Statewide Drug Policy Advisory Council

Public Meeting Book

February 02, 2023
8:30AM-10:30AM

Statewide Drug Policy Advisory Council (DPAC) Meeting

February 2, 2023
8:30 am to 10:30 am

Virtual Meeting via Microsoft Teams:
http://floridahealth.gov/DPACMeeting
Or call in (audio only)
850-792-1375
Phone Conference ID: 201 614 413#

AGENDA

Time	Item	Topic	Topic Facilitator/Presenter
8:30 am – 8:40 am	1	Welcome/Introductions/Opening Remarks	Joseph A. Ladapo, MD, PhD State Surgeon General Florida Department of Health
8:40 am – 8:50 am	2	Approval of October 27, 2022 Meeting Minutes	DPAC Members
8:50 am – 9:10 am	3	University of Florida College of Pharmacy – Kratom Research	Christopher McCurdy, PhD, F.A.A.P.S Professor of Medicinal Chemistry College of Pharmacy, University of Florida Abhisheak Sharma, M. Pharm., PhD Assistant Director of Translational Drug Development Core Assistant Professor of Pharmaceutics College of Pharmacy, University of Florida Jay McLaughlin, PhD Professor of Pharmacodynamics College of Pharmacy, University of Florida Oliver Grundmann, PhD Clinical Professor of Medicinal Chemistry College of Pharmacy, University of Florida
9:10 am – 10:00 am	4	Agency and Member Updates	DPAC Members
10:00 am – 10:15 am	5	Public Comment	
10:15 am – 10:30 am	6	Next Steps/Future Meeting Date/ Motion to Adjourn	Joseph A. Ladapo, MD, PhD State Surgeon General Florida Department of Health

Statewide Drug Policy Advisory Council
Meeting Minutes

October 27, 2022
8:30 am – 12:30 pm
Meeting Location:
4052 Bald Cypress Way, Conference Room 301
Tallahassee, FL 32399

Welcome/Introductions
Shay Chapman, BSN, MBA, State Surgeon General Designee, opened the Statewide Drug Policy Advisory Council (DPAC) meeting. Ms. Chapman thanked all members of DPAC, designated appointees, and other participants for their continