fatality involving kratom. J Forensic Sci 58:S278–S279.

Negus SS, Henriksen SJ, Mattox A, Pasternak GW, Portoghese PS, Takemori AE, Weinger MB, Koob GF (1993) Effect of antagonists selective for mu, delta and kappa opioid receptors on the reinforcing effects of heroin in rats. J Pharmacol Exp Ther 265:1245–1252.

O'Connor EC, Chapman K, Butler P, Mead AN (2011) The predictive validity of the rat self-administration model for abuse liability. Neurosci Biobehav Rev 35:912–938.

Pattison LP, McIntosh S, Budygin EA, Hemby SE (2012) Differential regulation of accumbal dopamine transmission in rats following cocaine, heroin and speedball self-administration. J Neurochem 122:138–146.

Pattison LP, McIntosh S, Sexton T, Childers SR, Hemby SE (2014) Changes in dopamine transporter binding in nucleus accumbens following chronic self-administration cocaine: heroin combinations. Synapse 68:437–444.

Peana AT, Muggironi G, Fois GR, Zinellu M, Vinci S, Acquas E (2011) Effect of opioid receptor blockade on acetaldehyde self-administration and ERK phosphorylation in the rat nucleus accumbens. Alcohol 45:773–783.

Piazza PV, Le Moal M (1998) The role of stress in drug self-administration. Trends Pharmacol Sci 19:67–74.

Pickens RW (1978) Drug self-administration: an analysis of the reinforcing effects of drugs. In: Iversen LL, Iversen SD, Snyder SH eds. Handbook of Psychopharmacology, pp. 1–37. Plenum Press: New York.

Piepponen TP, Kivastik T, Katajamaki J, Zharkovsky A, Ahtee L (1997) Involvement of opioid mu 1 receptors in morphine-induced conditioned place preference in rats. Pharmacol Biochem Behav 58:275–279.

Ponglux D, Wongseripipatana S, Takayama H, Kikuchi M, Kurihara M, Kitajima M, Aimi N, Sakai S (1994) A new indole alkaloid, 7 alpha-hydroxy-7H-mitragynine, from Mitragyna speciosa in Thailand. Planta Med 60:580–581.

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Prozialeck WC, Jivan JK, Andurkar SV (2012) Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J Am Osteopath Assoc 112:792–799.

Saingam D, Assanangkornchai S, Geater AF, Balthip Q (2013) Pattern and consequences of krathom (Mitragyna speciosa Korth.) use among male villagers in southern Thailand: a qualitative study. Int J Drug Policy 24:351–358.

Sheleg SV, Collins GB (2011) A coincidence of addiction to "Kratom" and severe primary hypothyroidism. J Addict Med 5:300–301.

Singh D, Muller CP, Vicknasingam BK (2014) Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. Drug Alcohol Depend 139:132–137.

Singh D, Narayanan S, Vicknasingam B (2016) Traditional and non-traditional uses of Mitragynine (Kratom): a survey of the literature. Brain Res Bull 126:41–46.

Stevenson GW, Canadas F, Zhang X, Rice KC, Riley AL (2000) Morphine discriminative control is mediated by the mu opioid receptor: assessment of delta opioid substitution and antagonism. Pharmacol Biochem Behav 66:851–856.

Stogner JM (2015) Predictions instead of panics: the framework and utility of systematic forecasting of novel psychoactive drug trends. Am J Drug Alcohol Abuse 41:519–526.

Sufka KJ, Loria MJ, Lewellyn K, Zjawiony JK, Ali Z, Abe N, Khan IA (2014) The effect of Salvia divinorum and Mitragyna speciosa extracts, fraction and major constituents on place aversion and place preference in rats. J Ethnopharmacol 151:361–364.

Suwanlert S (1975) A study of kratom eaters in Thailand. Bull Narc 27:21–27.

Suzuki T, Mori T, Tsuji M, Misawa M, Nagase H (1995) Discriminative stimulus properties of morphine mediated by mu 1-opioid receptors. Eur J Pharmacol 284:195–198.

Suzuki T, Yoshiike M, Mizoguchi H, Kamei J, Misawa M, Nagase H (1994) Blockade of delta-opioid receptors prevents morphine-induced place preference in mice. Jpn J Pharmacol 66:131–137.

Takayama H, Ishikawa H, Kurihara M, Kitajima M, Aimi N, Ponglux D, Koyama F, Matsumoto K, Moriyama T, Yamamoto LT, Watanabe K, Murayama T, Horie S (2002) Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. J Med Chem 45:1949–1956.

Varadi A, Marrone GF, Palmer TC, Narayan A, Szabo MR, Le Rouzic V, Grinnell SG, Subrath JJ, Warner E, Kalra S, Hunkele A, Pagirsky J, Eans SO, Medina JM, Xu J, Pan YX, Borics A, Pasternak GW, McLaughlin JP, Majumdar S (2016) Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit beta-arrestin-2. J Med Chem 59:8381–8397.

Vicknasingam B, Narayanan S, Beng GT, Mansor SM (2010) The informal use of ketum (Mitragyna speciosa) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. Int J Drug Policy 21:283–288.

Ward J, Rosenbaum C, Hernon C, McCurdy CR, Boyer EW (2011) Herbal medicines for the management of opioid addiction: safe and effective alternatives to conventional pharmacotherapy? CNS Drugs 25:999–1007.

Warner ML, Kaufman NC, Grundmann O (2016) The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. Int J Leg Med 130:127–138.

Wilson MC, Hitomi M, Schuster CR (1971) Psychomotor stimulant self administration as a function of dosage per injection in the rhesus monkey. Psychopharmacologia 22:271–281.

Yusoff NHM, Mansor SM, Muller CP, Hassan Z (2017) Opioid receptors mediate the acquisition, but not the expression of mitragynine-induced conditioned place preference in rats. Behav Brain Res 332:1–6.

Yusoff NH, Suhaimi FW, Vadivelu RK, Hassan Z, Rumler A, Rotter A, Amato D, Dringenberg HC, Mansor SM, Navaratnam V, Muller CP (2016) Abuse potential and adverse cognitive effects of mitragynine (kratom). Addict Biol 21:98–110.

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ORIGINAL INVESTIGATION

Abuse liability of mitragynine assessed with a self-administration procedure in rats

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Abstract

Rationale Substantial use of the plant kratom for psychoactive effects has driven interest in its abuse liability. Several place conditioning studies suggest abuse liability of the active ingredient mitragynine, though studies of its self-administration have not been published.

Methods Binding of mitragynine to rat brain mu, kappa, and delta opioid receptors was compared to that for heroin and morphine. Self-administration of mitragynine, heroin, methamphetamine, or saline was assessed during single-session substitutions in rats trained to self-administer methamphetamine (0.022 mg/kg/injection, i.v.) during 1-h daily sessions.

Results Mitragynine had > 2- or ~ 16-fold greater affinity for the mu opioid receptor than, respectively, for kappa or delta opioid receptors. Its affinity for the mu receptor was ~ 200-fold less than that for morphine. 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.

Conclusions 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.

Keywords Mitragynine · Kratom · Abuse liability · Self-administration · Methamphetamine · Heroin · Medical treatments · Opioid abuse · Rats

Significant use of the plant kratom for its psychoactive effects has prompted interest by the United States Drug Enforcement Agency (DEA) to temporarily place the active ingredients of the plant, mitragynine, and 7-hydroxymitragynine, into Schedule I of the Controlled Substances Act as an abusable substance (US Drug Enforcement Administration 2016). The notice of that intent by DEA was met with responses from the public, commercial, and legislative sectors which included testimonials though little scientific evidentiary support for those various responses (Henningfield et al. 2018).

Kratom is the commonly used term for the leaves of *Mitragyna speciosa*, which contain a variety of constituents. Mitragynine accounts for 66% of total alkaloid content in some geographical variants of the plant with variations among species studied and interactions among the various kratom constituents (Takayama 2004). 7-OH-Mitragynine is also present at lower levels with a 5- to 10-fold higher affinity for μ-opioid receptors (Kruegel et al. 2016). As levels in brain tissue after intravenous injection of mitragynine indicate suitable brain penetration from plasma (Kong et al. 2017), it is likely that mitragynine is the main pharmacologically active alkaloid in kratom (Kruegel and Grundmann 2018), though see the description below of a study of kratom extracts (Sufka et al. 2014).

Several studies in animal subjects have examined various behavioral effects including the abuse potential of mitragynine

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(see Hassan et al. 2017; Kruegel and Grundmann 2018 for reviews). A study of place conditioning (Sufka et al. 2014) administered different doses of mitragynine or an extract of *Mitragyna speciosa* leaves over eight conditioning sessions, half of which were preceded with mitragynine injection and half with vehicle. Significant place conditioning was obtained in rats administered 5 or 30 mg/kg of mitragynine though the effect eluded statistical significance at 10 mg/kg. Though the kratom extract increased place conditioning, it was not to a statistically significant extent. The authors interpreted the diminished effect of the extract as possibly due to lower concentrations of mitragynine in the extract or the presence of other plant constituents with effects interfering with the effect of mitragynine. Yusoff et al. (2016), using a similar procedure, found significant place conditioning in rats administered 10 or 30 mg/kg of mitragynine over ten conditioning sessions. In a subsequent study (Yusoff et al. 2017), the place conditioning induced by 10 mg/kg of mitragynine was blocked by the co-administration of naloxone (0.3 or 1.0 mg/kg), indicating that the place conditioning was mediated by opioid receptors. However, there are studies suggesting non-opioid effects of mitragynine (Kruegel and Grundmann 2018), and a recent report of baclofen blockade of mitragynine-induced place conditioning suggests potential $GABA_B$ receptor involvement in that effect (Yusoff et al. 2018).

Harun et al. (2015) compared the discriminative stimulus effects of mitragynine (15 mg/kg, i.p.) to those of morphine (5.0 mg/kg) in separate groups of rats each trained with one of the compounds. Both groups acquired discriminative control, though the morphine group acquired that control more rapidly. Each training drug produced a dose-related generalization to the training dose and each drug dose-dependently substituted for the other. Further 7-OH-mitragynine substituted for morphine more potently than did mitragynine. Interestingly, the discriminative effects of mitragynine were only incompletely antagonized by naloxone (Harun et al. 2015).

In a recent report (Hemby et al. 2018), rats were trained to reliably self-administer morphine (50 or 100 μg/infusion) under a fixed-ratio 3-response schedule, followed by replacement of drug with saline and extinction of responding. Following extinction, rats were allowed to self-administer different doses of mitragynine or 7-OH-mitragynine. No dose of mitragynine (25 to 150 μg/injection) maintained rates of responding significantly greater than those maintained by saline. In contrast, 7-OH-mitragynine maintained rates above those for saline at 2.5 to 20 μg/injection and also did so in a separate group of subjects without experience self-administering morphine. Both the μ-opioid receptor selective antagonist naloxonazine and the δ-opioid receptor antagonist naltrindole decreased self-administration of 7-OH-mitragynine but only naloxonazine decreased morphine self-administration.

The present study was designed to further assess the abuse liability of mitragynine using a self-administration procedure in rats. To confirm opioid activity, the displacement by mitragynine of opioid radioligands was studied using native rat tissue and compared to that produced by the standard opioids, morphine, and heroin. These binding affinities helped select doses tested to ensure that biologically active doses of mitragynine were studied.

Methods

Receptor binding assays Whole rat brain tissue excluding the cerebellum was thawed on ice, then homogenized in 50 mM Tris HCl, pH 7.5 using a Brinkman Polytron (setting 6 for 20 s), and centrifuged at 30,000 × g for 10 min at 4 °C. The supernatant was discarded and the pellet was resuspended in fresh buffer and spun at 30,000×*g* for 10 min. The supernatant was discarded and the pellet was resuspended to give 100 mg/ml original wet weight. Ligand-binding experiments were conducted in polypropylene assay tubes containing 0.5 ml Tris HCl buffer for 60 min at room temperature. [^{3}H]DADLE (final concentration 1 nM, PolyPeptide Laboratories, San Diego, CA), [^{3}H]DAMGO (final concentration 1 nM, PolyPeptide Laboratories, San Diego, CA), or [^{3}H]U-69,593 (final concentration 1 nM, Perkin Elmer Life Sciences, Waltham, MA) were used to determine binding at the delta, mu, and kappa opioid receptor sites, respectively. Unlabeled DAMGO (final concentration, 30 nM) was added to the delta receptor assay tubes to block the binding of the radioligand to mu opioid receptors. All assay tubes contained 100 μl homogenate suspension. Non-specific binding was determined using 0.01 mM naloxone for all assays. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.1% PEI (polyethyleneimine), using a Brandel R48 filtering manifold (Brandel Instruments, Gaithersburg, MA). The filters were washed twice with 5 ml cold buffer and transferred to scintillation vials. Cytoscint (MP BioMedicals, Santa Ana, CA) (3.0 ml) was added and the vials were counted the next day using a Perkin Elmer TriCarb liquid scintillation counter.

Data were analyzed by using GraphPad Prism software (San Diego, CA). Inhibition constants (K_i values) were calculated using the Cheng-Prusoff equation (Cheng and Prusoff 1973), with IC_{50} value of inhibitors used in the assay and the K_d value of the radioligand previously determined in this laboratory.

Subjects for behavioral experiments Six male Sprague-Dawley rats (obtained from the Animal Center of the Tongji Medical College of Hua Zhong University of Science & Technology, Wuhan, China) served as subjects and were acclimated to a temperature- and humidity-controlled room for

at least 1 week before any procedures. Food and water were available at all times in their home cages. The housing room was under a 12:12-h light/dark cycle with lights on at 7:00 AM. After acclimation, body weights of subjects were maintained at approximately 320 g. The experimental protocol was approved by an Institutional Review Committee for the use of Animal Subjects. All procedures and facilities were operated in accordance with the Guide for the Care and Use of Laboratory Animals of Jianghan University.

After the 1-week acclimation to the facility, a chronic intravenous catheter (3.5 cm in length, 0.58 mm inner diameter, 0.91 mm outer diameter, BPU-T30, Instech, Plymouth Meeting, PA, USA) was surgically implanted in the subject and secured to the right jugular vein under sodium pentobarbital (50 mg/kg, i.p.) anesthesia, as per Kai et al. (2014). Catheters exited dorsally in the mid-scapular region through a back mount that was secured subcutaneously. Following surgery, rats were housed individually in home cages and allowed at least 7 days of recovery during which they received daily intravenous infusions of gentamicin (0.16 mg/kg) followed by 0.2 ml of a heparinized (1%) sterile saline solution to minimize the likelihood of infection and the formation of clots or fibroids.

Behavioral procedures All self-administration experiments were conducted in operant-conditioning chambers (29 × 26 × 29 cm) enclosed in sound-attenuating and light-proof cubicles which were equipped with fans that provided ventilation (Anilab Software & Instruments Co., Ltd., China) (Zhang 2006). Two nose-poke operanda (ENV-114M; Med Associates, Fairfax, VT) were located 9 cm above the floor on the front panels of the chambers. A red stimulus light was mounted within each nose-poke hole and a white house light was mounted near the ceiling on the opposite wall. A syringe driver (model 22; Harvard Apparatus, Holliston, MA) containing a 10-ml syringe delivered injections. The syringe was connected by tubing to a fluid swivel (375 Series Single Channel Swivels, Instech Laboratories, Inc., Plymouth Meeting, PA) mounted on a balance arm above the chamber. Tubing, protected by a metal surrounding spring, connected the swivel to the subject's catheter.

Subjects were placed in chambers during daily 1-h experimental sessions in which subjects were initially trained with responses producing methamphetamine injections under a FR 5-response schedule (each fifth response produced a 0.022 mg/kg/injection of methamphetamine). During these sessions, the white house light was illuminated when methamphetamine injections were available. A single nose poke in the left hole turned on the red stimulus light within that hole for 0.5 s. Completion of each FR 5 requirement turned off the house light, delivered the methamphetamine injection, and was followed by a 20-s timeout (TO) period during which all lights were off and responses were recorded but had no scheduled consequences. After the TO, the house light was illuminated and the FR schedule was again in effect. When response rates were sufficiently high to produce 25 injections per session and were reliable from one session to the next, training sessions with methamphetamine (M) and saline (S) injections were conducted in a double-alternation sequence (e.g., ...MMSSMMSS..., where M—methamphetamine and S—saline).

When the response rates were reliably higher during methamphetamine sessions than during saline sessions, tests (T) of substitutions with saline or various doses of methamphetamine, heroin, or mitragynine were assessed by inserting those tests between repeats of the double-alternation sequence [e.g., ...MSTSMTMST...]. Each dose was tested once in each of the six subjects. Subsequently, the effects of mitragynine on heroin or methamphetamine self-administration were assessed by administering various mitragynine doses [saline, 0.03, 0.1, 0.3, 1 and 3 mg/kg, i.p.] 5 min before test sessions as described above in which different doses of either heroin or methamphetamine were available for self-administration. The sequence of mitragynine dose testing was balanced among rats using a Latin square design.

Numbers of responses were tabulated for each subject and analyzed with one-way analyses of variance (ANOVA) with drug dose as a factor. Post hoc analyses were conducted to assess contributions to significant effects using Holm-Sidak Multiple Comparisons versus saline. The levels of inactive responses were separately analyzed using one-way ANOVAs.

Drugs Mitragynine was obtained in "technical grade" from Carbosynth Limited (Compton, Berkshire, UK) and was dissolved in Tween 20 and DMSO, then diluted to the necessary concentration with 0.9% NaCl. Heroin HCl and methamphetamine HCl were obtained from the Hubei Public Security Bureau and were dissolved in 0.9% NaCl.

Results

Receptor binding assays The K_i value for the displacement of [^{3}H]DAMGO from the μ-opioid receptor by mitragynine was 502 nM, which indicated greater affinity for that receptor than that for κ- and δ-opioid receptors (Table 1). The K_i values for the displacement of [^{3}H]U-69,593 and [^{3}H]DADLE from κ- and δ-opioid receptors, respectively, were significantly greater than that for displacement of [^{3}H]DAMGO. The affinity of mitragynine for the μ-opioid receptor was substantially lower than that for either heroin or morphine (Table 1). Values for heroin are likely due entirely to the affinity of its metabolite 6-acetylmorphine (Inturrisi et al. 1983).

Drug self-administration The dose-effect curves for heroin and methamphetamine were biphasic for active responses

Table 1 K_i values (nM) calculated from displacement of the indicated radioligands for mitragynine compared to that for reference compounds (heroin, morphine) at mu, kappa, and delta opioid receptors. Values are means (± SEM) from at least three independent replications

Binding site	Mitragynine	Heroin	Morphine
Mu opioid receptor [^{3}H]DAMGO	502 ± 19.4	18.6 ± 2.78	2.33 ± 0.261
Kappa opioid receptor [^{3}H]U-69,593	1200 ± 79.7	263 ± 24.3	82.4 ± 3.92
Delta opioid receptor [^{3}H]DADLE	7910 ± 1140	281 ± 28.0	105 ± 11.5

(Fig. 1, center and right panels, filled symbols), with maximal effects at 0.01 and 0.022 mg/kg/injection, respectively. The ANOVA indicated that the differences in the mean values among heroin doses were greater than would be expected by chance ($F_{4,20} = 8.32$, $P < 0.001$). A similar result for dose was obtained with the ANOVA for methamphetamine ($F_{4,20} = 76.2$, $P < 0.001$). In contrast, no dose of mitragynine increased responding to levels greater than those obtained with saline (Fig. 1, left panel, filled symbols). However, the ANOVA indicated that the differences in the mean values among mitragynine doses were greater than would be expected by chance ($F_{5,25} = 3.05$, $P = 0.028$). Post hoc analysis indicated that the significance in the overall ANOVA was a result of the decreases in responding that were observed at the 3.0 mg/kg/injection dose (Holm-Sidak Multiple Comparisons versus saline ($t = 3.49$, $P = 0.009$). The levels of inactive responses (Fig. 1, open symbols) were uniformly low and were not different from saline with increases in dose per injection for any of the compounds.

Treatment with mitragynine before sessions at 3.0 mg/kg decreased the maximal levels of active responses maintained by heroin (Fig. 2, left panel). Lower doses (0.1 to 1.0 mg/kg) of mitragynine generally had little effect. The ANOVA indicated significant differences in the mean values for the different doses of heroin ($F_{3,32} = 13.7$, $P < 0.001$) and mitragynine ($F_{4,32} = 16.7$, $P < 0.001$). Mitragynine had no significant effect on inactive responses (data not shown).

In contrast to the effects on heroin self-administration, mitragynine did not significantly affect responding maintained by methamphetamine injection. The ANOVA indicated that the effect of mitragynine dose ($F_{3,15} = 1.69$, $P = 0.213$) was not larger than random sampling variability. The right panel of Fig. 2 shows the lack of effect on the maximal rates of responding maintained by 0.022 mg/kg/injection of methamphetamine (triangles) across the range of doses of mitragynine from those having no effect to those decreasing rates of responding maintained by heroin (circles).

Discussion

In the present study, the self-administration of mitragynine was assessed and compared to that of heroin in rats trained to self-administer methamphetamine. In contrast to heroin, mitragynine did not maintain response rates greater than those obtained with saline injection. In addition, the effects of presession injections of mitragynine were assessed on responding maintained by heroin and methamphetamine. Mitragynine dose-dependently decreased rates of responding maintained by heroin but had little effect on responding maintained by methamphetamine across the same range of mitragynine doses. These results suggest a limited liability for abuse of mitragynine, perhaps due to its activity as a biased agonist (Kruegel et al. 2016; Váradi et al. 2016) and the

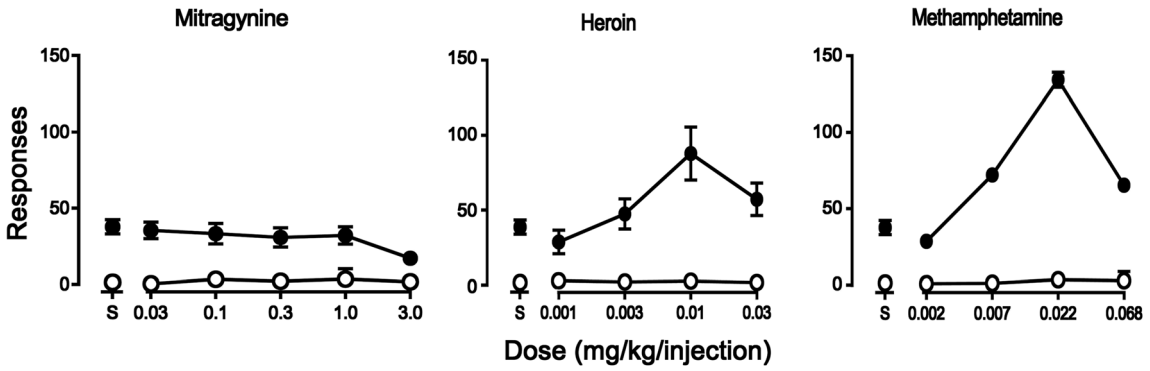

Fig. 1 Substitution of saline or a range of doses of mitragynine, heroin, or methamphetamine in rats trained to self-administer methamphetamine (0.022 mg/kg per i.v. injection) under an FR 5-response schedule of reinforcement. Ordinates: responses per session; abscissae: unit dose of substituted drug (mg/kg per i.v. injection), log scale. Filled points show active responses (left nose-poke hole); whereas, open points show inactive responses (right nose-poke hole). Each point represents the mean (± SEM) of six subjects. Note that both heroin and methamphetamine, but not mitragynine, maintained rates of response greater than those obtained with saline

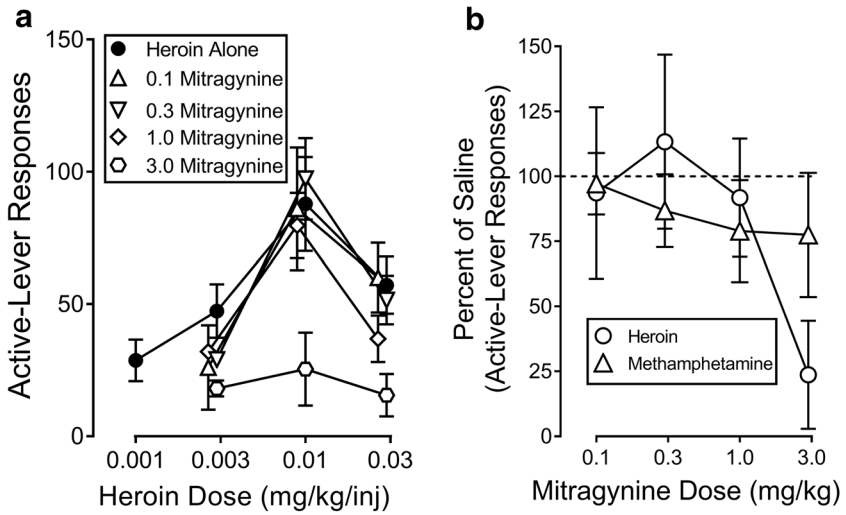

Fig. 2 Effects of presession treatments with mitragynine on self-administration of heroin under an FR 5-response schedule of reinforcement. **a** The effects of mitragynine pretreatment on the heroin self-administration dose-effect curve. Ordinates: number of active responses per session; abscissae: heroin unit dose (mg/kg per i.v. injection), log scale. Each point represents the mean (±SEM) of six subjects. Note that data points are displaced horizontally a minimal amount in order to better distinguish error bars. Mitragynine pretreatment decreased self-administration of heroin at a dose of 3.0 mg/kg. **b** A comparison of the effects of pretreatments with mitragynine on the maximal rates of responses maintained by heroin (0.01 mg/kg/inj) or methamphetamine (0.022 mg/kg/inj). Ordinates: number of active responses (left nose-poke hole) per session as a percentage of that obtained after saline pretreatment; abscissae: mitragynine dose (mg/kg), log scale. The control rates of responding maintained were 2.42 and 1.49 responses per minute during the 1-h session for methamphetamine and heroin, respectively. Note that the dose of mitragynine (3.0 mg/kg) that decreased self-administration of heroin had little effect on responses maintained by methamphetamine injection

possible specific reduction of opioid abuse by mitragynine treatment.

Hemby et al. (2018) also investigated mitragynine self-administration in rats. In that study, subjects trained to self-administer morphine did not self-administer mitragynine at doses approximating 0.07 to 0.43 mg/kg/injection (assuming 350-g rats). Those doses were at most 5.7-fold greater on a molar basis than the 50 μg/injection dose of morphine that maintained maximal response rates. The present study found an approximate 200-fold lower affinity of mitragynine than morphine at μ-opioid receptors in rat native tissue. Thus, the present study examined higher doses of mitragynine.

The comparison of mitragynine to heroin in the present study is complicated by the fact that heroin is a prodrug for morphine and 6-acetylmorphine (Inturrisi et al. 1983; Way et al. 1965) and is inactive in binding the μ-opioid receptor. The binding affinity obtained for heroin is likely entirely due to the affinity of the metabolite 6-acetylmorphine which can be detected in the binding assay tubes (Inturrisi et al. 1983). However, likely due to its lipophilicity (Way et al. 1960; Oldendorf et al. 1972), heroin is approximately 10-fold more potent than morphine (on a mg of the salt form basis) in a rat self-administration procedure (e.g., Hiranita et al. 2014). This potency difference renders the minimally effective dose of heroin the equivalent of morphine at 0.03 mg/kg/injection (or 0.04 μmol/kg/injection). The highest presently studied dose of mitragynine (3.0 mg or 7.53 μmol /kg/injection) approximates that necessary to ensure that a sufficient molar dose was studied. In addition, the highest tested dose per injection of mitragynine suppressed responding below levels obtained with saline, indicating that the range of mitragynine doses presently studied included those with biological activity.

There are several reasons to exercise caution in generalizing from the absence of mitragynine self-administration. First, the robust self-administration of several drugs of abuse occurs under some conditions but not others. Possibly the most pronounced example is nicotine for which there are numerous positive and negative outcomes (e.g., Caggiula et al. 2002; Kohut and Bergman 2016). Further, certain behavioral or pharmacological histories may predispose or mitigate robust self-administration (Young and Woods 1981; Hiranita et al. 2014). The use of an opioid rather than methamphetamine for training subjects may have facilitated mitragynine self-administration. However, a previous finding showed that several opioid agonists maintained responding comparably in subjects trained with methamphetamine or heroin (Hiranita et al. 2014). Nonetheless, it remains possible that circumstances may yet be found under which mitragynine is reliably self-administered. In addition, and as described above, there are several studies indicating place conditioning with mitragynine injections. Thus, while the present findings with a self-administration procedure suggest a relatively low abuse liability of mitragynine, further studies would add assurance to that conclusion.

In the present study, pretreatment with mitragynine dose-dependently decreased heroin self-administration, and those

decreases were more profound than those for the self-administration of methamphetamine. As methamphetamine has psychomotor stimulant effects, accumulation over the course of the session may have mitigated the response rate decreasing effects of mitragynine that were obtained with heroin self-administration. The total intake of methamphetamine within a session from the present study averaged about 0.054 mg/kg, distributed across a 1-h session. A single bolus dose of 0.1 mg/kg (i.p.) of methamphetamine has reliable direct behavioral effects on rats responding under ratio-type schedules (e.g., Mechner and Latranyi 1963), suggesting that accumulated methamphetamine did not offset the effects of mitragynine on response rates. Nonetheless, a comparison of effects of mitragynine on heroin self-administration with those on food-reinforced responding would add clarification to the selectivity of mitragynine.

Mitragynine at an active dose decreased the maximal self-administration of heroin rather than shifting the dose-effect curve rightward as is typically obtained by treatment with opioid antagonists (Bertalmio and Woods 1989; Harrigan and Downs 1978). The contrast among these effects along with the documented opioid-agonist effects of mitragynine indicates that the mechanism of mitragynine-induced decreases in heroin self-administration is not due to an antagonism of heroin effects. Previous studies of opioid pretreatments have produced similar decreases in maximal self-administration of opioid agonists (e.g., Hiranita et al. 2014; Winger et al. 1992). Noting the similarity of these downward shifts to the effects of food prefeeding on responding maintained by food reinforcement, Hiranita et al. (2014) suggested this outcome could reflect a satiating effect of the drug pretreatment on opioid self-administration (see also Zanettini et al. 2018). Satiation was suggested previously as explanation for the clinical efficacy of methadone in treating opioid abuse (Dole and Nyswander 1965).

Several reports have provided information that human self-administration of mitragynine is maintained by alleviation of opioid withdrawal symptoms (e.g., Grundmann 2017; Smith and Lawson 2017; Swogger and Walsh 2018). For example, Vicknasingam et al. (2010) reported that treatment of opioid withdrawal was self-reported by 62.5% and 46.9%, respectively, of short- and long-term kratom users in Malaysia. In addition, Cheaha et al. (2017) reported that an extract of *Mitragyna speciosa* suppressed naloxone-precipitated fecal excretions; however, it did not suppress naloxone-precipitated jumping in mice. Those results suggest some direct effects of mitragynine on opioid withdrawal, which has been historically used as evidence of its own potential to produce dependence (Himmelsbach 1941). However, the differences between the effects of mitragynine on the two different withdrawal signs in the Cheaha et al. (2017) study suggest some reservations regarding too extensive a conclusion. Further studies should examine the effects of the various pure alkaloids of the plant, both on precipitated withdrawal and that unfolding after cessation of agonist treatment. Studies over a range of doses, and with a wider variety of withdrawal signs and time frames would add substantially to consideration of kratom physiological dependence liability.

The present study suggests that mitragynine has limited abuse liability from the perspective of self-administration procedures. Those results should prompt other studies to further examine mitragynine self-administration across a broader range of conditions to assess the generality of the findings. Further mitragynine produced a decrease in self-administration of heroin at doses that did not affect self-administration of methamphetamine. These outcomes suggest potential for use of mitragynine in treating opioid abuse though it should be noted that mitragynine has a variety of other behavioral effects that may limit that potential (Hassan et al. 2017). Nonetheless, the current prevalence of opioid abuse and its consequent and multiple impacts on public health, it appears at present that mitragynine is deserving of more extensive exploration for the development of a therapeutic used for treating opioid abuse.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Bertalmio AJ, Woods JH (1989) Reinforcing effect of alfentanil is mediated by mu opioid receptors: apparent pA2 analysis. J Pharmacol Exp Ther 251:455–460

Caggiula AR, Donny EC, Chaudhri N, Perkins KA, Evans-Martin FF, Sved AF (2002) Importance of nonpharmacological factors in nicotine self-administration. Physiol Behav 77:683–687

Cheaha D, Reakkamnuan C, Nukitram J, Chittrakarn S, Phukpattaranont P, Keawpradub N, Kumarnsit E (2017) Effects of alkaloid-rich extract from Mitragyna speciosa (Korth) Havil on naloxone-precipitated morphine withdrawal symptoms and local field potential in the nucleus accumbens of mice. J Ethnopharmacol 208:129–137

Cheng Y, Prusoff WH (1973) Relationship between the inhibition constant (KI) and the concentration which causes 50% inhibition of an enzymatic reaction. Biochem Pharmacol 22:403–411

Dole VP, Nyswander M (1965) A medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. JAMA 193: 646–650

Grundmann O (2017) Patterns of kratom use and health impact in the US — results from an online survey. Drug Alcohol Depend 176:63–70

Harrigan SE, Downs DA (1978) Continuous intravenous naltrexone effects on morphine selfadministration in rhesus monkeys. J Pharmacol Exp Ther 204: 481–486

Harun N, Hassan Z, Navaratnam V, Mansor SM, Shoaib M (2015) Discriminative stimulus properties of mitragynine (kratom) in rats. Psychopharmacol 232:2227–2238

Hassan Z, Bosch OG, Singh D, Narayanan S, Kasinather BV, Seifritz E, Kornhuber J, Quednow BB, Müller CP (2017) Novel psychoactive substances — recent progress on neuropharmacological mechanisms of action for selected drugs. Front Psychiatry 8:152

Hemby SE, Mcintosh S, Cutler SJ, McCurdy CR (2018) Abuse liability of mitragynine and 7-hydroxymitragynine putative primary alkaloids of Mitragyna speciosa (kratom). Soc Neurosci Abstr 794:21

Henningfield JE, Fant RV, Wang DW (2018) The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacol 235: 573–589

Himmelsbach CK (1941) The effects of certain chemical changes on the addiction characteristics of drugs of the morphine, codeine series. J Pharmacol Exp Ther 71:41–48

Hiranita T, Kohut SJ, Soto PL, Tanda G, Kopajtic TA, Katz JL (2014) Preclinical efficacy of N-substituted benztropine analogs as antagonists of methamphetamine self-administration in rats. J Pharmacol Exp Ther 348:174–191

Inturrisi CE, Schultz M, Shin S, Umans JG, Angel L, Simon EJ (1983) Evidence from opiate binding studies that heroin acts through its metabolites. Life Sci 33(Suppl 1):773–776

Kai Y, Ma B, Chen L, Tian X, Ru Q, Gan Y, Wang D, Jin G, Li C (2014) l-Stepholidine, a naturally occurring dopamine D1 receptor agonist and D2 receptor antagonist, attenuates heroin self-administration and cue-induced reinstatement in rats. Neuroreport 25:7–11

Kohut SJ, Bergman J (2016) Reinforcing effectiveness of nicotine in nonhuman primates: effects of nicotine dose and history of nicotine self-administration. Psychopharmacol 233:2451–2458

Kong WM, Mohamed Z, Alshawsh MA, Chik Z (2017) Evaluation of pharmacokinetics and blood-brain barrier permeability of mitragynine using in vivo microdialysis technique. J Pharm Biomed Anal 143:43–47

Kruegel AC, Grundmann O (2018) The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacol 134:108–120

Kruegel AC, Gassaway MM, Kapoor A, Váradi A, Majumdar S, Filizola M, Javitch JA, Sames D (2016) Synthetic and receptor signaling explorations of the Mitragyna alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. J Am Chem Soc 138:6754–6764

Mechner F, Latranyi M (1963) Behavioral effects of caffeine, methamphetamine, and methylphenidate in the rat. J Exp Anal Behav 6: 331–342

Oldendorf WH, Hyman S, Braun L, Oldendorf SZ (1972) Blood-brain barrier: penetration of morphine, codeine, heroin, and methadone after carotid injection. Science 178:984–986

Smith KE, Lawson T (2017) Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. Drug Alcohol Depend 180:340–348

Sufka KJ, Loria MJ, Lewellyn K, Zjawiony JK, Ali Z, Abe N, Khan IA (2014) The effect of Salvia divinorum and Mitragyna speciosa extracts, fraction and major constituents on place aversion and place preference in rats. J Ethnopharmacol 151:361–364

Swogger MT, Walsh Z (2018) Kratom use and mental health: a systematic review. Drug Alcohol Depend 183:134–140

Takayama H (2004) Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, Mitragyna speciosa. Chem Pharm Bull (Tokyo) 52:916–928

US Drug Enforcement Administration (2016) Schedules of controlled substances: placement of mitragynine and 7-Hydroxymitragynine into schedule I. Federal Register. https://www.federalregister.gov/documents/2016/08/31/2016-20803/schedules-of-controlledsubstances-temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into. Accessed 10 April 2017

Váradi A, Marrone GF, Palmer TC, Narayan A, Szabó MR, Le Rouzic V, Grinnell SG, Subrath JJ, Warner E, Kalra S, Hunkele A (2016) Mitragynine/Corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β-Arrestin-2. J Med Chem 59:8381–8397

Vicknasingam B, Narayanan S, Beng GT, Mansor SM (2010) The informal use of ketum (Mitragyna speciosa) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. Int J Drug Policy 21:283–288

Way EL, Kemp JW, Young JM, Grassetti DR (1960) The pharmacologic effects of heroin in relationship to its rate of biotransformation. J Pharmacol Exp Ther 129:144–154

Way EL, Young JM, Kemp JW (1965) Metabolism of heroin and its pharmacologic implications. Bull Narc 17:25–33

Winger G, Skjoldager P, Woods JH (1992) Effects of buprenorphine and other opioid agonists and antagonists on alfentanil- and cocaine-reinforced responding in rhesus monkeys. J Pharmacol Exp Ther 261:311–317

Young AM, Woods JH (1981) Maintenance of behavior by ketamine and related compounds in rhesus monkeys with different self-administration histories. J Pharmacol Exp Ther 218:720–727

Yusoff NHM, Suhaimi FW, Vadivelu RK, Hassan Z, Rümler A, Rotter A, Amato D, Dringenberg HC, Mansor SM, Navaratnam V, Müller CP (2016) Abuse potential and adverse cognitive effects of mitragynine (kratom). Addict Biol 21:98–110

Yusoff NHM, Mansor SM, Müller CP, Hassan Z (2017) Opioid receptors mediate the acquisition, but not the expression of mitragynine-induced conditioned place preference in rats. Behav Brain Res 332:1–6

Yusoff NHM, Mansor SM, Müller CP, Hassan Z (2018) Baclofen blocks the acquisition and expression of mitragynine-induced conditioned place preference in rats. Behav Brain Res 345:65–71

Zanettini C, Wilkinson DS, Katz JL (2018) Behavioral economic analysis of the effects of N-substituted benztropine analogs on cocaine self-administration in rats. Psychopharmacol 235: 47–58

Zhang F (2006) SuperState: a computer program for the control of operant behavioral experimentation. J Neurosci Methods 155:194–201

Case Report

Unintentional Fatal Intoxications with Mitragynine and *O*-Desmethyltramadol from the Herbal Blend Krypton

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Abstract

The leaves of Kratom, a medicinal plant in Southeast Asia, have been used as an herbal drug for a long time. At least one of the alkaloids present in Kratom, mitragynine, is a mu-receptor agonist. Both Kratom and an additional preparation called Krypton are available via the internet. It seems to consist of powdered Kratom leaves with another mu-receptor agonist, *O*-desmethyltramadol, added. *O*-Desmethyltramadol is an active metabolite of tramadol, a commonly prescribed analgesic. We present nine cases of intoxication, occurring in a period of less than one year, where both mitragynine and *O*-desmethyltramadol were detected in the postmortem blood samples. Neither tramadol nor *N*-desmethyltramadol was present in these samples, which implies that the ingested drug was *O*-desmethyltramadol. The blood concentrations of mitragynine, determined by ultra-performance liquid chromatography–tandem mass spectrometry, ranged from 0.02 to 0.18 µg/g, and *O*-desmethyltramadol concentrations, determined by gas chromatography with nitrogen-specific detection, ranged from 0.4 to 4.3 µg/g. We believe that the addition of the potent mu-receptor agonist *O*-desmethyltramadol to powdered leaves from Kratom contributed to the unintentional death of the nine cases presented and conclude that intake of Krypton is not as harmless as it often is described on internet websites.

Introduction

Herbal drugs have always been popular because of their natural origin, and they are often thought of as safe alternatives to synthetic drugs. However, in recent years, several preparations sold as herbal drugs have actually been plant material spiked with synthetic active components. The most well-known series of preparations is Spice, which still is frequently used and which contains synthetic cannabinoid receptor agonists added to the dried leaves of plant material with little or no pharmacological effect (1–3).

Another example is the leaves of the medicinal plant *Mitragyna speciosa*, known as Kratom, which is native to Southeast Asia and has traditionally been used as a herbal drug for various indications (4–8). In low doses, it has a stimulant effect, and there are sedative and opioid-like effects after high doses (4). Even if more than 25 different alkaloids have been identified in this plant, the major constituent is mitragynine, which also is responsible for the opioid effects through the mu-receptor (9,10). Mitragynine has several diastereoisomers that also are present in various concentrations depending on the age and origin of the plant (9,10).

Currently, Kratom can easily be bought via the internet and is used worldwide. Even though Kratom has its own opioid effect, it is also available with another mu-agonist added. The preparation, called Krypton, consists of powdered Kratom leaves mixed with *O*-desmethyltramadol, the active metabolite of the commonly used analgetic tramadol (2,11). Tramadol is metabolized through O- and N-demethylation via cytochrome P-450 iso-enzymes. *O*-Desmethyltramadol, the only metabolite with pharmacological activity, has a higher affinity for the mu-receptor than tramadol itself (12). Although tramadol is considered a safe drug, there is an abuse potential and unintentional fatalities with tramadol have been described (13,14) even though they seem to be scarce. However, reports of its detection in autopsy cases and in the living confirm that there is an abuse potential (15,16).

The addition of another mu-receptor agonist makes Krypton more powerful than the leaves of Kratom alone. In addition, Krypton is sold in large quantities in containers with more than 50 g even though the dose recommended at the websites is as small as 0.5 g. The risk for unintentional overdose is

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therefore high. Since November 2009, we have identified nine cases of fatal overdose in which postmortem blood samples were positive for both mitragynine and *O*-desmethyltramadol without the parent drug. We believe that the intake of Krypton was the cause of these deaths and describe the circumstances in this paper.

Materials and Methods

Medicolegal autopsies are performed at six departments of forensic medicine in Sweden. At autopsy, samples of femoral blood, urine, and vitreous humor are routinely collected and submitted for toxicology screening to one central laboratory, the Department of Forensic Genetics and Forensic Toxicology in Linköping. Other samples, such as heart blood, muscle, hair, etc., are collected if routine samples are not available or if otherwise necessary. Potassium fluoride (1–2%) is added to the samples as a preservative. Mitragynine was obtained from ChromaDex (Irvine, CA), and LSD-d_3 was obtained from Cerilliant (Round Rock, TX). Speciogynine, speciociliatine, and mitraciliatine for identification of these mitragynine diastereoisomers were kind gifts from Professor Hans H. Maurer, Homburg, Germany.

Routine toxicological analyses

From more than 95% of the annual ~5000 medicolegal autopsies, samples were analyzed considering pharmaceuticals, including tramadol and metabolites. Alcohols and acetone were analyzed with headspace gas chromatography (GC) according to a previously described method (17). Narcotic drugs were analyzed in urine or blood using immunoassays and positive indications confirmed in blood with GC–mass spectrometry (MS) or liquid chromatography (LC)–tandem MS. About 150 different pharmaceutical drugs were analyzed by GC with nitrogen-specific detection (NPD), using an Agilent 5890 with original nitrogen-phosphorus detector and an Agilent 6890 with Blos bead detector. Two GC columns with different polarity, DB5 and DB17, were used to improve the identification of the analytical findings. The blood samples were extracted alkaline and neutral with butyl acetate (18). Tramadol and *O*-desmethyltramadol, included in this determination of pharmaceuticals, were extracted alkaline. Briefly described; 1.0 g blood was extracted with 0.4 mL buthyl acetate after adding 0.3 mL Tris-buffer (1 M, pH 11) and 30 µL internal standard (0.05 mg cyclizine). After extraction and centrifugation, an aliquot was analyzed with GC–NPD. Calibration curves for tramadol ranged from 0.05 to 5 µg/g blood and for *O*-desmethyltramadol from 0.1 to 5 µg/g blood. Calibrators and controls were made by adding standard solutions to drug-free blood. Long-term interday imprecision and accuracy for *O*-desmethyltramadol and tramadol are presented in Table I. *N*-Desmethyltramadol was also included in the analysis, although only qualitatively.

Table I. Long-Term Interday Imprecision and Accuracy for *O*-Desmethyltramadol and Tramadol in Blood

	N	Mean (µg/g)	CV (%)	Accuracy (%)
O-Desmethyltramadol				
Low 0.2 µg/g	183	0.22	14.7	110
High 1.0 µg/g	184	1.08	13.2	108
Tramadol				
Low 0.1 µg/g	184	0.10	6.0	100
High 3.0 µg/g	185	3.08	5.2	103

Analysis of mitragynine

Postmortem blood was prepared using liquid–liquid extraction with ethyl acetate under basic conditions. To 1.0 g blood,

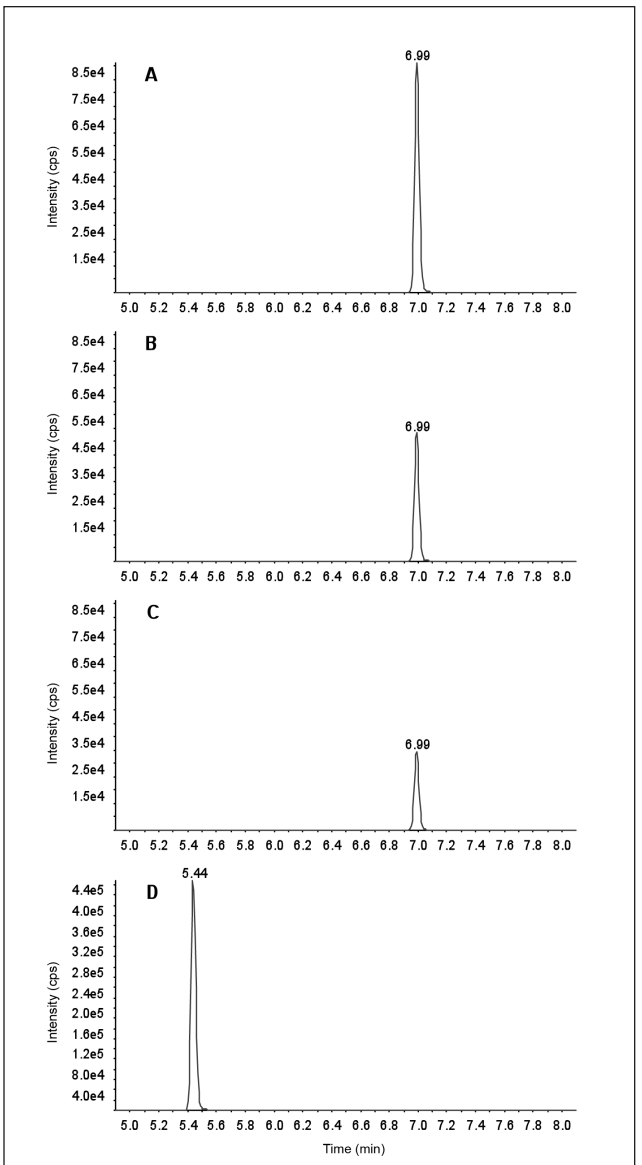

Figure 1. Chromatograms from a low quality control 0.01 µg mitragynine/g transitions 399/174 (A), 399/226 (B), and 399/159 (C) and internal standard, LSD-d_3, transition 327/226 (D).

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25 ng of LSD-d_3 was added as internal standard. After addition of 0.5 mL Tris-buffer (1 M, pH 11) and 3 mL ethyl acetate, the sample was shaken for 15 min and then centrifuged; the organic phase was evaporated and then reconstituted in a 50:50 mixture of mobile phases A and B. The LC–MS–MS system consisted of a Waters ACQUITY UPLC® (ultra-performance LC) with a Binary Solvent Manager, Sample Manager, and Column Manager (Waters, Milford, MA) connected to an API 4000™ triple-quadrupole instrument (AB SCIEX, Stockholm, Sweden) equipped with an electrospray interface (TURBO V™ source, TurboIonSpray® probe) operating in the multiple reaction monitoring (MRM) mode. Ion spray voltage was set to 4500 V. Nitrogen was used as the nebulizer gas (345 kPa), heater gas (517 kPa at 500°C), curtain gas (207 kPa), and as collision-activated dissociation gas (set on 5). UPLC was performed using an ACQUITY UPLC high-strength silica (HSS) T3 column (1.8 µm, 150 × 2.1 mm, Waters), preceded by a 0.2-µm column filter (Waters), and operated at 0.5 mL/min with a total run time of 12 min. Mobile phase A consisted of 0.05% formic acid in 10 mM ammonium formiate, and phase B was 0.05% formic acid in acetonitrile. The chromatographic system was run in a linear gradient from 1 to 50% phase B in 8 min, then increased to 95% phase B in 2 min, held at 95% phase B for 1 min, followed by a 0.9 min equilibration with 99% phase A. The injection volume was 1 µL, and the Column Manager temperature was set to 60°C. Instrument control, integration, and calculation were performed using Analyst™ 1.4.2 software. Quadratic regression analysis with 1/*x* weighting was used for the calibration curves. The final MRM method included three transitions 399/174, 399/226, and 399/159 for mitragynine and 327/226 for the internal standard, LSD-d_3,

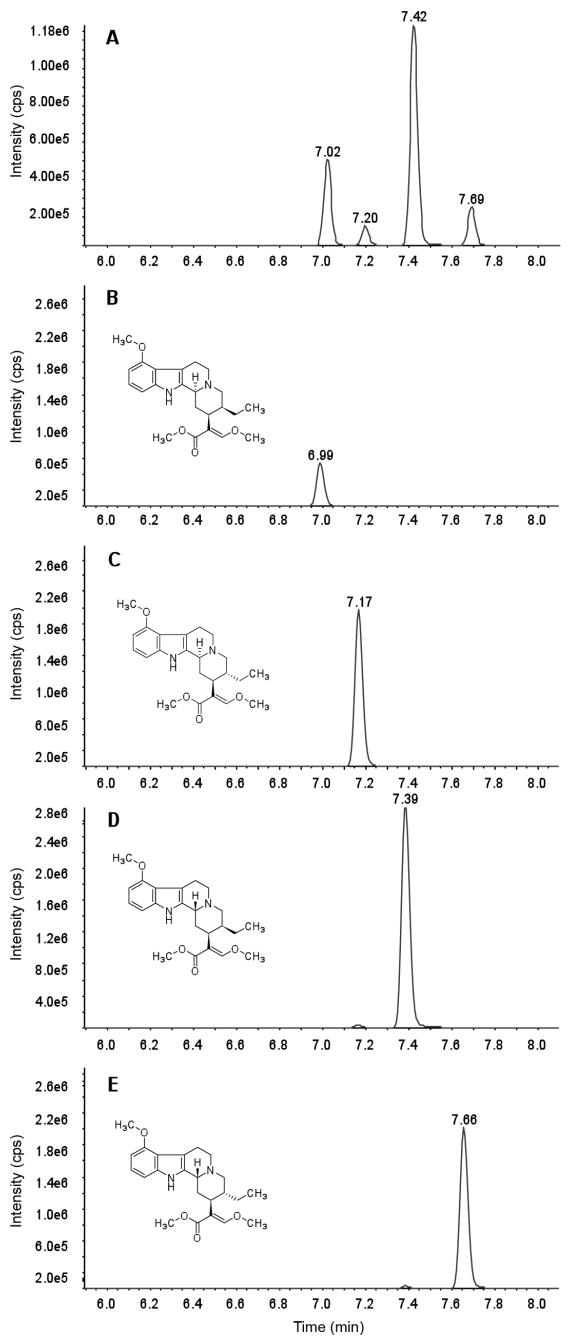

Figure 2. Chromatograms from case 7, (0.03 µg/g mitragynine) (A); mitragynine (MG), neat standard 0.02 µg/g, 399/174 (B); speciogynine (SG), neat standard 0.02 µg/g, 399/174 (C); speciociliatine (SC), neat standard 0.02 µg/g, 399/174 (D); and mitraciliatine (MC), neat standard 0.02 µg/g, 399/174 (E). In the chromatograms from some of the standards, there are small peaks at the retention times for the other stereoisomers. These are most likely impurities in the standards.

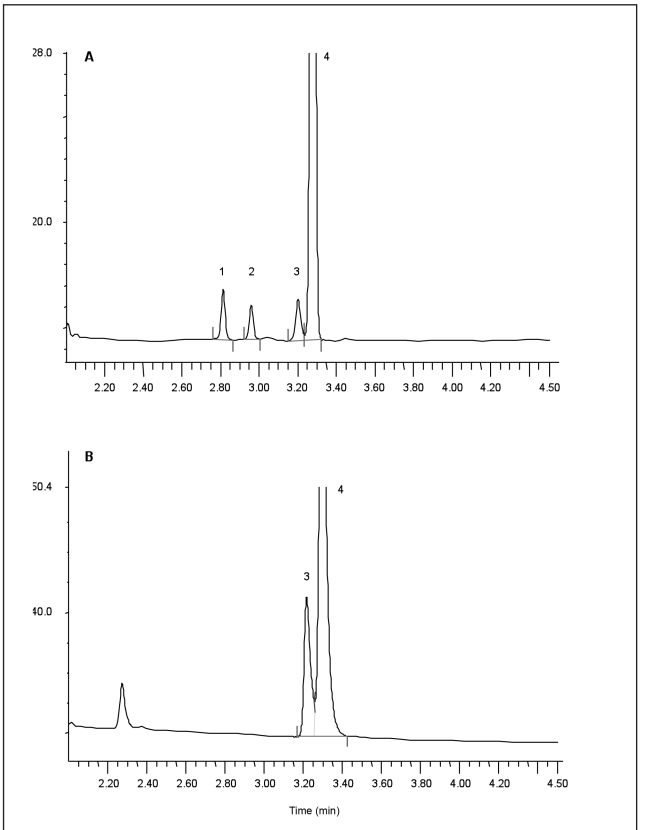

Figure 3. GC–NPD chromatograms from a control sample at 0.1 µg/g (A) and case 7 (B). Peak identification: 1, tramadol; 2, *N*-desmethyltramadol; 3, *O*-desmethyltramadol; and 4, internal standard.

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Table II. Toxicology and Demographic Data from Nine Cases of Accidental Drug Poisoning*

Case	Age/Sex (years)	Lung Weight (Right/Left) (g)	*O*-DMT† (µg/g)	Mitragynine (µg/g)	Other Drugs in Blood (µg/g)	Significant Autopsy Findings	Circumstances
1	22/male	R 828 L 732	0.4	0.07	0.14 alprazolam 0.09 ethanol‡	Congestion of lungs	Found dead at home. Previous history of drug abuse. Ordered Krypton via the Internet, probably for the first time.
2	35/male	R 804 L 722	0.7	0.16	0.3 alimemazine 0.1 DMA 0.7 venlafaxine 0.1 O-DMV	Edema and congestion of lungs	Found dead in mother's home. Previous history of drug abuse
3	30/female	R 625 L 590	0.5	0.04	0.6 fluoxetine 0.5 norfluoxetine 19.8 phenazon 0.2 olanzapine 0.3 diazepam 0.3 nordiazepam 5.0 pregabalin 0.04 amphetamine	Congestion of lungs Liver steatosis	Found dead at home. Previous history of drug abuse.
4	33/male	R 831 L 668	1.5	0.05	0.2 alimemazine 0.2 DMA 0.1 olanzapine 0.05 nordiazepam 0.002 THC	Edema and congestion of lungs Hepatitis Liver steatosis Mb Hodgkin Aspiration of stomach contents	Found dead in a friend's bedroom. Took Krypton, then fell asleep. Previous history of drug abuse.
5	27/male	R 695 L 640	4.3	0.18	0.2 alimemazine 0.1 mirtazapine 0.1 venlafaxine 0.09 diazepam 0.2 nordiazepam 0.0004 buprenorphine	Brain edema Lung edema	Found dead at home. Previous history of drug abuse.
6	27/male	R 712 L 690	1.2	0.05	0.04 zopiclone 0.01 ethanol‡	Brain edema Lung edema	Found dead at home. Ordered Krypton via internet. Previous history of drug abuse.
7	24/male	R + L 1456	1.1	0.03	0.14 alprazolam 0.20 amphetamine 0.0006 THC	Brain edema Congestion of lungs	Found dead in friend's home. Previous history of drug abuse.
8	25/female	R 620 L 410	0.8	0.02	1.0 venlafaxine 1.1 O-DMV 0.06 zopiclone	Congestion of lungs	Admitted to hospital unconscious with asystole 2 h after drinking tea made from Krypton.
9	32/male	R 848 L 770	1.1	0.05	0.8 citalopram 0.07 alprazolam 0.007 THC	Brain edema Lung edema	Found dead at home. Previous history of drug and alcohol abuse.

* The cause and manner of death was accidental drug intoxication in all cases.
† Abbreviations: O-DMT, O-desmethyltramadol; DMA, desmethylalimemazine; O-DMV, O-desmethylvenlafaxine; and THC, tetrahydrocannabinol.
‡ Ethanol reported at g/dL.

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with a dwell time of 75 ms for each transition. Criteria for identification were based on a qualifier ratio within 30% of the target ratio.

Method characteristics for the analysis of mitragynine

Matrix effects were evaluated using post-column infusion of mitragynine together with the injection of 10 different postmortem blood samples negative for mitragynine. Working range was verified by analysis of triplicates at seven concentrations from 0.008 to 0.20 µg/g blood. The within-day (n = 5) imprecision was estimated by analyzing five replicates at two concentrations, 0.01 and 0.15 µg/g blood. Calibrators and controls were made by adding standard solutions to drug-free blood. Final calibration concentrations were 0.008, 0.01, 0.05, 0.08, 0.10, 0.15, and 0.20 µg/g blood.

Identification of mitragynine diastereoisomers

Speciogynine, speciociliatine, and mitraciliatine, all three diastereoisomers of mitragynine, have been identified in urine samples from both humans and dosed rats (9,10). In the blood samples, we observed a cluster of four peaks with the same transitions. Therefore, we aimed at identifying these potential isomers. Each standard was analyzed separately and compared with the retention times of those in the peak cluster from the authentic samples.

Cases

The first case appeared in November 2009 and was recognized because of the presence of *O*-desmethyltramadol in the absence of the parent drug tramadol. Indeed, this was an unusual finding, even though tramadol itself is very commonly found in autopsy cases (19). Because of the reports available about Krypton, we analyzed and detected mitragynine in both blood and urine. During the spring 2010, several more cases were observed, and the current method for mitragynine, using a 150-mm column with a less-steep gradient was developed to increase the separation between the diastereoisomers. Also, LSD-d_3 was added as internal standard. Thus, the cases we present were not analyzed with the same chromatographic method for mitragynine.

Results

The LC–MS–MS method showed no matrix effects when investigating 10 different postmortem blood samples. The within-day imprecision of the mitragynine quantitation was 2.4% and 4.3% at the low and high level. A linear calibration model resulted in a variation less than 8% at the 7 levels, as well as accuracy between 97 and 102%. Chromatograms of a control sample at 0.1 µg/g are shown in Figure 1, and chromatograms from case 7 and the mitragynine diastereoisomers are shown in Figure 2. Figure 3 shows the GC–NPD chromatograms from case 7 and a control sample containing tramadol and its two demethylated metabolites. *O*-Desmethyltramadol precision data showed good performance over time as seen in Table I. The cases and their toxicological results are described in Table II. The autopsy findings were non-specific; in most cases, brain and lung edema and congestion of inner organs were noted. All blood samples, except case 3, were femoral blood. In summary, none of the cases presented with tramadol in blood, indicating that *O*-desmethyltramadol is not present in these cases as a metabolite but indeed was the ingested drug. This is further supported by the presence of mitragynine because they appear together in Krypton preparations. Several other psychotropic drugs were detected in each victim and could have contributed to death. The concentrations of *O*-desmethyltramadol ranged between 0.4 and 4.3 µg/g, and those of mitragynine ranged between 0.02 and 0.18 µg/g. The mitragynine diastereoisomers were identified in all cases.

Discussion

One of the most important conclusions from the present study is that the use of legal herb preparations might be associated with a high risk. In fact, the user has very little control over the contents of powders and plant material bought through the internet, because they might be spiked with one or more powerful synthetic drugs (1,3,20). A recent report on unintentional fatal intoxications with medications containing tramadol showed that only 17 cases were identified in Sweden over a 10-year period (14). However, the present study shows that over a period of less than one year, nine cases of poisoning with *O*-desmethyltramadol emerged. The potency of *O*-desmethyltramadol has been described as twice that of the parent compound tramadol (16). Femoral blood concentrations of tramadol higher than 1.0 µg/g are considered toxic and possibly fatal (14). Considering the higher potency of *O*-desmethyltramadol, the concentrations in the reported cases seem to be in the high range, suggesting overdose. The fact that Krypton is sold in packages containing large quantities even though the recommended dose is only 0.5 g supports this. The finding of heavy lungs in all cases but one also points towards respiratory depression and opiate overdose or a combination of *O*-desmethyltramadol and other drugs.

The absence of tramadol strongly suggests that the ingested drug was *O*-desmethyltramadol. During treatment, tramadol steady-state levels in blood are always higher than those for *O*-desmethyltramadol. Even though *O*-desmethyltramadol has a slightly longer half-life than tramadol, 7.4 h versus 6.3 h (16), detection of the metabolite only in the blood after tramadol use is unusual. The absence of *N*-desmethyltramadol is additional support for the ingestion of *O*-desmethyltramadol in the presented cases (Figure 3).

The contribution of mitragynine including its isomers in these cases is unclear because no reference data on blood concentrations are yet available. However, its agonist effects on the mu-receptor suggest that it may have contributed to the deaths. In addition, other alkaloids in Kratom have been investigated for their mu-receptor agonist properties, and 7-hy-

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droxymitragynine was found to have 30 times higher affinity than mitragynine in in vitro experiments as well as in an animal model (5,21,22).

Conclusions

We believe that the addition of the potent mu-receptor agonist *O*-desmethyltramadol to powdered leaves from Kratom contributed to the unintentional death of the nine cases presented. We conclude that intake of the herbal blend Krypton is not as harmless as it often is described on internet websites, and the large packages sold increase the risk for unintentional overdose.

References

1. V. Auwärter, S. Dresen, W. Weinmann, M. Müller, M. Pütz, and N. Ferreirós. 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? *J. Mass Spectrom*. **44:** 832–837 (2009).
2. S. Dresen, N. Ferreirós, M. Pütz, F. Westphal, R. Zimmermann, and V. Auwärter. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. *J. Mass Spectrom*. **45:** 1186–1194 (2010).
3. T. Sobolevsky, I. Prasolov, and G. Rodchenkov. Detection of JWH-018 metabolites in smoking mixture post-administration urine. *Forensic Sci. Int.* **200:** 141–147 (2010).
4. K.M. Babu, C.R. McCurdy, and E.W. Boyer. Opioid receptors and legal highs: *Salvia divinorum* and Kratom. *Clin. Toxicol. (Phila.)* **46:** 146–152 (2008).
5. S. Horie, F. Koyama, H. Takayama, H. Ishikawa, N. Aimi, D. Ponglux, K. Matsumoto, and T. Murayama. Indole alkaloids of a Thai medicinal herb, *Mitragyna speciosa*, that has opioid agonistic effect in guinea-pig ileum. *Planta Med.* **71:** 231–236 (2005).
6. T. Maruyama, M. Kawamura, R. Kikura-Hanajiri, H. Takayama, and Y. Goda. The botanical origin of kratom (*Mitragyna speciosa*; Rubiaceae) available as abused drugs in the Japanese markets. *J. Nat. Med.* **63:** 340–344 (2009).
7. E.J. Shellard, The alkaloids of Mitragyna with special reference to those of *Mitragyna speciosa*, Korth. *Bull. Narc.* **26:** 41–55 (1974).
8. H. Takayama, Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, *Mitragyna speciosa*. *Chem. Pharm. Bull. (Tokyo)* **52:** 916–928 (2004).
9. A.A. Philipp, D.K. Wissenbach, A.A. Weber, J. Zapp, S.W. Zoerntlein, J. Kanogsunthornrat, and H.H. Maurer. Use of liquid chromatography coupled to low- and high-resolution linear ion trap mass spectrometry for studying the metabolism of paynantheine, an alkaloid of the herbal drug Kratom in rat and human urine. *Anal. Bioanal. Chem.* **396:** 2379–2391 (2010).
10. A.A. Philipp, D.K. Wissenbach, S.W. Zoerntlein, O.N. Klein, J. Kanogsunthornrat, and H.H. Maurer. Studies on the metabolism of mitragynine, the main alkaloid of the herbal drug Kratom, in rat and human urine using liquid chromatography–linear ion trap mass spectrometry. *J. Mass Spectrom.* **44:** 1249–1261 (2009).
11. T. Arndt, U. Claussen, B. Güssregen, S. Schröfel, B. Stürzer, A. Werle, and G. Wolf. Krypton-Konsum als Ursache eines positiven *O*-desmethyltramadol-Nachweises im Urin einer Opiatabhängigen in der Entwöhnungstherapie. *Toxichem. Krimtech.* **77:** 23–28 (2010).
12. R.B. Raffa. Basic pharmacology relevant to drug abuse assessment: tramadol as example. *J. Clin. Pharm. Ther.* **33:** 101–108 (2008).
13. M. Tjäderborn, A.K. Jönsson, J. Ahlner, and S. Hägg. Tramadol dependence: a survey of spontaneously reported cases in Sweden. *Pharmacoepidemiol. Drug Saf.* **18:** 1192–1198 (2009).
14. M. Tjäderborn, A.K. Jönsson, S. Hägg, and J. Ahlner. Fatal unintentional intoxications with tramadol during 1995–2005. *Forensic Sci. Int.* **173:** 107–111 (2007).
15. K. De Decker, J. Cordonnier, W. Jacobs, V. Coucke, P. Schepens, and P.G. Jorens. Fatal intoxication due to tramadol alone: case report and review of the literature. *Forensic Sci. Int.* **175:** 79–82 (2008).
16. K.E. Goeringer, B.K. Logan, and G.D. Christian. Identification of tramadol and its metabolites in blood from drug-related deaths and drug-impaired drivers. *J. Anal. Toxicol.* **21:** 529–537 (1997).
17. A.W. Jones and J. Schuberth. Computer-aided headspace gas chromatography applied to blood-alcohol analysis: importance of online process control. *J. Forensic Sci.* **34:** 1116–1127 (1989).
18. H. Druid and P. Holmgren. A compilation of fatal and control concentrations of drugs in postmortem femoral blood. *J. Forensic Sci.* **42:** 79–87 (1997).
19. A.W. Jones, F.C. Kugelberg, A. Holmgren, and J. Ahlner. Five-year update on the occurrence of alcohol and other drugs in blood samples from drivers killed in road-traffic crashes in Sweden. *Forensic Sci. Int.* **186:** 56–62 (2009).
20. S. Dresen, N. Ferreirós, M. Pütz, F. Westphal, R. Zimmermann, and V. Auwärter. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. *J. Mass Spectrom.* **45:** 1186–1194 (2010).
21. K. Matsumoto, Y. Hatori, T. Murayama, K. Tashima, S. Wongseripipatana, K. Misawa, M. Kitajima, H. Takayama, and S. Horie, Involvement of mu-opioid receptors in antinociception and inhibition of gastrointestinal transit induced by 7-hydroxymitragynine, isolated from Thai herbal medicine *Mitragyna speciosa*. *Eur. J. Pharmacol.* **549:** 63–70 (2006).
22. K. Matsumoto, S. Horie, H. Ishikawa, H. Takayama, N. Aimi, D. Ponglux, and K. Watanabe, Antinociceptive effect of 7-hydroxymitragynine in mice: discovery of an orally active opioid analgesic from the Thai medicinal herb *Mitragyna speciosa*. *Life Sci.* **74:** 2143–2155 (2004).

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'COMPLEX SYMPHONY ORCHESTRA'

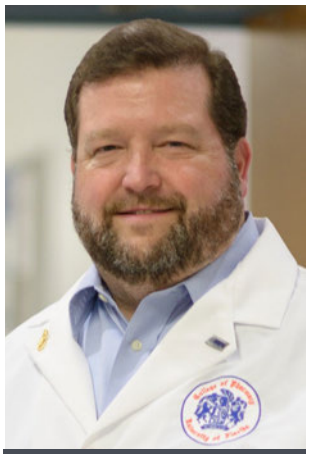
McCurdy Studies Whether Kratom Can Reduce Opioid Withdrawal, Ease Pain

BY DANA TALESNIK

It's a word now commonly spotted on smoke, vape and herbal shop signs across much of the country. But what exactly is kratom and is it safe to ingest?

Kratom is a tropical evergreen tree, from the same family as the coffee plant, whose leaves can be consumed in various forms. Its active compounds reportedly produce a range of stimulant, pain-relief and mood-enhancing effects.

Dr. Christopher McCurdy, professor of medicinal chemistry at the University of Florida (UF), became interested in the therapeutic potential of kratom from learning how it's been used in its native region.



Dr. Christopher McCurdy

"Kratom has been used by field workers in Southeast Asia to relieve pain and as a stimulant to improve their work capacity in the hot, tropical climate," he said. "Also, when they would run out of opium—for those who used it—they would use kratom in a

SEE **KRATOM**, PAGE 6

MILITARY, CIVILIAN DIMENSIONS

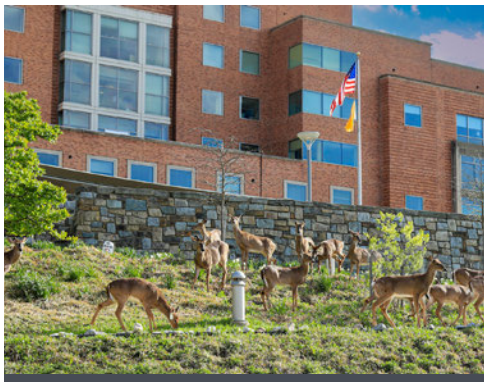
Stibbe Examines Effects of WWI Internment

BY ERIC BOCK

The internment of hundreds of thousands of soldiers and civilians during World War I gave governments a unique opportunity to experiment with different kinds of humanitarian assistance, said Dr. Matthew Stibbe, during a recent NLM History of Medicine talk. By studying the experiences of interned citizens in the 1910s, he hopes to gain insights into how isolation and uncertainty affect people, something that's relevant today.

From 1914 to 1918, roughly 8 million to 9 million soldiers became prisoners of war, said Stibbe, professor of modern European history at the United Kingdom's Sheffield

SEE **INTERNMENT**, PAGE 4



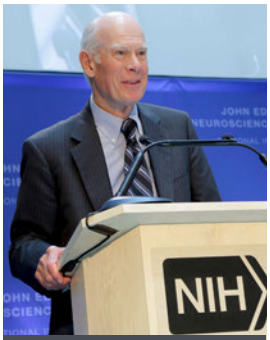
Volunteer vets issue important reminder about campus wildlife. See p. 2.

ALSO THIS ISSUE

'NO BETTER CHAMPION'

NIH Mourns Porter, Longtime Friend of Medical Research

"There is no better champion for medical research than John Porter." When then-NIAMS director Dr. Stephen Katz made that observation in 2011, legendary legislator Porter had been retired from Congress for a decade already. However, he'd never paused his efforts to increase support for NIH and for the medical research enterprise at large.



NIH champion John Porter in 2014

PHOTO: ERNIE BRANSON

Porter died on June 3 at age 87.

For 21 years, the Republican represented

SEE **PORTER**, PAGE 8

Bldg. 1's front lawn is once again awash in cyclists for Bike to Work Day.

PHOTO: MARLEEN VAN DEN NESTE

Bike to Work Day Back at NIH for 2022

NIH's main campus in Bethesda was once again one of nearly 100 pit stops in the Washington, D.C., metropolitan area for this year's Bike to Work Day, May 20. Forecast to be the hottest day of the year, BTWD dawned clear, but got muggy as thousands around the region pedaled to their job sites.

NIH's first BTWD observance since 2019—when more than 550 people pre-registered to

SEE **BIKE**, PAGE 12

SHARE YOUR FEEDBACK

Take the Federal Employee Viewpoint Survey

The 2022 Federal Employee Viewpoint Survey (FEVS) is currently open and will close on Friday, July 22. The annual government-wide survey gives eligible federal employees an opportunity to provide confidential feedback about their work satisfaction, organization and its leaders, and work/life balance.

The FEVS is available to full- and part-time permanent, non-seasonal employees, on board on or before Nov. 19, 2021. Eligible employees should check their inboxes for email from OPM. Results from the FEVS are used by leadership to develop specific plans aimed at making your institute, center or office a better place to work by incorporating professional and coaching development programs, listening sessions, interactive social events and more. For details about FEVS, visit https://hr.nih.gov/workforce/fevs or email NIHFEVS@nih.gov.

COSWD Issues RFI to Develop DEIA Prize

Respond By July 28

NIH's chief officer for scientific workforce diversity (COSWD) is currently seeking suggestions on the development of a prize competition to reward and promote inclusive excellence. The outreach is an outcome of UNITE, which was established to address structural racism within the NIH-supported and the greater scientific community.

The potential prize would recognize institutions of higher education that have implemented successful, innovative interventions for enhancing faculty and student diversity, equity, inclusion and accessibility (DEIA). These elements are essential to ensure equity and eliminate structural barriers to success among students and faculty in biomedical research.

Initiating such a prize is part of COSWD's commitment to increasing and sustaining biomedical research workforce diversity through institutional culture change.

The primary goal in establishing a competition is to reward transformative interventions developed by institutions to create research environments that promote and value DEIA. A secondary objective is to highlight evidence-based best practices proven to create more inclusive environments for students and faculty.

Recently, COSWD issued a request for information (RFI) seeking comments it may use to inform the potential prize competition. The COSWD team would like to hear from stakeholders throughout the scientific research community, DEIA experts, researchers and interested members of the public.

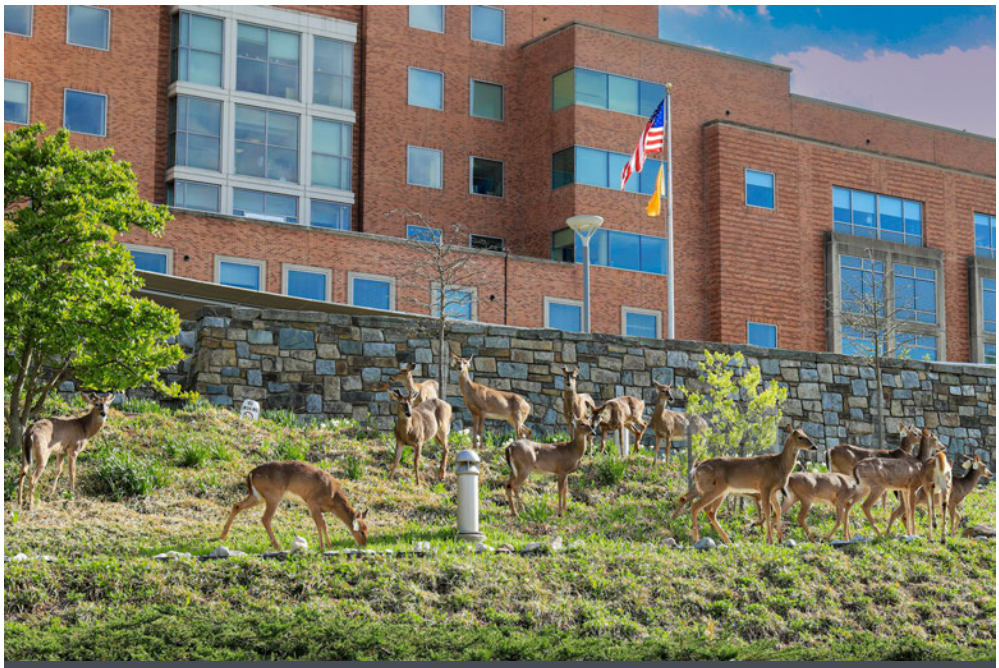
COSWD particularly wants input on the following:

- Competition structure
- Strategies for sharing information about the competition
- Judging criteria
- Amount of time needed to develop a prize submission
- Ways to disseminate approaches that promote inclusive excellence
- Reasons for and potential barriers to participating in the competition

To learn more, visit https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-109.html. All responses must be received by Thursday, July 28.

The COSWD team encourages everyone to take advantage of this opportunity to share thoughts on how NIH might recognize institutions that advance DEIA and create systemic change.

Send inquiries to: COSWDPrizeCompetition@nih.gov.



Deer graze on the lawn in front of the Clinical Research Center

PHOTO: DUSTIN HAYES, NEI

'KEEP WILDLIFE WILD'

Veterinary Volunteers Respond to Calls About Distressed/Injured Critters

Spring and summer are times when many wild animals on campus are busy raising their young.

The Wildlife Veterinary Volunteers Group wants to remind everyone to "Keep the Wildlife Wild" on NIH campuses while making sure that truly injured or distressed wildlife are cared for.

If you see any animal—no matter what species—that appears to be injured, distressed or acting aggressive, call the NIH Police non-emergency number (301) 496-5685. The NIH operator will call the volunteer veterinarian on duty to address the problem.

The group responds to calls about the Bethesda and Poolesville campuses.

The more information you can provide about the exact location of the animal, time found and activity of the animal, the better the team will be able to respond to the emergency.

Can Good Hydration Reduce Risk of Heart Failure?

NHLBI researchers Dr. Natalia Dmitrieva and Dr. Manfred Boehm and their colleagues in the Laboratory of Cardiovascular Regenerative Medicine are looking at whether staying well hydrated can stave off risks of heart failure.

NIH researchers have found that staying well hydrated may be associated with a reduced risk for developing heart failure. Their research, which appears in the *European Heart Journal*, suggests that consuming sufficient amounts of fluids throughout life not only supports essential body functioning, but may also reduce the risk of severe heart problems later on.

Heart failure, a chronic condition that develops when the heart does not pump enough blood for the body's needs, affects more than 6.2 million Americans. It's also more common among adults ages 65 and older.

After conducting preclinical research that suggested connections between dehydration and cardiac fibrosis, a hardening of the heart muscles, NHLBI researcher Dr. Natalia Dmitrieva and her team looked for similar associations in large-scale population studies.

To start, they analyzed data from more than 15,000 adults, ages 45-66, who enrolled in the Atherosclerosis Risk in Communities (ARIC) study between 1987-89 and shared information from medical visits over a 25-year period.

In selecting participants for their retrospective review, the scientists focused on those whose hydration levels were within a normal range and who did not have diabetes, obesity or heart failure at the start of the study. Approximately 11,814 adults were included in the final analysis and, of those, researchers found 1,366 (11.56 percent) later developed heart failure.

To determine potential links with hydration, the team assessed the hydration status of the participants using several clinical measures.

Looking at levels of serum sodium, which increases as the body's fluid levels decrease, was especially useful in helping to identify participants with an increased risk for developing heart failure. It also helped identify older adults at risk for developing both heart failure and left ventricular hypertrophy, an enlargement and thickening of the heart.

In a cohort of about 5,000 adults ages 70 to 90, those with serum sodium levels of 142.5-143 mEq/L at middle age were 62 percent more likely to develop left ventricular hypertrophy. Serum sodium levels starting at 143 mEq/L correlated with a 102 percent increased risk for left ventricular hypertrophy and a 54 percent increased risk for heart failure.

These early associations suggest good hydration may help prevent or slow the progression of changes within the heart that can lead to heart failure.

"Serum sodium and fluid intake can easily be assessed in clinical exams and help doctors identify patients who may benefit from learning about ways to stay hydrated," said NHLBI senior investigator Dr. Manfred Boehm, who leads the Laboratory of Cardiovascular Regenerative Medicine.

Fluids are essential for a range of bodily functions, including helping the heart pump blood efficiently, supporting blood vessel function and in orchestrating circulation. Yet many people take in far less than they need.

While fluid guidelines vary based on the body's needs, researchers recommended a daily fluid intake of 6-8 cups of water for women and 8-12 cups for men. R

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"Serum sodium and fluid intake can easily be assessed in clinical exams and help doctors identify patients who may benefit from learning about ways to stay hydrated."

-DR. MANFRED BOEHM

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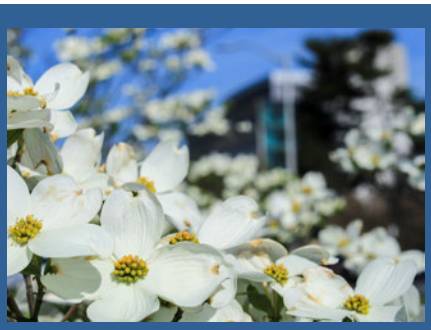

ON THE COVER: *Dogwood blossoms with Natcher Bldg. in background*

IMAGE: DUSTIN HAYES, NEI

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Turning Discovery Into Health

Internment

CONTINUED FROM PAGE 1

Hallam University and 2019 NLM Michael E. DeBakey fellow.

The experiences of the POWs varied greatly, Stibbe noted. Some soldiers were forced into physical labor near the frontlines. Others spent their time at guarded camps in more comfortable conditions. Neutral countries like Switzerland detained soldiers who strayed onto their lands. Across Europe, the death rate for these prisoners was around 11 percent, with considerable variations from country to country.

About 800,000 civilians also experienced internment. When war was declared in 1914, hundreds of thousands of citizens on both sides were imprisoned in detainment camps. British nationals living in Germany, for example, were seen as potential threats. These citizens were held captive, sometimes for the whole duration of the war.

"Military POWS were protected, in theory, by international legislation," he said. "Captive states were supposed to treat captured soldiers from the opposite side according to the same standards as their own enlisted men, in terms of food, accommodations and access to medical care."

Some civilian and military prisoners were also protected by the "reciprocity principle," in which "captor nations would not mistreat prisoners because they wanted to protect the interests of their own subjects in enemy captivity." Citizens interned by their own governments, however, had none of these protections.

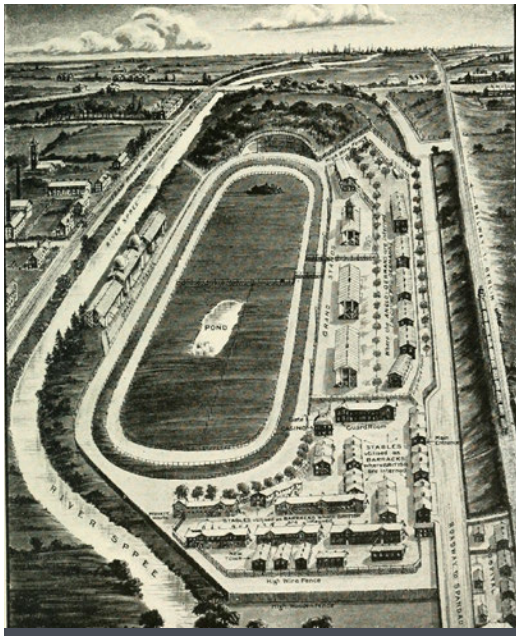
Captives had political and military value, said Stibbe. They were not just "useless eaters," although they were sometimes dubbed as such. Rather, they were bargaining chips, sources of intelligence and a labor force.

2019 NLM Michael E. DeBakey fellow Dr. Matthew Stibbe of United Kingdom's Sheffield University

Additionally, captor nations used POWs in propaganda to build support for the war.

Humanitarian organizations like the Geneva-based International Committee of the Red Cross campaigned for captor nations to treat civilian prisoners like military prisoners.

"There's a dilemma there," Stibbe argued. "If they were treated as military captives, civilians could experience disadvantages. They might not be able to excuse themselves from labor, for instance."



Stibbe showed this 1917 image of an internment camp of British prisoners near Berlin, from the book *In Ruhleben, Letters from a Prisoner to His Mother*.

IMAGE: WIKIMEDIA COMMONS

Certain groups, such as the British Quakers, thought that if they organized good things for German captives in Britain, that would encourage Germans to do the same. For example, the Quakers lobbied universities in Britain to give scientific equipment to German scientists in internment camps. In return, the Germans gave scientific equipment to detained British scientists.

As the war went on, countries began to standardize relief efforts, he said. Experts determined the amount of food, books and sports equipment each prisoner received. Neutral organizations like the Red Cross managed distribution of the packages.

"A lot of relief organizations decided that the typical prisoner was a literate, white male aged between 18 and 45," Stibbe noted. "There's a certain blindness towards the needs of particular groups."

In response, Dr. Elisabeth Rotten, a Swiss citizen with ties to the Quakers, created an organization to help enemy aliens in Germany who were in distress. Rotten believed those "who were most distressed were not the people who were in camps" but "the wives and children," Stibbe explained.

Exchange agreements were common. Soldiers with serious injuries were often traded. In 1917, some countries recognized that "barbed-wire disease," an "umbrella term for mental health conditions observed in long-term captives," could be grounds for exchange, he said.

A Swiss medic named Adolf Lukas Vischer wrote a book about the disorder. He argued, "It doesn't matter how good the conditions are in a camp. After a certain period of time, everybody in a prisoner of war camp will develop mental health symptoms, not just those who developed very obvious ones that necessitate their removal to a psychiatric institution." He further stated no one knew what the psychological implications of long-term internment might be.

The idea was controversial. Some medical experts thought diagnosing prisoners with barbed-wire disease would encourage others to claim they had the condition so they could go home. The Quakers criticized Vischer because they thought sending food and materials for arts and crafts was a good thing.

"Captivity itself had overlapping military and civilian dimensions, purposes and features," Stibbe said. "We cannot understand it holistically without understanding this overlapping of the military and civilian."

To view the talk, see: https://videocast.nih.gov/watch=44383.

For more information about the NLM Michael E. DeBakey Fellowship in the History of Medicine, see: https://www.nlm.nih.gov/hmd/get-involved/debakey-fellowship.html.

NEW PARTNERSHIP FORGED

Implementing Interventions for Environmental Health Equity

BY JENNIFER HARKER

Environmental health scientists forged a new partnership with implementation scientists to discuss how, together, they might address challenges and improve environmental health equity, during a 2-day workshop held earlier this year.

Implementation science studies methods to promote adoption of evidence-based practices, interventions and policies to improve population health. The field is part of NIEHS's strategic plan—Promoting Translation: Data to Knowledge to Action—to encourage application of strategies to reduce or avoid environmental exposures and resulting health impacts.

NIEHS's Dr. Lindsey Martin explained how implementation science and environmental health science can team up.

PHOTO: STEVE MCCAW/NIEHS

Real-World Example

Dr. Lindsey Martin, a health scientist administrator in the NIEHS Population Health Branch (PHB), and Dr. Rick Woychik, director of NIEHS and the National Toxicology Program, offered a real-world example from the Clean Cooking Implementation Science Network that applied implementation science to promote uptake of clean cooking technology to reduce household air pollution (HAP).

Unsafe cooking practices lead to HAP around the world and disproportionately affect the health of women and children in low- and middle-income countries. Researchers are studying strategies to promote appropriate use of cleaner cookstoves to replace HAP-generating instruments. Understanding the related individual, community, societal and policy factors is essential to supporting sustainable adoption.

Challenges to Implementation

"Could implementation science be the missing piece in addressing environmental health disparities through environmental justice research?" asked Dr. Melissa Smarr, a PHB health scientist administrator.

To achieve equity, barriers must first be worked through and understood. For example, structural racism may make implementation more difficult due to long-established interventions that might not serve all people equally. Therefore, de-implementation can be just as important a consideration, according to Dr. Rachel Shelton of Columbia University.

"We can introduce new programs and policies, but we also need to be thinking about how we de-implement programs, policies and practices that are already in place and are harmful," Shelton said. "This is a new and emerging area of implementation science."

Power of Green

Living in green spaces, surrounded by trees and grass, improves cardiovascular health and reduces air pollution, according to NIEHS grantee Dr. Aruni Bhatnagar, who leads the Green Heart Study at the University of Louisville.

A woman cooks indoors on a makeshift cookstove. Implementation science was used to promote uptake of an environmental health science intervention—clean cooking technology to reduce household air pollution.

PHOTO: MARVIN MINDER/SHUTTERSTOCK

Expanding on the health effects of greening urban areas, Dr. Eugenia South, director of the Urban Health Lab at the Perelman School of Medicine at the University of Pennsylvania, explained that the hardest hit areas stand to gain the most from environmental interventions.

"Gun violence is not immediately an outcome that people associate with thinking about neighborhood environments and environmental health, but I really want to get people thinking about that outcome," she said.

South's research suggests that revitalizing urban vacant lots with greenery resulted in a 29 percent reduction in gun violence and lowered self-reported depression by 41 percent.

'Never Too Early'

"A main takeaway is that it is never too early to think about implementation science," Martin said. "From better understanding issues of feasibility to planning for sustainability, you could incorporate implementation science throughout the research pathway."

The workshop featured panel discussions about four areas organizers say the fields of environmental health sciences and implementation science can grow together: environmental health disparities and environmental justice; prevention and interventions; climate change and disasters; community-engaged research.

"Equity is really the cornerstone and it needs to be front and center in how we think about science moving forward," added PHB chief Dr. Claudia Thompson, in closing remarks.

Martin, NCI program director for implementation science Dr. Gila Neta and OBSSR health scientist administrator Dr. Dara Blachman-Demner cochaired the workshop, which was a joint effort by NIEHS, NHLBI's Center for Translation Research and Implementation Science, NICHD, FIC, NCI, NIMH, NIMHD, Office of Behavioral and Social Sciences Research and Office of Disease Prevention.

Kratom

CONTINUED FROM PAGE 1

little bit higher doses to help avoid opioid withdrawal."

McCurdy wants to get to the root of the leaves' chemical properties and pharmacologic effects. He asks, as does the title of his recent NCCIH Integrative Medicine Research Lecture, "Can a controversial tree help end the opioid crisis?"

Drug of Concern

Despite an FDA import alert, an estimated 2,000 metric tons of kratom enter the U.S. monthly, mostly from Indonesia, suggesting millions of users across the country. Though federally legal, kratom is banned or restricted in multiple states. The U.S. Drug Enforcement Administration has classified kratom as a drug and chemical of concern, pending further study.

"We know that very few deaths are attributable to a kratom product alone, and for those that are, there could be extreme circumstances, in terms of overdosing, or it could be adulterated with synthetic compounds," such as fentanyl derivatives or other novel psychoactive substances that are unknown or undetected, said McCurdy.

A sign next to an organics market in North Bend, Oregon

PHOTO: THE IMAGE PARTY/SHUTTERSTOCK

Traditionally, in Thailand and elsewhere in Southeast Asia, kratom is consumed as a brewed tea. The fresh leaves are cut and boiled for hours.

In the U.S., though, kratom arrives as crushed leaves or powder and can come in different forms: capsules, energy shots, even gummies. McCurdy is collaborating with UF's Apopka campus to grow kratom trees and extrapolate the pharmacologic differences between fresh-leaf kratom and concentrated extracts.

McCurdy, with a screen background of kratom plants growing in a UF greenhouse, participates in a virtual Q&A with (from l) NCCIH communications director Catherine Law, NCCIH deputy director Dr. David Shurtleff and NCCIH director Dr. Helene Langevin.

"Collaboratively, we are trying to get a homegrown species to develop a product more similar to the traditional use for study in the U.S., [rather] than having to rely on these dried-leaf materials, which undergo post-harvest oxidation...and many times have changed the composition of the alkaloidal content," he said.

Therapeutic Potential

Kratom has opioid activity, said McCurdy, "but I'm going to show you that it's much more disruptive than just opioid activity. We've looked at it primarily as having the potential to replace several medications used during opioid detoxification."

McCurdy points to kratom having adrenergic (stimulant); serotonergic (mood-enhancing); analgesic (pain-relieving) and anxiolytic (anti-anxiety) activity. "If you could combine all those into one product," he said, "you might be able to improve medication adherence and completion of detoxification."

Another plus is that traditional kratom withdrawal tends to be mild. "It's in the upper end of mild," McCurdy said, "but it's not in moderate and it's certainly not in severe." He's working to get a standardized kratom product into clinical trials to evaluate its overall potential and therapeutic claims.

The Abundant Alkaloid

So far, investigators have isolated more than 40 alkaloids—organic compounds—in kratom. The predominant one, mitragynine

Kratom can be consumed in many forms, including brewed tea and capsules.

PHOTO: WASANAJAI / SHUTTERSTOCK

Dr. Brian Pearson of UF's department of environmental horticulture stands next to 1 of 100 in-ground kratom trees growing on the UF-Apopka campus. About 1,000 more are growing in a nearby greenhouse, allowing McCurdy to study the pharmacological properties of fresh-leaf kratom.

PHOTO COURTESY BRIAN PEARSON

(MG)—which gets its name from the plant's genus, *Mitragyna speciosa*—accounts for up to 66 percent of kratom's alkaloid content.

"It's the most abundant alkaloid in the plant, so it's the most easily extracted, isolated, purified and studied," said McCurdy.

MG occurs naturally in the plant. It's considered a partial opioid receptor agonist, though McCurdy said he wouldn't lump it in the traditional opioid category.

"We've collected data to show it has much less abuse and dependence liability than other opioid analgesics," he said.

What's more, MG's chemical composition pushes away some adverse side effects of traditional opioids, such as constipation and respiratory depression. "If you look at poison control center data," he added, "kratom overdoses resemble stimulants, not opioids."

In wild-type mice injected with a large dose of MG, McCurdy said the analgesic effect comes quickly, then dissipates after an hour. But this is just MG isolated.

★★★

"Kratom is a complex symphony orchestra of alkaloids, and what we generally tend to do in science is pluck each instrument out and listen to it at full blast and forget about the symphony it naturally occurs in."

-DR. CHRISTOPHER MCCURDY

★★★

"Kratom is a complex symphony orchestra of alkaloids, and what we generally tend to do in science is pluck each instrument out and listen to it at full blast and forget about the symphony it naturally occurs in," said McCurdy, urging listeners to take the data he presented in that context. "We're looking at these [elements] at full blast. These are big doses [given to the mice]...To achieve that in humans taking kratom just straight, it would make them vomit long before they would get to that level of efficacy."

Ingesting kratom whole, through the tea leaf, has good analgesic effects but is less robust than taking straight mitragynine orally, which can be as potent as codeine or morphine in some cases.

"MG by itself is that loud trumpet it wants to be," he said. "It does not appear to have abuse or addiction potential and reduces morphine and heroin intake in rats. These are of course desired characteristics of candidate pharmacotherapies for opiate addiction and withdrawal."

Molecule of Concern

One of the three known unnatural alkaloids in kratom, 7-hydroxymitragynine (7-HMG), can form when drying the leaves and it also metabolizes in the body. Not seen in fresh-leaf kratom, 7-HMG has high selectivity at opioid receptors.

"That's why we're so concerned about this molecule," said McCurdy.

He said his studies found 7-HMG "more potently substitutes for morphine...indicating that 7-hydroxy is potentially an abusable and addictive compound."

However, 7-HMG is unstable in human plasma and, taken orally, it does not appear to cross the blood-brain barrier very efficiently. New research shows equally promising news about the amount of MG converted to 7-HMG in the body.

"This is some of the hottest new data, refuting some work that's come out saying that 7-hydroxy is responsible for kratom's analgesic effects," McCurdy said. "We don't believe that to be the case. We don't believe the amount generated through metabolism is pharmacologically relevant."

McCurdy's research to date suggests kratom could help curb the opioid epidemic and manage pain and has other potential applications yet unexplored.

"There's so much anecdotal evidence out there in treatment of cardiovascular disease, diabetes and other avenues we haven't been able to tread into yet," he said during the Q&A. "Legitimate users are fighting to keep kratom legal; it's revolutionary for them."

In 2014, Porter and wife Amy celebrate completion of the research complex named for him at NIH.

PHOTO: ERNIE BRANSON

Porter

CONTINUED FROM PAGE 1

the North Shore of Chicago, northwest suburbs and eastern Lake County of Illinois in the U.S. House of Representatives, serving the 10th district from January 1980 until retiring in January 2001.

He was a member of the House Appropriations Committee and chaired its Subcommittee on Labor, Health and Human Services, Education and Related Agencies. The committee had jurisdiction over all of NIH's health programs, as well as those of other health-related federal agencies.

Over the period of 1998 to 2003, Congress doubled the NIH budget. Porter was widely recognized as the lead architect of that "remarkable legislative achievement," said NIH acting director Dr. Lawrence Tabak, addressing the Advisory Committee to the Director on June 9. "Mr. Porter was one of the greatest champions of NIH in the history of the agency. NIH has lost one of our most stalwart heroes."

Congressman Porter's numerous achievements as a visionary public servant cemented his legacy. Under his leadership, influence and advocacy, the educational and health-related programs of federal agencies such as NIH flourished.

In addition, Porter's commitment to the health and well-being of American citizens continued well after he left Congress. He chaired Research!America and served as vice chair of the Foundation for the NIH. He was a member of the Institute of Medicine of the National Academy of Sciences and the boards of the RAND Corporation and the American Heart Association.

Porter received 10 honorary degrees and more than 275 awards, including the Mary Woodard Lasker Award for Public Service in 2000.

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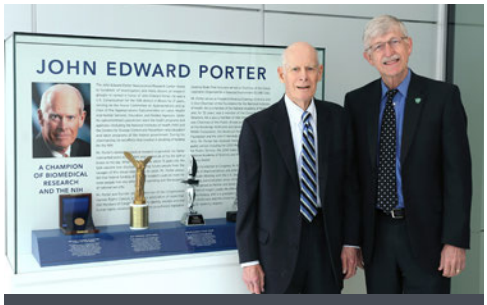
"Each one of us has to be involved. Let's work together to put science and research at our country's highest priority."

~JOHN EDWARD PORTER

◆ ◆ ◆



With Porter in 2019, NIH director Dr. Francis Collins unveils an exhibit about the ambassador for medical research.

PHOTO: CHIA-CHI CHARLIE CHANG

In January 2014, the National Academy of Sciences honored Porter with its esteemed Public Welfare Medal, "for being a tireless and effective advocate for scientific research over more than three decades, first in Congress and then in private life, thereby helping to maintain the preeminent status of biomedical research in the United States."

Later that spring, NIH hosted a scientific symposium and a dedication ceremony to celebrate completion of the John Edward Porter Neuroscience Research Center (PNRC) on the main Bethesda campus. The 500,000-square-foot, state-of-the-art complex had been built in 2 phases and brought together 800 neuroscientists from 10 institutes and centers across NIH in an effort to spur new advances in understanding the nervous system in health and disease. PNRC's footprint nearly matched that of its namesake.

In prescient remarks at the time, Porter called on investigators to defend research to the public and announced plans for a national campaign to reach all Americans about the importance of science.

"Each one of us has to be involved," he said. "Let's work together to put science and research at our country's highest priority. Now is the time to do it!"

DEIA Town Hall Set, June 29

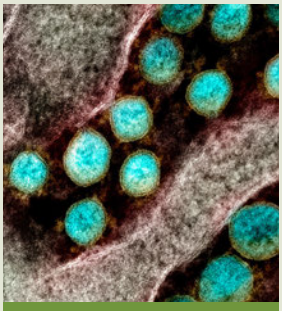
Join NIH acting director Dr. Lawrence Tabak on Wednesday, June 29 from 10:30 to 11:30 a.m. ET for a virtual Town Hall for all NIH staff, including employees, contractors, fellows and trainees to discuss NIH's diversity, equity, inclusion and accessibility (DEIA) efforts, share next steps on the NIH DEIA Strategic Plan and hear from Special Emphasis Program populations.

Also participating are Dr. Tara Schwetz, NIH acting principal deputy director; Dr. Marie Bernard, chief officer for scientific workforce diversity; Dr. Shelma Little, acting director, Office of Equity, Diversity and Inclusion; Julie Berko, chief people officer; and representatives of the following Special Emphasis Program populations: American Indian/Alaska Native, Black/African American, Asian/Native Hawaiian/Pacific Islander, Hispanic/Latino, sexual and gender minorities, people with disabilities and women.

Use this link to join: https://bit.ly/3O6IqHc. The meeting will include closed captioning and sign language interpreters. For other reasonable accommodation, contact Emma Wojtowicz (emma.wojtowicz@nih.gov, 301-451-2183) and/or the Federal Relay (1-800-877-8339).

Scientists Use Machine Learning to Better Identify Long Covid

An NIH-supported research team identified characteristics of people with long Covid and those likely to have it. Using machine learning techniques, scientists analyzed an unprecedented collection of electronic health records (EHRs) available for Covid-19 research to better identify who has long Covid.



Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient

IMAGE: NIAID

Exploring de-identified EHR data in the National Covid Cohort Collaborative (N3C), a centralized public database led by NCATS, the team found more than 100,000 likely long Covid cases as of October 2021 (as of May 2022, the count is more than 200,000). The findings appear in *The Lancet Digital Health.*

Long Covid is marked by wide-ranging symptoms, including shortness of breath, fatigue, fever, headaches, "brain fog" and other neurological problems that last for many months or longer after an initial Covid-19 diagnosis. Its symptoms mimic those of other diseases and conditions, often making it hard to identify.

The N3C data enclave currently includes information representing more than 13 million people nationwide, including nearly 5 million Covid-19-positive cases. The resource enables rapid research on emerging questions about Covid-19 vaccines, therapies, risk factors and health outcomes.

The new research is part of a related, larger trans-NIH initiative, Researching Covid to Enhance Recovery (RECOVER), which aims to improve understanding of the long-term effects of Covid-19, called post-acute sequelae of SARS-CoV-2 (PASC).

In the *Lancet* study, researchers examined patient demographics, health care use, diagnoses and medications in the health records of 97,995 adult Covid-19 patients in the N3C. They used this information, along with data on hundreds of long Covid patients from several clinics, to create three machine learning models.

In machine learning, scientists "train" computational methods to rapidly sift through large amounts of data to reveal new insights, patterns and clues.

The models focused on identifying potential long Covid patients among Covid-19 patients who were hospitalized and not hospitalized.

"Once you're able to determine who has long Covid in a large database of people, you can begin to ask questions about those people," said Dr. Josh Fessel, NCATS senior clinical advisor and a RECOVER scientific program lead. "Was there something different about those people before they developed long Covid? Did they have certain risk factors? Was there something about how they were treated during acute Covid that might have increased or decreased their risk for long Covid?"

The models searched for common features, including new medications, doctor visits and new symptoms in patients who were at least 90 days out from their acute infection. The research team hopes to use its long Covid patient classifier for clinical trial recruitment.

Study Looks at Antioxidant Effects on Dementia Risk

Some studies suggest that consuming high levels of antioxidants—compounds commonly found in vegetables and fruits that help protect cells from molecular damage—may help prevent the development of dementia.

In a new study, NIH researchers looked at associations between levels of certain antioxidants found in blood and the risk of developing dementia later in life. The compounds analyzed included carotenoids—antioxidant pigments found in plants—and some vitamins. The results were published in *Neurology*.

The team analyzed blood samples from more than 7,000 people between ages 45 and 90 who had enrolled in NHANES, an ongoing national study of nutrition, between 1988 and 1994. This data was linked with databases that tracked participants over an average of 16 years to find who later developed Alzheimer's disease or other dementias.

Overall, the team found that people with higher blood levels of carotenoids were less likely to develop dementia. However, when the researchers expanded their analyses to include lifestyle factors such as smoking and diet, and socioeconomic factors like education and income, the benefit of higher blood carotenoid levels disappeared.

Looking at individual carotenoids, blood levels of some of them were associated with a reduced risk of developing dementia after adjusting for other health, lifestyle and social factors. However, the size of the effect was reduced by these adjustments. The potentially protective carotenoids were lutein and zeaxanthin, which are found in green, leafy vegetables, and beta-cryptoxanthin, found in some orange-colored fruits.

A new study examined associations between levels of antioxidants in blood and the risk of developing dementia later in life.

PHOTO: TOM WANG / SHUTTERSTOCK

In contrast, blood levels of the antioxidant vitamins A, C and E weren't individually associated with dementia risk. Additional analyses suggested that high levels of vitamin A and E might actually counteract the effects of other antioxidants. The findings suggest that protective effects of some antioxidants may depend on the presence of other molecules in the body.

Around 6 million Americans are currently living with Alzheimer's disease or another type of dementia, a number expected to rise substantially in the coming decades as the population ages. More targeted preventive strategies are needed to help people stay cognitively healthy as they age.—adapted from *NIH Research Matters*

Researchers Identify High Costs of Living with SCD

Americans ages 64 and younger with commercial health insurance who live with sickle cell disease (SCD) pay almost quadruple the out-of-pocket medical costs over their lifetimes—a total of $44,000—as people living without the disease. And insurers pay $1.7 million on average for each person living with SCD, according to new NIH-supported research.

The health care spending analysis—published in *Blood Advances*—highlighted the financial toll that SCD—an inherited blood condition—has on patients, families and the health care system.

To calculate the lifetime out-of-pocket medical costs for people living with SCD, researchers analyzed commercial health insurance claims filed between 2007-2018 by 20,891 people living with SCD and compared those claims to those filed by 33,588 people of the same age and sex who did not have SCD.

Researchers found that people living with SCD had more medical appointments, urgent care and emergency medical visits, and prescriptions as well as higher out-of-pocket medical costs, which averaged about $1,300 annually.

SCD affects 100,000 people in the United States and millions worldwide. For more on this study, see: https://go.usa.gov/xJCjd.

NIDCD Clinical Director Van Waes Retires

BY PATRICIA BLESSING

Dr. Carter Van Waes, clinical director and chief of the Head and Neck Surgery Branch (HNSB) and tumor biology section at the National Institute on Deafness and Other Communication Disorders, will retire on June 30.

Dr. Carter Van Waes

Scientists, clinicians and colleagues honored his illustrious career at a symposium held May 13. NIDCD scientific director Dr. Lisa L. Cunningham presented Van Waes with the NIDCD Career Achievement Award for his outstanding leadership and scientific accomplishments. Many of the speakers were physician-scientists who were trained by Van Waes and spoke about how his mentorship influenced their professional careers. A common theme throughout the symposium was the inspiring role he played in training and nurturing future clinician-scientists and in advancing the NIDCD clinical research program.

"Dr. Van Waes's early and continued leadership in NIDCD's clinical program was instrumental in building the integrated clinical and basic research program that exists today," said NIDCD director Dr. Debara Tucci. "The NIDCD is extremely grateful for Van Waes's commitment to our institute over the past 29 years. His dedication to preclinical studies and clinical trials has led to the development of new therapies for the treatment of head and neck cancers that affect voice and speech and for inner ear tumors that cause hearing and balance disorders."

Van Waes earned a bachelor's degree from Earlham College in 1980, followed by an M.D. and a Ph.D. in the immunology of cancer from the University of Chicago. At the University of Michigan, he completed an NIH postdoctoral fellowship in molecular biology of head and neck cancer in 1990 and his residency in otolaryngology-head and neck surgery in 1993. He joined the NIDCD Division of Intramural Research in 1993 as a senior staff fellow and was promoted to acting chief of the tumor biology section and acting NIDCD clinical director in 1995. He was selected for the permanent position as NIDCD clinical director and HNSB chief in 2003.

In the branch's tumor biology section, Van Waes led studies that centered on developing approaches for preventing and treating cancerous tumors that affect human communication. This basic science work built the foundation for collaborating with other NIH institutes to conduct clinical trials pioneering the use of genetic and molecular-targeted treatments and combined therapies using immunotherapies, radiation and chemotherapy for head and neck cancers.

Van Waes credits his academic mentors and colleagues at NIH and the many students and fellows in the clinical program for their robust contributions to collectively improving the treatment of head and neck cancers.

"The most gratifying experience in my career has been to see more patients live to raise their children, work, enjoy retirement and be able to communicate," he said.

Over the course of Van Waes's career, his research was published in almost 200 peer-reviewed journals and cited more than 13,000 times. His work includes pioneering studies in head and neck cancer cell biology, immunology and genomics, with some of his discoveries translating directly to clinical studies and trials.

The cumulative body of work from HNSB and other laboratories provided an understanding of key genomic drivers of signal pathway and transcription factor networks in head and neck cancers, and ways these networks work to regulate the microenvironment that tumor cells create. Outlining these pathways from a systems biology perspective gave way to understanding how these networks and pathways were interacting at a molecular level.

These studies led Van Waes to work on the Cancer Genome Atlas (TCGA) program, which provided him with the opportunity to illustrate how genomic alterations fit within the pathways that he and others had previously defined.

Van Waes led a team of more than 50 TCGA researchers to compile research studies on the molecular characteristics that distinguish the genomic profiles of squamous cell carcinomas from the head, neck and other body sites. He, along with staff scientist Dr. Zhong Chen, now at the National Institute of Dental and Craniofacial Research, received the American Association for Cancer Research's Team Science Award in 2020 for their work, which is critical to the development of more effective diagnoses and targeted treatment strategies for head and neck cancers.

Van Waes's passion for mentoring and training the next generation of scientists was a constant force throughout his career. He was instrumental in developing the NIDCD clinical program into an environment that would attract surgeon-scientists eager for further training.

The Van Waes legacy continues today with the current NIDCD Otolaryngology Surgeon-Scientist Program, which provides opportunities for physicians to develop the skills necessary for cutting-edge, translational research on human communication processes in health and disease. He also mentored trainees in the NIH M.D./Ph.D. Partnership Training Program, the NIH Medical Scientist Training Program and the NIH Oxford-Cambridge Scholars Program. He tutored and mentored students and fellows in the NIH Clinical Research

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"Dr. Van Waes's early and continued leadership in the NIDCD's clinical program was instrumental in building the integrated clinical and basic research program that exists today."

-NIDCD DIRECTOR DR. DEBARA TUCCI

• • •

Training Program and the NIH Medical Research Scholars Program.

Van Waes participated in civil rights marches from the time he was in a stroller, so it is not surprising that he was involved early in developing NIDCD programs to recruit and mentor trainees from backgrounds underrepresented in biomedical research.

In 1994, in collaboration with the then-National Center on Minority Health and Health Disparities, Van Waes and NIDCD deputy director Dr. Jay Moskowitz developed the NIDCD Partnership Program, which was designed to create research opportunities within the institute for diverse groups of trainees. The program was initially piloted with four universities and later expanded to allow applicants from anywhere in the country. He continued to value and promote diversity in his clinical program and hopes that future initiatives will encourage more diversity in surgeon-scientist training programs.

Throughout his career, Van Waes received numerous awards for his contributions to diversity training programs, clinical care and research and scientific advances.

Past awards include the NIH Director's Award, NIH Clinical Center Director's Award for Excellence in Clinical Care, NIDCD Special Service Award for outstanding leadership as the clinical director in the establishment of a leading clinical program and numerous awards from professional organizations for head and neck cancers and clinical research.

In recognition of his outstanding leadership, expertise and mentorship, Van Waes will continue to serve NIH as a scientist emeritus.

Bernard Receives 2022 Hartford Foundation Award

NIH chief officer for scientific workforce diversity Dr. Marie A. Bernard was awarded the John A. Hartford Foundation Trustees Award for her many years of dedication to improving the lives of older adults through research, education and clinical practice improvement.

"Dr. Bernard has long been admired by the John A. Hartford Foundation, having been named to the first cohort of JAHF senior leadership scholars, chosen for their commitment to shaping the future of medicine and enhancing the health of older adults," said foundation president Dr. Terry Fulmer. "She is ensuring diverse representation in the research workforce, addressing critical issues in geriatric care—especially Alzheimer's disease—and has been a stellar educator and mentor to countless health care professionals. She is a true champion of older adults from all backgrounds."

The award recognizes Bernard for her work enhancing diversity in the sciences, especially in her current role as COSWD. The COSWD Office's mission is to be NIH's thought leader in the science of scientific workforce diversity, using evidence-based approaches to catalyze cultures of inclusive excellence. Bernard also co-leads NIH's UNITE initiative, which aims to identify and address structural racism within NIH and in the scientific community at large.

Established in 1929, the John A. Hartford Foundation has since 1982 awarded more than $625 million in grants to enhance the health and well-being of older people.

Adults with Covid-19 Sought

NIMHD researchers are recruiting adults newly diagnosed with Covid-19 (within 72 hours). The study will collect physical health data using a temperature patch and digital wristband that will be provided. Collected data will be uploaded to an app using a smartphone and will help researchers better understand how Covid-19 progresses and its long-term effects in groups with different demographics and risk profiles. Contact the Clinical Center Office of Patient Recruitment at (866) 444-2214 (TTY users dial 711) or ccopr@nih.gov. Refer to study #000315. Online: https://go.usa.gov/x676m.

Danazol Study Recruits Participants

NHLBI researchers are testing two low doses of danazol on individuals with short telomere disease and bone marrow disease, lung or liver disease. For more information, call the Office of Patient Recruitment (866) 444-2214 (TTY users dial 711). Online: https://go.usa.gov/xnPYm. Refer to study #18-H-0004.

Healthy Women Sought for Study

NICHD is seeking healthy women to compare with women who have experienced implantation failure and/or early or recurrent pregnancy loss. Researchers want to look at the uterine lining, the endometrium, to understand its role in implantation and miscarriage. Contact the Office of Patient Recruitment, (866) 444-2214 (TTY users dial 711) or ccopr@nih.gov. Online: https://go.usa.gov/xzE5. Refer to #000206-CH.

Adults with B-Cell Malignancies Sought

NHLBI opens a new clinical trial testing the drug NX-2127 for adults with relapsed/refractory B-cell malignancies. NX-2127 is an oral drug that degrades a protein in B-cell malignancies, Bruton's tyrosine kinase, instead of inhibiting or blocking it like other drugs. NX-2127 may also stimulate the body's immune T-cells to attack cancer cells. The study enrolls adults 18 years or older diagnosed with a B-cell malignancy that progressed after prior systemic therapies. Participation is at no cost and travel assistance may be available. Contact the Office of Patient Recruitment at (866) 444-2214 (TTY users dial 711) or email: ccopr@nih.gov. Refer to study #000326-H. Online: https://go.usa.gov/xuPDr.

Have Psoriasis? CC Needs Volunteers

Do you or someone you know have mild to moderate psoriasis? Researchers at the Clinical Center are testing a form of vitamin B3 dietary supplement to help improve immune system function in the blood and skin of people with mild to moderate psoriasis. Treatments and research procedures are provided at no cost. Refer to study #20-H-0044. Online: https://go.usa.gov/xdH2Y. For more information, call the Office of Patient Recruitment at (866) 444-2214 (TTY users dial 711) or email ccopr@nih.gov.

Above, Sean Cullinane (l) rocks the 2022 NIH souvenir T in cherry blossom pink. Below, it's got just two wheels and is leg-powered—count this scooter for BTWD!

PHOTOS: MARLEEN VAN DEN NESTE

Bike

CONTINUED FROM PAGE 1

bike to work on the designated day, this year's event seemed to be recovering in its own way from Covid-19. Safety precautions canceled the event in 2020 and 2021, interrupting its momentum from previous years. Participation in 2022 was also likely diminished as many employees remain on expanded telework schedules in the wake of the pandemic. Participants' enthusiasm remained high. They motivated by cycling's physical and mental health benefits as well as environmental benefits, according to several cyclists at the event.

"We had about 139 riders," said Frank Velez, NIDDK clinical research informatics analyst and NIH Bicycle Commuter Club (NIHBCC) president. "Our total mileage was 1,422 miles. We had 3 people tie for the longest ride in at 36 miles."

Riders from 17 institutes/centers, in addition to cyclists representing the Office of the Director, Office of Intramural Training and Education and Office of Research Services, checked in at NIH's pit stop in front of Bldg. 1. NCI had the highest number of unique commuters. The median commute was 8 miles and the average was 10.

"My commute was about 5 miles," said NIH acting principal deputy director Dr. Tara Schwetz, who pedaled from D.C. for BTWD. "I met up with Melissa Antman, who is on my team, and we rode most of the way together, going through some of the neighborhoods in Bethesda. We met around 9 a.m., and followed the bike route, so traffic wasn't really an issue. Last summer, I biked in almost once a week for several months. I may start doing it again since the weather is better."

FIC deputy director Dr. Peter Kilmarx, a longtime bicycle commuter, noted the change in his routine over the past 2 years.

"Before Covid-19, I biked every day year round," he said. "It's only about a mile from home to work across Old Georgetown Rd. Now I only come in once a week and I usually walk to get more steps, but I was in a hurry Friday, so I biked."

Since returning to work on site, NIHBCC member Kathy Kranzfelder, director of NIDDK's Office of Communications and Public Liaison, bikes in once or twice a week from Gaithersburg (32 to 36 miles round trip). She was one of more than 20 NIHBCC members who volunteered to help sign in cyclists, hand out t-shirts and otherwise facilitate riders at the pit stop.

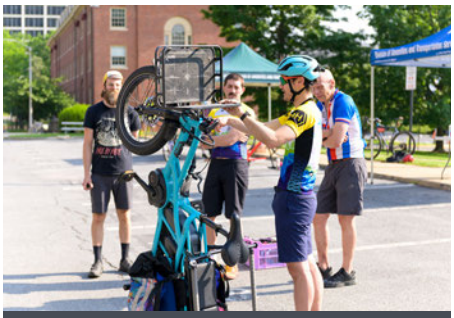
Kilmarx encourages "biking to work every day to improve health, reduce carbon footprint and pollution, relieve the parking burden on campus" and curtail overall traffic congestion in the region.

NIH'ers can find bicycling resources at: https://ors.od.nih.gov/pes/dats/NIHBicycleProgram/pages/default.aspx.

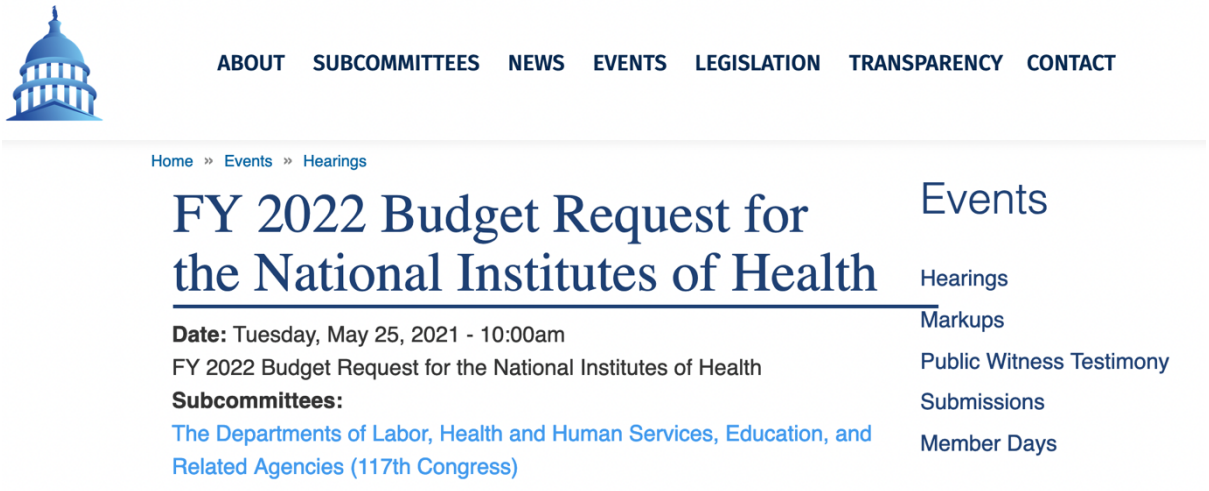
The League of American Bicyclists originated BTWD in 1956 to encourage bicycle commuting as a healthy and safe alternative to driving. NIH's observance is co-sponsored by NIHBCC and ORS's Division of Amenities and Transportation Services.—**Carla Garnett**

FIC deputy director Dr. Peter Kilmarx pedals to work.

Above, business is brisk at the sign-in table. Below, power pose on a beautiful day to bike to work



Above, a biker shows off a well-accessorized ride. Below, cyclists gather in front of Bldg. 1, after a 2-year BTWD hiatus.



https://appropriations.house.gov/events/hearings/fy-2022-budget-request-for-the-national-institutes-of-health

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Full length article

Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic

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ABSTRACT

Background: Kratom, a Southeast Asian plant with opioid-receptor mediated effects, has emerged as a potential substance of abuse, with limited data on its use and effects. This study characterized kratom user demographics, use patterns, and perceived drug effects.

Methods: A cross-sectional, anonymous online survey was conducted between January and December 2017.

Results: 2,798 kratom users – mean age 40 (SD = 12); predominantly White (90 %), female (61 %), and located in the US (97 %) – completed the survey. Kratom was primarily taken orally in doses of 1 – 3 g (49 %), with daily use (59 %) being most common. Kratom was used for pain (91 %), anxiety (67 %), and depression (65 %), with high ratings of effectiveness. 1,144 (41 %) used kratom to stop or reduce prescription or illicit opioid use, citing decreased opioid withdrawal and craving related to kratom use, with 411 reporting > 1-year continuous abstinence from opioids attributed to kratom use. Roughly one-third of respondents reported adverse effects of kratom, largely rated as mild in severity and lasting ≤ 24 h. Seventeen participants (0.6 %) sought treatment for adverse effects. Fifty-six individuals (2 %) met DSM-5 criteria for a past-year moderate or severe kratom-related substance use disorder (SUD). When asked how troubled they felt regarding their kratom use, the mean (SD) rating was 3.2 (9.8) on a scale from 0 to 100.

Conclusion: Kratom is used among White, middle-aged Americans for symptoms of pain, anxiety, depression, and opioid withdrawal. Although regular use was typical, kratom-related SUD and serious adverse effects were uncommon. Additional research on kratom epidemiology and pharmacology is imperative in light of the present opioid epidemic.

1. Introduction

Kratom (*Mitragyna speciosa*) is an evergreen tree in the coffee (*Rubiaceae*) family native to Southeast Asia (SEA), where it has a long history of traditional use (Hassan et al., 2013; Singh et al., 2016). Kratom leaf or extract are typically ingested orally for treating pain and other medical conditions, and to aid in the performance of agricultural and manual labor (Hassan et al., 2013; Singh et al., 2016). Kratom and its alkaloids have been classified as atypical opioids because they are structurally and biologically distinct from classical opioids (e.g., morphine) that are derived from the poppy (*Papaveraceae*) family (Raffa et al., 2018). Kratom has emerged as a natural product available for purchase over the internet (Babu et al., 2008; Prozialeck, 2016), and has been identified as a Drug of Concern by the US Drug Enforcement Administration (DEA, 2017). Surveys and case studies suggest many Americans are using kratom to self-medicate a range of conditions including pain and opioid withdrawal (Boyer et al., 2007; Coe et al., 2019; Grundmann, 2017; Henningfield et al., 2018; Smith and Lawson, 2017; Swogger et al., 2015), although there are limited empirical data available to support a therapeutic benefit for such use.

Kratom contains more than three dozen unique indole alkaloids, including its primary alkaloid mitragynine, which makes up approximately 66 % of the total alkaloids in kratom leaves (Kruegel and Grundmann, 2018; Takayama, 2004). Preclinical studies of mitragynine suggest it may hold potential toward developing new and efficacious pain medications (Kruegel and Grundmann, 2018; Macko et al., 1972; Takayama, 2004). Mitragynine is a G-protein-biased partial agonist of the mu-opioid receptor that does not recruit the β-arrestin signaling

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pathway like classical opioids (Kruegel et al., 2016; Váradi et al., 2016). It is thus hypothesized to confer analgesic effects with lower risk of respiratory depression than classical opioids (Kruegel et al., 2016; Siuda et al., 2017; Váradi et al., 2016). Mitragynine and kratom extracts have shown robust antinociceptive effects in rats, mice, and dogs, suppressing nociceptive response to both mechanical and thermal noxious stimuli with minimal respiratory depression (Hassan et al., 2013; Macko et al., 1972; Matsumoto et al., 1996; Sabetghadam et al., 2010). Furthermore, these antinociceptive effects are blocked by the opioid antagonist naloxone, suggesting an opioid-receptor mediated mechanism of action (Matsumoto et al., 1996; Sabetghadam et al., 2010). Abuse liability testing of mitragynine in rats has shown that it reduces morphine self-administration but does not substitute for morphine, and it does not engender or maintain intravenous self-administration, suggesting low abuse liability (Hemby et al., 2018). In addition, pretreating rats with mitragynine has also been shown to reduce heroin self-administration though mitragynine itself is not self-administered (Yue et al., 2018). However, 7-hydroxymitragynine, a minor alkaloid present at low levels (~2 % of alkaloids) in kratom leaves (Ponglux et al., 1994) has shown mu-opioid receptor-mediated analgesic effects (Matsumoto et al., 2004), and has been found to substitute for morphine and engender and maintain intravenous self-administration in rats in a dose-dependent manner (Hemby et al., 2018).

Survey studies indicate kratom has been used as a substitute for opioids and to alleviate opioid withdrawal both in SEA (Vicknasingam et al., 2010) and the US (Boyer et al., 2008; Coe et al., 2019; Grundmann, 2017). Internet-based studies have found that in the US, kratom is predominantly being used by White, middle-aged, middle-income, college-educated individuals for treatment of pain, opioid withdrawal, and mental health conditions, with relatively minor (e.g. stomach upset), dose-dependent adverse effects (Grundmann, 2017; Henningfield et al., 2018; Swogger et al., 2015). Among a sample of 8,049 kratom users in the US, more than a quarter of respondents reported using kratom to reduce illicit (e.g. heroin; n = 539) or prescription (e.g. opioid medication; n = 1813) drug dependence or withdrawal (Grundmann, 2017).

To date, the behavioral pharmacology and abuse liability of kratom have not been well-characterized in humans. One study conducted in Thailand that administered different doses of kratom tea to 10 chronic kratom-using males and evaluated blood and urine mitragynine levels found linear pharmacokinetics, time to maximum plasma concentration of roughly 1 h, and a terminal half-life of about one day (Trakulsrichai et al., 2015). Otherwise, no controlled laboratory research with kratom or its alkaloids has been conducted in humans. Given the lack of controlled human studies, it is important to understand more about kratom use patterns, users' motives, and outcomes following kratom exposure. This information can help inform prospective evaluations of kratom for different indications as well as regulatory decisions regarding scheduling. The present study collected demographic and self-report data from individuals who use kratom to extend the limited existing literature on contemporary kratom use.

2. Methods

2.1. Data collection

We conducted this cross-sectional, anonymous online survey to further characterize kratom user demographics, reasons for and patterns of kratom use, and perceived benefits of use. Self-reported adverse effects associated with kratom use were examined, including potential kratom withdrawal symptoms. Finally, indicators of abuse liability and problematic kratom use were assessed. All data were collected anonymously (no name or personally identifiable information recorded) using Qualtrics (Qualtrics, Provo, UT, USA). IP addresses were collected so the same person could not respond to the survey repeatedly, but were destroyed after data collection was completed. Between January 2017 and December 2017 participants were recruited using online advertisements and email announcements distributed via sites of interest to kratom users (e.g., American Kratom Association, Erowid, Reddit). Participants were required to be age 18 years or older, English language proficient, and have used kratom in the past year. Information about the purpose of the study was provided prior to beginning the survey, and by choosing to begin the survey respondents indicated their consent for voluntary participation. Participants who completed the initial pilot version of the survey through Amazon Mechanical Turk (n = 36) received $3.10 for completing the survey. Otherwise, no incentives were offered for study participation. Due to its confidential and anonymous nature, the Johns Hopkins University School of Medicine Institutional Review Board determined this did not qualify as human subjects research.

2.2. Measures

Participants provided demographic information (e.g., age, highest level of education, household income), location of residence, past-year use of licit (e.g., alcohol, nicotine), illicit (e.g., heroin, psychedelics), and prescription drugs (e.g., antidepressants, prescription opiates), and lifetime medical diagnoses. The 10-item Patient-Reported Outcomes Measurement Information System Global Health (PROMIS-GH) scale was used to assess general physical and mental health (Broderick et al., 2013). Chronic pain was assessed using the 15-item Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994).

Data regarding kratom use patterns, including age of kratom use initiation, frequency of use, typical dose of kratom, and route of administration were collected. Participants were asked to endorse whether they used kratom for specific conditions (e.g., pain, depression), if they would recommend kratom as a remedy for these conditions, and to rate how effective they considered kratom for these conditions using a visual analog scale (VAS) from 0 (not at all) to 100 (extremely). Participants were asked to report whether they had ever used kratom to help reduce or stop using heroin and/or licit or illicit use of pharmaceutical pain medications (e.g., Oxycontin, Percocet). Those who reported using kratom for this purpose then provided information on the perceived effectiveness of kratom to mitigate opioid use and ways in which kratom may have been useful in this capacity.

Incidence of self-reported adverse effects or side effects attributed to kratom was queried, and information on duration, severity, and medical treatment for adverse effects was collected. Similarly, potential kratom-related withdrawal was probed, with those endorsing possible kratom withdrawal completing the 16-item Subjective Opiate Withdrawal Scale (SOWS) to evaluate symptom severity (Handelsman et al., 1987). Participants rated typical subjective effects of kratom across 13 items from the Drug Effects Questionnaire (DEQ), assessing type, strength, and desirability of kratom effects associated with abuse liability (e.g., drug liking, euphoria, desire) using VAS from 0 (not at all) to 100 (extreme) (Morean et al., 2013). Additionally, participants were asked to rate how troubled or bothered they were by their kratom use using VAS from 0 (not at all) to 100 (extreme). Participants completed a DSM-5 substance use disorder (SUD) symptom checklist to assess whether past-year kratom use met diagnostic criteria for a kratom-related SUD (American Psychiatric Association, 2013; Hudziak et al., 1993).

2.3. Data analysis

Descriptive statistics were generated to determine the prevalence, means, and proportions of relevant variables. Chi-square (categorical variables) and Mann-Whitney U (continuous variables) tests were used to examine differences between those who used kratom to reduce opioid use and those who did not. To evaluate factors related to kratom use outcomes, we conducted four independent multivariate logistic regressions using Maximum Likelihood estimates for each of the

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following outcomes: negative effect of kratom use ≥1 lifetime/never lifetime); experience withdrawal from kratom use (≥1 symptom/0 symptoms); ever sought treatment for kratom use (yes/no); and lifetime use of kratom to reduce opioid use (yes/no). Several demographic and drug use variables were entered into the models as predictors, including: age, sex, race, relationship status, education, employment status, income, geographic region, past 12-month alcohol use, past 12-month opioid use, diagnosis of bipolar disorder, diagnosis of depression, age of first kratom use, kratom use frequency, number of kratom-related SUD symptoms, SOWS total, pain severity, experienced opioid withdrawal, and the total number of different types of opioids used in past 12 months. Data were analyzed using IBM Microsoft SPSS version 25 (IBM®, 2017), and Prism version 7.0 (GraphPad, La Jolla, CA, USA).

3. Results

3.1. Sample characteristics

Of the 4,302 individuals who began the survey, 2,826 (66 %) met all study inclusion criteria and completed the entire survey. Of these, 28 were removed due to inconsistent responses or technical issues, resulting in a final sample of 2,798 kratom users. Fifty-three percent of the final sample learned about the survey through the American Kratom Association and 44.2 % found it through Facebook or other social media websites.

Table 1 displays the means and proportions for demographic and substance use items. Respondents were on average 40.2 years old (SD = 11.8) and majority female (60.7 %). Most were married or in a committed relationship (66.5 %), employed (68.4 %), and had some college education (83.9 %). The median annual household income was between $50,000-$59,000. The largest geographic residential concentration for respondents was the U.S. South (41.0 %). Alcohol was the most commonly reported substance used in the past year (47.4 %), followed by tobacco (42.2 %), cannabis (37.2 %), and opioids (33.0 %). Roughly half the sample (52.9 %) reported ever experiencing opioid withdrawal symptoms or difficulty controlling opioid use.

3.2. Physical and psychological health

A majority of the sample (n = 1,924; 68.8 %) reported experiencing chronic pain over the past 3 months. Among this group, the mean (SD) BPI pain severity score was 4.1 (1.8), and the mean pain interference score was 4.9 (SD = 2.9), with possible scores ranging from 0 to 10 and greater scores indicating more pain or pain interference in daily activities. Pain was most commonly reported in the lower (53.8 %) and upper back (34.6 %), shoulders (33.1 %), and knees (31.3 %). Among this chronic pain group, 39.4 % reported currently taking a prescribed medication to treat pain, and 87.6 % reported current kratom use for pain.

Among the entire sample, the most commonly reported lifetime medical diagnoses (Table 1) included back pain (72.5 %), depression (65.0 %), muscle pain (62.9 %), neck pain (55.0 %), joint pain (54.5 %), panic attacks (48.1 %), and arthritis (43.8 %). PROMIS-GH physical health mean (SD) scores were 13.7 (3.2), and mental health scores were 12.8 (3.5), which both convert to standardized PROMIS-GH T-scores of approximately 45, slightly below the US general population mean of 50 (Hays et al., 2009).

3.3. Reasons for kratom use and use patterns

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

Table 1
Demographic characteristics and comparisons of respondents who did and did not report using kratom to reduce opioid use.[a]

Respondent Group				
Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Age in years, Mean ± SD	40.2 ± 11.8	39.8 ± 10.5	40.5 ± 12.6	.449
Sex, No. (%)				
Female	1,699 (60.7)	696 (60.8)	1,003 (60.6)	.916
Race, No. (%)				
American Indian/ Native Hawaiian	40 (1.4)	25 (2.2)	15 (0.9)	.013
Asian	14 (0.5)	4 (0.3)	10 (0.6)	
Black/African American	11 (0.4)	2 (0.2)	9 (0.5)	
More than one race/ some other race	176 (6.3)	60 (5.2)	116 (7.0)	
White	2,513 (89.8)	1,035 (90.5)	1,478 (89.4)	
Prefer not to respond	44 (1.6)	18 (1.6)	26 (1.6)	
Relationship status, No. (%)				
Single, never married	530 (18.9)	206 (18.0)	324 (19.6)	.671
In committed relationship/ married	1,860 (66.5)	775 (67.8)	1,085 (65.6)	
Separated/divorced	362 (12.9)	144 (12.6)	218 (13.2)	
Widowed	46 (1.6)	19 (1.7)	27 (1.6)	
Education, No. (%)				
Did not complete High school	51 (1.8)	22 (1.9)	29 (1.8)	.006
High school graduate or equivalent	401 (14.3)	189 (16.5)	212 (12.8)	
Some college	998 (35.7)	424 (37.1)	574 (34.7)	
College degree (e.g., AA, BS)	921 (32.9)	362 (31.6)	559 (33.8)	
Some graduate school	150 (5.4)	55 (4.8)	95 (5.7)	
Advanced degree (e.g., Ph.D.)	277 (9.9)	92 (8.0)	185 (11.2)	
Employment status, No. (%)				
Employed	1,915 (68.4)	785 (68.6)	1,130 (68.3)	< .001
Unemployed	313 (11.2)	148 (12.9)	165 (10.0)	
Student	109 (3.9)	27 (2.4)	82 (5.0)	
Other (e.g., disabled, retired)	461 (16.5)	184 (16.1)	277 (16.7)	
Household income, No. (%)				
< $10,000–$29,999	716 (25.6)	305 (26.7)	411 (24.8)	.098
$30,000–$49,999	608 (21.7)	266 (23.3)	342 (20.7)	
$50,000–$62,999	459 (16.4)	192 (16.8)	267 (16.1)	
$70,000–$99,999	483 (17.3)	180 (15.7)	303 (18.3)	
≥$100,000	532 (19.0)	201 (17.6)	331 (20.0)	
Geographic region, No. (%)				
Northeast	417 (14.9)	163 (14.2)	254 (15.4)	.132
Midwest	540 (19.3)	223 (19.5)	317 (19.2)	
South	1,147 (41.0)	495 (43.3)	652 (39.4)	
West	612 (21.9)	237 (20.7)	375 (22.7)	
Outside U.S./Prefer not to say	82 (2.9)	26 (2.3)	56 (3.4)	
Past 12-month substance use, No. (%)				
Alcohol	1,327 (47.4)	489 (42.7)	838 (50.7)	< .001
Antidepressants	787 (28.1)	296 (25.9)	491 (29.7)	.028
Benzodiazepines	702 (25.1)	327 (28.6)	375 (22.7)	< .001
Cannabis	1,041 (37.2)	419 (36.6)	622 (37.6)	.278
Cocaine	103 (3.7)	57 (5.0)	46 (2.8)	.002
Hallucinogens	161 (5.8)	51 (4.5)	110 (6.7)	.014
Opioids (prescribed or illicit)	922 (33.0)	550 (48.1)	372 (22.5)	< .001
Tobacco	1,180 (42.2)	573 (50.1)	607 (36.7)	< .001
Lifetime medical diagnoses, No. (%)				
Arthritis	1,225 (43.8)	532 (46.5)	693 (41.9)	.016
Back pain	2,028 (72.5)	875 (76.5)	1,153 (69.7)	< .001
Depression	1,818 (65.0)	797 (69.7)	1,021 (61.7)	< .001
Herniated disc	792 (28.3)	413 (36.1)	379 (22.9)	< .001
Joint Pain	1,526 (54.5)	664 (58.0)	862 (52.1)	.002
Menopause	538 (19.2)	187 (16.3)	351 (21.2)	.001

(*continued on next page*)

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Table 1 (*continued*)

Respondent Group				
Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Migraine/serious headaches	1,140 (40.7)	509 (44.5)	631 (38.1)	< .001
Muscle pain	1,760 (62.9)	774 (67.7)	986 (59.6)	< .001
Neck pain	1,540 (55.0)	669 (58.5)	871 (52.7)	.002
Ovarian cyst	550 (19.7)	261 (22.8)	289 (17.5)	< .001
Panic attacks	1,346 (48.1)	596 (52.1)	750 (45.3)	< .001
PTSD	711 (25.4)	327 (28.6)	384 (23.2)	.001
Restless leg syndrome	799 (28.6)	408 (35.7)	391 (23.6)	< .001
PROMIS-GH				
Physical health,[c] Mean ± SD	13.7 ± 3.2	13.8 ± 3.0	13.6 ± 3.3	.203
Mental health,[c] Mean ± SD	12.8 ± 3.5	13.0 ± 3.4	12.7 ± 3.5	.014

Abbreviation: No, number; SD, standard deviation; PTSD, Post-Trumatic Stress Disorder; PROMIS-GH, Patient-Reported Outcomes Measurement Information System Global Health scale.

[a] Opioid reduction users were classified as those who responded affirmatively to the question, "Have you ever used kratom to help you cut down or stop using heroin or prescription pain medications (such as Vicodin, Percocet, Oxycontin, etc.)?".

[b] P values calculated using chi-square and 2-tailed Mann-Whitney U tests.

[c] Range = 4–20. Greater values indicate better physical / mental health.

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.

The mean (SD) age for kratom use initiation was 38 (12.2) years (Table 2). The majority of respondents reported using kratom ≥100 times in their lifetime (76.2 %), and most had used kratom in the 24 h before completing the survey (80.7 %). The most commonly reported typical dose range per occasion was 1−3 grams (49.0 %), followed by 4−6 g (33.4 %). Daily use was reported by the majority of respondents (59.1 %), with a mean (SD) of 2.7 (1.3) doses used per day. Ingesting kratom orally in powder form was the most common method of administration (43.6 %) followed by drinking as a prepared beverage (e.g., tea, smoothie; 37.0 %).

3.4. Kratom adverse effects

Approximately 19 % of participants reported adverse effects from kratom use (Table 2), with an additional 12.8 % reporting possible kratom-related adverse effects. Among those reporting definite or possible adverse effects, only 1 % (n = 9) indicated serious to extreme severity, and 1.9 % (n = 17) reported seeking medical treatment for adverse effects. Most adverse effects were rated mild in severity (63.2 %) and lasted ≤1 day (86.1 %). Kratom-related withdrawal symptoms were reported by 9.5 % of respondents with another 17.5 % reporting possible kratom-related withdrawal. The overall logistic regression model fit was significantly improved by including the abovementioned predictor variables (χ^2 = 580.73, $p < .001$). Logistic regression revealed that adverse effects of kratom use were significantly associated with younger age (aOR > 1.20 for people 65 years or younger; 95 % CI: 0.18, 13.42)[1], male sex (female aOR = 0.75; 95 % CI: 0.59, 0.95), having less education (aOR > 0.90 for people without a graduate/professional degree; 95 % CI: 0.35, 2.07), and lower income (aOR > 1.20 for people earning < $250k annually; 95 % CI: 0.44, 6.14), as well as past 12-month alcohol use (aOR = 0.61 for no alcohol in past 12 months; 95 % CI: 0.48, 0.76), past 12-month opioid use (aOR = 0.59 for no opioid use in past 12 months; 95 % CI: 0.45, 0.76), kratom-related withdrawal (i.e., SOWS total; aOR < 0.01 for SOWS total < 50; 95 % CI: 0.00, 1.21 × 10^{10}), and the number of opioids used in the past 12-months (aOR > 2.45 for people whose used 8+ different types of opioids; 95 % CI: 0.00, 1.44 × 10^{13}). Self-reported depression (aOR = 0.68 for no depression; 95 % CI: 0.54, 0.87), pain severity (χ^2 = 9240.28, $p < .001$), and kratom-related DSM-5 SUD symptoms (χ^2 = 149.93, $p < .001$) were also related to kratom adverse effects.

3.5. Symptoms of withdrawal following kratom abstinence

The mean (SD) SOWS score among these individuals was 8.8 (8.4), indicating mild opiate withdrawal symptoms (i.e., SOWS score < 11). Most respondents (87.7 %) did not meet diagnostic criteria for a past-year kratom-related substance use disorder (SUD) based on the DSM-5 symptom checklist. Less than 3 % met diagnostic criteria for moderate and severe kratom-related SUD. When asked how troubled or bothered they were by their kratom use on a scale from 0 (not at all) to 100 (extremely), the mean (SD) response across the entire study sample was 3.2 (9.8). The most highly rated subjective effects of kratom on a 0–100 VAS (Table 2) included 'good effects' (M = 86.4; SD = 23.0) and 'drug liking' (M = 85.7; SD = 23.7), followed by 'alert' (M = 49.8; SD = 30.9) and 'stimulated' (M = 41.3; SD = 28.6), with lower ratings of 'euphoric' (M = 25.1; SD = 27.1) and 'high' (M = 12.0; SD = 20.1), suggesting potential differences in subjective effects profiles of kratom from classic opioids (Walsh et al., 2008). The overall logistic regression model fit was significantly improved by including the abovementioned predictor variables (χ^2 = 4015.85, $p < .001$). Logistic regression analyses revealed that experiencing kratom withdrawal was significantly predicted by the number of kratom-related DSM-5 SUD symptoms (χ^2 = 3301.90, $p < .001$), sex (female aOR = 0.21; 95 % CI: 0.09, 0.47), total SOWS score (χ^2 = 77.25, $p < .001$), and having experienced opioid withdrawal (aOR = 0.14 for never experiencing opioid withdrawal; 95 % CI: 0.05, 0.36). Seeking treatment for kratom use was also significantly predicted by the number of kratom-related DSM-5 SUD symptoms (all aOR < 0.01 for < 9 DSM-5 SUD symptoms; 95 % CI: 0.00, < 0.01) and SOWS total (all aOR < 0.01 for SOWS total < 50; 95 % CI: 0.00, < 0.01).

3.6. Kratom for opioid use reduction

A subsample of 1,144 individuals (40.9 %) reported using kratom to reduce or stop opioid use, including prescription opioid medications and heroin. Kratom was endorsed by this group as effectively treating their opioid withdrawal symptoms (87.3 %; n = 999), addressing underlying pain related to opioid use (86.1 %; n = 985), reducing opioid cravings (79.6 %; n = 911), and improving mood while tapering off opioids (72.0 %; n = 824). Kratom was widely reported to reduce opioid withdrawal symptoms among this group, including anxiety (86.5 %; n = 989), body aches (86.5 %; n = 989), restlessness (86.4 %; n = 988), and insomnia (79.5 %; n = 910).

Among these respondents, Percocet (33.2 %; n = 380) and Vicodin (32.3 %; n = 369) were the most commonly used opioids in the past year, and heroin exhibited the least past-year use (5.8 %; n = 66). Among this group 122 (10.7 %) reported past-year Suboxone use, 89 (7.8 %) reported past-year methadone use, and 411 (35.9 %) reported no past-year opioid use. Most of these respondents (74.2 %; n = 849) reported achieving ≥6 months of abstinence from opioids attributed to kratom use. The large majority of these participants (99.2 %; n = 1,135) said they would recommend kratom as an opioid withdrawal treatment. The overall logistic regression model fit was significantly

[1] Adjusted odds ratios (aOR) are included where data showed a significant monotonic relationship. χ^2 values are included where the predictor variable had a significant non-linear relationship to the dependent variable. Where multiple categories exist for a variable, the 95% CI shows the range of minimum-to-maximum for all catgeories.

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Table 2
Kratom use patterns and comparisons of respondents who did and did not report using kratom to reduce opioid use.[a]

Respondent Group				
Kratom Use Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Reasons for kratom use,[c] No. (%)				
Treatment of mood-related or psychiatric symptoms	1,975 (70.6)	873 (76.3)	1,102 (66.7)	< .001
Anxiety	1,881 (67.2)	827 (72.3)	1,054 (63.7)	< .001
Depression	1,804 (64.5)	814 (71.2)	990 (59.9)	< .001
Bipolar Mood	687 (24.6)	340 (29.7)	347 (21.0)	< .001
Post-traumatic Stress Disorder (PTSD)	829 (29.6)	402 (35.1)	427 (25.8)	< .001
For treatment of pain	2,554 (91.3)	1,078 (94.2)	1,476 (89.2)	< .001
To reduce or stop using prescription or illicit opioids	1,144 (40.9)	1,144 (100.0)	0 (0)	< .001
Age of kratom use initiation, Mean ± SD	38.0 ± 12.2	37.3 ± 11.0	38.4 ± 12.9	.107
Has used kratom ≥100 times, No. (%)	2,133 (76.2)	939 (82.1)	1,194 (72.2)	< .001
Last time of kratom consumption, No. (%)				
Past 24 h	2,258 (80.7)	990 (86.5)	1,268 (76.7)	< .001
Past week	300 (10.7)	88 (7.7)	212 (12.8)	
Past month	129 (4.6)	33 (2.9)	96 (5.8)	
Past Year	111 (4.0)	33 (2.9)	78 (4.7)	
Typical dose in grams, No. (%)				
< 1	242 (8.6)	60 (5.2)	182 (11.0)	< .001
1–3	1,372 (49.0)	542 (47.4)	828 (50.1)	
4–6	935 (33.4)	424 (37.1)	509 (30.8)	
7 or more	249 (8.9)	118 (10.3)	135 (8.2)	
Number of doses per day, Mean ± SD	2.7 ± 1.3	3.1 ± 1.3	2.4 ± 1.3	< .001
Past-year frequency of use, No. (%)				
≤1 time per month	109 (3.9)	26 (2.3)	83 (5.1)	< .001
2–4 times per month	152 (5.4)	27 (2.4)	125 (7.6)	
2–3 times per week	375 (13.4)	99 (8.7)	276 (16.7)	
4–6 times per week	508 (18.2)	197 (17.2)	311 (18.8)	
Daily	1,654 (59.1)	795 (69.5)	859 (51.9)	
Route of administration, No. (%)				
Capsule/pill	530 (18.9)	214 (18.7)	316 (19.1)	< .001
Prepared as tea/beverage	1,035 (37.0)	373 (32.6)	662 (40.0)	
Ingested powder	1,221 (43.6)	550 (48.1)	671 (40.6)	
Other (e.g., smoked, IV/SC, consumed as extract)	12 (0.4)	7 (0.6)	5 (0.3)	
Experienced adverse effects from kratom, No. (%)				
Yes	540 (19.3)	198 (17.3)	342 (20.7)	.045
Maybe	357 (12.8)	140 (12.2)	217 (13.1)	
No	1,901 (67.9)	806 (70.5)	1,095 (66.2)	
Adverse effect severity, No. (%)				
Not at all	274 (9.8)	95 (8.3)	179 (10.8)	.589
Mild	567 (20.3)	219 (19.1)	348 (21.0)	
Moderate	47 (1.7)	20 (1.7)	27 (1.6)	
Serious to Extreme	9 (0.3)	4 (0.3)	5 (0.3)	
Sought medical treatment due to adverse effects	17 (0.6)	9 (0.8)	8 (0.5)	.311
Duration of adverse effects, No. (%)				
≤1 day	772 (27.6)	288 (25.2)	484 (29.3)	.476
2–6 days	76 (2.7)	28 (2.4)	48 (2.9)	
1–12 weeks	30 (1.1)	14 (1.2)	16 (1.0)	
4–11 months	6 (0.2)	4 (0.3)	2 (0.1)	
≥1 year	13 (0.5)	4 (0.3)	9 (0.5)	
Has experienced kratom-related withdrawal symptoms, No. (%)				
Yes	267 (9.5)	140 (12.2)	127 (7.7)	< .001
Maybe	491 (17.5)	251 (21.9)	240 (14.5)	
No	2,040 (72.9)	753 (65.8)	1,287 (77.8)	
SOWS Score,[d] Mean ± SD	8.8 ± 8.4	9.2 ± 8.4	8.3 ± 8.5	.017
Past-year DSM-5 kratom-related SUD criteria, No. (%)				
No criteria met	2,454 (87.7)	981 (85.8)	1,473 (89.1)	.043
Mild	276 (9.9)	131 (11.5)	145 (8.8)	
Moderate	51 (1.8)	26 (2.3)	25 (1.5)	
Severe	17 (0.6)	6 (0.5)	11 (0.7)	
How troubled or bothered by kratom use?[e] Mean ± SD	3.2 ± 9.8	3.4 ± 9.9	3.1 ± 9.8	.034
Ratings of typical kratom effects,[e] Mean ± SD				
Drug Effect	27.3 ± 29.8	25.9 ± 29.3	28.2 ± 30.1	.061
Drug Liking	85.7 ± 23.7	87.3 ± 22.5	84.6 ± 24.4	< .001
High	12.0 ± 20.1	11.1 ± 18.9	12.6 ± 20.8	.265
Good Effects	86.4 ± 23.0	86.7 ± 23.5	86.2 ± 22.6	.009
Bad Effects	11.5 ± 15.7	10.8 ± 15.5	12.0 ± 15.9	.036
Desire	30.1 ± 28.9	33.3 ± 29.3	27.9 ± 28.4	< .001
Stimulated	41.3 ± 28.6	42.5 ± 27.9	40.6 ± 29.0	.066
Euphoric	25.1 ± 27.1	24.7 ± 26.6	25.4 ± 27.4	.981
Sick	6.2 ± 12.3	5.8 ± 11.8	6.5 ± 12.6	.094

(*continued on next page*)

Table 2 (*continued*)

Respondent Group				
Kratom Use Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Dizzy	4.8 ± 10.9	4.9 ± 11.4	4.7 ± 10.5	.703
Alert	49.8 ± 30.9	52.5 ± 30.7	47.9 ± 30.8	< .001
Anxious	3.9 ± 9.6	3.8 ± 8.6	4.0 ± 10.3	.385
Sleepy	22.3 ± 23.6	20.4 ± 22.0	23.6 ± 24.7	.009

Abbreviation: No, number; SD, standard deviation; SOWS, Subjective Opioid Withdrawal Scale; SUD, Substance Use Disorder.

[a] Opioid reduction users were classified as those who responded affirmatively to the question, "Have you ever used kratom to help you cut down or stop using heroin or prescription pain medications (such as Vicodin, Percocet, Oxycontin, etc.)?".

[b] P values calculated using chi-square and 2-tailed Mann-Whitney U tests comparing Opioid reduction users (n = 1,144) and Other users of kratom (n = 1,654).

[c] Respondents could identify multiple reasons for use.

[d] SOWS scores can range from 0 to 64, with scores 0–10 = mild, 11–20 = moderate, > 20 = severe.

[e] Possible scores range 0 (not at all) to 100 (extremely).

improved by including the abovementioned predictor variables (χ^2 = 2988.20, $p < .001$). Kratom use for opioid use reduction was significantly associated with age of first kratom use (aOR > 8.87×10^4 for starting use at age 65 or younger; 95 % CI: 0.00, 12.92×10^6), lifetime kratom use on < 100 occasions (aOR = 0.26; 95 % CI: 0.13, 0.52), frequency of current kratom use (χ^2 = 10.64, $p = .031$), never having experienced opioid withdrawal (aOR < 0.01; 95 % CI: 0.00, < 0.01), greater number of opioids used in the past 12-months (χ^2 =644.46, $p < .001$), and past 12-month opioid use (aOR = 5.89; 95 % CI: 3.35, 10.39).

3.7. Comparison of kratom users by motivation for use

Tables 1 and 2 show between-groups comparisons of individuals who reported using kratom to reduce opioid use (n = 1,144), and those who reported using kratom for other reasons such as pain or depression (n = 1,654). These groups were similar in many respects including age, sex, relationship status, and geographic location (Table 1). However, groups differed significantly in education and employment status, with those using kratom for opioid use reduction showing lower rates of college or advanced degrees, fewer current students, and greater unemployment.

Those who used kratom to reduce opioid use were less likely to have used alcohol ($p < .001$), antidepressants ($p = .028$), and hallucinogens ($p = .014$), but more likely to have used tobacco ($p < .001$), opioids ($p < .001$), benzodiazepines ($p < .001$), and cocaine ($p = .002$) in the past year (Table 1). Individuals who used kratom to reduce opioid use reported significantly greater lifetime prevalence across a variety of medical diagnoses including back pain, depression, and panic attacks, with menopause being the only diagnosis more common among those using kratom for purposes other than opioid use reduction. Respondents who used kratom to reduce their opioid use also showed significantly higher rates of endorsing kratom use for anxiety, depression, post-traumatic stress, bipolar mood, and pain.

Those who reported using kratom for opioid use reduction exhibited greater likelihood of having used kratom in the 24 h prior to completing the survey, higher dose used per occasion, more doses used per day, greater frequency of use, and higher prevalence of kratom-related withdrawal symptoms (Table 2). Between-group differences in typical subjective effects of kratom were also observed, with opioid reduction users reporting significantly greater drug liking, good effects, alertness, and desire for kratom, and significantly less sleepiness. Those who reported using kratom for opioid reduction were slightly more likely to meet DSM-5 criteria for mild or moderate kratom-related SUD in the past year.

4. Discussion

The current study collected data on kratom user demographics, use patterns, and perceived therapeutic and adverse effects. Participants in the present study were predominantly White, middle-aged, female, with some college education, in a committed relationship, and employed. Physical and psychological health in the current sample was on average slightly below US general population means (Hays et al., 2009), though lifetime pain and depression diagnoses were highly prevalent among respondents. These findings are congruent with observed comorbidity between opioid use disorder, pain, and psychiatric conditions such as depression (Conway et al., 2006; Fischer et al., 2012). Interestingly, respondents who reported using kratom for opioid use reduction had a higher life-time prevalence of depression, but were less likely to use antidepressants than other respondents. It is possible that these individuals use kratom as an alternative to antidepressant medications, though this might also be related to lack of access to medical care, which was not explicitly probed in this survey and should be examined in future studies. Consistent with other recent research (Boyer et al., 2007; Coe et al., 2019; Grundmann, 2017; Henningfield et al., 2018; Smith and Lawson, 2017; Swogger et al., 2015), these data suggest individuals in the US are using kratom to self-treat medical conditions such as pain, depression, anxiety, and opioid withdrawal symptoms, and reporting robust effectiveness for these indications.

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 (Henningfield et al., 2018; Raffa et al., 2018).

The major limitation of this and other internet-based surveys of kratom users is the self-selected convenience sample queried. Because data were collected online, and recruitment was conducted through websites of interest to kratom users, the sample likely exhibits selection bias towards individuals who are younger, more affluent, and more

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positively inclined towards kratom. Therefore, these results may underrepresent individuals from lower socio-economic status backgrounds, older and less technologically-fluent people, and those with negative experiences using kratom (e.g., who discontinued use due to adverse effects and are no longer part of the kratom-using online community). Thus, adverse effects may be underestimated, and benefits overestimated. It was also impossible to distinguish medically prescribed from illicit use of opioid medications in the current dataset, representing another significant limitation of the present study.

Kratom is currently unscheduled in the US, although the US Drug Enforcement Administration and Food and Drug Administration have raised the possibility of Schedule I classification of kratom and its alkaloids, which would strongly deter research and pose a significant public health risk for individuals currently using kratom in place of other opioids (DEA, 2017; Henningfield et al., 2018; Prozialeck, 2016). The rationale for Schedule I classification includes 44 possible kratom-related deaths worldwide over the past decade, most of which are known to involve other substances and/or preexisting medical conditions (Henningfield et al., 2018). The current scope of kratom use in the US remains unknown, and only one controlled human laboratory study of kratom has been conducted to date (Trakulsrichai et al., 2015), highlighting a notable lack of empirical information about the epidemiology and pharmacological effects of kratom in humans. Nationally-representative epidemiological research is needed, along with controlled studies of the potential risks, benefits, medication interactions, and abuse liability of kratom in humans prior to any Scheduling action that may confer unintended, but deleterious, public health consequences. There is a high likelihood that banning kratom or its constituents would compel individuals who are presently using kratom for pain relief or opioid use reduction to return to using prescription or illicit opioids with a known risk of dependence and possible lethal overdose.

With nearly 49,000 opioid-related overdose deaths in the US in 2017, the current opioid epidemic has reached unprecedented levels (Ahmad et al., 2018). Prescription opioid use has increased more than 4-fold since 1999 (Frenk et al., 2015), comprising 245 million prescriptions for opioid medications in 2014 (Levy et al., 2015; Rudd et al., 2016), and contributing to almost half of current US opioid overdose deaths (Ahmad et al., 2018; Rudd et al., 2016). The majority of pharmaceutical opioids are prescribed for the management of acute pain. However, prescription opioid misuse, diversion, and use disorder represent rapidly growing public health concerns (Vowles et al., 2015), highlighting an urgent need for novel pain management options that are safer, and less addictive than current medications (Volkow and McLellan, 2016). If controlled research in humans finds that kratom exhibits analgesic effects with minimal abuse liability and risk of respiratory depression, this could provide a much-needed avenue towards the development of novel medications for pain management and potentially OUD. Thus, additional investigation of kratom and its alkaloids is both timely and promising, and may have critical public health ramifications in the midst of the current opioid crisis.

Contributors

Dr. Garcia-Romeu made substantial contributions to the conception and design of the study, the acquisition, analysis, and interpretation of the data, and the drafting of the manuscript. Dr. Cox made substantial contributions to the analysis of the data, and made critical revisions to the manuscript. Dr. Smith made substantial contributions to the design of the study, the analysis of the data, and made critical revisions to the manuscript. Dr. Dunn made substantial contributions to the conception and design of the study, the acquisition and interpretation of the data, and made critical revisions to the manuscript. Dr. Griffiths made substantial contributions to the conception and design of the study and made critical revisions to the manuscript. All authors read and approved the final version of this manuscript, and agree to be accountable for all aspects of the work.

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Declaration of Competing Interest

The authors have no conflicts of interest to report.

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References

Ahmad, F.B., Rossen, L.M., Spencer, M.R., Warner, M., Sutton, P., 2018. Provisional Drug Overdose Death Counts. National Center for Health Statistics [WWW Document]. URL https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm (Accessed 2.21.19).

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.

Babu, K.M., McCurdy, C.R., Boyer, E.W., 2008. Opioid receptors and legal highs: salvia divinorum and Kratom. Clin. Toxicol. 46 (2), 146–152.

Boyer, E.W., Babu, K.M., Adkins, J.E., McCurdy, C.R., Halpern, J.H., 2008. Self-treatment of opioid withdrawal using kratom (Mitragynia speciosa korth). Addiction 103 (6), 1048–1050.

Boyer, E.W., Babu, K.M., Macalino, G.E., Compton, W., 2007. Self-treatment of opioid withdrawal with a dietary supplement, kratom. Am. J. Addict. 16 (5), 352–356.

Broderick, J.E., DeWitt, E.M., Rothrock, N., Crane, P.K., Forrest, C.B., 2013. Advances in patient-reported outcomes: the NIH PROMIS® measures. Egems 1 (1).

Cleeland, C.S., Ryan, K.M., 1994. Pain assessment: global use of the brief pain inventory. Ann. Acad. Med. Singapore 23 (2), 129–138.

Coe, M.A., Pillitteri, J.L., Sembower, M.A., Gerlach, K.K., Henningfield, J.E., 2019. Kratom as a substitute for opioids: results from an online survey. Drug Alcohol Depend. 202, 24–32.

Conway, K.P., Compton, W., Stinson, F.S., Grant, B.F., 2006. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J. Clin. Psychiatry 67 (2), 247–257.

Drug Enforcement Administration, 2017. Drugs of Abuse: a DEA Resource Guide. Drug Enforcement Administration, US Department of Justice [WWW Document] URL https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf#page=84 (Accessed 2.12.19).

Fischer, B., Lusted, A., Roerecke, M., Taylor, B., Rehm, J., 2012. The prevalence of mental health and pain symptoms in general population samples reporting nonmedical use of prescription opioids: a systematic review and meta-analysis. J. Pain 13 (11), 1029–1044.

Frenk, S.M., Porter, K.S., Paulozzi, L., 2015. Prescription Opioid Analgesic Use Among Adults: United States, 1999-2012 189. US Department of Health and Human Services, Centers for Disease Control and Prevention. National Center for Health Statistics Data Brief, pp. 1–8.

Grundmann, O., 2017. Patterns of kratom use and health impact in the US—results from an online survey. Drug Alcohol Depend. 176, 63–70.

Handelsman, L., Cochrane, K.J., Aronson, M.J., Ness, R., Rubinstein, K.J., Kanof, P.D., 1987. Two new rating scales for opiate withdrawal. Am. J. Drug Alcohol Abuse 13 (3), 293–308.

Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N.H., Suhaimi, F.W., Vadivelu, R., et al., 2013. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. Neurosci. Biobehav. Rev. 37 (2), 138–151.

Hays, R.D., Bjorner, J.B., Revicki, D.A., Spritzer, K.L., Cella, D., 2009. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual. Life Res. 18 (7), 873–880.

Hemby, S.E., McIntosh, S., Leon, F., Cutler, S.J., McCurdy, C.R., 2018. Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. Addict. Biol. https://doi.org/10.1111/adb.12639.

Henningfield, J.E., Fant, R.V., Wang, D.W., 2018. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology 235 (2), 573–589.

Hudziak, J.J., Helzer, J.E., Wetzel, M.W., Kessel, K.B., McGee, B., Janca, A., Przybeck, T., 1993. The use of the DSM-III-R checklist for initial diagnostic assessments. Compr. Psychiatry 34 (6), 375–383.

Kruegel, A.C., Gassaway, M.M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., et al., 2016. Synthetic and receptor signaling explorations of the Mitragyna alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. J. Am.

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Chem. Soc. 138 (21), 6754–6764.
Kruegel, A.C., Grundmann, O., 2018. The medicinal chemistry and neuropharmacology of kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology 134, 108–120.
Levy, B., Paulozzi, L., Mack, K.A., Jones, C.M., 2015. Trends in opioid analgesic–prescribing rates by specialty, US, 2007–2012. Am. J. Prev. Med. 49 (3), 409–413.
Macko, E., Weisbach, J.A., Douglas, B., 1972. Some observations on the pharmacology of mitragynine. Arch. Int. Pharmacodyn. Ther. 198 (1), 145–161.
Matsumoto, K., Horie, S., Ishikawa, H., Takayama, H., Aimi, N., Ponglux, D., Watanabe, K., 2004. Antinociceptive effect of 7-hydroxymitragynine in mice: discovery of an orally active opioid analgesic from the Thai medicinal herb Mitragyna speciosa. Life Sci. 74 (17), 2143–2155.
Matsumoto, K., Mizowaki, M., Suchitra, T., Takayama, H., Sakai, S., Aimi, N., Watanabe, H., 1996. Antinociceptive action of mitragynine in mice: evidence for the involvement of supraspinal opioid receptors. Life Sci. 59 (14), 1149–1155.
Morean, M.E., de Wit, H., King, A.C., Sofuoglu, M., Rueger, S.Y., O'Malley, S.S., 2013. The drug effects questionnaire: psychometric support across three drug types. Psychopharmacology 227 (1), 177–192.
Ponglux, D., Wongseripipatana, S., Takayama, H., Kikuchi, M., Kurihara, M., Kitajima, M., et al., 1994. A new indole alkaloid, 7 α-hydroxy-7H-mitragynine, from Mitragyna speciosa in Thailand. Planta Med. 60 (6), 580–581.
Prozialeck, W.C., 2016. Update on the pharmacology and legal status of kratom. J. Am. Osteopath. Assoc. 116 (12), 802–809.
Raffa, R.B., Pergolizzi, J.V., Taylor, R., Ossipov, M.H., NEMA Research Group, 2018. Nature's first "atypical opioids": kratom and mitragynines. J. Clin. Pharm. Ther. 43 (3), 437–441.
Rudd, R.A., Aleshire, N., Zibbell, J.E., Gladden, R.M., 2016. Increases in drug and opioid overdose deaths—United States, 2000–2014. Am. J. Transplant. 16 (4), 1323–1327.
Sabetghadam, A., Ramanathan, S., Mansor, S.M., 2010. The evaluation of antinociceptive activity of alkaloid, methanolic, and aqueous extracts of Malaysian Mitragyna speciosa Korth leaves in rats. Pharmacognosy Res. 2 (3), 181.
Singh, D., Narayanan, S., Vicknasingam, B., 2016. Traditional and non-traditional uses of Mitragynine (Kratom): a survey of the literature. Brain Res. Bull. 126, 41–46.
Siuda, E.R., Carr III, R., Rominger, D.H., Violin, J.D., 2017. Biased mu-opioid receptor ligands: a promising new generation of pain therapeutics. Curr. Opin. Pharmacol. 32, 77–84.
Smith, K.E., Lawson, T., 2017. Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. Drug Alcohol Depend. 180, 340–348.
Swogger, M.T., Hart, E., Erowid, F., Erowid, E., Trabold, N., Yee, K., et al., 2015. Experiences of kratom users: a qualitative analysis. J. Psychoactive Drugs 47 (5), 360–367.
Takayama, H., 2004. Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, Mitragyna speciosa. Chem. Pharm. Bull. 52 (8), 916–928.
Trakulsrichai, S., Sathirakul, K., Auparakkitanon, S., Krongvorakul, J., Sueajai, J., Noumjad, N., et al., 2015. Pharmacokinetics of mitragynine in man. Drug Des. Devel. Ther. 9, 2421–2429.
Váradi, A., Marrone, G.F., Palmer, T.C., Narayan, A., Szabó, M.R., Le Rouzic, V., et al., 2016. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β-arrestin-2. J. Med. Chem. 59 (18), 8381–8397.
Vicknasingam, B., Narayanan, S., Beng, G.T., Mansor, S.M., 2010. The informal use of ketum (Mitragyna speciosa) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. Int. J. Drug Policy 21 (4), 283–288.
Volkow, N.D., McLellan, A.T., 2016. Opioid abuse in chronic pain—misconceptions and mitigation strategies. N. Engl. J. Med. 374 (13), 1253–1263.
Vowles, K.E., McEntee, M.L., Julnes, P.S., Frohe, T., Ney, J.P., van der Goes, D.N., 2015. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 156 (4), 569–576.
Walsh, S.L., Nuzzo, P.A., Lofwall, M.R., Holtman Jr, J.R., 2008. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. Drug Alcohol Depend. 98 (3), 191–202.
Yue, K., Kopajtic, T.A., Katz, J.L., 2018. Abuse liability of mitragynine assessed with a self-administration procedure in rats. Psychopharmacology 235 (10), 2823–2829.

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

THE KRATOM CONSUMER PROTECTION ACT

A bill to regulate the preparation, distribution, and sale of kratom products; to prohibit the preparation, distribution, and sale of adulterated or contaminated kratom products; to prescribe fines and penalties; and to provide for the powers and duties of certain state governmental officers and entities.

Sec. 1. This act shall be known and may be cited as the "[INSERT NAME OF STATE] Kratom Consumer Protection Act".

Sec. 2. Definitions. As used in this act:

(a) "Processor" means a person that sells, prepares, manufactures, distributes, or maintains kratom products, or advertises, represents, or holds itself out as selling, preparing, or maintaining kratom products.

(b) "Food" means a food, food product, food ingredient, dietary ingredient, dietary supplement, or beverage for human consumption.

(c) "Kratom product" means a food product or dietary ingredient containing any part of the leaf of the plant Mitragyna speciosa or an extract of it; is manufactured as a powder, capsule, tablet, beverage, or other edible form; and all kratom products are foods.

(d) “Kratom Extract” means a food product or dietary ingredient containing any part of the leaf of the plant Mitragyna Speciosa that has been extracted or concentrated in order to provide more standardized product content.

(e) “Retailer” means any person that sells, distributes, advertises, represents, or holds itself out as selling or maintaining kratom products.

Sec. 3. Kratom product limitations. A processor shall not prepare, distribute, sell, or expose for sale any of the following:

(a) A kratom product that is adulterated with a dangerous non-kratom substance. A kratom product is adulterated with a dangerous non-kratom substance if the kratom product is mixed or packed with a non-kratom substance and that substance affects the quality or strength of the kratom product to such a degree as to render the kratom product injurious to a consumer.

(b) A kratom product that is contaminated with a dangerous non-kratom substance. A kratom product is contaminated with a dangerous non-kratom substance if the kratom product contains a poisonous or otherwise deleterious non-kratom ingredient, including, but not limited to, the substances listed in section [INSERT THE RELEVANT LOCATION OF THE STATE’S CONTROLLED SUBSTANCES LIST] and analogues of those substances.

(c) A Kratom Extract that contains levels of residual solvents higher than is allowed in USP 467.

(d) a kratom product containing a level of 7-hydroxymitragynine in the alkaloid fraction that is greater than 2% of the overall alkaloid composition of the product.

(e) a kratom product containing any synthetic alkaloids including synthetic mitragynine, synthetic 7-hydroxymitragynine, or any other synthetically derived compounds of the kratom plant.
(f) that does not provide labeling directions necessary for safe use by consumers, including a recommended serving size.

Sec. 4. Age limits. A processor shall not distribute, sell, or expose for sale a kratom product to an individual under [insert 18 or 21] years of age.

Sec. 5. Violations.

(a) A processor that violates section 3 is subject to an administrative fine of not more than [insert amount] for the first offense and not more than [insert amount] for the second or subsequent offense. Upon the request of a person to whom an administrative fine is issued, the director shall conduct a hearing in accordance with the [INSERT THE RELEVANT CODE SECTION].
(b) A retailer does not violate section 3 if it is shown by a preponderance of the evidence that the retailer relied in good faith upon the representations of a manufacturer, processor, packer, or distributor of food represented to be a kratom product.

Enacting section
This act takes effect [INSERT THE APPROPRIATE ENACTMENT DATE].

Kratom Science Update: Evidence-Based Facts

Jack Henningfield, PhD,[1] Marilyn Huestis, PhD,[2] Oliver Grundmann, PhD,[3] Albert Garcia-Romeu, PhD[4]

Preface

Kratom science has been increasing almost exponentially over the past decade with more than 100 new published studies addressing kratom safety, benefits, and abuse potential since early 2018. The science provides evidence to guide consumer safety leading to kratom regulations now passed into law in seven states, with many more states considering such laws. As discussed below, these new scientific findings also led the United States Department of Health and Human Services (US DHHS) to reverse its position on Controlled Substances Act (CSA) scheduling and, in August 2018, to rescind its earlier scheduling recommendation to the Drug Enforcement Administration (DEA). More recently, and with still more evidence, in 2021, the World Health Organization Expert Committee on Drug Dependence (WHO ECDD), reviewed the evidence for international scheduling and concluded that there was not sufficient evidence to recommend scheduling, meaning the available data did not show public health risks of kratom warranting international restrictions.

What is clearly needed is balanced regulation to ensure that kratom products purchased by consumers are pure and unadulterated, in other words meeting the same types of standards that apply to other food products, and even bottled water. Steps toward such standards were taken in states that passed their own versions of kratom consumer protection act laws. Ultimately, the Food and Drug Administration (FDA) needs to develop national performance standards for kratom as it does for other products. Such standards will help ensure access to kratom products that are appropriately marketed and are without contaminants and adulterants that might pose safety risks.

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Specific regulatory and policy approaches supported by new evidence.

The DHHS request to schedule kratom and mitragynine was reversed by its lead official charged with Controlled Substances Act recommendations to the DEA, namely, the Assistant Secretary of Health, Dr. Brett Giroir. Dr. Giroir requested a review of the evidence pertaining to kratom scheduling and safety, and concluded in August 2018, that the evidence did not support Schedule I placement. See a summary of the findings of the review in Dr. Giroir's formal 2018 scheduling rescission letter to the DEA at https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/60145eab6df59e7e36a7cfc1/1611947693695/dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf.

As discussed in the scheduling rescission letter, the evidence was not sufficient to support scheduling, but was sufficient to support the conclusion that many thousands of kratom consumers use kratom as a path away from opioids. This led to the public health concern that "[Scheduling would lead to] … kratom users switching to highly lethal opioids… risking thousands of deaths…". Dr. Giroir raised other concerns including that placing kratom and mitragynine in Schedule I would discourage pregnant women and others from talking to their health care providers about their kratom use, discourage research, and more.

The conclusions of the Assistant Secretary of Health were consistent with those of the National Institute on Drug Abuse (NIDA), which states on its Kratom Facts webpage that "While there are no uses for kratom approved by the FDA, people report using kratom to manage drug withdrawal symptoms and cravings (especially related to opioid use), pain, fatigue and mental health problems. NIDA supports and conducts research to evaluate potential medicinal uses for kratom and related chemical compounds." NIDA substantially expanded its kratom research support since 2017 and this research portfolio is rapidly expanding the evidence base for kratom regulation and possibly new kratom derived medicines in the years to come.

Similarly, at the international level, the large evidence base was reviewed in 2021 by the World Health Organization Expert Committee on Drug Dependence (WHO ECDD) to determine if kratom met criteria for being placed on a critical review pathway for international scheduling. The WHO ECDD came to essentially the same conclusions as had the Assistant Secretary of Health and NIDA. After conducting a thorough pre-review and a public hearing with input from leading international experts, the ECDD reported to the United Nations Office of Drug Control that there was insufficient evidence to recommend kratom for critical review but that it should be kept under surveillance. It also stated, "(k)ratom is used for self-medication for a variety of disorders but there is limited evidence of abuse liability in humans…"[i]

Addressing overdose risks, the ECDD noted: "Although mitragynine has been analytically confirmed in a number of deaths, almost all involve use of other substances, so the degree to which kratom use has been a contributory factor to fatalities is unclear." Both the Assistant Secretary, and the WHO ECDD also acknowledge beneficial uses to abstain from opioids. Without labeling this as "therapeutic use", the Assistant Secretary clearly acknowledges such use and the public health risks of banning kratom. This nuanced recognition of benefits of use, along with risks of banning access to use by Assistant Secretary Giroir, was absent in the 2017 and early 2018 position of FDA, but was since recognized by the Secretary of Health Becerra in a letter to Senator Mike Lee and Congressman Mark Pocan on March 16, 2022.[1]

What is the current state of kratom science and evidence?

Kratom has been studied for decades, primarily in Southeast Asia (SEA), where kratom trees grow in

[1] https://assets.website-files.com/61e07df312afed13238eb7f1/6261ab303b46bb88f21b6d1a_HHS%20Kratom%20Response.pdf

abundance, but research escalated substantially in the US and globally with support by NIDA, SEA countries, and philanthropies. New science over the past 5-10 years includes investigations on kratom/mitragynine chemistry and medicinal development, neuropharmacology, brain imaging, preclinical and clinical studies, and surveys in the US and SEA. The rate of published kratom research continues to increase, along with presentations and symposia at national and international scientific meetings, such as the College on Problems of Drug Dependence in June 2022 that included a kratom symposium and a clinical study report in the late breaking hot topics research sessions.

New evidence.

What is the new evidence that is so compelling to result in the Assistant Secretary's withdrawal of an earlier scheduling recommendation, and support the WHO ECDD findings accepted by the United Nations Office of Drug Control? In short, more than 100 new studies since early 2018 addressing kratom safety, abuse potential, mechanisms of action, and reasons for use, with most kratom users reporting that use is primarily motivated by health and well-being related benefits and not for recreational purposes. Much of this research was supported by NIDA and conducted in the US, but extensive additional research was conducted internationally with generally similar findings.

The following summary and conclusions are based on peer-reviewed scientific publications, many conducted by international leaders in kratom research and supported by NIDA. A bibliography with links to the articles is provided.

What is kratom?

Kratom is a tree in the coffee family. Not surprisingly, its diverse effects include coffee-like alerting, stimulating, and mood enhancing effects, which are quite distinct from the effects of morphine-type opioids. It also has some opioid-like effects that include pain relief, possible opioid withdrawal symptoms after chronic frequent use and unpleasant side effects like constipation, but without the potentially lethal respiratory depressing or highly addictive brain rewarding effects that are driving the opioid epidemic.

Is kratom an opioid?

While some naturally occurring substances in kratom act on opioid receptors, kratom is not a prototypical opioid based on its chemical structure, botanical origins, or law – nationally or internationally. Like many natural products it has diverse effects and mechanisms of action that contribute to these effects and the reasons people use kratom. Some kratom constituents bind to opioid receptors and relieve pain whereas others do not. Unlike opioids which sedate and can impair mental functioning, kratom is used by many people in place of coffee for its alerting, mental focusing, and occupational performance enhancing effects. Animal and human studies, as well as neuropharmacology mechanisms of action studies, show that kratom does not carry the substantial opioid-like risks of deadly respiratory depression or powerfully addictive euphoria. A misunderstanding of one of kratom's self-reported beneficial uses, recognized by researchers and NIDA, providing relief of opioid withdrawal, is sometimes interpreted as evidence that it must be an opioid. In fact, the nonopioid adrenergic blocking drugs developed for treating high blood pressure, clonidine and lofexidine, were prescribed for decades to treat opioid withdrawal. FDA approved lofexidine (Lucemyra) for treating opioid withdrawal in 2018. Mitragynine and other kratom constituents also produce adrenergic effects.

Who uses kratom and why?

According to surveys in the US, most consumers report are White adults, aged 35-55, with jobs and health care insurance, who report that their consumption is primarily for health and well-being. This includes consumption as an alternative to caffeinated products for alertness and increased focus, for the self-management of pain, and to improve mood. Many consumers state that kratom worked better for them, had fewer side-effects than the FDA-approved medicines that had been taken, and/or that they preferred natural products. A

smaller but especially important fraction of consumers are people who consider kratom as a "life-line" or a path away from opioids. They use kratom to manage opioid withdrawal and reduce or eliminate opioid use.

What led to increased kratom use in the United States?

Although kratom has been taken as a natural traditional medicine in SEA for centuries, its use in the US was largely limited to Asian immigrants from the early 1970s through the 1990s. In the early 2000s, with a rising general interest in natural products as alternatives to conventional medicines and growing public access to information via the Internet, kratom use began to increase. Reasons for use appear generally similar from the US to SEA; as an alternative to coffee and tea for its alerting and mild stimulant effects, to improve mood and relieve pain, and to manage withdrawal and help people to reduce or discontinue use of opioids, alcohol and other addictive substances. Many survey respondents report that kratom was either more effective, carried fewer side effects of concern such as the sedating effects of opioid pain relivers, and/or that they prefer natural products over conventional medicine. Estimates of the present market vary widely. By 2014, there were an estimated 3-5 million kratom consumers, and marketing and SEA export estimates suggest that the present market is 15 million or more in the US. One federal survey estimated between 2-3 million kratom consumers, which might reflect its panel of respondents. The federal survey is designed to track substance abuse and might underrepresent middle aged and older people with lower rates of recreational substance use who might use kratom for other reasons.

Does kratom contain dangerous substances?

Like its botanical cousin coffee, kratom contains many substances referred to as alkaloids, which tend to be somewhat alkaline and bitter in flavor. More than 40 alkaloids are identified in kratom to date, with most having little or no known pharmacological effect, or occurring at such low levels as to be of little cause for harm or benefit. However, as is the case with other natural products, the naturally occurring mixture of substances likely contributes to the overall effects and natural variations in alkaloid composition may lead to varying pharmacological effects. The main ingredient currently thought to account for most of the effects reported by kratom consumers is mitragynine, which does not have strong rewarding and addictive effects, nor respiratory depressant effects like opioids and conventional stimulants.

The second most widely recognized substance is 7-hydroxymitragynine that has stronger opioid effects but occurs at non-detectable levels in fresh kratom leaves. However, 7-hydroxymitragynine is also a product of mitragynine metabolism. In the absence of kratom regulation, some kratom makers boosted 7-hydroxymitragynine content far higher than that found in the native plant material. States passing kratom consumer protection act laws ensure that legally marketed kratom does not contain boosted 7-hydroxymitragine levels, contaminants, or other adulterants, thereby reducing public health risks. Additionally, dangerous substances like fentanyl, heroin, and morphine were found in adulterated kratom products, and these can be harmful. Regulation is needed from FDA to ensure that all US consumers are protected from risky exposure to contaminated or adulterated products.

Respiratory effects of kratom.

It is well understood that kratom's respiratory effects are not like those of morphine-like opioids; however, studies since 2018 support the conclusion that kratom is not simply weaker than opioids with respect to respiratory depression. Specifically, mitragynine and other alkaloids in kratom act as partial agonists at opioid receptors, meaning that their maximal effects reach a ceiling beyond which higher doses produce little additional effect.[ii] This was demonstrated in several animal species (including cats, dogs, mice, and rats) with mitragynine doses increased to levels far beyond what is or can be consumed by even high intake

chronic kratom consumers. The most recent study employed a sophisticated rodent model developed by FDA to compare a broad range of mitragynine doses to therapeutic and toxic oxycodone doses across blood gases and other parameters. Whereas oxycodone produced the signature dose-related plummeting blood oxygen levels and deaths, mitragynine produced no evidence of respiratory depression at any dose, and no life-threatening effects.

Can you overdose on kratom?

It is possible that kratom contributed to some deaths occurring in kratom consumers but the overall risk appears at least 1,000 times lower for kratom as compared to opioids. There were no deaths in which either the FDA or CDC confirmed as appropriately categorized as due to kratom consumption, though the possibility cannot be ruled out. Kratom consumers should not assume that kratom is without risk. Nonetheless, the CDC did not list kratom as a cause of any of the more than one hundred and eight thousand drug overdose deaths in 2021, or in any other year of which we are aware. In contrast, opioids were concluded by the CDC and NIDA to account for more than 80,000 overdose deaths in 2021. Overdose is possible with many readily available consumer substances, including caffeine, but kratom's most common side-effect, transient stomach upset and nausea, also limits intake and is discomforting but not seriously harmful. In February 2018, after announcing that kratom carried opioid-like death risk, the FDA noted that only one of 44 deaths occurring in kratom consumers did not involve other respiratory depressing substances. Further investigation found that the final cause was a motor vehicle fatality involving a kratom consumer.

In fact, NIDA, FDA, US DHHS, and WHO ECDD all concluded that most kratom-associated deaths involved other substances. This is also true in SEA where scientists' conclusions were similar to those of the US Assistant Secretary of Health, Dr. Brett Giroir. As summarized by Dr. Giroir in the previously mentioned 2018 DHHS scheduling rescission letter, "There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses."

Is kratom fueling the opioid overdose epidemic?

The US has the world's most sophisticated and multi-pronged substance abuse and product safety monitoring network detecting signals of gateway drug use and ways in which one substance may contribute to the abuse and risks of another. US monitoring systems include the National Survey on Drug Use and Health (NSDUH), Monitoring the Future (MTF), Treatment Episodes Data Set, and the DEA's National Forensic Laboratory Information System (NFLIS). It also includes the Drug Abuse Warning Network (DAWN) which reported a variety of potential signals of emerging substance threats while kratom use was rapidly increasing from the 1990s through its pre-2012 reports, as well as the "new" DAWN system that reported on 2021 data in its 2022 report. None of these systems, nor more than 20,000 comments to the DEA, suggested that kratom contributed to the opioid epidemic. Kratom was also never listed in DEA's annual National Drug Threat Assessment, though DEA routinely monitors kratom as a "chemical of concern" Despite over 10 years of monitoring, DEA has not listed kratom or mitragynine or 7-hydroxymitragynine as a national drug threat.

Key scientific findings in the past five years:

- Multiple state of the art animal studies found that kratom has low abuse potential. For example, mitragynine produces weaker rewarding effects compared to morphine and heroin. The authors of this fact sheet urge that as a precaution, consumers should monitor their kratom consumption to reduce the risk of dependence development.

- Surveys indicate that some people can become dependent upon kratom; however, many of

these people were using kratom to abstain from opioids and/or other substances. Disentangling prior substance use disorders from kratom is not always clear. Most people who report kratom dependence or withdrawal state that it is more readily self-manageable than dependence and withdrawal from opioids and other drugs of abuse.

- Mitragynine treatment results in reduced opioid (e.g., morphine and heroin) drug seeking and self-administration in animal models assessing the potential effectiveness of drug use disorder reduction and cessation. These findings are consistent with human reports that kratom consumption reduces their opioid cravings and served as a path away from opioids.

- In animals made physically dependent on morphine, kratom pretreatment reduced morphine withdrawal symptoms in several models for evaluating efficacy in the treatment of withdrawal. This is consistent with human reports that kratom consumption helps to manage opioid withdrawal and reduce opioid craving.

- Similarly, an intracranial brain self-stimulation study suggested low rewarding effects of kratom alkaloids as compared to drugs of abuse.

- Several national internet surveys found that kratom use was helpful in managing opioid withdrawal, reducing opioid cravings, and achieving abstinence from opioids.

- None of the national surveys relied upon by the FDA, Centers for Disease Control (CDC), NIDA, and DEA to determine if a substance poses an abuse-related threat to public health suggested that kratom poses a known or imminent risk to public health. Consistent with this, the DEA never listed kratom as a threat to public health in its annual National Drug Threat Assessment reports.[iii]

- Safety studies in several animal species demonstrated that even at extraordinarily high doses, mitragynine and kratom produced little evidence of respiratory depression or life-threatening effects in contrast to opioids such as morphine and oxycodone which produced substantial dose related decreases in respiration.

Disclosure:

Through Pinney Associates, Drs. Henningfield and Huestis provide scientific and regulatory advising on new medicines, dietary supplements, cannabinoids, and tobacco/nicotine products for FDA regulation. This paid work includes leading the development and drafting of this kratom science facts summary for the American Kratom Association. Dr. Grundmann is a member of the advisory board of the Kratom Vendors Association and has received an honorarium from the American Kratom Foundation for participation in a scientific discussion forum about kratom dependence. Dr. Garcia-Romeu is a paid scientific advisor to ETHA Natural Botanicals and has received a speaking honorarium from the American Kratom Foundation.

Annotated Bibliography

Expert evaluations of kratom policy and regulation and risks & public health

United Nations Commission on Narcotic Drugs, WHO Expert Committee on Drug Dependence (2021). Implementation of the international drug control treaties: changes in the scope of control of substances Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD), 11–15 October 2021: Kratom, mitragynine, 7-hydroxymitragynine. https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf. *Note: This is a summary of the WHO Expert Committee on Drug Dependence pre-review of kratom concluding that the evidence does not support initiation of a full review of kratom for international drug scheduling considering its effects, safety, abuse related- risks and public health factors.*

Assistant Secretary of Health Dr. Brett P. Giroir, Admiral (August 16, 2018). Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to rescind previous support to permanently place mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2018 [Available from: https://images.go02.informamarkets.com/Web/Informa02/%7b548e6d56-2ea4-4da4-9404-0348b56e9a88%7d_dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf. *Note: This formal DHHS scheduling rescission letter summarizes review of the evidence for FDA's 2017 recommendation to schedule kratom and concluded that FDA did not provide sufficient evidence to support scheduling, and also failed to consider the adverse public health consequences of Scheduling and thereby banning legal consumer access to kratom.*

Prozialeck, W., Avery, B., Boyer, E., Grundmann, O., Henningfield, J., Krueger A., McMahon, L., McCurdy, C., Swogger, M., Veltri, C., and Singh, D. (2019). Kratom Policy: The challenge of balancing therapeutic potential with public safety. International Journal of Drug Policy, 70:70–77. *Note: Leading kratom researchers discuss policy implications of state-of-the-art knowledge related to kratom's effects, uses, risks, and real-world public health benefits and risks.*

Swogger MT, Smith KE, Garcia-Romeu A, Grundmann O, Veltri CA, Henningfield J, Busch LY (2022) Understanding kratom use: a guide for healthcare providers. Front Pharmacol 13:801855. *Although there are no FDA approved uses for kratom, which is the case for most dietary supplements, this expert opinion article provides practical information for consideration by health care professionals whose patients are consuming kratom.*

Henningfield JE, Grundmann O, Babin JK, Fant RV, Wang DW, Cone EJ (2019) Risk of death associated with kratom use compared to opioids. Prev Med. 128:105851. *Note: This article compared estimates from FDA of deaths associated with kratom consumption in comparison with deaths associated with nonmedical opioid use concluding that the risk of death associated with kratom use is at least 1,000 times less than for opioids.*

Henningfield JE, Wang DW, Huestis MA (2022) Kratom abuse potential 2021: an updated eight factor analysis. Front Pharmacol 12:775073. *Note: This article is a published version of an assessment of kratom abuse potential according to the 8-factor analysis required for permanent scheduling by the Controlled Substances Act. It concludes that on the basis of all factors, including decades of surveillance in the US, and decades more globally, kratom does not warrant scheduling and, in fact, that scheduling kratom would carry adverse public health consequences. This is consistent with the position of the WHO Expert Committee on Drug Dependence and the DHHS review led by Assistant Secretary Giroir.*

Kratom reasons for use surveys

Note: Whereas there are several surveys that provide estimates of how many people use kratom with estimates ranging from about 2 to more than 15 million, those surveys provide no information about why people use kratom, or the consequence of their kratom use (See Henningfield JE, Grundmann O, Garcia-Romeu A, Swogger MT. We Need Better Estimates of Kratom Use Prevalence. Am J Prev Med. 2022;62(1):132-133). The following surveys are focused on why people use kratom and provide insights as to the risks and benefits of kratom consumption. Specifically, these surveys show that although there is some recreational use of kratom, most people use for reasons related to health and well-being including as approaches to self-manage opioid and other drug withdrawal and to reduce and discontinue opioid and other addictive drug use.

Coe MA, Pillitteri JL, Sembower MA, Gerlach KK, Henningfield JE. Kratom as a substitute for opioids: Results from an online survey. Drug Alcohol Depend. 2019;202:24-32.

Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RR. Kratom (Mitragyna speciosa): User demographics, use patterns, and implications for the opioid epidemic. Drug Alcohol Depend. 2020;208:107849.

Grundmann O. Patterns of Kratom use and health impact in the US-Results from an online survey. Drug Alcohol Depend. 2017;176:63-70.

Smith KE, Rogers JM, Dunn KE, et al. Searching for a Signal: Self-Reported Kratom Dose-Effect Relationships Among a Sample of US Adults With Regular Kratom Use Histories. Front Pharmacol. 2022;13:765917.

Smith KE, Rogers JM, Schriefer D, Grundmann O. Therapeutic benefit with caveats?: Analyzing social media data to understand the complexities of kratom use. Drug Alcohol Depend. 2021;226:108879.

Swogger MT, Walsh Z. Kratom use and mental health: A systematic review. Drug Alcohol Depend. 2018;183:134-40.

Kratom abuse potential and assessment for treatment of dependence and withdrawal

Note: The following studies found that mitragynine is characterized by low abuse potential in classic models as compared to morphine and heroin. The Hemby et al. and Yue et al. studies also showed that mitragynine administration led to decreases in morphine and heroin self-administration, which is consistent with survey reports that kratom helps relieve opioid craving and discontinuation of opioid use. Hassan et al. is one of several recent studies demonstrating that (a) mitragynine withdrawal is less severe than morphine withdrawal, and (b) mitragynine provides effective relief of opioid withdrawal, which is a common use of kratom that is acknowledged by NIDA and claimed by many kratom consumers in the surveys of why people use kratom. Wilson et al. demonstrates that a kratom tea like preparation was of relatively low risk and effective at reducing opioid withdrawal symptoms. It is also important to note that animal studies of single substances such as mitragynine cannot be interpreted as showing that kratom has no abuse or dependence potential – it does carry some abuse and dependence risk in humans as documented in the surveys, but these appear relatively low for most consumers as compared to opioids. These studies are also contrary to FDA's 2017 claims that mitragyine carried narcotic opioid like risks.

Behnood-Rod A, Chellian R, Wilson R, Hiranita T, Sharma A, Leon F, et al. Evaluation of the rewarding effects of mitragynine and 7-hydroxymitragynine in an intracranial self-stimulation procedure in male and female rats. Drug Alcohol Depend. 2020;215:108235.

Hassan R, Pike See C, Sreenivasan S, Mansor SM, Müller CP, Hassan Z. Mitragynine attenuates morphine withdrawal effects in rats-a comparison with methadone and buprenorphine. Front Psychiatry. 2020;11:411.

Hemby SE, McIntosh S, Leon F, Cutler SJ, McCurdy CR. Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. Addict Biol. 2019;24(5):874-85.

Yue K, Kopajtic TA, Katz JL. Abuse liability of mitragynine assessed with a self-administration procedure in rats. Psychopharmacology (Berl). 2018;235(10):2823-9.

Wilson LL, Harris HM, Eans SO, Brice-Tutt AC, Cirino TJ, Stacy HM, et al. Lyophilized kratom tea as a therapeutic option for opioid dependence. Drug Alcohol Depend. 2020;216:108310.

Kratom pharmacology studies help understand its effects that contribute to reasons for use and safety

Note: The following studies are representative of several dozen other studies published since 2018 that help understand the effects, and potential benefits and risks of kratom's constituents including mitragynine. At kratom doses far higher than those consumed by humans, respiratory depressant effects are substantially lower than opioids. This does not mean that kratom does not carry risks but rather that its overall risks appear lower than those associated with drugs such as opioids that kratom substitutes for. Balanced regulation could help consumers minimize the risks of kratom use by banning medical claims, providing accurate labeling and warning labels, as is being implemented in states that passed kratom consumer protection act laws.

Avery BA, Boddu SP, Sharma A, Furr EB, Leon F, Cutler SJ, et al. Comparative pharmacokinetics of mitragynine after oral administration of Mitragyna speciosa (kratom) leaf extracts in rats. Planta Med. 2019;85(4):340-6.

Chakraborty S, DiBerto JF, Faouzi A, Bernhard SM, Gutridge AM, Ramsey S, et al. A novel mitragynine analog with low-efficacy mu opioid receptor agonism displays antinociception with attenuated adverse effects. J Med Chem. 2021;64(18):13873-92.

Hill R, Kruegel AC, Javitch JA, Lane JR, Canals M. (2022) The respiratory depressant effects of mitragynine are limited by its conversion to 7-OH mitragynine. Br J Pharmacol. 179(14):3875-3885.

Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. Neuropharmacology. 2018;134(Pt A):108-20.

Macko E, Weisbach JA, Douglas B (1972) Some observations on the pharmacology of mitragynine [in cats, dogs and monkeys]. Arch Int Pharmacodyn Ther 198(1):145.

Maxwell EA, King TI, Kamble SH, Raju KSR, Berthold EC, Leon F, et al. Pharmacokinetics and safety of mitragynine in beagle dogs. Planta Med. 2020;86(17):1278-85.

Obeng S, Kamble SH, Reeves ME, Restrepo LF, Patel A, Behnke M, Chear NJ, Ramanathan S, Sharma A, León F, Hiranita T, Avery BA, McMahon LR, McCurdy CR. Investigation of the Adrenergic and Opioid Binding Affinities, Metabolic Stability, Plasma Protein Binding Properties, and Functional Effects of Selected Indole-Based Kratom Alkaloids. J Med Chem. 2020 Jan 9;63(1):433-439.

Obeng S, Wilkerson JL, Leon F, Reeves ME, Restrepo LF, Gamez-Jimenez LR, et al. Pharmacological comparison of mitragynine and 7-hydroxymitragynine: In vitro affinity and efficacy for mu-opioid receptor and opioid-like behavioral effects in rats. J Pharmacol Exp Ther. 2021;376(3):410-27.

Sharma A, McCurdy CR. Assessing the therapeutic potential and toxicity of Mitragyna speciosa in opioid use disorder. Expert Opin Drug Metab Toxicol. 2021;17(3):255-7.

Vicknasingam B, Chooi WT, Rahim AA, Ramachandram D, Singh D, Ramanathan S, et al. Kratom and pain tolerance: A randomized,

placebo-controlled, double-blind study. Yale J Biol Med. 2020;93(2):229-38.

Chakraborty S, DiBerto JF, Faouzi A, Bernhard, SM, Guttridge, AM, Ramsey, S et al.(2021). A Novel Mitragynine Analog with Low-Efficacy Mu Opioid Receptor Agonism Displays Antinociception with Attenuated Adverse Effects. J Med Chem. 2021;64(18):13873-13892.

McCurdy C, Grundmann O, McLaughlin J (2020) Kratom Resources. Department of Pharmacodynamics, College of Pharmacy, University of Florida. https://pd.pharmacy.ufl.edu/research/kratom/. Accessed 8 March 2022. *Note: this is a living and evolving repository of factual scientific information that may be useful to policy makers, regulators, consumers, and other researchers. It is an example of what would ideally be provided by NIH and FDA*.

[i] Neither the US Food Drug and Cosmetic Act, nor the US CSA or the international drug control treaties define "therapeutic use" as being approved as drugs by FDA or the equivalent regulatory agencies in other countries. However that has become the de facto standard of the FDA, which therefore ignores self-reported beneficial use by dietary supplement consumers and states that they have no recognized therapeutic use, and thus, widespread use of kratom to stay off opioids was ignored as a benefit. The authors of this science update and the American Kratom Association agree that specific health claims should not be made by kratom marketers without supporting evidence, but neither should policy makers simply dismiss the benefits of kratom and the risks of removing licit kratom by millions of kratom consumers.

[ii] Contributing to the misunderstanding that kratom carries opioid-like risks of overdose and addiction is a misunderstanding of potency and strength. Strength refers to the maximum effect that a substance can produce, whereas potency refers to how much of the substance it takes to produce a given effect. Thus, alcohol is strong and actually results in approximately 2,000 overdose deaths annually in the US, however, it is relatively low in potency among central nervous system active substances and requires the equivalent rapid consumption of a quart or more of high percentage (proof) alcohol to produce death, though for young people it may take much less as suggested by fraternity hazing related deaths every year in the US. At the other extreme is fentanyl which can produce extremely strong euphoriant effects in humans, reinforcing effects in animals, and lethal respiratory depressant effects at very low doses of just a few mg. Kratom's primary active alkaloid, mitragynine is both relatively weak and low in potency with respect to respiration as compared to morphine. In fact, it is a partial agonist with respect to respiratory depression, meaning that its maximal effects at all tested doses do not produce lethal respiratory depression. The mitragynine metabolite 7-hydroxymitragynine is more potent than morphine on the guinea pig ileum muscle twitching test but that test is not necessarily relevant to lethality, and 7-hydroxymitragynine, also appears to be a partial agonist with respect to its respiratory effects.

[iii] DEA has included kratom on its list of "drugs and chemicals of concern", for the past decade, first listing it following reports of overdose deaths in Sweden among consumers of a kratom product that was later concluded to have been adulterated with lethal doses of O-desmethyltramadol. However, as mentioned in this science update, DEA never listed kratom as a threat to public health in its annual National Drug Threat Assessment reports. In fact, it has not listed kratom in its annual National Forensic Laboratory Reports since 2016, apparently, because the reports have remained low and not at the "threshold for reporting." Whether and when DEA will remove kratom or kratom alkaloids from its drugs and chemicals of concern list is not clear since researchers agree that kratom use and epidemiology should continue to be monitored, but unfortunately, this listing implies a higher level of concern than has been expressed by any other DEA action since it withdrew its scheduling proposal in 2016.

Kratom Misinformation in Medical Journals

Heidi Sykora DNP, GNP-BC

Kratom is a natural plant growing in southeast Asia that has been used by the local population for hundreds of years for pain and anxiety relief. The plant is a combination of alkaloids working together to provide the desired effect. The use of Kratom in the United States has become popular as an alternative to opioids for pain relief and as a reported safer alternative for those with opioid addictions.

Despite the reported health benefits and potential lifesaving alternative to opioids, misinformation in published peer-reviewed medical journals and online health sources abound. The types of misinformation fall into three general categories: Online health information with references that do not support the actual content and conclusions of the references cited, medical journal titles and abstracts that disingenuinely summarize the content and conclusions of the article, and Journal articles that draw conclusions not supported by the facts presented in the article.

The following are examples of each of the above types of misinformation:

An example of the first category of misinformation is from the Mayo Clinic Consumer Health Information online, Kratom: Unsafe and ineffective - Mayo Clinic. For example, this article lists many side effects that are not supported by any of the references listed. The article provides nothing but misinformation from the title and the content their claims regarding Kratom are unsubstantiated and false. In addition, there is no author(s) listed.

An article by Nelsen JL, et.al., "Seizure and coma following Kratom (Mitragynina speciosa Korth) exposure" is an illustration of an article title and abstract that disingenuinely summarizes the content and conclusions of the article. The content of this article states that the patient's drug screen was positive for multiple other substances including Datura, yet the article title and abstract only mentions kratom. The authors acknowledge this in the content of the article by stating…" it remains a leap to infer there is causality based on an association."

Castillo et al, "Posterior reversible leukoencephalopathy syndrome after kratom ingestion,"
Is an example of a journal article that draws conclusions not supported by the facts presented in the article. This article states, "His drug screen was positive for amphetamine, benzodiazepine (lorazepam given in local emergency room), cannabinoids, and opiates (morphine given in local emergency room). His urine was **not** tested for kratom." The patient tested positive for multiple other substances that might explain his symptoms yet the title and abstract mention kratom alone. In fact, the article doesn't provide any evidence or report that the patient took kratom. This is obviously very deceptive.

Despite all the rhetoric in the media regarding medical misinformation there is no accountability to hold authors liable for their egregious lies regarding kratom.

I implore all representatives of the people of Wisconsin and other states to pass the Kratom Consumer Protection Act to protect the safe and effective use of kratom.

References:

Austin Castillo, BS, J. Drew Payne, DO, and Kenneth Nugent, MD. Proc (Bayl Univ Med Cent) 2017;30(3):355–357.

Castillo A, et al. Posterior reversible leukoencephalopathy syndrome after kratom ingestion. Baylor University Medical Center Proceedings. 2017;30:355.

Nelsen JL, Lapoint J, Hodgman MJ, Aldous KM. Seizure and coma following Kratom (Mitragynina speciosa Korth) exposure. J Med Toxicol. 2010 Dec;6(4):424-6. doi: 10.1007/s13181-010-0079-5. PMID: 20411370; PMCID: PMC3550469.

Kratom Abuse Potential by the Eight Factors of the Controlled Substances Act: Latest Science and Public Health Findings

Jack E. Henningfield, PhD

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

and

Professor, Adjunct, Behavioral Biology, Department of Psychiatry and Behavioral Sciences,
The Johns Hopkins University School of Medicine

Former Chief, Clinical Pharmacology Research Branch
and Biology of Dependence & Abuse Potential Section
National Institute on Drug Abuse, National Institutes of Health (NIDA, NIH)

For Presentation at the Wisconsin Controlled Substances Board Meeting
Regarding the Legislature Agenda Request: Status of Kratom
Meeting on November 11, 2022, at 9:30 a.m. in N133 and N134,

Disclosure & Experience

50 years experience in scientific studies of the abuse and dependence potential of substances and drugs and their appropriate regulation, nationally and internationally.

My NIDA work included representing NIDA in CSA scheduling determinations with FDA and DEA.

At PinneyAssociates, my focus is pharmaceutical abuse potential assessments for FDA filings addressing a broad range of pharmaceutical products, dietary supplements, cannabinoids, kratom, and noncombustible tobacco/nicotine products for FDA regulation. This includes advising the American Kratom Association on kratom science and abuse potential assessment.

Basis for Conclusions and Recommendations

1. ***More than 100 abuse potential related studies in the past 5 years***, largely supported by NIDA, with many studies by the University of Florida, Columbia University, Malaysia Center for Drug Research, and more recently commercially sponsored safety and abuse related research for kratom products and potential mitragynine analogs for new medicines development
2. ***Regular meetings with other global kratom research leaders***, e.g., June 2022 College on Problems of Drug Dependence, and virtual meeting, as well as collaborations with researchers worldwide
3. ***Evaluations by the Assistant Secretary of Health, charged with US DHHS scheduling recommendations to DEA (2018), and the WHO Expert Committee on Drug Dependence*** **for international drug control convention scheduling actions (2021).**
4. **Kratom has never been included in DEA Annual National Drug Threat Assessment Reports**
5. ***See summary in October 2021 Kratom Science Update (Henningfield, Huestis, Grundman & Garcia-Romeu)*** for the American Kratom Association. This includes recent peer-reviewed publications and reviews including the 2022 kratom 8-Factor Analysis published in Frontiers in Pharmacology (Henningfield, Wang & Huestis, 2022) and an annotated bibliography. All articles are available online and I can provide them on request.

Eight Factors of the Controlled Substances Act

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.

Factors 4, 5 & 6 are determinative of "known or imminent public health threat" used to justify temporary/"emergency" scheduling and "permanent" scheduling

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. Note: This is a factual or administrative determination based on prior scheduling actions and chemical structures and synthesis of the substances. – ***Note: Neither kratom nor any of its alkaloids or metabolites are opioids, previously scheduled substances, or precursors of controlled substances***

Kratom Alkaloid Facts

Is kratom an opioid? No. Not by nature, chemistry, pharmacology, typical use or safety, or by the CSA or International Drug Control Conventions. Kratom does not have the two main effects that account for the US opioid crisis: powerful addicting euphoria and deadly respiratory depressant effects

Mitragynine is the main kratom constituent that accounts for kratom's effects including caffeine-like alerting effects and also pain-relieving and mood enhancing effects. Other substances that vary by strain, growing conditions and other effects may contribute to the kratom experience as is the case for coffee and tea***. Nonopioid actions (possibly alpha adrenergic like lofexidine [1st nonopioid approved for opioid withdrawal relief] may contribute to or possibly primarily mediate kratom's opioid withdrawal relieving effects)***

7-hydroxymitragynine (7OHMG) occurs at very low levels that do not appear to directly substantially contribute to the effects of natural kratom. 7OHMG is a mitragynine metabolite that gradually occurs in the body and likely contributes to kratom's effects but without apparent safety risks. It is important to regulate kratom to prevent product adulteration by spiked or boosted 7OHMG levels

International: Commission on Narcotic Drugs, 2021

Summary of recommendations of the 44th October 2021, WHO Expert Committee on Drug Dependence (ECDD), on kratom

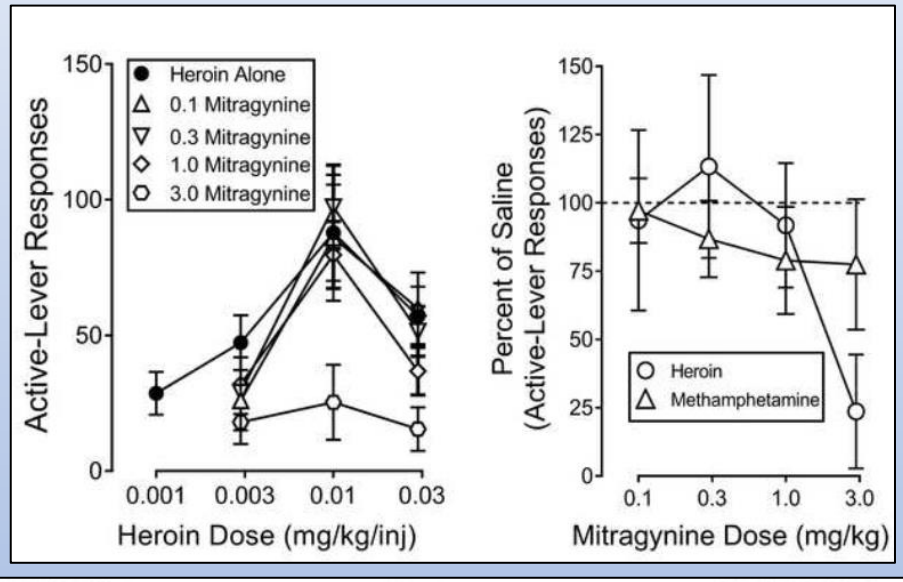
Therapeutic usefulness & public health was a consideration: People report using kratom to self-medicate a variety of disorders and conditions, including pain, opioid withdrawal, opioid use disorder, anxiety and depression. Kratom is being used as a part of traditional medicine in some countries

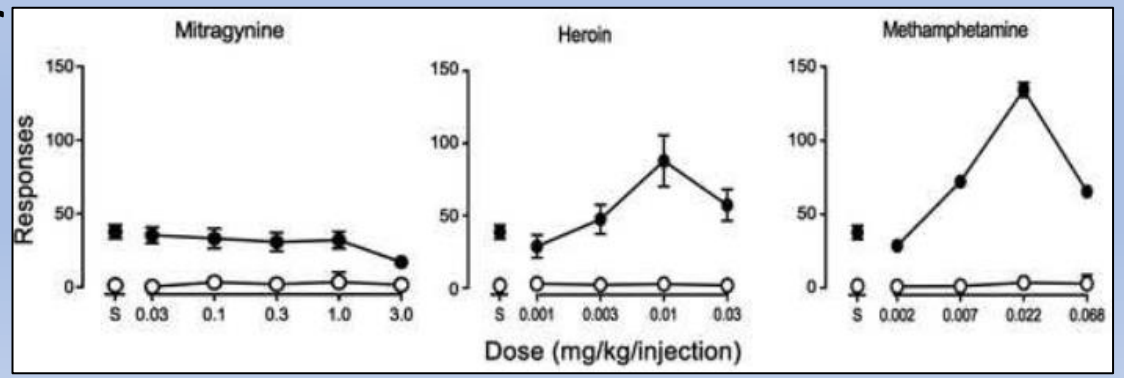
Conclusion: The Committee concluded that there is insufficient evidence to recommend a critical review (i.e., scheduling pathway) of kratom, MG, or 7OHMG

Recommendation: The Committee recommended kratom, MG, and 7OHMG be kept under surveillance by the WHO Secretariat and NOT scheduled in the international treaties (1961 Single Drug or 1971 Psychotropic)

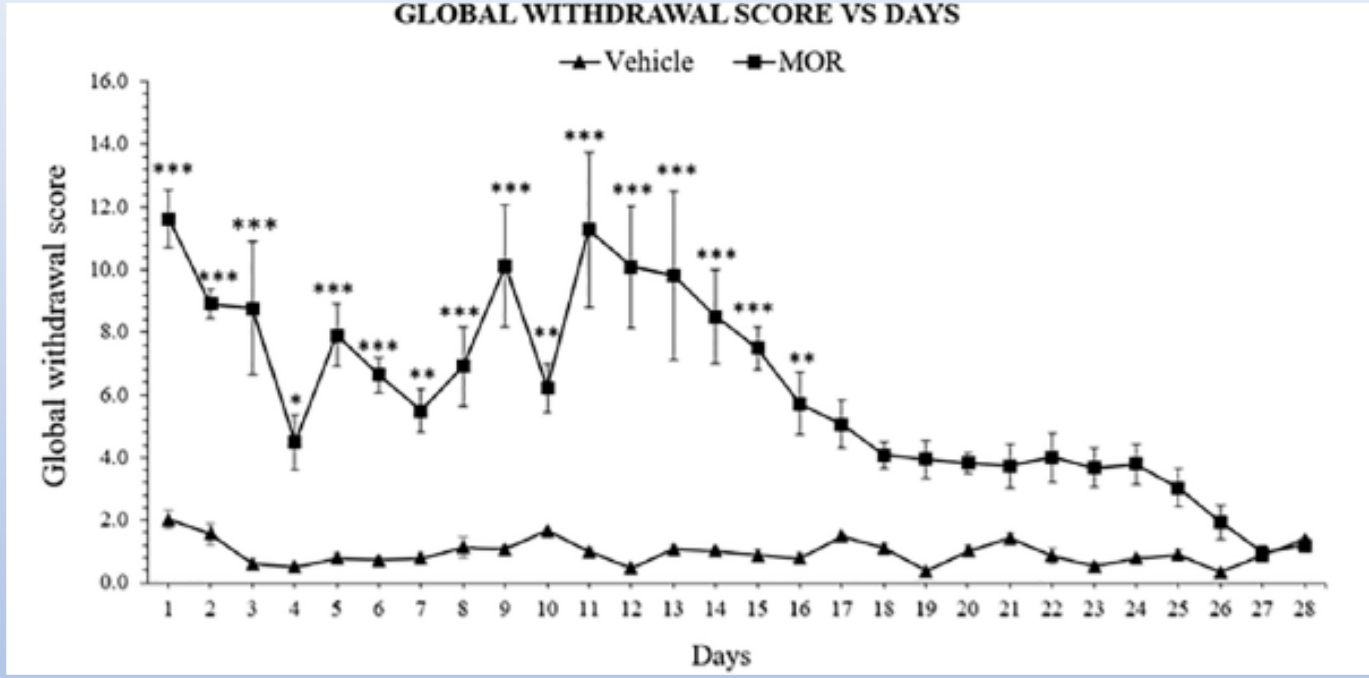
Abuse Liability of Mitragynine Assessed with a Self-Administration Procedure in Rats (Yue, Kopajtic & Katz, 2018-Collaboration of NIDA IRP with Jianghan University, China)

CONCLUSIONS: No rewarding effects by mitragynine compared to heroin or methamphetamine: "The present study suggests that mitragynine has limited abuse liability from the perspective of self-administration procedures….[and]…it appears at present that mitragynine is deserving of more extensive exploration for the development of a therapeutic use for treating opioid abuse."





Animal Studies Confirm Kratom and Mitragynine's Potential to Relieve Opioid Withdrawal (Hassan, See, Sreenivasan et al., 2020 - Malaysia CDR)



Conclusion: Weak withdrawal from kratom compared to morphine and *"Four-day replacement treatment with mitragynine attenuated morphine withdrawal symptoms significantly, suggesting that mitragyine is able to reduce morphine withdrawal symptoms similarly to methadone and buprenorphine"* (p.9)

Recent Comparison of Mitragynine Respiratory Effects following FDA Model by Xu et al. 2020 & 2021

Henningfield, Magnuson, Rodricks & Huestis, Oct. 2022 Psychopharmacology:
Respiratory Effects of Oral Mitragynine and Oxycodone in a Rodent Model

First study employing FDA model for comparing the respiratory effects of substances singly and in combination to oral oxycodone using FDA's doses, measures, and basic protocol. We evaluated 5 MG doses from 20 mg/kg (high Human Equivalent Dose) to 400 mg/kg (maximum oral dose based on solubility and ethical limitation of volume per gastric administration).

Oxycodone produced expected dose-related plummeting blood oxygen, and strong behavioral effects including deaths.

MG did not produce dose-related effects on any blood gas measures or life-threatening effects. Transient locomotor impairment was observed at 400 mg/kg.

Extends earlier findings in dogs, mice, monkeys & rats.

Note: The study results were presented to the FDA model development team (Xu et al.) and NIDA leadership before presentation at meetings, submission for publication or shared with the sponsor, AKA. AKA provided unrestricted funding for the study that the authors independently conceived, designed, evaluated and published. Mountain West Research did the study and iC42 Bioanalytics at the University of Colorado did the bioanalytics (led by Prof. Uwe Christians)



Absence of Withdrawal Symptoms After Stopping 14 Daily Kratom Leaf, Extract or Mitragynine Isolate Doses in a Controlled Clinical Study

Late Breaking Session,
College on Problems of Drug Dependence, Minneapolis, MN

Marilyn Huestis[1], Jack Henningfield[2], Dan Wang[2] & Ramsey Atallah[3]
[1]Thomas Jefferson University, [2]PinneyAssociates, [3]NP Biotech, LLC

Phase I Study of the Safety, Tolerability & Pharmacokinetics of Three Kratom Formulations

- Escalating single & repeated (14 days) oral doses of kratom leaf powder, leaf extract & MG isolate (3-4 doses of each formulation)
- 30 clinical site visits per kratom naïve healthy adult (n=198), 47 days
- Key endpoints:
  - Adverse events, blood gases & laboratory assessment of clinical chemistry (including liver & kidney function) & hematology
  - Clinical Opiate Withdrawal Scale (COWS) by clinician & Subjective Opiate Withdrawal Scale (SOWS) self-administered by participant
  - Mitragynine & 7-OH-mitragynine pharmacokinetics
  - Drug effect questionnaire
- **Findings: No evidence of abuse potential or withdrawal**
- **PK, including MG and 7OHMG analyses, are underway**
- **Extends Vicknasingam et al. (2020) COWS & SOWS findings at higher doses in cold pressor test evaluation of MG**

Abuse Potential & Scheduling Relevant Main Conclusions

- Kratom/MG is not appropriately characterized as an “opioid” by nature, chemistry, pharmacology, or by the US CSA or International Drug Conventions
- Animal behavioral pharmacology is generally consistent with human reports suggesting low reinforcing effects, less severe withdrawal than morphine, and by therapeutic potential for Opioid Used Disorder and Opioid Withdrawal
- MG and 7OHMG do not have opioid-like respiratory effects but respiratory depression in combination with other substances or disease conditions, and adulterated products cannot be ruled out. Users should not assume “no risk”. Regulation is needed to provide product standards, labeling, and warnings
- Kratom “dependence” and withdrawal can occur in heavy chronic use but appears most likely in people with prior opioid use – more research is needed
- As concluded by 2018 US DHHS & 2021 WHO ECDD, surveys do not indicate an imminent public health threat, e.g., considered by Factors 4, 5 & 6
- Taken together, the evidence does not meet the 8-factor criteria for scheduling

AUG 16 2018

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

Dear Mr. Dhillon:

Pursuant to the Controlled Substances Act (CSA), 21 U.S.C. § 811, I am rescinding our prior recommendation dated October 17, 2017, that the substances mitragynine and 7-hydroxymitragynine be permanently controlled in Schedule I of the CSA. HHS is instead recommending that mitragynine and 7-hydroxymitragynine not be controlled at this time, either temporarily or permanently, until scientific research can sufficiently support such an action. Mitragynine and 7-OH-mitragynine are two of the constituents of the plant *Mitragyna speciosa* (*M. speciosa*), commonly referred to as *kratom*. This decision is based on many factors, in part on new data, and in part on the relative lack of evidence, combined with an unknown and potentially substantial risk to public health if these chemicals were scheduled at this time. Further research, which I am proposing be undertaken, should provide additional data to better inform any subsequent scheduling decision.

Procedural History

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

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

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

Analysis

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

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

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

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

21 U.S.C. § 811(c).

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

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

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

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

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

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

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

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

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

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

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

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

Sincerely yours,

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

Psychopharmacology
https://doi.org/10.1007/s00213-022-06244-z

ORIGINAL INVESTIGATION

Respiratory effects of oral mitragynine and oxycodone in a rodent model

Jack E. Henningfield[1,2] · Joseph V. Rodricks[3] · Aaron M. Magnuson[4] · Marilyn A. Huestis[5]

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Abstract

Rationale Kratom derives from *Mitragyna speciosa* (Korth.), a tropical tree in the genus *Mitragyna* (Rubiaceae) that also includes the coffee tree. Kratom leaf powders, tea-like decoctions, and commercial extracts are taken orally, primarily for health and well-being by millions of people globally. Others take kratom to eliminate opioid use for analgesia and manage opioid withdrawal and use disorder. There is debate over the possible respiratory depressant overdose risk of the primary active alkaloid, mitragynine, a partial μ-opioid receptor agonist, that does not signal through ß-arrestin, the primary opioid respiratory depressant pathway.

Objectives Compare the respiratory effects of oral mitragynine to oral oxycodone in rats with the study design previously published by US Food and Drug Administration (FDA) scientists for evaluating the respiratory effects of opioids (Xu et al., Toxicol Rep 7:188–197, 2020).

Methods Blood gases, observable signs, and mitragynine pharmacokinetics were assessed for 12 h after 20, 40, 80, 240, and 400 mg/kg oral mitragynine isolate and 6.75, 60, and 150 mg/kg oral oxycodone hydrochloride.

Findings Oxycodone administration produced significant dose-related respiratory depressant effects and pronounced sedation with one death each at 60 and 150 mg/kg. Mitragynine did not yield significant dose-related respiratory depressant or life-threatening effects. Sedative-like effects, milder than produced by oxycodone, were evident at the highest mitragynine dose. Maximum oxycodone and mitragynine plasma concentrations were dose related.

Conclusions Consistent with mitragynine's pharmacology that includes partial μ-opioid receptor agonism with little recruitment of the respiratory depressant activating β-arrestin pathway, mitragynine produced no evidence of respiratory depression at doses many times higher than known to be taken by humans.

Keywords Kratom · Mitragynine · Oxycodone · Safety · Respiratory depression · Rat · Animal model · Pharmacokinetics · Pharmacodynamics · Opioid overdose epidemic

Introduction

Kratom products are used globally for health and well-being, improved mood, sleep, attention, and coffee-caffeine-like alerting effects (Grundmann, 2017; Henningfield et al. 2018, 2022; Swogger et al. 2022). There is recreational use; however, many people who use opioids recreationally report kratom as a poor substitute for producing opioid-like euphoria but do find it useful to self-manage withdrawal and discontinue opioid use (Coe et al. 2019; Garcia-Romeu et al. 2020; Prozialeck et al. 2019; Swogger et al. 2022). Estimates of incidence and prevalence of intake vary from 2 to 16 million in the United States (US) (American Kratom Association 2019; Covvey et al. 2020; Henningfield et al. 2021; Palamar 2021; Schimmel et al. 2021) and many millions

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more globally, with the highest prevalence in Southeast Asia and Indonesia where kratom grows in abundance and has been widely consumed for centuries (Brown et al. 2017; Cinosi et al. 2015; Prozialeck et al. 2021; WHO ECDD 2021; Vicknasingam et al. 2010).

Deaths attributed directly to kratom use in the US and globally are rare and were not documented in Southeast Asia (Prozialeck et al. 2019; Ramanathan and McCurdy 2020). Analyses of kratom-associated deaths found that most of such deaths are more likely attributed to the use of other substances and causes not related to kratom (Gershman et al. 2019; Henningfield et al. 2019; National Institute on Drug Abuse 2020; Olsen et al. 2019).

Provisional estimates from the US Centers for Disease Control and Prevention (CDC) indicated that nearly 76,000 of more than 100,000 drug overdose deaths in 2021 were attributable to opioids (CDC 2021). In October 2021, the US Department of Health and Human Services (US DHHS) announced that drug overdose prevention efforts would include a substantial increase in harm reduction efforts to reduce opioid and other drug overdose deaths (US DHHS 2021). Kratom was not mentioned in the 2021 US DHHS announcement; however, US national surveys indicated that kratom is increasingly taken as a harm reduction strategy by thousands of opioid users to reduce and/or eliminate their opioid use related to pain and/or opioid use disorder (Grundmann 2017; Grundmann et al. 2018; Coe et al. 2019; Garcia-Romeu et al. 2020; Prozialeck et al. 2019, 2020, 2021; Swogger et al. 2022).

Oral mitragynine was investigated because mitragynine is the only alkaloid present at potentially biologically active levels in many widely marketed and consumed kratom products that also include mitragynine isolates. Many products have low or nondetectable concentrations of other alkaloids that may contribute to respiratory and other effects (Chakraborty et al. 2021; Sharma et al. 2019; Sharma and McCurdy 2021). Furthermore, unlike opioids and other substances widely used recreationally that are taken intravenously, insufflated, or inhaled (e.g., O'Brien 2015), kratom is taken almost exclusively by the oral route as dried kratom leaf powder teas, foods, or beverages to mask its bitter unpleasant taste, or leaf powder-filled capsules (Cinosi et al. 2015; Henningfield et al. 2018, 2022; Ramanathan and McCurdy 2020; Singh et al. 2016).

Earlier studies concluded that mitragynine has low respiratory depressant potential as compared to morphine or other μ-opioid agonists but did not include blood oxygen and related blood gas measures. Macko et al. (1972) measured respiratory rate in cats and dogs following morphine and/or codeine or mitragynine administration and found fewer effects from mitragynine. In another recently published study (Hill et al. 2022), 3 to 90 mg/kg mitragynine doses were compared to 3, 10, and 30 mg/kg morphine doses administered by oral gavage to mice tested in plethysmography chambers enabling measurement of minute respiratory volumes. Morphine produced dose-dependent decreases in minute volumes. The maximal effect of 90 mg/kg mitragynine was between that obtained with 10 to 30 mg/kg morphine.

The present study was designed to further evaluate mitragynine's respiratory effects including effects on blood gases. The same basic approach as FDA utilized in its own studies comparing a broad range of substances to a prototypic respiratory depressing opioid, oxycodone (Xu et al. 2020, 2021) was employed. Oxycodone was selected by the FDA as the prototypic opioid for comparison and the dosing strategy was typical of what FDA often recommends to drug developers, namely inclusion of the therapeutic dose equivalent, and two or more supratherapeutic doses of oxycodone (6.75, 60, and 150 mg/kg).

The rational for selection of the mitragynine doses was to begin with a low dose utilized by other investigators (20 mg/kg), then systematically increase the dose until the highest tolerable dose or the highest chemically feasible dose due to ethical limitations followed by the laboratory on oral gavage (10.0 mL/kg or about 3.5 mL maximum) and limited mitragynine solubility. The laboratory determined that 400 mg/kg was the maximum dose based on solubility in Tween 20 solvent in a volume of approximately 3.5 mL (adjusted individually per animal based on actual body weight). The 400 mg/kg dose is substantially larger than the highest dose employed in most animal studies and is equivalent to 64.5 mg/kg in humans (dividing by 6.2 for allometric scaling). This is many times higher than is consumed by humans, whose typical per serving intake ranges from approximately 0.35 to 2.0 mg/kg per serving (Prozialeck et al. 2020; Singh et al. 2016; Swogger et al. 2022).

Respiratory effect measures were partial pressure carbon dioxide (pCO2), oxygen saturation (sO2), partial pressure oxygen (pO2), bicarbonate (HCO3), pH, and lactate in rat blood after oral mitragynine and oxycodone. Observable signs of drug effects for 12 h after dosing by veterinary-trained technicians with extensive experience in rat safety and pharmacokinetics studies are also reported (see details in the "Methods" section). The full pharmacokinetics of oxycodone and mitragynine will be reported elsewhere, whereas the present article reports maximum concentrations (C_{max}) and time of C_{max} (T_{max}), confirming dose-dependent increases in oxycodone and mitragynine.

Methods

Animals

Adult male Sprague Dawley rats ($n = 48$) approximately 80 days old weighed between 350 and 375 g at the time of surgical placement of carotid artery catheters at Charles

River Laboratories. Actual body weights on dosing days ranged from 323.0 to 372.8 g. Animals were acclimated for 1 day at the CARE research facility due to concerns about the patency of the arterial catheters for collecting the primary blood gas and pharmacokinetic parameters. To ensure catheter patency, the catheters were flushed with heparinized saline every other day. A small amount of heparinized saline was left in the catheter as a "locking solution" to prevent clots from forming.

Rats were single-housed in a temperature-controlled room (20–26 °C) under a 12:12 h light/dark cycle, with 15–70% humidity and corn cob bedding. Animals had ad libitum access to Teklad Rodent Chow 2018 and filtered tap water, and no other medications were administered.

Animal care procedures were approved by the CARE Research Institutional Animal Care and Use Committee and animal welfare complied with the US Department of Agriculture's (USDA) Animal Welfare Act (9 CFR Parts 1, 2, and 3), the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences 2011), and laboratory standard operating procedures. Animals were euthanized and disposed of without necropsy in accordance with accepted American Veterinary Medical Association guidelines (Underwood and Anthony 2020).

Drug preparation and administration

All drug doses were administered by oral gavage in maximum volumes of 10 mL/kg based on pre-session body weights for each animal following the ethical limitations of the laboratory. Table 1 includes doses and the number of days from delivery of the animals to Care Research from Charles River Labs that each dose was administered. Oxycodone hydrochloride from Sigma-Aldrich (Product Number O1378-500 mg) was dissolved in sterile water the morning of each test day. Doses were based on the weight of 100% pure oxycodone hydrochloride (6.75, 60.0, and 150.0 mg/kg). Mitragynine, 99.9% pure, extracted from Mitragyna Speciosa from Coryn Pharmaceuticals (Product Number 5057), was dissolved, or suspended in 20% Tween 20, because it is not water soluble. Mitragynine dissolved poorly in 20% Tween 20 above concentrations of roughly 10 to 15 mg/mL, requiring mitragynine doses to be prepared individually for each animal immediately before testing using vortex and sonication. To achieve the 240 and 400 mg/kg doses, the solution was in the form of a suspension, mixed well by vortex, and administered within 1 min of each preparation. Mitragynine was stored at room temperature in the dark and used within 62 days of receipt, with study completion within seven days from the first to the last dose.

The three initial mitragynine doses (20, 40, and 80 mg/kg) were the same as in earlier rat studies (Avery et al. 2019; de Moraes et al. 2009; Jagabalan et al. 2019), where data suggested maximum tolerable doses might be several times higher than 80 mg/kg. Drs. Henningfield and Huestis were briefed by the study director (Dr. Magnuson) 12 h after dosing each test day to determine if the next provisionally planned dose was likely tolerable and/or if it should be adjusted to document the dose–response curve as fully as possible. Because there were no observed behavioral effects, adverse events, or changes in blood gases at 80 mg/kg, the next dose was adjusted to 240 mg/kg, and the highest dose set to the maximum chemically feasible dose of 400 mg/kg.

Table 1 Administered doses, sequence of drug dosing, and the day following rat receipt the session was conducted. Test sessions were initiated between 7:30 and 8:30 AM during the light cycle

Group # drug dose mg/kg*	Sequence	Days after rats delivered for session
1. Oxycodone 6.75	5	8**
2. Oxycodone 60	4	4
3. Oxycodone 150	3	2
4. Mitragynine 20	1	1
5. Mitragynine 40	1	1
6. Mitragynine 80	2	2
7. Mitragynine 240	5	8**
8. Mitragynine 400	4	4

*Doses were calculated for each animal based on its pre-session body weight

**Blood gas analyzer failure required testing after a 4-day washout

Test session sequence

Two groups were tested each day. Table 1 shows the dosing sequence and the days after the animals were delivered to the laboratory. Mitragynine doses increased from the lowest to highest doses, while oxycodone doses descended from the highest to lowest doses. Due to a malfunction of the blood gas analyzer, animals dosed with oxycodone 60 mg/kg and mitragynine 240 mg/kg had blood gases measured for only 2 h. No data from these doses were utilized, and the animals underwent a 4-day washout period. The oxycodone 60 mg/kg dose was administered the next day to naïve rats. Animals originally dosed with 60 mg/kg oxycodone were re-dosed with 6.75 mg/kg oxycodone after the 4-day washout, and animals originally dosed with 240 mg/kg mitragynine were re-dosed with 240 mg/kg mitragynine after the 96 h washout. Protocol changes were approved by the ethical committee and permitted rats adequate recovery from the few blood collections performed.

Test session protocol

Animals were removed from their home cages for weighing at approximately 6 am each day and at 24 h post-dose, for drug administration and blood collections, and immediately returned to their home cages. Blood collections occurred pre-dose between 7:30 and 8:30 am and 1, 2, 4, 6, 8, and 12 h post-dose. A total of 300 µL whole blood (EDTA anticoagulant) was drawn at each time point (2.1 mL total). Approximately 100 µL was for blood gas analysis with a portable blood gas testing device (VetScan i-STAT Alinity V Handheld Analyzer with CG4 + cartridges (Zoetis/Abaxis/Abbott)) at 7 time points following procedures described by Xu et al. (2020). Blood gases were measured within 10 min after each blood collection.

A single blood gas measurement obtained data for all blood gas parameters at each time point for each animal and at each dose. A two-way ANOVA with multiple comparisons was performed, with the Dunnett test accounting for multiple comparisons, and significance set to $p < 0.05$. The remaining 200 µL blood was processed immediately for subsequent plasma oxycodone or mitragynine analyses, with storage at − 60 °C or below. Arterial ports were flushed with saline-heparin after each blood draw and every other day.

Observable signs were collected by the two veterinary-trained session monitors who identified and recorded adverse events and deviations from normal behavior. Observable signs included general activity (lethargy, impaired motor function, and righting response), response to stimulus (finger snap or clap near the animal), abnormal behaviors such as bracing (defined as a rigid posture with limbs slightly splayed), and apparent increases or decreases in respiration from normal/control. These items were given special attention as effects commonly observed in mu-agonist opioid studies, and our interest in comparing mitragynine's effects to those of oxycodone, a prototypical mu-agonist opioid. Observations were conducted at each blood collection and monitored closely following dosing, and anytime an abnormality was observed by one of the two veterinary-trained session monitors. Observations were detailed in writing by the technician who made them. The technician observers were not blinded to treatments.

Six animals received each dose; 200 µL (K_2EDTA) blood was processed to obtain plasma (~ 100 µL) for pharmacokinetic analysis. A total of 336 samples were analyzed for oxycodone and mitragynine in two separate validated LC–MS/MS assays. Pharmacokinetic analyses were performed with a non-compartment model (WinNonlin Phoenix professional, Version 8.3, Certara, Princeton, NJ) to determine pharmacokinetic parameters. The maximum plasma concentration (C_{max}) and time of maximum plasma concentration (T_{max}) following 6.75, 60, and 150 mg/kg oxycodone and 20, 40, 80, 240, and 400 mg/kg/d mitragynine group are presented. Due to space limitations and the many pharmacodynamic findings in this manuscript, a separate report will describe complete oxycodone and mitragynine pharmacokinetics.

Results

Oxycodone and mitragynine pharmacokinetics

Table 2 shows the maximum observed plasma concentrations (C_{max}) for oxycodone and mitragynine. C_{max} increased by dose from 20 to 400 mg/kg, but each dose increase did not produce a significant increase based on a one-way ANOVA with Tukey's post hoc analysis and a significance value of $p < 0.05$. Mitragynine C_{max} results were significantly different between the 20 and 40 mg/kg doses and the 240 and 400 mg/kg mitragynine doses, and the 80 mg/kg dose and the 400 mg/kg dose. Although the 240 mg/kg mean C_{max} was 5601 and the 400 mg/kg mean C_{max} was 7982 ng/mL, this increase was not statistically significant.

The maximum plasma concentration generally occurred within 1–2 h (T_{max}) but varied across animals, occurring as late as 12 h in some animals. Three animals were not included in the pharmacokinetic or pharmacodynamic analyses due to two animals not achieving concentrations below the limit of quantification (one in 150 mg/kg oxycodone group and one in the 240 mg/kg mitragynine group) after a 4-day washout period prior to redosing. One animal in the 240 mg/kg mitragynine group had a catheter blockage and tail blood was collected at time points 6, 8, and 12 h; however, for unexplained reasons, the blood analytic result was

Table 2 Median maximum plasma concentrations (C_{max}), with the minimum and maximum plasma concentration observed by drug and dose

Dose mg/kg	*n*	Median C_{max} ng/mL	Range ng/mL
Oxycodone			
6.75	6	33.5	10.7–51.5
60	6	39.9	34.5–1179
150	5*	131	93.2–5532
Mitragynine			
20	6	723	317–1010
40	6	1720	1043–2032
80	6	2497	1538–3125
240	4**	5182	3783–7444
400	6	7513	4404–10,096

*One animal's data were not included in the analysis due to incomplete washout prior to redosing

**Another animal's data were not included in the analysis due to incomplete washout prior to redosing and one eliminated due to extreme outlier for C_{max}

an extreme outlier for C_{max} at 23,425 ng/mL—a concentration threefold higher than any obtained with the 400 mg/kg dose. This result failed the outlier test and was not included in any analyses.

Respiratory blood gas results

Figure 1 presents the change from pre-dose baseline levels over time of oxycodone and mitragynine on the partial pressure of carbon dioxide (pCO2), which Xu et al. (2021) suggested is more sensitive than partial pressure of oxygen (pO2). None of the three blood gas parameters significantly deviated from baseline at the therapeutic 6.75 mg/kg oxycodone dose. The pCO2 was significantly increased relative to baseline at 1, 4, and 6 h for the 60 mg/kg oxycodone dose and at 1, 2, and 4 h for the 150 mg/kg oxycodone dose. There was a rapid decrease in sO2 and pO2 following the 60 and 150 mg/kg oxycodone doses, with the sO2 significantly depressed at 1, 4, and 6 h for the 60 mg/kg oxycodone dose and 1, 2, 4, and 6 h for the 150 mg/kg oxycodone dose, while no statistically significant decreases in pO2 were observed for either 60 or 150 mg/kg oxycodone. By 8 h post-drug administration, pCO2, sO2, and pO2 were no longer significantly different from baseline for higher oxycodone doses. There were no significant differences in pCO2, sO2, and pO2 following

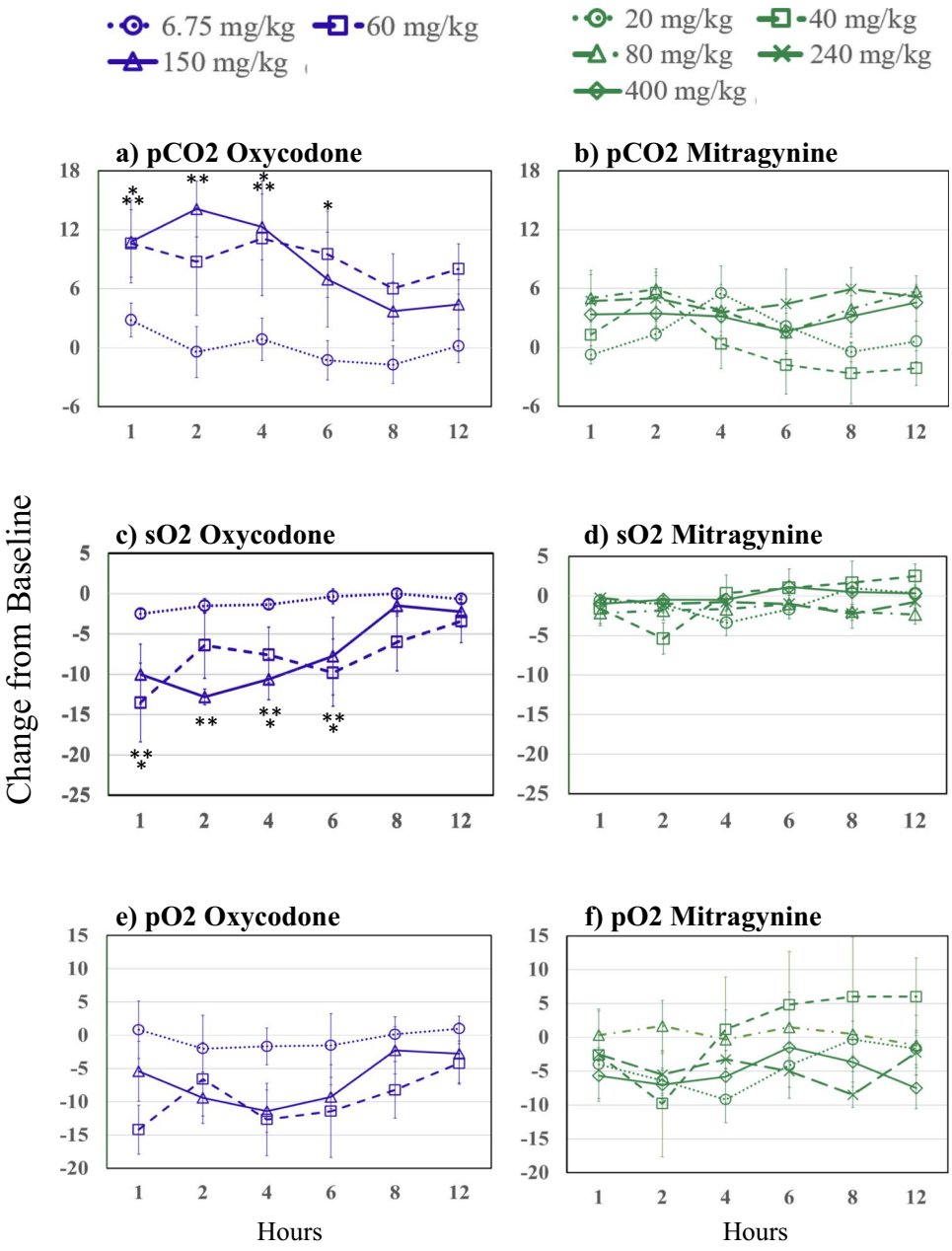

Fig. 1 Changes from baseline over time following oxycodone in **a** partial pressure of carbon dioxide (pCO2), **c** oxygen saturation (sO2), and **e** partial pressure of oxygen (pO2); and changes from baseline over time following mitragynine **b** partial pressure of carbon dioxide (pCO2), **d** oxygen saturation (sO2), and **f** partial pressure of oxygen (pO2). Asterisks indicate significant differences from baseline ($p \leq 0.05$, one asterisks (*) 60 and two asterisks (**) 150 mg/kg oxycodone). Oxycodone is shown in purple. 6.75 mg/kg, dotted lines and circles; 60 mg/kg, dashed lines and squares; 150 mg/kg, solid lines and triangles. Mitragynine is shown in green; 20 mg/kg, dotted lines and circles; 40 mg/kg, short dashes and squares; 80 mg/kg, dashed and dotted lines and triangles; 240 mg/kg, long dashed lines and Xs; 400 mg/kg, solid lines and diamonds

20, 40, 80, 240, or 400 mg/kg mitragynine from baseline to 12 h.

Figure 2 presents oxycodone and mitragynine effects on blood lactate, bicarbonate (HCO_3), and pH. No mitragynine or oxycodone dose produced any statistically significant changes in HCO_3 concentrations for 12 h after drug administration with the exception of the 400 mg/kg at 12 h post-drug administration. There were no significant changes from baseline in blood lactate following any oxycodone or mitragynine dose. Following 150 mg/kg oxycodone, the pH dropped significantly compared to baseline from 1–4 h and at 1 h after the 60 mg/kg oxycodone dose. There were no significant changes from baseline in pH after any mitragynine dose.

Observable signs including potential drug-related adverse effects

There was no evidence of opioid or other drug effects or any behavioral observation in any of the animals receiving 6.75 mg/kg oxycodone or 20, 40, 80, and 240 mg/kg mitragynine that was visibly apparent to staff monitoring the animals.

Following 60 and 150 mg/kg oxycodone, the trained observers recorded numerous reports of behavioral effects including decreased activity, lethargy, apparently decreased respiration, and impairments to motor function. Four of the six animals at 60 mg/kg oxycodone showed overt signs of

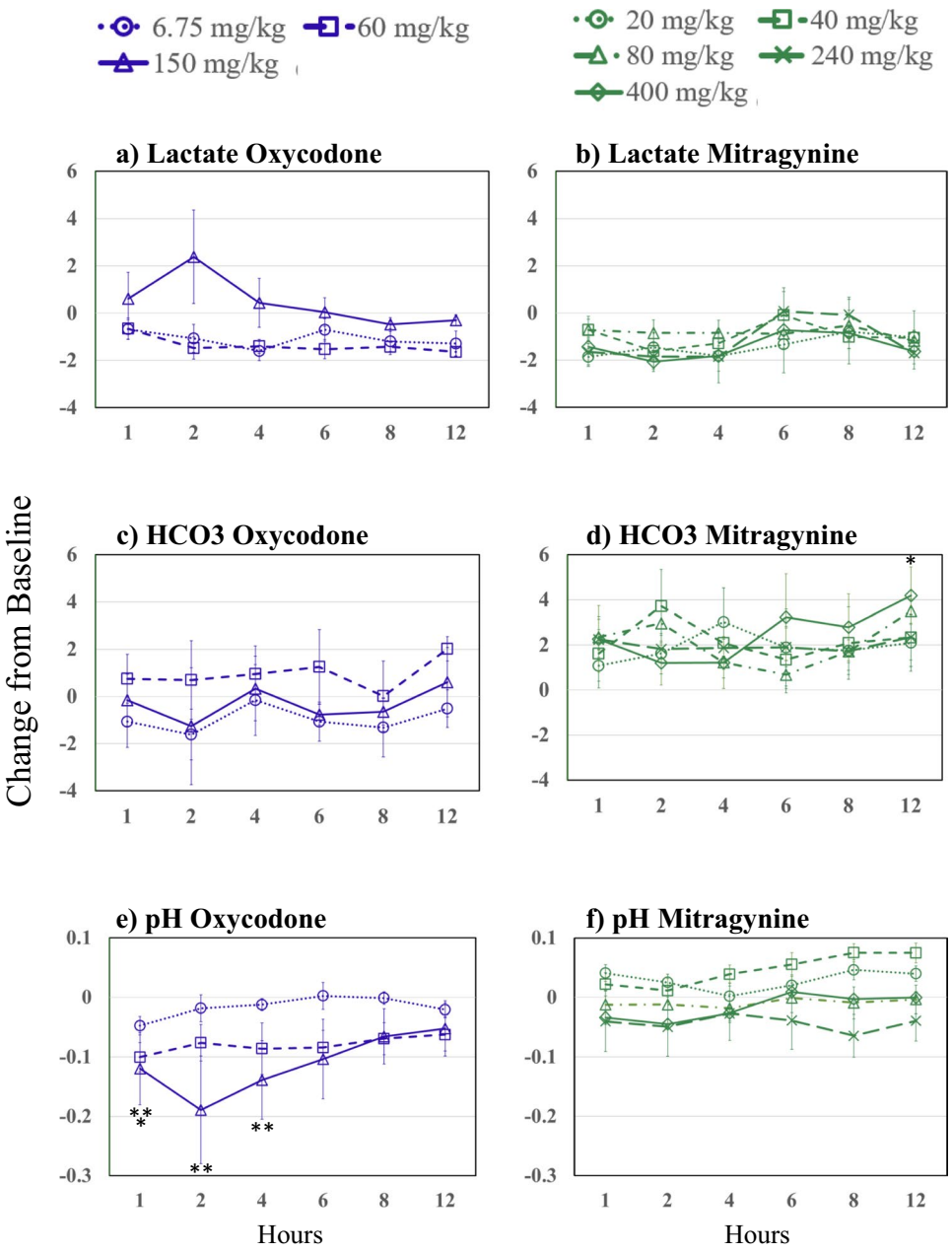

Fig. 2 Changes from baseline over time and by dose (see key) following oxycodone on the left side panels (blue) and mitragynine on the right side panels (green) for lactate (top panels), bicarbonate (HCO3) (middle panels), and pH (bottom panels). Asterisks indicate significant differences from baseline ($p \leq 0.05$, one asterisk (*) 60 and two asterisks (**) 150 mg/kg oxycodone)

opioid exposure including pronounced behavioral effects and lethargy typical of opioids. One animal receiving 60 mg/kg oxycodone died between the 2 and 4 h time points, apparently as a result of the animal pulling its catheter and causing internal bleeding. These data were not used in the results. Four of the five remaining animals in the 60 mg/kg group appeared normal at 24 h, while one animal was found dead at 7:53 AM the next morning, almost 24 h following drug exposure.

The 150 mg/kg oxycodone dose produced notably stronger behavioral effects and lethargy typical of opioids with observable signs occurring in all 6 animals at 1–2 h. At 4 h post-dose, 3 of the 6 animals appeared normal. However, one of those animals was subsequently found dead approximately 5 h post-drug exposure. Two of the remaining 5 animals continued to exhibit behavioral signs at 6, 8, and 12 h, while all others returned to normal by 6 h. All 5 remaining animals appeared normal at 24 h.

The 400 mg/kg mitragynine dose produced milder observable signs than 60 and 150 mg/kg oxycodone. These observations included alteration of motor behavior, lethargy, and/or incoordination in 5 of 6 animals, with no observed abnormal behavior in the sixth animal. The slowed behavior suggested potentially decreased respiratory rate at 2 and 4 h in five animals.

Approximately 40 min after the 400 mg/kg mitragynine dose, one animal displayed "full body spasms" when picked up to be removed from the home cage for blood collection. Under observation (away from home cage) at approximately 1 h post-mitragynine dose, the animal exhibited what was described as a seizure-like activity for approximately 30 s that was described as moderate. No further seizure-like behavior was observed.

Discussion

The purpose of this study was to evaluate the respiratory effects of kratom's primary alkaloid, mitragynine, in comparison to oxycodone, a prototypic opioid that reliably produces dose-related respiratory depression and death in humans, rats, and other species. As far as we are aware, this is the first study of mitragynine's respiratory effects that followed the approach published previously by Xu et al. (2020, 2021) that utilized blood gas assessment of respiratory function. The respiratory effects of a 20-fold range of mitragynine doses were compared to those of therapeutic and supratherapeutic doses of oxycodone for comparative assessments of the respiratory effects of drugs. The main finding was that mitragynine produced no evidence of respiratory depression at doses many times higher than typical human doses, whereas oxycodone produced the expected dose-related respiratory depressant effects consistent with its strong morphine-opioid (i.e., μ-opioid) receptor-mediated effects. These findings are consistent with mitragynine's pharmacology that includes partial μ-opioid receptor agonism with little recruitment of the respiratory depressant activating β-arrestin pathway (Kruegel et al. 2016, 2019; Váradi et al. 2016).

Observable signs and blood pharmacokinetics confirmed that the administered doses produced the dose-related pharmacodynamic and pharmacokinetic results expected, namely, higher plasma concentrations and stronger behavioral effects.

The blood gas assessments revealed striking dose and drug-related effects. We found that oxycodone, in the same oral doses used by Xu et al. (2020), did not produce significant respiratory depressant effects at the therapeutic equivalent dose of 6.75 mg/kg, and had strongly depressant effects at 60 mg/kg and more severe and longer lasting effects at 150 mg/kg. In contrast, mitragynine did not produce dose-related respiratory depression or life-threatening effects at any dose, and there were no dose-related trends in blood oxygen or carbon dioxide. Consistent with the conclusion of Xu et al. (2021), pCO2 appeared to be a more sensitive measure of the respiratory depressant effects of oxycodone than blood oxygen measures; however, none of the blood gas measures showed dose-related changes associated with mitragynine administration.

This is not the first study to conclude that mitragynine does not produce opioid-like dose-dependent respiratory depressant effects. This was also demonstrated by Macko et al. (1972), and Hill et al. (2022) found no respiratory depressant effect at 3 mg/kg but did find some respiratory depression at 10 mg/kg, which they reported did not change at higher doses. Whether this difference from the present finding is unique to mice, measurement techniques or another factor is not known. In addition, Váradi et al. (2016, p. 7) reported that, in contrast to the dose-dependent respiratory depressant effects of morphine, a mitragynine analog "shows a lower propensity to cause respiratory depression and constipation compared with the canonical opioid, morphine."

The human equivalent doses (HEDs) of those tested in this rat study are based on estimated body surface area dividing the rat doses by 6.2 (Nair and Jacob 2016). Based on this conversion, the HEDs of 20, 40, 80, 240, and 400 mg/kg are 3.2, 6.6, 12.9, 38.7, and 64.5 mg/kg respectively. Manufacturers of mitragynine-containing kratom extracts state that about 25 mg per serving or about 0.35 mg/kg in a 70 kg human is the minimal amount that provides sufficient self-reported benefits by consumers to support repeat sales. Some marketed products are labeled with this amount and commonly marketed products in Southeast Asia in the form of tea-like decoctions typically contain 22.5 to 75 mg but with wide variation across marketed products (Brown

et al. 2017; Cinosi et al. 2015; Prozialeck et al. 2020; WHO ECDD 2021). Thus, it appears that the mitragynine doses administered in the present study range from the high end of consumer use (e.g., at the 20 mg/kg dose) to levels many times higher than would be voluntarily consumed or considered desirable or tolerable, regardless of their apparent limited effects on respiratory function. Some people who are self-treating chronic pain and/or using to maintain opioid abstinence may consume larger doses of 2–5 mg/kg 2–4 times per day (Cinosi et al. 2015; Figura et al. 2020; European Monitoring Centre 2015; McCurdy et al. 2020; Ramanathan and McCurdy 2020; Sharma and McCurdy 2021; Swogger et al. 2022; WHO ECDD 2021).

Self-report data posted on internet websites were summarized in several kratom use reviews (e.g., Cinosi et al 2015; Henningfield et al. 2018, 2022; Swogger and Walsh 2018; Veltri and Grundmann 2019). These data suggest that kratom intake is typically limited by non-life-threatening but discomfort-producing gastrointestinal symptoms and/or undesirable lethargy. Furthermore, for most kratom consumers, higher doses do not produce the powerful euphoria-like highs sought by people who recreationally use opioids, cocaine, and amphetamine and that is an incentive for the frequent dose escalation that contributes to the high risk of overdose deaths associated with such drugs (Swogger et al. 2022; Swogger and Walsh 2018; Henningfield et al. 2018, 2022).

An important caveat to the foregoing observations is that it should not be concluded that kratom is without life-threatening risks under some conditions and in some people, any more than such assumption should be made for any dietary or consumer product. It is possible, if not plausible, that in some yet-to-be documented combination with other drugs or underlying health conditions, high-dose kratom consumption could pose a serious risk. Therefore, it is prudent, as discussed elsewhere (e.g., Swogger et al. 2022) to not consume kratom with other drugs or in high dosages. For example, buprenorphine is a partial agonist that is approved for the treatment of pain and opioid use disorder and also produces little evidence of life-threatening depression over a broad range of doses. Buprenorphine did not produce life-threatening respiratory depression in humans even after a 16 mg intravenous dose (Umbricht et al. 2004; Huestis et al. 2013). However, buprenorphine is associated with overdose deaths when combined with benzodiazepines and other sedative-hypnotic drugs (Pergolizzi et al. 2015; Pergolizzi and Raffa 2019; Schuman-Olivier et al. 2013).

The absence of evidence for respiratory depressant effects in rats documented here does not rule out the possibility of respiratory depressant effects in some human conditions and in combination with other substances. Mitragynine in isolation and kratom produce diverse opioid and nonopioid mediated effects that warrant further study (Ahmad et al. 2022; Harun et al. 2022; Behnood-Rod et al. 2020; Hemby et al. 2019; Henningfield et al. 2018, 2022; Reeve et al. 2020; Sharma and McCurdy 2021; Wilson et al. 2020; Yue et al. 2018). However, as compared to opioids and other substances that contributed to the 2021 annualized rate of 108,000 drug overdose deaths, the relative risk of kratom appears to be far lower than that of opioids, methamphetamine and cocaine, alcohol, and many other substances of abuse (CDC 2021; Giroir 2018; Henningfield et al. 2019; United Nations Commission on Narcotic Drugs 2021).

The risk of kratom producing seizures is real but low and extensive surveillance to determine the conditions under which kratom may increase the risk may be necessary. For example, Boyer et al. (2008) reported a seizure in a person with no history of seizures following the ingestion of 100 mg modafinil combined with an unknown amount of kratom. Follow-up evaluation including computerized tomography and magnetic resonance brain imaging was normal. Modafinil itself can lower the seizure threshold and possibly cause seizures (Artsy et al. 2012; Bahramnjead et al. 2018). Thus, it is not known if kratom contributed but an interaction cannot be ruled out.

Current findings in the context of recent advances in understanding the pharmacology of mitragynine

The finding that a broad range of mitragynine doses did not produce respiratory depression is not novel in itself because there are earlier studies of mitragynine across diverse doses and conditions, albeit at generally lower doses of 20–56 mg/kg in rats. These studies did not as intensively evaluate respiratory effects, and most did not include a pharmacokinetic assessment of mitragynine in comparison to a prototypic opioid. Several studies administered mitragynine to mice and dogs in experimental models with behaviorally functioning animals in conditioned place preference, self-administration, and intracranial self-stimulation models, reviewed recently by Henningfield et al. (2022), Ramanathan and McCurdy (2020), Sharma and McCurdy (2021), and WHO ECDD (2021). None of these studies reported life-threatening effects of mitragynine of 20–56 mg/kg and higher (e.g., Avery et al. 2019; Behnood-Rod et al. 2020; Maxwell et al. 2020; Obeng et al. 2021; Gutridge et al. 2020; Hassan et al. 2021; Kamble et al. 2021; Suhaimi et al. 2021; Todd et al. 2020). For example, a pharmacokinetics and safety study in beagle dogs reported a "mild transient sedation" lasting about 2–4 h after 5 mg/kg oral mitragynine but without clinically significant effects on vital signs (Maxwell et al. 2020). Váradi et al. (2016) found that morphine, but not a mitragynine analog, dose-dependently decreased respiratory rate in rats.

The main strengths of the present study include its dose-related comparison of oxycodone to substantially higher doses of mitragynine than were tested in most other studies

and by close adherence to the protocol used in two published studies for evaluating respiratory effects (Xu et al. 2020, 2021). Its main limitation with respect to its goals was that the limit of tolerability, as defined by life-threatening effects, was not discovered and was limited by dosing restrictions. Future studies will consider alternative oral dosing approaches to enable the administration of higher doses. It is also possible that the two groups of animals that were not mitragynine naïve due to the blood gas analyzer failure were affected by their prior mitragynine exposure despite the 4-day washout period. Nor does this single ascending dose (SAD) approach address the effects of chronic dosing as can be informed by multiple ascending dose (MAD) studies. Future studies will help better understand the generalizability of the present findings, although the overall findings that the respiratory effects of mitragynine are weak albeit at lower doses as compared to morphine-like opioids are not novel. It also is important to evaluate the effects of mitragynine in combinations with drugs commonly taken with kratom including opioids, sedatives, alcohol, and stimulants. Further studies of mitragynine and other kratom constituents and analytes are clearly warranted to continue to advance science and public health.

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Declarations

Conflict of interest Jack E. Henningfield is an employee of PinneyAssociates which provides scientific and regulatory consulting to the American Kratom Association (AKA) and its affiliated American Kratom Foundation (AKF), as well as to the developers of potential kratom-based dietary supplements and medicines. Marilyn A. Huestis consults with PinneyAssociates, including the AKA and AKF, as well as to the developers of potential kratom-based dietary supplements and medicines. Aaron Magnuson is an employee of Mountain West Research, LLC (formerly CARE Research, LLC) which was awarded the contract to conduct the study following a competitive bidding process. Joseph V Rodricks, PhD, is a consulting toxicologist currently employed by Ramboll Health and Environment providing global consulting services evaluating the safety and toxicology of dietary ingredients.

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References

Ahmad I, Prabowo WC, Arifuddin M, Fadraersada J, Indriyanti N, Herman H, Purwoko RY, Nainu F, Rahmadi A, Paramita S, Kuncoro H, Mita N, Narsa AC, Prasetya F, Ibrahim A, Rijai L, Alam G, Mun'im A, Dej-adisai S, (2022) Mitragyna species as pharmacological agents: from abuse to promising pharmaceutical products. Life 12:193. https://doi.org/10.3390/life12020193

American Kratom Association (2019) The increase in consumer use of kratom in the United States, June 2019. https://assets.website-files.com/61858fcec654303987617512/619dd9d68bd48315873c4952_Kratom_Population_2019.pdf. Accessed 19 Oct 2022

Artsy E, McCarthy DC, Hurwitz S, Pavlova MK, Dworetzky BA, Lee JW (2012) Use of modafinil in patients with epilepsy. Epilepsy Behav 23(4):405–408. https://doi.org/10.1016/j.yebeh.2012.02.011

Avery BA, Boddu SP, Sharma A, Furr EB, Leon F, Cutler SJ (2019) McCurdy CR (2019) Comparative pharmacokinetics of mitragynine after oral administration of Mitragyna speciosa (Kratom) leaf extracts in rats. Planta Med 85(4):340–346. https://doi.org/10.1055/a-0770-3683

Bahramnjead E, Kazemi Roodsari S, Rahimi N, Etemadi P, Aghaei I, Dehpour AR (2018) Effects of modafinil on clonic seizure threshold induced by pentylenetetrazole in mice: involvement of glutamate, nitric oxide, GABA, and serotonin pathways. Neurochem Res 43:2025–2037. https://doi.org/10.1007/s11064-018-2623-7

Behnood-Rod A, Chellian R, Wilson R, Hiranita T, Sharma A, Leon F, McCurdy CR, McMahon LR, Bruijnzeel AW (2020) Evaluation of the rewarding effects of mitragynine and 7-hydroxymitragynine in an intracranial self-stimulation procedure in male and female rats. Drug Alcohol Depend 215:108235. https://doi.org/10.1016/j.drugalcdep.2020.108235

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

Brown PN, Lund JA, Murch SJ (2017) A botanical, phytochemical and ethnomedicinal review of the genus Mitragyna korth: implications for products sold as kratom. J Ethnopharmacol 202:302–325. https://doi.org/10.1016/j.jep.2017.03.020

Centers for Disease Control and Prevention (CDC), National Center for Health statistics (2021) Drug Overdose Deaths in the U.S. Top 100,000 Annually. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm. Accessed 8 March 2022

Chakraborty S, DiBerto JF, Faouzi A, Bernhard SM, Guttridge AM Ramsey, S, et al (2021) A novel mitragynine analog with low

efficacy mu opioid receptor agonism displays antinociception with attenuated adverse effects. J Med Chem 64(18):13873–13892
Cinosi E, Martinotti G, Simonato P, Singh D, Demetrovics Z, Roman-Urrestarazu A, Bersani FS, Vicknasingam B, Piazzon G, Li JH, Yu WJ, Kapitány-Fövény M, Farkas J, Di Giannantonio M, Corazza O (2015) Following "the roots" of Kratom (Mitragyna speciosa): the evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in Western countries. Biomed Res Int 2015:968786. https://doi.org/10.1155/2015/968786
Coe MA, Pillitteri JL, Sembower MA, Gerlach KK, Henningfield JE (2019) Kratom as a substitute for opioids: results from an online survey. Drug Alcohol Depend 202:24–32. https://doi.org/10.1016/j.drugalcdep.2019.05.005
Covvey JR, Vogel SM, Peckham AM, Evoy KE (2020) Prevalence and characteristics of selfreported kratom use in a representative US general population sample. J Addict Dis 38(4):506–513
de Moraes NV, Moretti RA, Furr EB III, McCurdy CR, Lanchote VL (2009) Determination of mitragynine in rat plasma by LC–MS/MS: application to pharmacokinetics. J Chromatogr B Analyt Technol Biomed Life Sci 877(24):2593–2597. https://doi.org/10.1016/j.jchromb.2009.06.023
Epilepsy Foundation (2020) Triggers of seizures: over-the-counter medications. https://www.epilepsy.com/learn/triggers-seizures/over-counter-medications. Accessed 8 March 2022
European Monitoring Centre for Drugs and Drug Addiction (2015) Kratom drug profile. https://www.emcdda.europa.eu/publications/drug-profiles/kratom_en. Accessed 7 March 2022
Figura C, Barrett M, Atkinson TJ (2020) A kratom primer: miracle medicine or herb of abuse? Pract Pain Manag 20(5). https://www.practicalpainmanagement.com/treatments/pharmacological/non-opioids/kratom-primer-miracle-medicine-herb-abuse. Accessed 8 March 2022
Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RR (2020) Kratom (Mitragyna speciosa): user demographics, use patterns, and implications for the opioid epidemic. Drug Alcohol Depend 208:107849. https://doi.org/10.1016/j.drugalcdep.2020.107849
Gershman K, Timm K, Frank M, Lampi L, Melamed J, Gerona R, Monte AA (2019) Deaths in Colorado attributed to kratom. N Engl J Med 380(1):97–98. https://doi.org/10.1056/NEJMc1811055
Giroir BP (2018) Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to Rescind Previous Support to Permanently Place Mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2018. https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/60145eab6df59e7e36a7cfc1/1611947693695/dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf. Accessed 8 March 2022
Grundmann O (2017) Patterns of Kratom use and health impact in the US—results from an online survey. Drug Alcohol Depend 176:63–70. https://doi.org/10.1016/j.drugalcdep.2017.03.007
Grundmann O, Brown PN, Henningfield J, Swogger M, Walsh Z (2018) The therapeutic potential of kratom. Addiction 113(10):1951–1953. https://doi.org/10.1111/add.14371
Gutridge AM, Robins MT, Cassell RJ, Uprety R, Mores KL, Ko MJ, Pasternak GW, Majumdar S, van Rijn RM (2020) G protein-biased kratom-alkaloids and synthetic carfentanil-amide opioids as potential treatments for alcohol use disorder. Br J Pharmacol 177(7):1497–1513. https://doi.org/10.1111/bph.14913
Harun N, Kamaruzaman NA, Mohamed Sofian Z, Hassan Z (2022) Mini review: potential therapeutic values of mitragynine as an opioid substitution therapy. Neurosci Lett 773:136500. https://doi.org/10.1016/j.neulet.2022.136500
Hassan R, Sreenivasan S, Müller CP, Hassan Z (2021) Methadone, buprenorphine, and clonidine attenuate mitragynine withdrawal in rats. Front Pharmacol 12:708019. https://doi.org/10.3389/fphar.2021.708019
Hemby SE, McIntosh S, Leon F, Cutler SJ, McCurdy CR (2019) Abuse liability and therapeutic potential of the Mitragyna speciosa (Kratom) alkaloids mitragynine and 7-hydroxymitragynine. Addict Biol 24(5):874–885. https://doi.org/10.1111/adb.12639
Henningfield JE, Fant RV, Wang DW (2018) The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology 235(2):573–589. https://doi.org/10.1007/s00213-017-4813-4
Henningfield JE, Grundmann O, Babin JK, Fant RV, Wang DW, Cone EJ (2019) Risk of death associated with kratom use compared to opioids. Prev Med 128:105851. https://doi.org/10.1016/j.ypmed.2019.105851
Henningfield JE, Grundmann O, Garcia-Romeu A, Swogger MT (2021) We need better estimates of kratom use prevalence. Am J Prev Med 62:132–133. https://doi.org/10.1016/j.amepre.2021.07.022
Henningfield JE, Wang DW, Huestis MA (2022) Kratom abuse potential 2021: an updated eight factor analysis. Front Pharmacol 12:775073. https://doi.org/10.3389/fphar.2021.775073
Hill R, Kruegel AC, Javitch JA, Lane JR, Canals M (2022) The respiratory depressant effects ofmitragynine are limited by its conversion to 7-OH mitragynine. Br J Pharmacol 179(14):3875–3885. https://doi.org/10.1111/bph.15832
Huestis MA, Cone EJ, Pirnay SO, Umbricht A, Preston KL (2013) Intravenous buprenorphine and norbuprenorphine pharmacokinetics in humans. Drug Alcohol Depend 131(3):258–262. https://doi.org/10.1016/j.drugalcdep.2012.11.014
Jagabalan Y, Zainal H, Al Ganaby A, Murugaiyah V, Ramanathan S (2019) Pharmacokinetic modeling of single dose Kratom (mitragynine) in rats. *Conference Abstract: International Conference on Drug Discovery and Translational Medicine 2018, Putrajaya, Malaysia.* Front Pharmacol. https://doi.org/10.3389/conf.fphar.2018.63.00087
Kamble SH, Berthold EC, King TI, Raju Kanumuri SR, Popa R, Herting JR, León F, Sharma A, McMahon LR, Avery BA, McCurdy CR (2021) Pharmacokinetics of eleven kratom alkaloids following an oral dose of either traditional or commercial kratom products in rats. J Nat Prod 84(4):1104–1112. https://doi.org/10.1021/acs.jnatprod.0c01163
Kruegel AC, Gassaway MM, Kapoor A, Váradi A, Majumdar S, Filizola M, Javitch JA, Sames D (2016) Synthetic and receptor signaling explorations of the Mitragyna alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. J Am Chem Soc 138(21):6754–6764. https://doi.org/10.1021/jacs.6b00360
Kruegel AC, Uprety R, Grinnell SG, Langreck C, Pekarskaya EA, Le Rouzic V, Ansonoff M, Gassaway MM, Pintar JE, Pasternak GW, Javitch JA, Majumdar S, Sames D (2019) 7-Hydroxymitragynine is an active metabolite of mitragynine and a key mediator of its analgesic effects. ACS Cent Sci 5(6):992–1001. https://doi.org/10.1021/acscentsci.9b00141
Macko E, Weisbach JA, Douglas B (1972) Some observations on the pharmacology of mitragynine. Arch Int Pharmacodyn Ther 198(1):145
Maxwell EA, King TI, Kamble SH, Raju KS, Berthold EC, León F, Avery BA, McMahon LR, McCurdy CR, Sharma A (2020) Pharmacokinetics and safety of mitragynine in beagle dogs. Planta Med 86(17):1278–1285. https://doi.org/10.1055/a-1212-5475
McCurdy C, Grundmann O, McLaughlin J (2020) Kratom Resources. Department of Pharmacodynamics, College of Pharmacy, University of Florida. https://pd.pharmacy.ufl.edu/research/kratom/. Accessed 8 March 2022
Nair AB, Jacob S (2016) A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm 7(2):27–31. https://doi.org/10.4103/0976-0105.177703

National Academy of Sciences (2011) Guide for the Care and Use of Laboratory Animals: Eighth Edition, 2011. Washington, DC: The National Academies Press. https://doi.org/10.17226/12910.

National Institute on Drug Abuse (2020). Kratom Drug Facts. National Institutes of Health, Bethesda, MD. https://www.drugabuse.gov/publications/drugfacts/kratom. Accessed 8 March 2022

Obeng S, Wilkerson JL, León F, Reeves ME, Restrepo LF, Gamez-Jimenez LR, Patel A, Pennington AE, Taylor VA, Ho NP, Braun T, Fortner JD, Crowley ML, Williamson MR, Pallares VLC, Mottinelli M, Lopera-Londoño C, McCurdy CR, McMahon LR, Hiranita T (2021) Pharmacological comparison of mitragynine and 7-hydroxymitragynine: in vitro affinity and efficacy for μ-opioid receptor and opioid-like behavioral effects in rats. J Pharmacol Exp Ther 376(3):410–427. https://doi.org/10.1124/jpet.120.000189

O'Brien CP (2015). Drug addiction. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. McGraw Hill. https://accessmedicine.mhmedical.com/content.aspx?bookid=1613&sectionid=102159667

Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N (2019) Notes from the field: unintentional drug overdose deaths with kratom detected—27 states, July 2016–December 2017. MMWR Morb Mortal Wkly Rep 68(14):326–327 https://doi.org/10.15585/mmwr.mm6814a2

Palamar JJ (2021) Past-Year kratom use in the U.S.: Estimates from a nationally representative sample. Am J Prev Med 61(2):240-245. https://doi.org/10.1016/j.amepre.2021.02.004

Pergolizzi JV Jr, Raffa RB (2019) Safety and efficacy of the unique opioid buprenorphine for the treatment of chronic pain. J Pain Res 12:3299–3317. https://doi.org/10.2147/JPR.S231948

Pergolizzi JV Jr, Scholten W, Smith KJ, Leighton-Scott J, Willis JC, Henningfield JE (2015) The unique role of transdermal buprenorphine in the global chronic pain epidemic. Acta Anaesthesiol Taiwan 53(2):71–76. https://doi.org/10.1016/j.aat.2015.06.001

Prozialeck WC, Avery BA, Boyer EW, Grundmann O, Henningfield JE, Kruegel AC, McMahon LR, McCurdy CR, Swogger MT, Veltri CA, Singh D (2019) Kratom policy: the challenge of balancing therapeutic potential with public safety. Int J Drug Policy 70:70–77. https://doi.org/10.1016/j.drugpo.2019.05.003

Prozialeck WC, Edwards JR, Lamar PC, Plotkin BJ, Sigar IM, Grundmann O, Veltri CA (2020) Evaluation of the mitragynine content, levels of toxic metals and the presence of microbes in kratom products purchased in the western suburbs of Chicago. Int J Environ Res Public Health 17(15):5512. https://doi.org/10.3390/ijerph17155512

Prozialeck WC, Lamar PC, Krupp M 2nd, Moon M, Phelps LE, Grundmann O (2021) Kratom use within the context of the evolving opioid crisis and the COVID-19 pandemic in the United States. Front Pharmacol 12:729220. https://doi.org/10.3389/fphar.2021.729220

Ramanathan S, McCurdy CR (2020) Kratom (Mitragyna speciosa): worldwide issues. Curr Opin Psychiatry 33(4):312–318. https://doi.org/10.1097/YCO.0000000000000621

Reeve ME, Obeng S, Oyola FL, Behnke M, Restrepo LF, Patel A, Ho NP, Williamson MR, Jimenez LR, McCurdy CR, McMahon LR (2020) The adrenergic a2 receptor-mediated discriminative-stimulus effects of mitragynine, the primary alkaloid in Kratom (Mitragyna speciosa) in rats. FASEB J 34(S1):1. https://doi.org/10.1096/fasebj.2020.34.s1.05233

Schimmel J, Amioka E, Rockhill K, Haynes CM, Black JC, Dart RC, Iwanicki JL (2021) Prevalence and description of kratom (Mitragyna speciosa) use in the United States: a cross-sectional study. Addiction 116(1):176–181. https://doi.org/10.1111/add.15082

Schuman-Olivier Z, Hoeppner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ (2013) Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. Drug Alcohol Depend 132(3):580–586. https://doi.org/10.1016/j.drugalcdep.2013.04.006

Sharma A, Kamble SH, León F, Chear NJ, King TI, Berthold EC, Ramanathan S, McCurdy CR, Avery BA (2019) Simultaneous quantification of ten key Kratom alkaloids in Mitragyna speciosa leaf extracts and commercial products by ultra-performance liquid chromatography-tandemmass spectrometry. Drug Test Anal 11(8):1162–1171. https://doi.org/10.1002/dta.2604

Sharma A, McCurdy CR (2021) Assessing the therapeutic potential and toxicity of Mitragyna speciosa in opioid use disorder. Expert Opin Drug Metab Toxicol 17(3):255–257. https://doi.org/10.1080/17425255.2021.1853706

Singh D, Narayanan S, Vicknasingam B (2016) Traditional and non-traditional uses of Mitragynine (Kratom): a survey of the literature. Brain Res Bull 126(Pt 1):41–46. https://doi.org/10.1016/j.brainresbull.2016.05.004

Suhaimi FW, Hassan Z, Mansor SM, Müller CP (2021) The effects of chronic mitragynine (Kratom) exposure on the EEG in rats. Neurosci Lett 745:135632. https://doi.org/10.1016/j.neulet.2021.135632

Swogger MT, Walsh Z (2018) Kratom use and mental health: a systematic review. Drug Alcohol Depend 183:134–140. https://doi.org/10.1016/j.drugalcdep.2017.10.012

Swogger MT, Smith KE, Garcia-Romeu A, Grundmann O, Veltri CA, Henningfield J, Busch LY (2022) Understanding kratom use: a guide for healthcare providers. Front Pharmacol 13:801855. https://doi.org/10.3389/fphar.2022.801855

Todd DA, Kellogg JJ, Wallace ED, Khin M, Flores-Bocanegra L, Tanna RS, McIntosh S, Raja HA, Graf TN, Hemby SE, Paine MF (2020) Chemical composition and biological effects of kratom (Mitragyna speciosa): in vitro studies with implications for efficacy and drug interactions. Sci Rep 10(1):19158. https://doi.org/10.1038/s41598-020-76119-w

U.S. Department of Health and Human Services (2021) Overdose Prevention Strategy. https://www.hhs.gov/overdose-prevention/. Accessed 8 March 2022

U.S. Drug Enforcement Administration (DEA) (2016) DEA Rulemaking Docket, Comment on FR Doc # 2016–24659, Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine into Schedule I. Public comments on FR Doc # 2016–24659 (23,220 public comments). https://www.regulations.gov/docket/DEA-2016-0015/comments. Accessed 8 March 2022

Umbricht A, Huestis MA, Cone EJ, Preston KL (2004) Effects of high-dose intravenous buprenorphine in experienced opioid abusers. J Clin Psychopharmacol 24(5):479–487. https://doi.org/10.1097/01.jcp.0000138766.15858.c6

Underwood W, Anthony R (2020) AVMA guidelines for the euthanasia of animals: 2020 edition. American Veterinary Medical Association. https://www.spandidos-publications.com/var/AVMA_euthanasia_guidelines_2020.pdf. Accessed 9 March 2022

United Nations Commission on Narcotic Drugs (2021) Implementation of the international drug control treaties: changes in the scope of control of substances Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD), 11–15 October 2021: Kratom, mitragynine, 7-hydroxymitragynine. https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf. Accessed 10 March 2022

Váradi A, Marrone GF, Palmer TC, Narayan A, Szabó MR, Le Rouzic V, Grinnell SG, Subrath JJ, Warner E, Kalra S, Hunkele A, Pagirsky J, Eans SO, Medina JM, Xu J, Pan YX, Borics A, Pasternak GW, McLaughlin JP, Majumdar S (2016) Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β-arrestin-2. J Med Chem 59(18):8381–8397. https://doi.org/10.1021/acs.jmedchem.6b00748

Veltri C, Grundmann O (2019) Current perspectives on the impact of Kratom use. Subst Abuse Rehabil 10:23–31. https://doi.org/10.2147/SAR.S164261

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

Wilson LL, Harris HM, Eans SO, Brice-Tutt AC, Cirino TJ, Stacy HM, Simons CA, León F, Sharma A, Boyer EW, Avery BA (2020) Lyophilized kratom tea as a therapeutic option for opioid dependence. Drug Alcohol Depend 216:108310. https://doi.org/10.1016/j.drugalcdep.2020.108310

World Health Organization, Expert Committee on Drug Dependence (WHO ECDD) (2021) Pre-review report: kratom (*Mitragyna speciosa*), mitragynine, and 7-hydroxymitraginine for the forty-fourth meeting of the ECDD, Geneva, 11–15 October 2021. https://www.who.int/publications/m/item/kratom-mitragynine-7-hydroxymitragynine-critical-review-report. Accessed 8 March 2022

Xu L, Chockalingam A, Stewart S, Shea K, Matta MK, Narayanasamy S, Pilli NR, Volpe DA, Weaver J, Zhu H, Davis MC, Rouse R (2020) Developing an animal model to detect drug-drug interactions impacting drug-induced respiratory depression. Toxicol Rep 7:188–197. https://doi.org/10.1016/j.toxrep.2020.01.008

Xu L, Krishna A, Stewart S, Shea K, Racz R, Weaver JL, Volpe DA, Pilli NR, Narayanasamy S, Florian J, Patel V, Matta MK, Stone MB, Zhu H, Davis MC, Strauss DG, Rouse R (2021) Effects of sedative psychotropic drugs combined with oxycodone on respiratory depression in the rat. Clin Transl Sci 14(6):2208–2219. https://doi.org/10.1111/cts.13080

Yue K, Kopajtic TA, Katz JL (2018) Abuse liability of mitragynine assessed with a self-administration procedure in rats. Psychopharmacology 235(10):2823–2829. https://doi.org/10.1007/s00213-018-4974-9

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REVIEW
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Kratom Abuse Potential 2021: An Updated Eight Factor Analysis

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Drugs are regulated in the United States (US) by the Controlled Substances Act (CSA) if assessment of their abuse potential, including public health risks, show such control is warranted. An evaluation via the 8 factors of the CSA provides the comprehensive assessment required for permanent listing of new chemical entities and previously uncontrolled substances. Such an assessment was published for two kratom alkaloids in 2018 that the Food and Drug Administration (FDA) have identified as candidates for CSA listing: mitragynine (MG) and 7-hydroxymitragynine (7-OH-MG) (Henningfield et al., 2018a). That assessment concluded the abuse potential of MG was within the range of many other uncontrolled substances, that there was not evidence of an imminent risk to public health, and that a Schedule I listing (the only option for substances that are not FDA approved for therapeutic use such as kratom) carried public health risks including drug overdoses by people using kratom to abstain from opioids. The purpose of this review is to provide an updated abuse potential assessment reviewing greater than 100 studies published since January 1, 2018. These include studies of abuse potential and physical dependence/withdrawal in animals; *in-vitro* receptor binding; assessments of potential efficacy treating pain and substance use disorders; pharmacokinetic/pharmacodynamic studies with safety-related findings; clinical studies of long-term users with various physiological endpoints; and surveys of patterns and reasons for use and associated effects including dependence and withdrawal. Findings from these studies suggest that public health is better served by assuring continued access to kratom products by consumers and researchers. Currently, Kratom alkaloids and derivatives are in development as safer and/or more effective medicines for treating pain, substances use disorders, and mood disorders. Placing kratom in the CSA via scheduling would criminalize consumers and possession, seriously impede research, and can be predicted to have serious adverse public health consequences, including potentially thousands of drug overdose deaths. Therefore, CSA listing is not recommended. Regulation to minimize risks of contaminated, adulterated, and inappropriately marketed products is recommended.

Keywords: dietary supplement, safety, abuse potential, epidemiology, substance use disorder treatment, opioid pharmacology, Controlled Substances Act

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1 INTRODUCTION

This is an update to the Henningfield et al. (2018) assessment of the abuse potential of kratom based on the eight factors of the United States Controlled Substances Act (US CSA) (Henningfield et al., 2018a) and summarizes new scientific findings from January 2018 through August 2021. The CSA eight factors evaluate pharmacological actions in the brain or central nervous system (CNS) that may lead to dependence, substance use disorders, or addictions (American Psychiatric Association, 2013; National Institute on Drug Abuse, 2019; World Health Organization, 1994; O'Brien et al., 2011). Abuse potential assessments determine whether substances and medicinal products should be controlled by the CSA (scheduled), and if so the restrictiveness or level of control. Substances are only placed in Schedule I (heroin, LSD, cannabis) when there is no FDA approved therapeutic use and sufficient abuse potential to merit control. Substances with approved therapeutic uses and sufficient abuse potential must be placed in Schedules II–V. By law, an eight-factor analysis (8-FA) provides the primary pharmacological and public health basis for drug scheduling (Food and Drug Administration, 2017a; Belouin and Henningfield, 2018; Johnson et al., 2018). This assessment focuses on kratom and its alkaloids, in particular mitragynine (MG), the primary alkaloid in kratom present in sufficient amounts to account for its effects.

Kratom and its alkaloids are not approved for any therapeutic use by the FDA, are not federally controlled in the US, nor in the International Drug Control Conventions; however some countries do control kratom and/or its two primary alkaloids, MG and 7-OH-MG (Prozialeck et al., 2019; International Narcotics C, 2020a; International Narcotics C, 2020b). Six states in the US (Alabama, Arkansas, Indiana, Tennessee, Vermont and Wisconsin) have banned kratom, while five have passed consumer protection legislation to ensure consumer access to kratom with a framework for regulatory oversight (Arizona, Georgia, Nevada, Oklahoma and Utah). Maryland rejected a proposed ban and passed a minimum age of purchase law (age 21), and at this writing, several states are considering their own kratom consumer protection laws to ensure consumer access but with regulatory oversight. In 2021, Thailand decriminalized kratom farming, possession and sales. In December, 2021, the World Health Organization Expert Committee on Drug Dependence concluded "there is insufficient evidence to recommend a critical review of kratom mitragynine and 7-hydroxymitragynine" [for potential scheduling] but should be kept under surveillance (Commission on Narcotic Drugs, 2021).

In August 2016 the US Drug Enforcement Agency (DEA) proposed scheduling kratom on a temporary "emergency" basis but withdrew the proposal due to thousands of comments from kratom consumers and bipartisan members of Congress, and out of concern that people who were managing their opioid use disorder with the aid of kratom would return to opioid use. The DEA requested that FDA perform a full 8-FA and develop its own independent recommendations related to scheduling (Ingraham, 2016a; Ingraham, 2016b). Subsequently, Dr. Henningfield and his colleagues at PinneyAssociates were commissioned by the American Kratom Association's legal regulatory counsel to develop an 8-FA (Pinney Associates (2016)) for submission to DEA by December 2, 2016. In November 2017, FDA Commissioner Scott Gottlieb announced that kratom carried "narcotic like" risks of addiction and death but did not make public its October 17th recommendation to DEA to permanently place MG and 7-OH-MG in Schedule I of the CSA (Food and Drug Administration, 2017b; Food and Drug Administration, 2017c).

DEA typically responds to formal 8-FA scheduling requests within 90 days, though there is no legal timeline; however, a formal scheduling rescission order was issued on August 18, 2018 from the Assistant Secretary of Health, US Department of Health and Human Services (DHHS) (Giroir, 2018). The order included conclusions based on a DHHS review consistent with those of the Henningfield et al. (2018) 8-FA (Henningfield et al., 2018a). The DHHS rescission letter stated "mitragynine does not satisfy the first of the three statutory requisites for Schedule I"; "There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses"; and "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." The letter also raised concerns about "the stifling effect of classification in Schedule l on critical research needed on the complex and potentially useful chemistry of components of kratom." This letter was not made public until January 2021.

In 2017, the National Institute on Drug Abuse (NIDA) substantially increased its active research program on kratom's alkaloids and derivatives as potentially safer and less abusable medicines for pain and addiction and other disorders. The purpose of this review is to provide an update of our 2018 article on the abuse potential of kratom. It includes more than 100 new studies related to kratom abuse potential, safety, patterns of use, and potential therapeutic and public health benefits.

2 METHODS

The intent was to include all new studies published in English relevant to kratom abuse potential, safety and mechanisms of action published in since January 1, 2018 with some essential earlier studies mentioned and referenced to our 2018 review.[1] This was by comprehensive online literature searches, and direct requests to leading kratom researchers worldwide. To be concise, factors 4, 5, and 6 are considered a single group of public health related factors.[2] (Henningfield et al., 2018a; Johnson et al., 2018). Factor 8 is unchanged as neither kratom nor its constituents are scheduled.

[1]The authors welcome communications from readers on abuse-potential and safety related kratom research published since 2018 that we might have missed.

[2]For formal FDA submissions Factors 4, 5, and 6 are considered separately (see Henningfield et al., 2018a and Johnson, Griffiths, Hendricks and Henningfield, 2018 as examples), however, for temporary (also known as "emergency") scheduling, determining if a substance poses an imminent health risk is based on the analysis of all three factors combined similarly to our approach in this review.

3 RESULTS

3.1 Factor 1: Actual or Relative Potential for Abuse

A summary of the references used, along with main findings and comments from the authors of this review are included in **Table 1**.

3.1.1 Summary of 2018 Findings

There were no animal intravenous drug self-administration (IV DSA), intracranial self-stimulation (ICSS) brain reward, or physical dependence/withdrawal studies of kratom's alkaloids; however, other data suggested relatively low abuse potential as compared to opioids and other drugs of abuse (Henningfield et al., 2018a). There was evidence of morphine opioid receptor (MOR) mediated effects, and preliminary drug discrimination and conditioned place preference (CPP) studies with rats suggested abuse related effects at high intolerable human dose equivalents.

Survey data from the US and field studies in Southeast Asia (SEA) showed most kratom use was for health-related benefits, and to facilitate occupational performance. Data indicated that problem abuse and addiction were not common and was generally more tolerable and readily self-manageable as compared to opioids. A frequent reason for use was as an opioid substitute for pain and self-management of opioid, alcohol, and other drug dependence.

3.1.2 Factor 1 Science Updates

3.1.2.1 Intravenous Drug Self-Administration Trials

Rates of MG self-administration were similar to those of saline, and MG pretreatment produced dose-related reductions in morphine self-administration rates (Hemby et al., 2019). The authors concluded "The present findings indicate that MG does not have abuse potential and reduces morphine intake, desired characteristics of candidate pharmacotherapies for opiate addiction and withdrawal … ". 7-OH-MG was self-administered at high doses and pretreatment increased morphine self-administration.

MG self-administration rates in rats did not exceed those obtained with saline and MG pretreatment decreased heroin self-administration, with little effect on methamphetamine self-administration (Yue et al., 2018). The authors noted "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." These results 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; Coe et al., 2019; Prozialeck et al., 2019; Garcia-Romeu et al., 2020).

Intracranial Self-Stimulation

In the ICSS model, rats equipped with brain electrodes self-deliver rewarding electrical brain stimulation. Opioids, amphetamine-like stimulants, cocaine, and other classic drugs of abuse reduce the stimulation threshold and increase the strength of the rewarding effects of drugs on ICSS (Negus and Miller, 2014). Neither MG nor 7-OH-MG showed evidence of brain rewarding effects, whereas morphine robustly and dose-dependently decreased the stimulation threshold (Behnood-Rod et al., 2020). Thus, the ICSS results suggest lower brain rewarding effects of MG as compared to morphine.

Drug Discrimination Studies

The discriminative stimulus effects of MG were evaluated in studies designed to assess generalization to morphine as well as the delta-opioid receptor agonist SNC80 and kappa-opioid receptor agonist U69593, alpha adrenergic agonists lofexidine, clonidine and phenylephrine, alpha adrenergic antagonists yohimbine and atipamezole, and the cannabinoid agonist Δ-9-tetrahydrocannabinol (Reeve et al., 2020). The strongest generalization was to lofexidine and phenylephrine, both unscheduled drugs: phenylephrine is in some over-the-counter cold medicines; lofexidine is approved for several indications including the first nonopioid for alleviating opioid withdrawal.

In a comparison of MG and 7-OH-MG across studies that included *in vitro* receptor binding and an antinociception test, MG partially generalized to morphine, whereas 7-OH-MG fully generalized to morphine in rats (Obeng et al., 2021). Similarly, Hiranita et al. (2020) found only partial generalization of oral MG to i.p. morphine in rats (Hiranita et al., 2020).

3.1.2.4 Conditioned Place Preference

Various MG preparations produced mixed CPP effects with some suggesting abuse potential at high doses. A low priming injection of MG or morphine reinstated CPP after establishment with either drug, suggesting rewarding effects for both (Japarin et al., 2021). Baclofen pretreatment prevented the acquisition and expression of MG-induced CPP (Yusoff et al., 2018). CPP was achieved in mice with a high dose methanolic extract of kratom leaves (Vijeepallam et al., 2019). In a fourth study (see also Factor 2), lyophilized (freeze-dried) kratom tea (LKT), a potential treatment for pain and opioid dependence, did not induce CPP in mice (Wilson et al., 2020).

3.1.2.5 Physical Dependence and Withdrawal

Discontinuation of morphine administration produced response rate disruptions indicating significant signs of spontaneous withdrawal, whereas discontinuation of MG administration did not produce significant signs of spontaneous withdrawal. Naloxone administration did precipitate response rate disruptions indicating withdrawal in both MG and morphine treated rats, however, this withdrawal effect was weaker and shorter lived in MG treated rats as compared to morphine treated rats (Harun et al., 2020). MG treatment also reduced naloxone precipitated withdrawal in animals receiving chronic morphine, consistent with human reports. Hassan, Pike, See, Sreenlivasan et al. (2020) compared the efficacy of MG to methadone for treating morphine withdrawal in rats concluding that MG treatment attenuated withdrawal symptoms significantly, similar to methadone and buprenorphine, and potentially with less undesired effects (Hassan et al., 2020).

TABLE 1 | Summary of references.

Factor/Description	Citations	Main findings	Comments
Factor 1: Actual or relative potential for abuse			
Intravenous Self-Administration (IV SA)	(Prozialeck et al., 2019), (Grundmann et al., 2018; Yue et al., 2018; Coe et al., 2019; Hemby et al., 2019; Garcia-Romeu et al., 2020)	No evidence of reward	MG pretreatment reduced morphine self-administration
Intracranial Self-Stimulation (ICSS)	(Negus and Miller, 2014)-(Behnood-Rod et al., 2020)	No evidence of reward for MG or 7-OH-MG	
Drug Discrimination	(Hiranita et al., 2020; Reeve et al., 2020; Obeng et al., 2021)	MG showed partial generalization to multiple drugs, including morphine 7-OH-MG showed full generalization to morphine	Strongest generalization of MG was to unscheduled drugs: phenylephrine and lofexidine
Conditioned Place Preference (CPP)	(Yusoff et al., 2018; Vijeepallam et al., 2019; Wilson et al., 2020; Japarin et al., 2021)	Mixed evidence of CPP	
Physical Dependence/ Withdrawal	(Harun et al., 2020; Hassan et al., 2020; Johari et al., 2021; Hassan et al., 2021; Hassan et al., 20211778; Harun et al., 2021a)	Mixed evidence of weak withdrawal across studies relative to morphine	MG reduces morphine withdrawal and differs from morphine withdrawal on some measures
Survey Data	(Prozialeck et al., 2019), (Grundmann et al., 2018; Coe et al., 2019; Garcia-Romeu et al., 2020), (Singh et al., 2014; Galbis-Reig, 2016; Swogger and Walsh, 2018; Smith et al., 2019; Harun et al., 2021b)	Majority use is for health benefits, not recreational use or to get high. Use is almost exclusively oral, without the tendency of many recreational substance to smoke, inject, and/or nasally insufflate	Most people reporting "kratom addiction" found it weaker and more tolerable and acceptable than "drug" addiction and were more likely so use it to manage other addictions than to use addictively
Factor 2: Scientific evidence of pharmacological effect			
Potential Therapeutic Effects	(Behnood-Rod et al., 2020; Obeng et al., 2021), (Vicknasingam et al., 2020; Chakraborty et al., 2021a)	Kratom's antinociceptive effects appear to be mediated at least partly by 7-OH-MG metabolite formation	Animal study findings are consistent for use to manage opioid use disorder and withdrawal, pain and suggest exploration for other disorders
Mechanisms of Action	(Prozialeck et al., 2019), (Behnood-Rod et al., 2020), (Hassan et al., 2019; Hiranita et al., 2019; Kruegel et al., 2019; Gutridge et al., 2020; Todd et al., 2020; Suhaimi et al., 2021)	Kratom alkaloids, including 7-OH-MG may interact with opioid receptors, but do not recruit β-arrestin 2	These are consistent with little or no respiratory depression across a broad range of doses and conditions
Kratom Minor Alkaloids and Metabolites	(Kruegel et al., 2019; Chakraborty et al., 2021a; León et al., 2021; Sharma and McCurdy, 2021), (Newman and Cragg, 2016; Sharma et al., 2019; Domnic et al., 2021a; Domnic et al., 2021b; Chear et al., 2021)	Most minor kratom alkaloids and metabolites are in de minimis levels	Some minor alkaloids might influence kratom's pharmacological effects and merit evaluation for potential therapeutic uses at much higher doses than provided by kratom
Metabolism and Metabolite Profiling	(Kamble et al., 2019; Kamble et al., 2020a; Kamble et al., 2020b)	7-OH-MG appears to metabolize differently in humans than in other species (e.g., rats, dogs, monkeys)	Animal models for kratom alone may not be fully predictive of human effects
Factor 3: Current state of scientific knowledge			
MG and 7-OH-MG PK/PD	(Hiranita et al., 2020), (Avery et al., 2019; Jagabalan et al., 2019; Maxwell et al., 2020)	Greater exposure observed with natural kratom formulations than with oral MG	
Minor Alkaloids PK/PD	(King et al., 2020; Berthold et al., 2021; Kamble et al., 2021)	Approximately one third of minor alkaloids are characterized	
Clinical Studies	(Singh et al., 2018a; Singh et al., 2018b; Singh et al., 2019a; Singh et al., 2020a; Leong Bin Abdullah et al., 2020; Leong Abdullah et al., 2021)	Long term users of kratom have no significant differences in most physiological measures compared to nonusers	These should not be considered definitive safety data but provide a foundation for further studies
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			
U.S. National and Federal Survey Data	(National Institute on Drug Abuse, 2019), (Coe et al., 2019)-(Garcia-Romeu et al., 2020), (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020; Grundmann, 2017; Drug Abuse Warning Network, 2020; Drug Enforcement Adm, 2020a; Substance Abuse and Menta,	NSDUH Lifetime Use: 1.4%; Past Year Use 0.7%. Little evidence of use on other federal surveys either because kratom was not specifically included or did not meet the threshold for reporting	Federal survey data provide no evidence that kratom poses an imminent threat to public health but merits continuing monitoring to better understand trends in use

(Continued on following page)

TABLE 1 | (*Continued*) Summary of references.

Factor/Description	Citations	Main findings	Comments
Kratom Use Prevalence	2020; Drug Enforcement Adm, 2020b; Grundmann et al., 2021; Miech et al., 2021) (U.S. Department of Health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020), (Botanical Education Alliance, 2016)	Estimates range from 1.8 million to over 16 million users in the US	It appears likely that there are at least 10 million kratom users in the US but more definitive studies are needed
Kratom Use Associated Mortality	(National Institute on Drug Abuse, 2019), (Giroir, 2018), (Food and Drug Admini, 2018; Gershman et al., 2019; Henningfield et al., 2019; Olsen et al., 2019)	Risk of kratom associated death appears to be at least a thousand times lower than for morphine-like opioids	Approximately 80% of kratom positive or "involved" deaths also detected other drugs of abuse or the decedent had a history of substance use disorders in one study contribution by other drugs not possible to rule out
Mortality Risks Projected as a Result of Banning Licit Kratom	(Henningfield et al., 2018a), (Ingraham, 2016b), (Giroir, 2018), (Grundmann et al., 2018; Coe et al., 2019; Garcia-Romeu et al., 2020), (Grundmann, 2017), (Henningfield et al., 2018b; Henningfield et al., 2018c; Henningfield et al., 2018d; Prozialeck et al., 2020)	Surveys suggest that it is likely that some kratom users would return to opioid use if kratom use and possession is banned	Fears of relapse to opioid use was a serious concern voiced by thousands of users in surveys and comments to DEA and FDA
Public Health and Individual Benefits of Kratom	(Henningfield et al., 2018a), (Prozialeck et al., 2019), (Coe et al., 2019)-(Garcia-Romeu et al., 2020), (Swogger and Walsh, 2018), (Grundmann, 2017), (Drug Enforcement Adm, 2016), (Raffa, 2014)-(Pain News Network, 2018)	Kratom is used by millions of people in the US to manage substance use disorders, pain, mood disorder, and for energy and improved mental focus and alertness	Reasons for use of kratom rather than FDA approved medications included better efficacy, presumed lower risks and because it is more accessible and tolerable, and/or preferred as a "natural product". Note: such data should not be used to support therapeutic claims in labeling or marketing
Kratom Use for Managing Opioid Use/Withdrawal and Other Health Reasons	(Coe et al., 2019), (Grundmann, 2017), (Singh et al., 2019b; Singh et al., 2020b; Singh et al., 2020c)	Surveys in US and SEA report kratom is used mostly for its health benefits, including opioid withdrawal	Although management of opioid use and withdrawal is prominent, nonclinical data suggest that use for other substance use disorder management and many other disorders merit further exploration
Comment on Therapeutic Use in Context of FDA Standards	(Katz, 2004; DiMasi et al., 2016; Food and Drug Admini, 2016; Dabrowska and Thaul, 2018; Wouters et al., 2020)	While research has yet to meet FDA's standard for therapeutic efficacy (NDA), there is substantial evidence of its use and efficacy in treating opioid withdrawal symptoms, and other disorders	
Factor 7—The psychic or physiological dependence liability			
Science Updates	(Hemby et al., 2019), (Coe et al., 2019)-(Garcia-Romeu et al. 2020), (Swogger and Walsh, 2018), (Harun et al., 2021b)-(Vicknasingam et al., 2020), (Grundmann, 2017), (Grundmann et al., 2021), (Swogger et al., 2015; Smith and Lawson, 2017; Singh et al., 2018c; Leong Bin Abdullah et al., 2021)	Some chronic, frequent kratom users report dependence/addition and/or withdrawal, but this is generally more readily self-managed compared to use disorders of other drugs of abuse	

Although MG withdrawal signs are weak in rats compared to those from morphine withdrawal, there does appear to be evidence of physical dependence; however, MG withdrawal unlike morphine was not associated with anxiogenic-like subjective symptoms. When using a pentylenetetrazol (PTZ) discrimination trial to evaluate anxiogenic signs in rats after MG or morphine withdrawal precipitated by naloxone, MG showed no substitution to the PTZ discriminative stimulus, while morphine produced a dose-related PTZ-like stimulus, further supporting MG as a novel pharmacotherapeutic intervention for managing opioid use disorder (Johari et al., 2021).

Other studies of opioid or MG withdrawal suggested that specific brain proteins might serve as more sensitive biomarkers for physiological dependence in rats as compared to behavioral signs (Hassan et al., 2021). Clonidine treatment may attenuate MG withdrawal signs in rats (Hassan et al., 2021). Another recent study employed an open-field test and an elevated-plus maze test to evaluate naloxone-precipitated withdrawal from MG as compared to morphine, and provided additional evidence confirming that MG can induce physical dependence and measurable signs of withdrawal in rats (Harun et al., 2021a). Overall, the research is consistent with human reports that

kratom withdrawal is generally more modest and more readily self-manageable than that produced by opioids (e.g., 22 and as discussed in Factor 7).

3.1.2.6 Real World Evidence of Abuse and Dependence

Factors 4–6 discuss the public health aspects of kratom use; however, many of the same studies address Factor 1 concerning evidence for abuse and are mentioned here.

As reported by Henningfield, et al. (2018), although surveys and anecdotal reports in the US and SEA confirm that some kratom consumers reported "addiction" those studies also indicated that use "to get high" is relatively low as compared to opioids and other recreational drugs of abuse, and that use by smoking, injecting, and/or insufflating was rare as compared to opioids, stimulants and other recreational drugs (Henningfield et al., 2018a). Recent studies confirm that kratom intake can lead to 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 drugs such as opioids, alcohol, and stimulants (Singh et al., 2014; Galbis-Reig, 2016; Swogger and Walsh, 2018; Prozialeck et al., 2019).

A variety of reports confirm kratom use to self-manage opioid withdrawal and that abstinence from high chronic kratom use is typically associated with milder symptomatology than abstinence from classical opioids (Grundmann et al., 2018; Smith et al., 2019; Garcia-Romeu et al., 2020). The conclusion of Prozialeck et al. (2019) and Grundmann et al. (2018) (Grundmann et al., 2018; Prozialeck et al., 2019) were further strengthened by two published US surveys which found that the overwhelming majority of kratom consumers reported that their use was for various health benefits and not for recreational purposes (Coe et al., 2019; Garcia-Romeu et al., 2020; Harun et al., 2021b).

3.1.3 Factor 1 Updated Conclusion

Diverse scientific approaches were employed to profile MG's abuse potential, finding no evidence of rewarding effects in the IV self-administration and ICSS models, and weak evidence of potential reward in the CPP procedure. MG only partially generalizes to morphine and more fully generalizes to the nonscheduled alpha-adrenergic agonists, phenylephrine and lofexidine. The new data suggest relatively low abuse potential as compared to morphine-like opioids, stimulants, and other 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. These findings are generally consistent with human reports that MG has a relatively low abuse and withdrawal potential as compared to recreationally used 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 (also discussed in Factors 4, 5, and 6). New studies discussed in Factors 2–7 contribute further to the understanding of kratom's abuse potential, including its public health risks and benefits, that are part of the 8-factor abuse potential assessment.

3.2 Factor 2—Scientific Evidence of its Pharmacological Effects

3.2.1 Summary of 2018 Findings

MG and 7-OH-MG have some MOR mediated effects, but 7-OH-MG occurs at low concentrations in kratom leaves and is absent in many kratom product derivatives suggesting that the effects reported by kratom consumers are due primarily to MG. Some kratom effects were shown to be naloxone reversible (e.g., "pain" tolerance); however, MG and 7-OH-MG mechanisms of action were diverse and mediated by non-opioid transmitters and pathways (Kruegel and Grundmann, 2018). Thus, characterization of MG as an opioid "analog" or "narcotic like opioid" is not consistent with the overall evidence, leading Henningfield et al. (2018) to conclude "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 occur in marketed products and brewed extracts" (Henningfield et al., 2018a).

3.2.2 Factor 2 Science Updates

3.2.2.1 Potential Therapeutic Effects

Although neither kratom nor any of its alkaloids are approved for therapeutic use for any disorder, surveys discussed in *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* and elsewhere (Henningfield et al., 2018a; Grundmann et al., 2018; Swogger and Walsh, 2018; Coe et al., 2019; Prozialeck et al., 2019; Garcia-Romeu et al., 2020) show individuals in the US and around the world describe using kratom for its health benefits. Research characterizing kratom's effects, mechanisms of action, and therapeutic kratom alkaloid use rapidly advanced since 2018. In a placebo-controlled cold pressor task evaluating anti-nociceptive effects, pain tolerance was significantly increased following consumption of a kratom tea-type decoction similar to Malaysian preparations (Vicknasingam et al., 2020). These data provided "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".

Consistent with Vicknasingam et al. (2020)'s clinical findings, oral LKT administration to mice produced dose-related antinociceptive effects at doses that did not alter locomotion or produce CPP; there were brief, non-life threatening decreases in respiration (Behnood-Rod et al., 2020). Repeated LKT administration produced no physical dependence, but significantly decreased naloxone-precipitated withdrawal in morphine dependent mice, confirming MOR agonist activity and therapeutic LKT effect for treating pain and opioid physical dependence.

After investigating *in vitro* receptor binding affinity and *in vivo* morphine discrimination, antinociception in the "heated plate" pain test, and naloxone challenge tests in rats, the authors concluded "At human m-opioid receptor (MOR) *in vitro*, mitragynine has low affinity and is an antagonist . . . ". Overall, 7-OH-MG had stronger MOR mediated effects including antinociception (Obeng et al., 2021). An extensive series of tests characterized several minor indole and oxindole alkaloids that the authors suggest are insufficient in abundance to account for the biological effects of kratom but may show promise for the development of potential medicines including potential new chemical entities (Chakraborty et al., 2021a).

Several of these studies showed MOR mediated antinociceptive effects with little evidence of respiratory depression suggesting the potential to contribute to new generations of nonopioid analgesics.

3.2.2.2 Mechanisms of Action

Although kratom produces some effects in common with opioids, and some of its alkaloid's actions are mediated by MOR receptors, its effects and mechanisms of action are diverse and include non-opioid mechanisms of action and non-opioid acting constituent alkaloids, as discussed in earlier reviews (Henningfield et al., 2018a; Kruegel and Grundmann, 2018; Prozialeck et al., 2019). In 2021, Leon et al. (2021) investigated several alkaloids, including mitragynine, paynantheine and speciogynine that produce serotonergic effects potentially mediated by their metabolites. As the authors discuss, such actions would be consistent with some of the mood enhancing effects attributed to kratom (Kruegel and Grundmann, 2018; Sharma and McCurdy, 2021).

Kratom contains approximately 1–2% MG by weight, as well as other alkaloids (including 7-OH-MG) that typically are present at such low levels in kratom leaf material that it is uncertain if they contribute to kratom effects (Prozialeck et al., 2019). 7-OH-MG is present in low concentrations in natural kratom products, but gradually emerges *in vivo* as a MG metabolite. Kruegel et al. (2019) studied its role as a mediator of MG effects (Kruegel et al., 2019) summarizing "7-hydroxymitragynine is formed from mitragynine in mice and . . . brain concentrations of this metabolite are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of mitragynine . . . it suggests a possible explanation for the seemingly improved safety profile of mitragynine compared to classical opioid agonists . . . 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." Hiranita, Sharma, Oyola et al. (2020) reported although "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" (Behnood-Rod et al., 2020).

Kratom is commonly consumed to enhance occupational performance and as a coffee substitute for energy at low doses. In an animal model of spatial learning and memory, high doses impaired memory (Hassan et al., 2019). Suhaimi, Hassan, Mansor and Müller (2021) reported changes in brain electroencephalogram (EEG) activity after acute and chronic MG exposure in rats, with strong effects on some measures at high doses, supporting the importance of more research on brain function and potential cognitive effects (Suhaimi et al., 2021).

Gutridge et al. (2020) pharmacologically characterized interactions between kratom extracts, kratom alkaloids, and synthetic carfentanil-amide opioids with G-proteins and beta-arrestin at mu, delta and kappa opioid receptors *in vitro,* and assessed whether they had rewarding properties and the degree to which they reduced alcohol intake (Gutridge et al., 2020). The authors concluded 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." These findings were further supported by the findings by Todd et al. (2020) who concluded "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" (Todd et al., 2020).

Hiranita et al. (2019) compared the effects of MG to morphine in behavioral and antinociception assays in rat models finding "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" (Hiranita et al., 2019).

3.2.2.3 Studies of Kratom Minor Alkaloids and Their Metabolites, and Analogs

Advances in analytical methods are accelerating our understanding of the effects of numerous kratom alkaloids including liquid chromatography–tandem mass spectrometry assays that quantify kratom alkaloids in kratom leaf extracts and commercial products (Sharma et al., 2019).

Most of these alkaloids are present at de minimis levels with respect to human experience, effects, and safety; however, it is possible that while the majority of natural plant-based kratom preparation effects are mediated by MG, one or more minor alkaloids may also play a minor role and account for differences in kratom strains (Kruegel et al., 2019; Chear et al., 2021).

An *in vitro* pharmacological characterization of five kratom based minor alkaloids found that their low abundance made it unlikely that these alkaloids play a major mediating role in the biological actions of kratom consumed by humans, but this research may contribute to furthering the understanding of kratom mechanisms of action and opioid receptor function (Chakraborty et al., 2021a).

Kratom alkaloids are of interest as templates for novel synthesized molecules (i.e., analogs) for new medicines. One third to one half of FDA-approved medicines are based on natural plant product substances from which novel chemical entities were developed (Newman and Cragg, 2016; Domnic et al., 2021a). Such efforts are actively in progress characterizing a variety of indole and oxindole alkaloids, determining their chemical structures, and binding affinities for opioid and other receptors (Chear et al., 2021). One approach to the synthesis of novel MG analogs produced several partial MOR agonists with low G-protein activation (Chakraborty et al., 2021b). These analogs demonstrated robust analgesic effects but low respiratory depressant, locomotor, and conditioned place preference suggesting lower adverse effects including abuse potential.

Combinations of kratom alkaloids may inhibit cell proliferation and migration of nasopharyngeal carcinoma cells suggesting alkaloid or new analogs as potential cancer treatments (Domnic et al., 2021b).

3.2.2.4 MG Metabolism and Metabolite Profiling

Thirteen MG metabolites were identified in human liver microsomes (HLM) and S9 fraction studies (Kamble et al., 2019), and potential MG and other kratom alkaloids drug interactions were investigated including with pharmaceutic products (Kamble et al., 2020a).

7-OH-MG can be converted to pseudoindoxyl-MG in human plasma to a greater extent than is produced in mice, rats, dogs and cynomolgus monkeys, possibly explaining potential human effects and benefits that may not be predicted in animal studies alone (Kamble et al., 2020b).

3.2.3 Factor 2 Updated Conclusion

Kratom's main effects are due to the consumption of MG, but other minor alkaloids and metabolites, including 7-OH-MG, may also contribute to effects reported by consumers. Since 2018, many scientific advances improved our understanding of how these alkaloids and metabolites interact. Some alkaloids that contribute little to the effects of kratom 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 this rapidly advancing science is explaining how kratom works, and why its pain relieving, and other benefits occur with relatively low levels of abuse, dependence, and harmful decreases in respiration compared to opioids.

3.3 Factor 3—The State of Current Scientific Knowledge Regarding the Drug

3.3.1 Summary of 2018 Findings

The 2018 8-FA highlighted kratom's pharmacodynamic effects. Preclinical anti-nociceptive studies suggested that MG and 7-OH-MG produced such effects mediated by MOR receptors. Most information about the effects of long-term use in humans on various physiological, and cognitive parameters was based on anecdotal reports, case histories, and preliminary field studies in SEA. A two-compartment model best described human oral MG pharmacokinetics (Trakulsrichai et al., 2015).

3.3.2 Factor 3 Science Updates

New kratom pharmacokinetics studies in rats, mice and dogs document plasma MG, 7-OH-MG, and other alkaloids and minor metabolites over 12 h or more, with accompanying safety assessments. Six new clinical studies following long-term kratom use provide safety data on health, and organ and brain function were also conducted.

3.3.2.1 Pharmacokinetics and Pharmacodynamics Findings Related to MG and 7-OH-MG Safety

After oral administration of traditional or other natural kratom formulations to rats, greater systemic exposure was observed than that of an equivalent oral MG dose alone; no adverse events were reported (Avery et al., 2019).

Administration of 5 mg/kg oral MG (equivalent to approximately 3 mg/kg in humans) and 0.1 mg/kg IV MG to beagle dogs was well tolerated and produced no adverse events or major abnormalities in clinical parameters (Maxwell et al., 2020).

The estimated MG clearance (CL/F) was 2.21 L/h, absorption rate (Ka) 0.82/h, and volume of distribution (Vd) 30.8 L after oral 20, 40, and 80 mg/kg MG doses to rats (Jagabalan et al., 2019). Oral 55 mg/kg MG produced 85 ng/ml Cmax for 7-OH-MG, 14 times lower than the MG Cmax. Anti-nociception after IV MG and 7-OH-MG suggested that 7-OH-MG was more potent and efficacious than MG, and metabolic formation of 7-OH-MG contributes to *in vivo* MOR mediated effects of oral MG (Hiranita et al., 2020).

3.3.2.2 Pharmacokinetic and Pharmacodynamic Findings With Kratom's Minor Alkaloids

MG, 7-OH-MG, corynantheidine, speciogynine, speciociliatine, paynantheine, corynoxine, corynoxine-B, mitraphylline, ajmalicine, and isospeciofoline were analyzed in rat plasma after a variety of oral kratom products, with only MG, 7-OH-MG, speciociliatine, and corynantheidine quantifiable at 8 h (Kamble et al., 2021).

Speciociliatine pharmacokinetics were characterized following IV and oral dosing to help understand the potential contribution of this alkaloid to *in vivo* kratom administration effects (Berthold et al., 2021). Speciociliatine had higher systemic exposure and lower clearance compared to the other kratom alkaloids mitragynine and corynantheidine. Similarly, the pharmacokinetics of corynanthidine, a minor kratom alkaloid and perhaps a MOR antagonist, were determined after 2.5 mg/kg IV and 20 mg/kg oral doses to rats, yielding a 50% oral bioavailability, a 4.1 h Tmax and extensive distribution including in brain corpus callosum and hippocampus regions (King et al., 2020).

3.3.2.3 Safety Assessments From Clinical Studies

Kratom's anti-nociceptive effects in the cold pressor test are described in Factor 2 and its potential for physiological dependence and withdrawal are discussed in Factor 7 (Vicknasingam et al., 2020). This section summarizes six new clinical studies that assessed health and safety endpoints.

Leong Bin Abdullah et al. (2020) studied the lipid profiles, liver function and blood chemistries in 100 chronic kratom users and 100 healthy nonusers in Malaysia finding that 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."

Singh, Muller, Murugaiyah et al. (2018) studied various hematological and clinical-chemistry parameters of kratom users in Malaysia (Singh et al., 2018a). They interviewed and collected blood samples from 58 "regular kratom users" and 19 "healthy controls." Findings showed 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 users. 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.

Singh, Narayanan, Grundmann et al. (2020), studied the long-term effects of kratom use in thirteen people in Malaysia who used kratom longer than 20 years in a cross-sectional pilot study (Singh et al., 2020a). 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 ≥87.54 mg mitragynine) kratom consumption was not associated with altered biochemical levels, although prolonged and chronic, frequent use (>3 glasses daily) may result in cardiovascular risks." Note that this study was not designed to determine if kratom or other factors contributed to higher lipid values.

Singh, Chye, Suo et al. (2018) conducted 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. They reported "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. 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" (Singh et al., 2018b).

Singh, Narayanan, Muller et al. (2019) studied potential long-term cognitive effects associated with kratom use in kratom uses in Malaysia with assessments performed using the Cambridge Neuropsychological Test Automated Battery (Singh et al., 2019a). Relative to control participants, higher consumption (>3 glasses daily or mitragynine doses between 72.5 and 74.9 mg) of kratom tea was selectively associated with impaired performance on the Paired Associates Learning task of the Cambridge Neuropsychological Test Automated Battery, reflecting deficits in visual episodic memory and new learning.

Leong Bin Abdullah, Tan, et al., evaluated the prevalence of ECG abnormalities and QTc intervals in kratom users without histories of illicit drug use. Sinus tachycardia was higher in kratom users. Daily kratom consumption was associated with borderline QTc intervals (Leong Abdullah et al., 2021). Another study by Leong Bin Abdullah and Singh found that people who consumed four or more glasses of kratom tea daily had higher MG concentrations than lower intake consumers and this higher intake was associated with prolonged QTc intervals (Leong Bin Abdullah and Singh, 2021a). The same authors published a comprehensive review of the cardiovascular and cardiotoxic effects of kratom and came to the conclusion that limitations in studies to date do not permit definitive conclusions about the cardiovascular risks (Leong Bin Abdullah and Singh, 2021b).

3.3.3 Factor 3 Updated Conclusion

Pharmacokinetics and safety data from multiple species, kratom preparations, alkaloids, and metabolites; advances in bioanalytical assays providing more accurate and reliable findings; and data from multiple studies with MG doses many times higher than those human kratom users take are now available. These studies add to those described in Factors 1 and 2 confirming little evidence of serious adverse or life-threatening effects over a broad range of doses, dosage forms, and in four species (mouse, rat, dog, and monkey).

Other major advances in kratom science come from six clinical studies of long term kratom use effects and safety, as well as the study of anti-nociceptive effects of kratom and physiological dependence described in Factors 2 and 7. These important advances in kratom science 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 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.

3.4 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

3.4.1 Summary of 2018 Findings

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. The Henningfield et al., 2018 8-FA considered all major relevant federal surveys, as well as data from internet monitoring, and more than 20,200 comments to the DEA, and concluded that there was no evidence of an imminent public health threat associated with kratom (Henningfield et al., 2018a). To the contrary, the review concluded that there were foreseeable health risks including opioid overdose and deaths if lawful kratom was banned and possession criminalized. Moreover, although kratom is not approved as safe and effective for therapeutic use, it was evident that most kratom use in the US was for health and well-being by people who personally found kratom to be more effective, tolerable, accessible and/or preferred a natural product as compared to FDA approved medicines.

3.4.2 Factors 4, 5, and 6 Science Updates

3.4.2.1 U.S. National and Federal Survey Data

Table 2 summarizes the main findings from the major national and federal surveys and other data sources. Overall, there are more similarities than differences with respect to demographics reported in this table as well as in other demographics reported in the published survey results. Prevalence appears to be substantially underestimated by the NSDUH and RADARS surveys (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021).

NSDUH, RADARS, and Covvey et al. did not report reasons for use; however, many kratom users reported past or present use of opioids and/or drug addiction treatment consistent with past findings that self-management of addiction and withdrawal is a common reason for kratom use (National Institute on Drug Abuse, 2019; Coe et al., 2019; Garcia-Romeu et al., 2020; U.S. Department of health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020; Grundmann, 2017). Survey data incidence reports for DAWN, MTFS, NFLIS, and TEDS are apparently below the threshold for reporting as confirmed in an inquiry to NFLIS (Drug Enforcement Administration, 2020a; Drug Abuse Warning Network, 2020; Substance Abuse and Mental, 2020).

These findings do not support the conclusion that kratom use represents an imminent health threat and in fact kratom is not listed in the most recent DEA National Drug Threat Assessment (Drug Enforcement Administration, 2020b). There is no evidence that kratom is "fueling" or otherwise contributing to the opioid epidemic, though the survey data suggest that it is an informal self-management approach supporting the efforts of many opioid users to reduce and discontinue opioid use (Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020; Grundmann et al., 2021).

3.4.2.2 Kratom Use Prevalence

As mentioned in **Table 2**, the NSDUH and RADARS surveys may greatly underestimate the US prevalence and incidence of kratom use, with estimates of past year kratom use of 1,790,00–2,040,000.[3] (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021). In contrast, a credible estimate based on market data suggested prevalence of 3–5 million in 2014–2015 (Botanical Education Allia, 2016).

Experts and marketers agree that the kratom market substantially expanded since that time, with kratom export data from Indonesia to the US and major marketer consensus finding that the US consumer base was likely 10–16 million. This is consistent with a nationally projectable survey estimate from 2020 concluding past year kratom use as 4.1% or 10,500,000 kratom users (Covvey et al., 2020).

3.4.2.3 Kratom Use Associated Mortality

The two most widely cited estimates of kratom associated mortality are based on world-wide reports over nearly 10 years (Food and Drug Administration, 2018; Olsen et al., 2019). FDA's statement noted that all but one involved other substances, and that case was under further investigation.[4] Medical examiners or coroners reported kratom as the cause of death in 91 (59.9%) of 152 kratom positive decedents (out of 27,338 overdose deaths in 27 states), including seven for whom kratom was the only substance positive on postmortem toxicology, although other substances could not be ruled out (Olsen et al., 2019). In approximately 80% of kratom positive or "involved" deaths, decedents had a history of "substance misuse", with 65% of cases listing fentanyl as the cause of death, 32.9% heroin, followed by benzodiazepines, prescription opioids, and cocaine. An earlier study (Gershman et al., 2019) cautioned that comprehensive toxicology might identify other substances contributing or causing death. We are not aware that any of the 93,000 drug overdoses estimated for 2020 included deaths due to kratom. That does not mean that there were no deaths in which kratom was the primary cause or a contributing factor; however, the signal is clearly low.

An assessment of various survey data concluded that the risk of kratom associated death was at least a thousand times lower than for morphine-like opioids (Henningfield et al., 2019). This is consistent with NIDA's position (National Institute on Drug Abuse, 2019) and with the 2018 DHHS kratom scheduling rescission letter and the conclusions drawn by Assistant Secretary of Health Brett P. Giroir, MD, ADM who stated:

[3]Note in a summary of RADARS data presented a few months after the Schimmel et al., 2020 publication, it was reported that the national projected past year prevalence estimate was 3.35 million.

[4]FDA never reported the results of that investigation, however, the US DHHS review that led to the 2018 withdrawal of the 2017 MG and 7-OH-MG CSA scheduling recommendation determined that the incident in question was an automobile crash not attributable to kratom use.

TABLE 2 | Summary of data sources.

Survey/Data source	Main results and comment	Other comments
Drug Abuse Warning Network (Drug Abuse Warning Networ, 2020)	No reports in DAWN from 1970 to 2011 "New DAWN" began in 2019 and has not listed kratom	
Monitoring the Future Study (Miech et al., 2021)	Kratom use is not assessed	Note that 9% of NSDUH Reports were from age 12–17 year olds
National Forensic Laboratory Information Service (Drug Enforcement Adm, 2020a)	Since 2016 NFLIS did not include MG/kratom reports because the rates are below the threshold for inclusion	
National Survey on Drug Use and Health (U.S. Department of health and Human Services, 2020)	Paid responders on national panel (n = 67,625).[6] 2019 Prevalence Lifetime Use: 1.4%; Past Year Use: 0.7%	See Grundmann et al., 2021 and Henningfield et al., 2021 comment on apparent underestimation of kratom use prevalence (Grundmann et al., 2021; Henningfield et al., 2021)
Treatment Episodes Data Set (Substance Abuse and Menta, 2020)	No reports. This does not mean there were no reports but suggests subthreshold signal	Internet chatrooms and SUD treatment clinic advertising suggests some kratom users are seeking cessation assistance
Coe et al. (2019) (Coe et al., 2019)	Internet Survey of self-identified kratom users age ≥18 (n = 2,867) 48% use for self-management of pain 10% for self-management of opioid UD or withdrawal 22% use for mood management 2.4% use to get high	
Garcia-Romeu et al. (2020) (Garcia-Romeu et al., 2020)	Internet Survey of self-identified kratom users, age ≥18 (n = 2,798) 91% use for self-management of pain 41% for self-management of opioid UD or withdrawal 67% for management of anxiety 65% for depression <3% report kratom dependence	2% met DSM-5 criteria for past-year moderate or severe kratom-related SUD, but it was rated very low on scale of concern and adverse impact
Covvey et al. (2020) (Covvey et al., 2020)	Nationally representative Internet survey of persons aged 18–59 (n = 1842) 112 (6%) reported lifetime kratom use 72% were 25–44 years old, male, employed, and at higher educational levels 24–47% of respondents indicated self-reported diagnoses for any addiction, and 43% reported previously received treatment for addiction	Similar demographics as Grundmann 2017, Coe et al., 2019 and Garcia-Romeu et al., 2020 but may have underestimated % over 50 due to 59 year old upper age limit of survey. ((Coe et al., 2019), (Garcia-Romeu et al., 2020), (Grundmann, 2017)) Reasons for use were not asked, e.g., to self-manage pain, addiction, mood
Schimmel et al. (2021) (Schimmel et al., 2021)	RADARS® survey of paid survey responder on national panel age >18 (n = 59,714) 0.8% lifetime use 44% age >35 61% male 59% past year opioid use	Reasons for use were not asked, e.g., pain, addiction, mood. See Grundmann et al., 2021 and Henningfield et al., 2021 comment on apparent under estimation of kratom use prevalence (Grundmann et al., 2021; Henningfield et al., 2021)

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

3.4.2.4 Mortality Risks Projected as a Result of Banning Licit Kratom

Surveys and more than 20,000 comments to the DEA suggest that many kratom users fear resumption of opioid use and the need to resort to illicit kratom markets (Drug Enforcement Adm, 2016; Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020). It is not possible to project how many people would relapse to opioids and potentially overdose (Henningfield et al., 2018a; Henningfield et al., 2018b; Henningfield et al., 2018c; Henningfield et al., 2018d; Grundmann et al., 2018; Prozialeck et al., 2020). This was a concern of the DEA in withdrawing its 2016 kratom scheduling proposal (Ingraham, 2016b) and in the US DHHS kratom scheduling recission letter (Giroir, 2018).

3.4.2.5 Public Health and Individual Benefits of Kratom

In 2018, a systematic review of kratom use and mental health by Swogger and Walsh concluded ". . .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" (Swogger and Walsh, 2018). The

therapeutic potential of kratom based on surveys, anecdotal reports, and nonclinical research supports the plausibility of such benefits as discussed by other reviewers (Prozialeck et al., 2019; Hemby et al., 2019; Yue et al., 2018; Grundmann et al., 2018; Kruegel and Grundmann, 2018; Sharma and McCurdy, 2021; Swogger et al., 2018; Prozialeck et al., 2021).

The most important public health benefits with respect to mortality are widely agreed upon by kratom experts and surveys, and that is its use to self-manage opioid and other drug addiction and withdrawal symptoms, and thereby reduce use and overdose from far deadlier substances. This type of use is not unique in the US but was long reported in SEA (Raffa, 2014; Henningfield et al., 2018a). This was also reported in the first major US Internet survey of kratom use (Grundmann, 2017), as well as in subsequent surveys (Coe et al., 2019; Garcia-Romeu et al., 2020; Pain News Network (2018)). This was also a conclusion of a systematic review of 13 studies addressing kratom use and mental health in the US, SEA, and other countries and regions of the world, and a review by an international consortium of kratom researchers (Swogger and Walsh, 2018; Prozialeck et al., 2019).

While the opioid epidemic represents a highly visible and deadly epidemic in its own right, it is important to recognize that many millions use kratom as their preferred approach to managing other life-threatening disorders including pain, depression, anxiety, post-traumatic stress, fibromyalgia and more (Drug Enforcement Adm, 2016; Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020).

3.4.2.6 Kratom Use for Managing Opioid Use/Withdrawal and Other Health Reasons

In the first half-year of the COVID-19 pandemic, there was uncertainty about kratom supply by vendors and consumers, however, overall US supply was not affected. The main reasons for kratom use are pain relief (48%), anxiety, "PTSD" or depression (22%), increase energy or focus (10%), and "help cut down on opioid use and/or relieve withdrawal" (10%) (Coe et al., 2019). Side effects were generally minor, e.g., stomach upset, rarely required medical attention and rates and severity of "bad reactions" were generally similar to those reported by Grundmann (Grundmann, 2017).

Field studies with face-to-face interviews in Malaysia provide complementary evidence to US Internet surveys regarding reasons for use and potential benefits (Singh et al., 2019b). Motives related to mood and other factors in 116 regular kratom users employed the Drinking Motives Questionnaire (DMQ) to measure motives for kratom use, reported "heavy" kratom use as drinking more than three glasses daily (estimating that 1 glass contains 48.24–50.4 mg of mitragynine), with use associated with significantly higher means scores on the Coping and Enhancement scales. A field face-to-face survey of 92 long-term male kratom users found that 72 participants (78%) reported using kratom to "enhance sexual performance" and all but one found did their sexual performance did improve. Interestingly, among participants who described kratom intake for other reasons, 35% reported enhanced sexual performance (Singh et al., 2020b).

Patterns and reasons for use and demographics were investigated in 142 current and 62 former opioid polydrug users in Malaysia (Singh et al., 2020c). The alkaloid content of a kratom street sample was primarily MG, followed by paynantheine, speciociliatine, speciogynine, and "low levels" of 7-OH-MG. There were no significant differences in demographic characteristics between current and former opioid polydrug users except with respect to marital status, with current kratom users having a higher odds ratio of being single. 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; however, former opioid users were more likely to use kratom for mood elevating effects.

3.4.2.7 Comment on Therapeutic Use in Context of FDA Standards

It is important to note that the benefits documented in published surveys do not constitute the basis for therapeutic claims and no kratom product or kratom alkaloid is approved for therapeutic use in the US. The FDA and other federal agencies state that there is no proven therapeutic use for kratom despite evidence that millions of people in the US and many more in SEA use kratom primarily for therapeutic, beneficial use. That evidence includes peer reviewed surveys and field studies in the US and SEA, clinical and preclinical studies showing that MG's mechanisms of action are consistent with such effects. Moreover, several animal models used to predict efficacy for treating opioid use disorder, opioid withdrawal and pain demonstrated efficacy.

None of this research meets FDA's standard for therapeutic efficacy that is determined by evaluation of a New Drug Application (NDA). The NDA must be supported by "substantial evidence of effectiveness," and is defined as "evidence consisting of adequate and well-controlled investigations" (Katz, 2004; Dabrowska and Thaul, 2018). The time and cost to develop and achieve FDA approval of a product as therapeutically effective and acceptably safe varies widely but is often approximated at 10 years and 1 billion dollars (DiMasi et al., 2016; Wouters et al., 2020). Only two botanical substances, Veregen® (sinecatechins) and Mytesi™ (crofelemer), were developed as drug products consistent with FDA's Botanical Drug Guidance and both are available only as prescription drugs that is typical of new drug approvals (Food and Drug Admini, 2016).

3.4.3 Factor 4, 5, and 6 Updated Conclusions

The most important finding from new US survey evidence is that the conclusion that kratom products and kratom's primary active alkaloid, MG, pose a "serious imminent threat to public health" is not supported. This extensive survey update agrees with the Henningfield et al. (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" (Henningfield et al., 2018a).

The evidence shows that millions of people in the US purchase and use kratom products for improving health 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. Assistant Secretary Dr. Giroir noted "... 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).

3.5 Factor 7—The Psychic or Physiological Dependence Liability

3.5.1 Summary of 2018 Findings

Recently, psychic dependence is referred to simply as "dependence" or "substance use disorder" and more commonly as "addiction" though definitions of addiction vary widely (American Psychiatric Asso, 1994; World Health Organization, 1994). Physiological dependence is often used interchangeably with the most common measure of physiological dependence, namely "withdrawal" which is also considered a clinical disorder (American Psychiatric Asso, 2013).

In the 2018 8-FA, Henningfield, Fant and 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 employing the drug self-administration and physical dependence/withdrawal model been conducted (see Factor 2 in this report)".

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 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."

3.5.2 Factor 7 Science Updates

In addition to the animal laboratory studies predictive of abuse potential, dependence, and withdrawal summarized in Factor 1, there are several new studies, surveys, and expert reviews addressing the risk and factors associated with dependence and withdrawal. A major category of kratom use is related to the typically mild and tolerable dependence and withdrawal that occurs in some frequent kratom users and the resulting use of kratom as an approach to self-management. In this context, kratom provides a harm reduction alternative to opioids in particular, but also potentially for alcohol, methamphetamine, and other drugs.

Dependence and withdrawal were addressed in a systematic review of kratom use for mental health reasons that concluded "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 ... kratom use does not appear to result in significant respiratory depression" (Swogger and Walsh, 2018). A major category of kratom use globally was to self-manage substance use disorders, consistent with the findings discussed in Factor 1 that demonstrated low abuse and physical dependence potential, and that MG administration reduced morphine and heroin self-administration, and withdrawal signs (Hemby et al., 2019; Harun et al., 2021b).

The Vicknasingam et al. (2021) study included in Factor 2 also assessed potential withdrawal signs using the Clinical Opiate Withdrawal Scale (COWS), comparing scores when participants were administered placebo or 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 was likely that people using kratom multiple times per day for many years would have experienced pronounced withdrawal symptoms. The authors concluded "None of the participants reported withdrawal symptoms either using spontaneous self-report or had significant withdrawal symptoms based on the COWS scores... 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 h, no participant reported or displayed discomfort, symptoms, or signs of potential withdrawal symptoms."

100 long term kratom users and 100 non-users in Malaysia were interviewed to assess potential symptoms related to kratom dependence and withdrawal (Leong Bin Abdullah et al., 2021). Kratom use longer than 6 years and 3 or more times per day were more likely to be associated with dependence, reduced quality of life and/or withdrawal symptoms when kratom use is discontinued. However, the authors noted that the study did not allow causative conclusions as to whether quality of life reductions are a

result of increased kratom use or if such quality of life and other demographic factors contribute to more frequent kratom use.

An internet survey assessing reasons for use and effects of use in 2,798 present and past kratom users included questions about kratom dependence, withdrawal symptoms associated with discontinuation, and use to self-manage opioid dependence (Garcia-Romeu et al., 2020). Kratom-related withdrawal symptoms were reported by 9.5% of respondents with another 17.5% reporting possible kratom-related withdrawal. This supports results of previous studies (Swogger et al., 2015; Grundmann, 2017; Smith and Lawson, 2017; Coe et al., 2019) 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.

Coe et al. (2019) conducted an internet survey (2,867 current, 157 former kratom users) that included similar questions as Garcia-Romeu et al. and Grundmann (2017) (Grundmann, 2017; Garcia-Romeu et al., 2020), related to opioid use and effects. Kratom use was less likely to interfere with social, family, and occupational functioning compared to conventional opioids. Kratom was used by many to reduce or completely replace prescription and nonprescription opioid withdrawal and was generally considered "very effective" for managing opioid withdrawal. Relief of anxiety (including associated with post-traumatic stress disorder), depression, as well as to increase focus or energy were other major reasons for use. The foregoing conclusions are also consistent with those of Grundmann, Babin, Henningfield et al. (2021) who stated: "Some user reports suggest that regular kratom consumption carries risks of dependency and addiction, though with generally self-manageable withdrawal" (Grundmann et al., 2021).

Singh, Narayanan, Muller et al. (2018) 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 apparently frequent chronic kratom consumers in Malaysia (Singh et al., 2018c). Most respondents (70%) experienced symptoms of mild anxiety, while 81% reported 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 less. Cessation from regular and long-term kratom tea consumption was not associated with symptoms of high anxiety or depression.

3.5.3 Factor 7 Updated Conclusion

Kratom's potential to produce psychic dependence (aka "dependence" or "use disorder") and physiological dependence (aka, "withdrawal") advanced considerably due to surveys, and preclinical and clinical studies. 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 (Henningfield et al., 2018a). Some kratom users report dependence/addiction and/or withdrawal with a greater likelihood with 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 compared to dependencies to opioids, alcohol, stimulants and other drugs of abuse.

It is also important to note that there is wide individual variability, and some people do experience what they consider to be strong addiction and withdrawal to kratom. At present, it appears likely that many if not most individuals had prior histories of dependence to opioids and/or other drugs. Their conditions remain of concern nonetheless and is another area warranting further study. People for whom kratom use is considered a serious problem should have the same access to treatment as anyone 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 judicious in people seeking help to manage their kratom use disorder and/or withdrawal. If they formerly or are 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, treating with buprenorphine or methadone may introduce individuals to opioids and may not be the best option. This could be like treating unwanted caffeine dependence with amphetamine to replace the caffeine.

4 DISCUSSION AND CONCLUSION

In 2018, there was sufficient evidence to conclude that there was no imminent public health threat nor high degree of pharmacological abuse potential that would justify scheduling, taking into consideration the serious foreseeable adverse public health consequences of thousands of former opioid users returning to opioids and risking overdose, as well as the *de facto* criminalization of millions of US citizens. Approximately 8 months after the Henningfield et al. 8-FA was published, the US DHHS came to the same conclusion and rescinded the 2017 recommendation to place MG and 7-OH-MG in Schedule I of the CSA (Giroir, 2018). Since January 2018, there was remarkable research relevant to the abuse potential and safety of kratom from the perspective of the CSA eight factors.

Two intravenous drug self-administration studies showed that MG did not substitute for morphine (Hemby et al., 2019) or heroin (Yue et al., 2018), and that MG pretreatment reduced morphine and heroin self-administration. An intracranial brain self-stimulation (ICSS) study showed that whereas morphine produced robust decreases in the brain stimulation threshold, MG and 7-OH-MG did not (Behnood-Rod et al., 2020).

In the evaluation of physical dependence and withdrawal potential, four studies showed MG did not carry morphine-like physical dependence or withdrawal potential (Harun et al., 2020; Hassan et al., 2020; Wilson et al., 2020; Johari et al., 2021). Moreover, MG pretreatment of animals reduced spontaneous

morphine withdrawal (Hassan et al., 2020). In MG physically dependent animals, withdrawal signs were qualitatively different and much weaker than morphine, consistent with its mixed mechanisms of action (Johari et al., 2021). In a mouse physical dependence model (Wilson et al., 2020), naloxone precipitated withdrawal in morphine- but not MG LKT-maintained animals, while LKT pretreatment significantly reduced withdrawal in the morphine-maintained mice.

These findings are consistent with new US survey data showing relatively low self-reported kratom addiction rates, with most people describing MG use to manage pain, depression, anxiety, opioid and other drug use disorders and withdrawal, and to increase alertness, focus and work performance. In addition, kratom dependence and withdrawal are generally weaker and more readily self-managed relative to opioids.

Extensive *in vitro* and *in vivo* animal neuropharmacology studies of the mechanisms of action of MG, 7-OH-MG and other alkaloids illustrate that they are not appropriately designated as opioids, opioid analogs, or "atypical opioids," though some are partial agonists with low potential to recruit beta arrestin and produce respiratory depression. 7-OH-MG produces stronger MOR mediated opioid effects on abuse potential related measures and antinociception, but naturally occurs at levels so low as to not contribute meaningfully to kratom effects. This supports recommendations that regulations should prohibit kratom products with 7-OH-MG concentrations greater than occur safely in nature.[5]

Safety assessments in pharmacokinetic and pharmacodynamic studies confirm that kratom based extracts and individual alkaloids at far higher doses than consumed by humans do not appear to carry substantial mortality risk, with one analysis suggesting a mortality risk at least 1000 times less than illicit opioids (Henningfield et al., 2019). Results support the US DHHS conclusion that "experts disagree on whether kratom by itself causes overdose deaths" (Giroir, 2018; National Institute on Drug Abuse, 2019). This does not imply that kratom does not carry a mortality risk—most substances do under certain conditions and exposure levels, another important area for further research.

As to the question of whether or not kratom poses an imminent public health threat, no analysis of factors 4–6 of the 8 CSA factors, including the FDA analysis (Food and Drug Administration, 2017b), revealed kratom to pose an imminent public health risk. The US has the most comprehensive survey data to address the need for temporary or "emergency" placement of substances into CSA Schedule I. Yet none of the major surveillance systems identified such a public health threat. This includes the old and new Drug Abuse Warning Network, Monitoring the Future, National Survey on Drug Use and Health, RADARS®, or the Treatment Evaluation Data Set. DEA's National Forensic Laboratory Information System mentioned kratom reports from 2010–2016 but none thereafter because the signal remained low. Neither has kratom been included in any DEA Annual National Drug Threat Reports.

The primary public health consequences of kratom use are well documented by four surveys of more than 20,000 kratom consumers summarized in this review, by Henningfield et al., 2018 (Henningfield et al., 2018a), and more than 20,000 comments to DEA (Drug Enforcement Adm, 2016) suggesting that millions of US citizens use kratom for health and well-being and many to self-manage opioid and other drug withdrawal and use disorders as their preferred approach. Many kratom users believe kratom is more effective, tolerable and/or accessible than other pharmaceuticals (Grundmann et al., 2018; Swogger and Walsh, 2018; Prozialeck et al., 2019; Prozialeck et al., 2020).

There are problems with kratom product purity (e.g., Prozialeck et al., 2020) (Prozialeck et al., 2020) and adulteration (Prozialeck et al., 2019) in the consumer marketplace. A scheduling imposed kratom ban would likely worsen these problems because kratom marketing would not discontinue and consumer demand would not cease, rather marketing would switch from regulatable lawful to illicit kratom suppliers. More states and ideally the US federal government could address these issues by product performance standards and regulatory approaches guided by science and informed through a federal rule-making approach.

Remarkably, as discussed in several reports (Henningfield et al., 2019; Prozialeck et al., 2019; Henningfield et al., 2021), there has yet to emerge a generally accepted estimate of the number of current US kratom consumers, which current ranges from approximately 2 to more than 10 million (see factors 4–6 and Henningfield et al., 2021) (Henningfield et al., 2021). As noted by Henningfield et al., 2018 and bluntly stated in the US DHHS scheduling rescission letter (Giroir, 2018), surveys need to address such issues before any action to ban consumer kratom sales and possession is contemplated. As stated in the DHHS letter:

"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:

- 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 among people with intractable pain, psychological distress, risk for suicide; and/or people who might transition to proven deadly opioids such as prescription opioids, heroin, or fentanyl.

[5]Five states (AZ, GA, NV, OK, and UT) have taken this approach in their kratom consumer protection regulations and law but setting actual performance standards to address the variety of kratom based products would be seem best done by FDA which has extensive experience in such matters and could take a federal rule making approach that ensures input from diverse stakeholders representing science, public health, consumers, and the industry that prepares and manufactures kratom products.

- 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 and 6)" (Giroir, 2018).

By law, scheduling considers diverse evidence including chemistry and pharmacology, level of abuse potential, physiological dependence determined in animal and human studies, as well as assessment of individual and public health risks and benefits. Taking all of these factors into account, this review provides stronger evidence than was available to Henningfield et al., or the US DHHS in 2018 (Henningfield et al., 2018a; Giroir, 2018) to recommend not only that CSA scheduling is not warranted but that CSA scheduling carries a substantial foreseeable risk of thousands of opioid overdose deaths as well as depriving millions of US citizens of one of their preferred health management assets. The fact that possession of kratom by millions of US citizens would be criminalized as a heroin-like drug felony offense is not a CSA consideration but should not be ignored.

In conclusion, we do not recommend scheduling kratom or any of its alkaloids in the CSA. We do recommend accelerated research to address the many questions raised in this review, including support of the potential development of new medicines with potential better safety and/or efficacy profiles for a variety of diseases. Finally, we recommend that the US federal government and other nations consider approaches to kratom regulation as are presently being pioneered in five US states.

AUTHOR CONTRIBUTIONS

JH was the primary scientist/investigator, and lead the identification of articles, writing, and analysis. DW supported writing, research, and analysis. MH provided toxicological analysis of articles and supported writing and analysis.

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REFERENCES

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition. Arlington, VA: DSM-IV.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders*. 5th Edition. Arlington, VA: DSM-5.

Avery, B. A., Boddu, S. P., Sharma, A., Furr, E. B., Leon, F., Cutler, S. J., et al. (2019). Comparative Pharmacokinetics of Mitragynine after Oral Administration of Mitragyna Speciosa (Kratom) Leaf Extracts in Rats. *Planta Med.* 85 (4), 340–346. doi:10.1055/a-0770-3683

Behnood-Rod, A., Chellian, R., Wilson, R., Hiranita, T., Sharma, A., Leon, F., et al. (2020). Evaluation of the Rewarding Effects of Mitragynine and 7-hydroxymitragynine in an Intracranial Self-Stimulation Procedure in Male and Female Rats. *Drug Alcohol Depend* 215, 108235. doi:10.1016/j.drugalcdep.2020.108235

Belouin, S. J., and Henningfield, J. E. (2018). Psychedelics: Where We Are Now, Why We Got Here, what We Must Do. *Neuropharmacology* 142, 7–19. doi:10.1016/j.neuropharm.2018.02.018

Berthold, E. C., Kamble, S. H., Raju, K. S., King, T. I., Popa, R., Sharma, A., et al. (2021). Preclinical Pharmacokinetic Study of Speciociliatine, a Kratom Alkaloid, in Rats Using an UPLC-MS/MS Method. *J. Pharm. Biomed. Anal.* 194, 113778. doi:10.1016/j.jpba.2020.113778

Botanical Education Alliance (2016). *Results of Survey of Kratom Venders to Estimate the Number of Venders, and Size of the Market by Consumers and Kratom Product Venders*. Washington, DC.

Chakraborty, S., DiBerto, J. F., Faouzi, A., Bernhard, S. M., Gutridge, A. M., Ramsey, S., et al. (2021). A Novel Mitragynine Analog with Low-Efficacy Mu Opioid Receptor Agonism Displays Antinociception with Attenuated Adverse Effects. *J. Med. Chem.* 64 (18), 13873–13892. doi:10.1021/acs.jmedchem.1c01273

Chakraborty, S., Uprety, R., Daibani, A. E., Rouzic, V. L., Hunkele, A., Appourchaux, K., et al. (2021). Kratom Alkaloids as Probes for Opioid Receptor Function: Pharmacological Characterization of Minor Indole and Oxindole Alkaloids from Kratom. *ACS Chem. Neurosci.* 12 (14), 2661–2678. doi:10.1021/acschemneuro.1c00149

Chear, N. J., León, F., Sharma, A., Kanumuri, S. R. R., Zwolinski, G., Abboud, K. A., et al. (2021). Exploring the Chemistry of Alkaloids from Malaysian Mitragyna Speciosa (Kratom) and the Role of Oxindoles on Human Opioid Receptors. *J. Nat. Prod.* 84 (4), 1034–1043. doi:10.1021/acs.jnatprod.0c01055

Coe, M. A., Pillitteri, J. L., Sembower, M. A., Gerlach, K. K., and Henningfield, J. E. (2019). Kratom as a Substitute for Opioids: Results from an Online Survey. *Drug Alcohol Depend* 202, 24–32. doi:10.1016/j.drugalcdep.2019.05.005

Commission on Narcotic Drugs (2021). Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD). Available at: https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf (Accessed October 11–15, 2021).

Covvey, J. R., Vogel, S. M., Peckham, A. M., and Evoy, K. E. (2020). Prevalence and Characteristics of Self-Reported Kratom Use in a Representative US General Population Sample. *J. Addict. Dis.* 38 (4), 506–513. doi:10.1080/10550887.2020.1788914

Dabrowska, A., and Thaul, S. (2018). How FDA Approves Drugs and Regulates Their Safety and Effectiveness: Congressional Research Service. Case Report Prepared for Members and Committees of Congress. Available from: https://fas.org/sgp/crs/misc/R41983.pdf.

DiMasi, J. A., Grabowski, H. G., and Hansen, R. W. (2016). Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs. *J. Health Econ.* 47, 20–33. doi:10.1016/j.jhealeco.2016.01.012

Domnic, G., Narayanan, S., Mohana-Kumaran, N., and Singh, D. (2021). Kratom (Mitragyna Speciosa Korth.) an Overlooked Medicinal Plant in Malaysia. *J. Substance Use* 26 (1), 1–6. doi:10.1080/14659891.2021.1885515

Domnic, G., Jeng-Yeou Chear, N., Abdul Rahman, S. F., Ramanathan, S., Lo, K. W., Singh, D., et al. (2021). Combinations of Indole Based Alkaloids from Mitragyna Speciosa (Kratom) and Cisplatin Inhibit Cell Proliferation and

Migration of Nasopharyngeal Carcinoma Cell Lines. *J. Ethnopharmacol* 279, 114391. doi:10.1016/j.jep.2021.114391

Drug Abuse Warning Network (2020). *Preliminary DAWN Data Review*. Rockville, Maryland, United States: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

Galbis-Reig, D. (2016). A Case Report of Kratom Addiction and Withdrawal. *WMJ* 115 (1), 49–53.

Garcia-Romeu, A., Cox, D. J., Smith, K. E., Dunn, K. E., and Griffiths, R. R. (2020). Kratom (Mitragyna Speciosa): User Demographics, Use Patterns, and Implications for the Opioid Epidemic. *Drug Alcohol Depend* 208, 107849. doi:10.1016/j.drugalcdep.2020.107849

Gershman, K., Timm, K., Frank, M., Lampi, L., Melamed, J., Gerona, R., et al. (2019). Deaths in Colorado Attributed to Kratom. *N. Engl. J. Med.* 380 (1), 97–98. doi:10.1056/NEJMc1811055

Giroir, B. P. (2018). Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to Rescind Previous Support to Permanently Place Mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2018. Available from: https://images.go02.informamarkets.com/Web/Informa02/%7b548e6d56-2ea4-4da4-9404-0348b56e9a88%7d_dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf.

Grundmann, O., Babin, J. K., Henningfield, J. E., Garcia-Romeu, A., Kruegel, A. C., Prozialeck, W. C., et al. (2021). Kratom Use in the United States: a Diverse and Complex Profile. *Addiction* 116 (1), 202–203. doi:10.1111/add.15173

Grundmann, O., Brown, P. N., Henningfield, J., Swogger, M., and Walsh, Z. (2018). The Therapeutic Potential of Kratom. *Addiction* 113 (10), 1951–1953. doi:10.1111/add.14371

Grundmann, O. (2017). Patterns of Kratom Use and Health Impact in the US-Results from an Online Survey. *Drug Alcohol Depend* 176, 63–70. doi:10.1016/j.drugalcdep.2017.03.007

Gutridge, A. M., Robins, M. T., Cassell, R. J., Uprety, R., Mores, K. L., Ko, M. J., et al. (2020). G Protein-Biased Kratom-Alkaloids and Synthetic Carfentanil-Amide Opioids as Potential Treatments for Alcohol Use Disorder. *Br. J. Pharmacol.* 177 (7), 1497–1513. doi:10.1111/bph.14913

Harun, N., Johari, I. S., Japarin, R. A., Bakar, S. N. S., Mat, N. H., Hassan, Z., et al. (2021). Naloxone-precipitated Mitragynine Withdrawal Did Not Associate with Increased Anxiety-like Behaviour in Rats. *Malays J. Biochem. Mol. Biol.* 24 (1), 100–107.

Harun, N., Johari, I. S., Japarin, R. A., Suhaimi, F. W., Hassan, Z., and Shoaib, M. (2021). Current Perspectives on the Therapeutic Potential of Mitragyna Speciosa and its Derivatives on Animal Model. *TJPS* 45 (3), 195–201.

Harun, N., Johari, I. S., Mansor, S. M., and Shoaib, M. (2020). Assessing Physiological Dependence and Withdrawal Potential of Mitragynine Using Schedule-Controlled Behaviour in Rats. *Psychopharmacology (Berl)* 237 (3), 855–867. doi:10.1007/s00213-019-05418-6

Hassan, R., Othman, N., Mansor, S. M., Müller, C. P., and Hassan, Z. (2021). Proteomic Analysis Reveals Brain Rab35 as a Potential Biomarker of Mitragynine Withdrawal in Rats. *Brain Res. Bull.* 172, 139–150. doi:10.1016/j.brainresbull.2021.04.018

Hassan, R., Pike See, C., Sreenivasan, S., Mansor, S. M., Müller, C. P., and Hassan, Z. (2020). Mitragynine Attenuates Morphine Withdrawal Effects in Rats-A Comparison with Methadone and Buprenorphine. *Front. Psychiatry* 11, 411. doi:10.3389/fpsyt.2020.00411

Hassan, R., Sreenivasan, S., Müller, C. P., and Hassan, Z. (2021). Methadone, Buprenorphine, and Clonidine Attenuate Mitragynine Withdrawal in Rats. *Front. Pharmacol.* 12, 708019. doi:10.3389/fphar.2021.708019

Hassan, Z., Suhaimi, F. W., Ramanathan, S., Ling, K. H., Effendy, M. A., Müller, C. P., et al. (2019). Mitragynine (Kratom) Impairs Spatial Learning and Hippocampal Synaptic Transmission in Rats. *J. Psychopharmacol.* 33 (7), 908–918. doi:10.1177/0269881119844186

Hemby, S. E., McIntosh, S., Leon, F., Cutler, S. J., and McCurdy, C. R. (2019). Abuse Liability and Therapeutic Potential of the Mitragyna Speciosa (Kratom) Alkaloids Mitragynine and 7-hydroxymitragynine. *Addict. Biol.* 24 (5), 874–885. doi:10.1111/adb.12639

Henningfield, J. E., Babin, J., Boyer, E. W., Brown, P., Garcia-Romeu, A., Griffiths, R. R., et al. Critique of the FDA's 8-Factor Analysis of Kratom, Specifically, Mitragynine and 7-hydroxymitragyine 2018. Available from: https://www.americankratom.org/images/file/Scientists-Response-to-FDA-Kratom-8FA–28-Nov-2018-FINAL.pdf.

Henningfield, J. E., Fant, R. V., and Wang, D. W. (2018). The Abuse Potential of Kratom According the 8 Factors of the Controlled Substances Act: Implications for Regulation and Research. *Psychopharmacology (Berl)* 235 (2), 573–589. doi:10.1007/s00213-017-4813-4

Henningfield, J. E., Grundmann, O., Babin, J. K., Fant, R. V., Wang, D. W., and Cone, E. J. (2019). Risk of Death Associated with Kratom Use Compared to Opioids. *Prev. Med.* 128, 105851. doi:10.1016/j.ypmed.2019.105851

Henningfield, J. E., Grundmann, O., Garcia-Romeu, A., and Swogger, M. T. (2021). We Need Better Estimates of Kratom Use Prevalence. *Am. J. Prev. Med* 62 (1), 132–133. doi:10.1016/j.amepre.2021.07.022

Henningfield, J. E., Swogger, M. T., Walsh, Z., Kruegel, A. C., Grundmann, O., Garcia-Romeu, A., et al. (2018). Kratom Science Letter to Congressional Leaders. Available from: https://www.americankratom.org/images/16_Kratom_Scientist_Letter_to_Congressional_Leaders_June_21_2018_FINAL.pdf.

Henningfield, J. E., Swogger, M. T., Walsh, Z., Kruegel, A. C., Grundmann, O., Garcia-Romeu, A., et al. (2018). *Kratom Science Letter to the White House*. US: American Kratom Association. Available from: http://www.americankratom.org/images/file/Document%2019%20Science%20Letter%20on%20Kratom%20Sent%20to%20WH%20and%20DEA%20Feb%208%202018.pdf.

Hiranita, T., Leon, F., Felix, J. S., Restrepo, L. F., Reeves, M. E., Pennington, A. E., et al. (2019). The Effects of Mitragynine and Morphine on Schedule-Controlled Responding and Antinociception in Rats. *Psychopharmacology (Berl)* 236 (9), 2725–2734. doi:10.1007/s00213-019-05247-7

Hiranita, T., Sharma, A., Oyola, F. L., Obeng, S., Reeves, M. E., Restrepo, L. F., et al. (2020). Potential Contribution of 7-Hydroxymitragynine, a Metabolite of the Primary Kratom (Mitragyna Speciosa) Alkaloid Mitragynine, to the μ-Opioid Activity of Mitragynine in Rats. *FASEB j.* 34 (S1), 1. doi:10.1096/fasebj.2020.34.s1.05180

Ingraham, C. (2016). DEA Defies Senators' Appeal to Reconsider 'unprecedented' Kratom Ban. *The Wash. Post*.

Ingraham, C. (2016). The DEA Is Withdrawing a Proposal to Ban Another Plant after the Internet Got Really Mad. *Wash. Post*.

International Narcotics Control Board (2020). *List of Narcotic Drugs under International Control: Yellow List*. 59th ed. Vienna, Austria: International Narcotics Control Board.

International Narcotics Control Board (2020). *List of Psychotropic Substances under International Control: Green List*. Vienna, Austria: International Narcotics Control Board.

Jagabalan, Y., Zainal, H., Al Ganaby, A., Murugaiyah, V., and Ramanathan, S. (2019). "Pharmacokinetic Modeling of Single Dose Kratom (Mitragynine) in Rats. Front Pharmacol," in International Conference on Drug Discovery and Translational Medicine 2018 (ICDDTM '18) "Seizing Opportunities and Addressing Challenges of Precision Medicine, Putrajaya, Malaysia, 03 Dec 2018.

Japarin, R. A., Yusoff, N. H., Hassan, Z., Müller, C. P., and Harun, N. (2021). Cross-reinstatement of Mitragynine and Morphine Place Preference in Rats. *Behav. Brain Res.* 399, 113021. doi:10.1016/j.bbr.2020.113021

Johari, I. S., Harun, N., Sofian, Z. M., and Shoaib, M. (2021). Pentylenetetrazol-like Stimulus Is Not Produced Following Naloxone-Precipitated Mitragynine Withdrawal in Rats. *Psychopharmacology Berl* 238, 3183–3191. doi:10.1007/s00213-021-05934-4

Johnson, M. W., Griffiths, R. R., Hendricks, P. S., and Henningfield, J. E. (2018). The Abuse Potential of Medical Psilocybin According to the 8 Factors of the Controlled Substances Act. *Neuropharmacology* 142, 143–166. doi:10.1016/j.neuropharm.2018.05.012

Kamble, S. H., Berthold, E. C., King, T. I., Raju Kanumuri, S. R., Popa, R., Herting, J. R., et al. (2021). Pharmacokinetics of Eleven Kratom Alkaloids Following an Oral Dose of Either Traditional or Commercial Kratom Products in Rats. *J. Nat. Prod.* 84 (4), 1104–1112. doi:10.1021/acs.jnatprod.0c01163

Kamble, S. H., León, F., King, T. I., Berthold, E. C., Lopera-Londoño, C., Siva Rama Raju, K., et al. (2020). Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases its Opioid Potency and Efficacy. *ACS Pharmacol. Transl Sci.* 3 (6), 1063–1068. doi:10.1021/acsptsci.0c00075

Kamble, S. H., Sharma, A., King, T. I., Berthold, E. C., León, F., Meyer, P. K. L., et al. (2020). Exploration of Cytochrome P450 Inhibition Mediated Drug-Drug

Interaction Potential of Kratom Alkaloids. *Toxicol. Lett.* 319, 148–154. doi:10.1016/j.toxlet.2019.11.005

Kamble, S. H., Sharma, A., King, T. I., León, F., McCurdy, C. R., and Avery, B. A. (2019). Metabolite Profiling and Identification of Enzymes Responsible for the Metabolism of Mitragynine, the Major Alkaloid of Mitragyna Speciosa (Kratom). *Xenobiotica* 49 (11), 1279–1288. doi:10.1080/00498254.2018.1552819

Katz, R. (2004). FDA: Evidentiary Standards for Drug Development and Approval. *NeuroRx* 1 (3), 307–316. doi:10.1602/neurorx.1.3.307

King, T. I., Sharma, A., Kamble, S. H., León, F., Berthold, E. C., Popa, R., et al. (2020). Bioanalytical Method Development and Validation of Corynantheidine, a Kratom Alkaloid, Using UPLC-MS/MS, and its Application to Preclinical Pharmacokinetic Studies. *J. Pharm. Biomed. Anal.* 180, 113019. doi:10.1016/j.jpba.2019.113019

Kruegel, A. C., and Grundmann, O. (2018). The Medicinal Chemistry and Neuropharmacology of Kratom: A Preliminary Discussion of a Promising Medicinal Plant and Analysis of its Potential for Abuse. *Neuropharmacology* 134 (Pt A), 108–120. doi:10.1016/j.neuropharm.2017.08.026

Kruegel, A. C., Uprety, R., Grinnell, S. G., Langreck, C., Pekarskaya, E. A., Le Rouzic, V., et al. (2019). 7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of its Analgesic Effects. *ACS Cent. Sci.* 5 (6), 992–1001. doi:10.1021/acscentsci.9b00141

León, F., Obeng, S., Mottinelli, M., Chen, Y., King, T. I., Berthold, E. C., et al. (2021). Activity of Mitragyna Speciosa ("kratom") Alkaloids at Serotonin Receptors. *J. Med. Chem.* 64 (18), 13510–13523. doi:10.1021/acs.jmedchem.1c00726

Leong Abdullah, M. F. I., Tan, K. L., Narayanan, S., Yuvashnee, N., Chear, N. J. Y., Singh, D., et al. (2021). Is Kratom (Mitragyna Speciosa Korth.) Use Associated with ECG Abnormalities? Electrocardiogram Comparisons between Regular Kratom Users and Controls. *Clin. Toxicol. (Phila)* 59 (5), 400–408. doi:10.1080/15563650.2020.1812627

Leong Bin Abdullah, M. F. I., and Singh, D. (2021). Assessment of Cardiovascular Functioning Among Regular Kratom (Mitragyna Speciosa Korth) Users: A Case Series. *Front. Pharmacol.* 12, 723567. doi:10.3389/fphar.2021.723567

Leong Bin Abdullah, M. F. I., and Singh, D. (2021). The Adverse Cardiovascular Effects and Cardiotoxicity of Kratom (Mitragyna Speciosa Korth.): A Comprehensive Review. *Front. Pharmacol.* 12, 726003. doi:10.3389/fphar.2021.726003

Leong Bin Abdullah, M. F. I., Tan, K. L., Mohd Isa, S., Yusoff, N. S., Chear, N. J. Y., and Singh, D. (2020). Lipid Profile of Regular Kratom (Mitragyna Speciosa Korth.) Users in the Community Setting. *PLoS One* 15 (6), e0234639. doi:10.1371/journal.pone.0234639

Leong Bin Abdullah, M. F. I., Yuvashnee, N., and Singh, D. (2021). Effect of Regular Kratom (Mitragyna Speciosa Korth.) Use on Quality of Life of People Who Use Kratom. *Subst. Abus*, 1–12. doi:10.1080/08897077.2021.1876809

Maxwell, E. A., King, T. I., Kamble, S. H., Raju, K. S. R., Berthold, E. C., León, F., et al. (2020). Pharmacokinetics and Safety of Mitragynine in Beagle Dogs. *Planta Med.* 86 (17), 1278–1285. doi:10.1055/a-1212-5475

Miech, R. A., Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., and Patrick, M. E. (2021). *Monitoring the Future National Survey Results on Drug Use, 1975–2020: Volume I, Secondary School Students*. Ann Arbor: Institute for Social Research, The University of Michigan.

National Institute on Drug Abuse (2019). *Kratom DrugFacts*. Bethesda, MD: National Institutes of Health. Available from: https://www.drugabuse.gov/publications/drugfacts/kratom.

Negus, S. S., and Miller, L. L. (2014). Intracranial Self-Stimulation to Evaluate Abuse Potential of Drugs. *Pharmacol. Rev.* 66 (3), 869–917. doi:10.1124/pr.112.007419

Newman, D. J., and Cragg, G. M. (2016). Natural Products as Sources of New Drugs from 1981 to 2014. *J. Nat. Prod.* 79 (3), 629–661. doi:10.1021/acs.jnatprod.5b01055

O'Brien, C. P. (2011). "Drug Addiction," in *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. Editors L. L. Brunton, B. A. Chabner, and B. C. Knollman 12th ed. (New York: McGraw Hill Medical), 649–668.

Obeng, S., Wilkerson, J. L., León, F., Reeves, M. E., Restrepo, L. F., Gamez-Jimenez, L. R., et al. (2021). Pharmacological Comparison of Mitragynine and 7-Hydroxymitragynine: *In Vitro* Affinity and Efficacy for μ-Opioid Receptor and Opioid-like Behavioral Effects in Rats. *J. Pharmacol. Exp. Ther.* 376 (3), 410–427. doi:10.1124/jpet.120.000189

Olsen, E. O., O'Donnell, J., Mattson, C. L., Schier, J. G., and Wilson, N. (2019). Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected - 27 States, July 2016-December 2017. *MMWR Morb Mortal Wkly Rep.* 68 (14), 326–327. doi:10.15585/mmwr.mm6814a2

Pain News Network (2018). Kratom Survey. Available from: https://www.painnewsnetwork.org/kratom-survey.

Pinney Associates (2016). *Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation*, Bethesda, MD.

Prozialeck, W. C., Avery, B. A., Boyer, E. W., Grundmann, O., Henningfield, J. E., Kruegel, A. C., et al. (2019). Kratom Policy: The challenge of Balancing Therapeutic Potential with Public Safety. *Int. J. Drug Pol.* 70, 70–77. doi:10.1016/j.drugpo.2019.05.003

Prozialeck, W. C., Edwards, J. R., Lamar, P. C., Plotkin, B. J., Sigar, I. M., Grundmann, O., et al. (2020). Evaluation of the Mitragynine Content, Levels of Toxic Metals and the Presence of Microbes in Kratom Products Purchased in the Western Suburbs of Chicago. *Int. J. Environ. Res. Public Health* 17 (15). doi:10.3390/ijerph17155512

Prozialeck, W. C., Lamar, P. C., Krupp, M., 2nd, Moon, M., Phelps, L. E., and Grundmann, O. (2021). Kratom Use within the Context of the Evolving Opioid Crisis and the COVID-19 Pandemic in the United States. *Front. Pharmacol.* 12, 729220. doi:10.3389/fphar.2021.729220

R. B. Raffa (Editor) (2014). *Kratom and Other Mitragynines: The Chemistry and Pharmacology of Opioids from a Non-opium Source* (Boca Raton: CRC Press, Taylor & Francis).

Reeve, M. E., Obeng, S., Oyola, F. L., Behnke, M., Restrepo, L. F., Patel, A., et al. (2020). The Adrenergic a 2 Receptor-Mediated Discriminative-Stimulus Effects of Mitragynine, the Primary Alkaloid in Kratom (Mitragyna Speciosa) in Rats. *FASEB j.* 34 (S1), 1. doi:10.1096/fasebj.2020.34.s1.05233

Schimmel, J., Amioka, E., Rockhill, K., Haynes, C. M., Black, J. C., Dart, R. C., et al. (2021). Prevalence and Description of Kratom (Mitragyna Speciosa) Use in the United States: a Cross-Sectional Study. *Addiction* 116 (1), 176–181. doi:10.1111/add.15082

Sharma, A., Kamble, S. H., León, F., Chear, N. J., King, T. I., Berthold, E. C., et al. (2019). Simultaneous Quantification of Ten Key Kratom Alkaloids in Mitragyna Speciosa Leaf Extracts and Commercial Products by Ultra-performance Liquid Chromatography-Tandem Mass Spectrometry. *Drug Test. Anal.* 11 (8), 1162–1171. doi:10.1002/dta.2604

Sharma, A., and McCurdy, C. R. (2021). Assessing the Therapeutic Potential and Toxicity of Mitragyna Speciosa in Opioid Use Disorder. *Expert Opin. Drug Metab. Toxicol.* 17 (3), 255–257. doi:10.1080/17425255.2021.1853706

Singh, D., Chye, Y., Suo, C., Yücel, M., Grundmann, O., Ahmad, M. Z., et al. (2018). Brain Magnetic Resonance Imaging of Regular Kratom (Mitragyna Speciosa Korth.) Users: a Preliminary Study. *Malays J. Med. Heal Sci.* 14 (Suppl. 1), 65–70.

Singh, D., Müller, C. P., Murugaiyah, V., Hamid, S. B. S., Vicknasingam, B. K., Avery, B., et al. (2018). Evaluating the Hematological and Clinical-Chemistry Parameters of Kratom (Mitragyna Speciosa) Users in Malaysia. *J. Ethnopharmacol* 214, 197–206. doi:10.1016/j.jep.2017.12.017

Singh, D., Müller, C. P., and Vicknasingam, B. K. (2014). Kratom (Mitragyna Speciosa) Dependence, Withdrawal Symptoms and Craving in Regular Users. *Drug Alcohol Depend* 139, 132–137. doi:10.1016/j.drugalcdep.2014.03.017

Singh, D., Narayanan, S., Grundmann, O., Chear, N. J. Y., Murugaiyah, V., Hamid, S. B. S., et al. (2020). Long-term Effects of Kratom [mitragyna Speciosa] Use. *Mal J. Med. Health Sci.* 16 (4), 64–72.

Singh, D., Narayanan, S., Müller, C. P., Swogger, M. T., Chear, N. J. Y., Dzulkapli, E. B., et al. (2019). Motives for Using Kratom (Mitragyna Speciosa Korth.) Among Regular Users in Malaysia. *J. Ethnopharmacol* 233, 34–40. doi:10.1016/j.jep.2018.12.038

Singh, D., Narayanan, S., Müller, C. P., Swogger, M. T., Rahim, A. A., Leong Bin Abdullah, M. F. I., et al. (2018). Severity of Kratom (Mitragyna Speciosa Korth.) Psychological Withdrawal Symptoms. *J. Psychoactive Drugs* 50 (5), 445–450. doi:10.1080/02791072.2018.1511879

Singh, D., Narayanan, S., Müller, C. P., Vicknasingam, B., Yücel, M., Ho, E. T. W., et al. (2019). Long-term Cognitive Effects of Kratom (Mitragyna Speciosa

Korth.) Use. *J. Psychoactive Drugs* 51 (1), 19–27. doi:10.1080/02791072.2018.1555345

Singh, D., Yeou Chear, N. J., Narayanan, S., Leon, F., Sharma, A., McCurdy, C. R., et al. (2020). Patterns and Reasons for Kratom (Mitragyna Speciosa) Use Among Current and Former Opioid Poly-Drug Users. *J. Ethnopharmacol* 249, 112462. doi:10.1016/j.jep.2019.112462

Singh, D., Grundmann, O., Murugaiyah, V., Rahim, A. B. M., Chawarski, M., and Balasingam, V. (2020). Improved Sexual Functioning of Long-Term Daily Users of Mitragyna Speciosa (Korth.). *J. Herbal Med.* 19, 100293. doi:10.1016/j.hermed.2019.100293

Smith, K. E., and Lawson, T. (2017). Prevalence and Motivations for Kratom Use in a Sample of Substance Users Enrolled in a Residential Treatment Program. *Drug Alcohol Depend* 180, 340–348. doi:10.1016/j.drugalcdep.2017.08.034

Smith, L. C., Lin, L., Hwang, C. S., Zhou, B., Kubitz, D. M., Wang, H., et al. (2019). Lateral Flow Assessment and Unanticipated Toxicity of Kratom. *Chem. Res. Toxicol.* 32 (1), 113–121. doi:10.1021/acs.chemrestox.8b00218

Substance Abuse and Mental Health Services Administration (2020). *Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2018. Admissions to and Discharges from Publicly Funded Substance Use Treatment.* Rockville, MD: Substance Abuse and Mental Health Services Administration.

Suhaimi, F. W., Hassan, Z., Mansor, S. M., and Müller, C. P. (2021). The Effects of Chronic Mitragynine (Kratom) Exposure on the EEG in Rats. *Neurosci. Lett.* 745, 135632. doi:10.1016/j.neulet.2021.135632

Swogger, M. T., Hart, E., Erowid, F., Erowid, E., Trabold, N., Yee, K., et al. (2015). Experiences of Kratom Users: A Qualitative Analysis. *J. Psychoactive Drugs* 47 (5), 360–367. doi:10.1080/02791072.2015.1096434

Swogger, M. T., Smith, K. E., Garcia-Romeu, A., Grundmann, O., Veltri, C., Henningfield, J., et al. Understanding Kratom Use: A Guide for Healthcare Providers. *Front. Pharmacol.*

Swogger, M. T., and Walsh, Z. (2018). Kratom Use and Mental Health: A Systematic Review. *Drug Alcohol Depend* 183, 134–140. doi:10.1016/j.drugalcdep.2017.10.012

Todd, D. A., Kellogg, J. J., Wallace, E. D., Khin, M., Flores-Bocanegra, L., Tanna, R. S., et al. (2020). Chemical Composition and Biological Effects of Kratom (Mitragyna Speciosa): *In Vitro* Studies with Implications for Efficacy and Drug Interactions. *Sci. Rep.* 10 (1), 19158. doi:10.1038/s41598-020-76119-w

Trakulsrichai, S., Sathirakul, K., Auparakkitanon, S., Krongvorakul, J., Sueajai, J., Noumjad, N., et al. (2015). Pharmacokinetics of Mitragynine in Man. *Drug Des. Devel Ther.* 9, 2421–2429. doi:10.2147/DDDT.S79658

U.S. Department of health and Human Services (2020). *U.S. Departmentof Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality*. National Survey on Drug Use and Health 2019 (NSDUH-2019-DS0001). Rockville, MD.

U.S. Drug Enforcement Administration (2020). National Drug Threat Assessment: U.S. Department of Justice. [Available from: https://www.dea.gov/sites/default/files/2021-02/DIR-008-21%202020%20National%20Drug%20Threat%20Assessment_WEB.pdf.

U.S. Drug Enforcement Administration (2020). *National Forensic Laboratory Information System: NFLIS-Drug 2019 Annual Report*. Springfield, VA: U.S. Drug Enforcement Administration.

U.S. Drug Enforcement Administration Temporary Placement of Mitragynine and 7-Hydroxymitragynine into Schedule I; Withdrawal. Docket No. DEA-2016-0015-0006 2016 Available from: https://www.regulations.gov/document/DEA-2016-0015-0006.

U.S. Food and Drug Administration (2017). *Assessment of Abuse Potential of Drugs: Guidance for Industry. Silver Spring*. MD,US: Center for Drug Evaluation and Research, Food and Drug Administration.

U.S. Food and Drug Administration (2016). *Botanical Drug Development: Guidance for Industry. Silver Spring*. MD,US: U.S. Department of Health and Human Services, Center for Drug Evaluation and Research. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/botanical-drug-development-guidance-industry.

U.S. Food and Drug Administration (2017). Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to Permanently Place Mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2017. Available from: https://www.documentcloud.org/documents/5031552-HHS-kratom-letter.html.

U.S. Food and Drug Administration (2018). Statement from FDA Commissioner Scott Gottlieb. M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse 2018 Available from: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds.

U.S. Food and Drug Administration (2017). Statement from FDA Commissioner Scott Gottlieb, M.D. On FDA Advisory about Deadly Risks Associated with Kratom. Available from: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fda-advisory-about-deadly-risks-associated-kratom.

Vicknasingam, B., Chooi, W. T., Rahim, A. A., Ramachandram, D., Singh, D., Ramanathan, S., et al. (2020). Kratom and Pain Tolerance: A Randomized, Placebo-Controlled, Double-Blind Study. *Yale J. Biol. Med.* 93 (2), 229–238.

Vijeepallam, K., Pandy, V., Murugan, D. D., and Naidu, M. (2019). Methanolic Extract of Mitragyna Speciosa Korth Leaf Inhibits Ethanol Seeking Behaviour in Mice: Involvement of Antidopaminergic Mechanism. *Metab. Brain Dis.* 34 (6), 1713–1722. doi:10.1007/s11011-019-00477-2

Warner, M. L., Kaufman, N. C., and Grundmann, O. (2016). The Pharmacology and Toxicology of Kratom: from Traditional Herb to Drug of Abuse. *Int. J. Leg. Med* 130 (1), 127–138. doi:10.1007/s00414-015-1279-y

Wilson, L. L., Harris, H. M., Eans, S. O., Brice-Tutt, A. C., Cirino, T. J., Stacy, H. M., et al. (2020). Lyophilized Kratom tea as a Therapeutic Option for Opioid Dependence. *Drug Alcohol Depend* 216, 108310. doi:10.1016/j.drugalcdep.2020.108310

World Health Organization (WHO) (1994). *The ICD-10 Classification of Mental and Behavioural Disorders: Conversion Tables between ICD-8, ICD-9 and ICD-10, Rev*, 1. Geneva, Switzerland: World Health Organization.

Wouters, O. J., McKee, M., and Luyten, J. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA* 323 (9), 844–853. doi:10.1001/jama.2020.1166

Yue, K., Kopajtic, T. A., and Katz, J. L. (2018). Abuse Liability of Mitragynine Assessed with a Self-Administration Procedure in Rats. *Psychopharmacology (Berl)* 235 (10), 2823–2829. doi:10.1007/s00213-018-4974-9

Yusoff, N. H. M., Mansor, S. M., Müller, C. P., and Hassan, Z. (2018). Baclofen Blocks the Acquisition and Expression of Mitragynine-Induced Conditioned Place Preference in Rats. *Behav. Brain Res.* 345, 65–71. doi:10.1016/j.bbr.2018.02.039

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Kratom: A Legal Drug That's Dangerously Addictive

childmind.org/article/kratom-a-legal-drug-thats-dangerously-addictive

Kratom use among teenagers is rising. Because it’s legal and made from a plant, they assume it’s safe — but it's not.

Writer: Christina Frank

Clinical Expert: Michael P. Milham, MD, PhD

Marianne Chai, MD, director of the Center for Living in New York, first encountered kratom a few years ago when a teenage boy came to her office for addiction treatment. “He had been drinking it as a tea to help with anxiety and ultimately ended up in the school’s student health center in acute opioid withdrawal,” she says.

Kratom is a substance derived from the leaves of a plant native to Southeast Asia. At low doses, it produces stimulant effects comparable to medications commonly used to treat ADHD; at higher doses, the substance functions as an opioid. However, kratom doesn’t require a prescription, and unlike “street” opioids such as heroin, it is currently legal and easy to purchase. And there’s the rub: Because it’s legal and made from a plant, there’s a misperception that kratom is safe. In fact, it’s addictive.

“High school and college students are surrounded by kratom these days — in smoke shops and on the internet, says Mike Milham, MD, PhD, a child and adolescent*psychiatrist*

at the Child Mind Institute. “For students especially, you can imagine the allure of the stimulant effects, but once you start experiencing the euphoria of the opioid aspect, you’re at risk for addiction.”

Students say kratom helps them study and counters anxiety. “Initially it helps you with your all-nighters, and it helps you with your stress,” says Dr. Milham. “But then you’re stuck.”

What is in kratom?

Kratom is sold in powder form and can be taken in capsules or made into a tea: some states even have “bars” devoted to it.

One of the substances found in kratom leaves, mitragynine, interacts with receptor systems in the brain to produce stimulant effects. Mitragynine and another compound, 7-α-hydroxymitragynine, interact with opioid receptors in the brain, producing the pleasurable, pain-reducing effects of opioids, especially when users consume large amounts of the plant.

It is sometimes advertised as “safe kratom,” and touted as able to relieve everything from anxiety to diabetes. Proponents believe kratom can be a lifesaver for opioid addicts since you don’t need a prescription to get it, and it may help reduce withdrawal symptoms. To date, however, there have been no well-controlled scientific studies showing that kratom is effective for opioid abuse withdrawal or any other conditions in humans. There is also no research on how kratom may interact with other medications.

Kratom addiction

David Seitz, MD, the medical director of Ascendant, a New York based rehab program, reports seeing an increase in cases of kratom addiction. “I think the major challenge is a perceptual one,” he notes. Young people using think it’s harmless because it’s touted as natural. “They don’t consider it a drug until they get into trouble with it.”

One father reports that his son started using kratom in boarding school, where he was introduced to it in his dorm and was told it was a tea. He started using it for social anxiety, but then he got addicted. “We noticed that he seemed angrier and had an explosive temper,” his dad said. “He realized he had a problem and stopped, but had some relapses before stopping completely. It was a scary thing.”

Kratom addiction is also particularly challenging to treat. There are a lot of substances in kratom, Dr. Seitz explains, “some of which haven’t even been properly identified.” Among those other substances, he says, seems to be something that acts like a benzodiazepine, an anti-anxiety medication.

When you treat a patient withdrawing from kratom with medications used for opioid addiction, like Methadone or Suboxone, they deal with the opioid effect but not with the effects other substances in the plant. Patients withdrawing from kratom may become so anxious they give up on treatment. “It appears that just treating the opioid effect is often not enough,” Dr. Seitz says. “If you just use the Suboxone, the person is likely to leave treatment.”

Dr. Seitz, who is also a diplomate of the American Society of Addiction Medicine, notes that few physicians realize how complicated kratom is. He reports hearing from other doctors and medical students who are frustrated with their kratom patients.

“They’re seeing the patient and they’re like, ‘I’m giving opioids and you can’t be having the symptoms you’re having because I’m giving you this.’ And it just doesn’t work that way. There’s another effect in there.”

Kratom and regulation

Kratom is not regulated by the Food and Drug Adminstration (FDA), so there’s no way to know how potent any given amount is, or if a batch contains other substances as well; in April 2019, the FDA released results of a laboratory analysis that found significant levels of lead and nickel in 30 kratom products — enough to potentially cause heavy metal poisoning.

Dr. Milham, who is also the founding director of the Center for the Developing Brain at the Child Mind Institute, acknowledges that there are challenges in determining how exactly kratom should be regulated or classified.

“Making it completely illegal isn’t necessarily a good idea, because at this point you do have portions of the community that actually are using it to help with opioid withdrawal, and to just make it illegal and take it completely off schedule doesn’t really make sense.”

The best solution, says Dr. Milham, is to make kratom a Schedule II drug — a classification by the Drug Enforcement Administration that’s applied to medications “with a high potential for abuse, with use potentially leading to severe psychological or physical dependence.”

With that classification, kratom could be used in a controlled fashion, with reliable quantities of active ingredients. “Drugs with addictive potential,” he argues, “should be in the hands of the healthcare providers to prescribe.”

What should parents do?

In addition to the fact that it’s easy to purchase over-the-counter, kratom stands out because it does not show up on standard drug tests, further increasing its appeal for some users. Testing can be done by certain labs, but this is expensive, and, at the moment, kratom is not something most people think to test for.

Dr. Milham’s takeaway for parents: “Educate yourself, and don’t be fooled if your child dismisses your concerns, saying it’s just a tea, it’s legal and sold in stores.”

It’s important that parents have a conversation with teenage children about kratom, to let them know what the dangers are, whether or not they are aware that a child is using the drug. Dr. Chai notes that parents are very often unaware of the extent of

their child's substance use. "Parents don't realize until their kid has progressed much further along to the point of having consequences," she says. "Parents are often the last to know what their child is really doing."

If you suspect your child might be developing a kratom addiction, here are some of the symptoms to be on the lookout for, according to Dr. Chai:

- Runny nose
- Muscle aches
- Joint and bone pain and spastic, jerky movements
- Mood swings
- Depression
- Anxiety
- Irritability
- Tremors, chills, sweating, pin-point pupils, gooseflesh (typical of opioid withdrawal)

If your teen or young adult child is using kratom, the conversation should be not only about why they should stop using it, but what it's doing for them, and how they might find healthier alternatives. "You need to be able to figure out," as Dr. Seitz puts it, "if your kid is using it, why is your kid using it?"

If eliminating kratom proves to be difficult, or if your child is struggling with withdrawal symptoms, then an evaluation by an addiction professional is in order.

Dr. Seitz notes that it's important to have open communication with kids about drug use, to keep it from being driven underground. "It can become sort of a cat-and-mouse game, where what parents are concerned about is catching their kid. And then it doesn't serve any function."

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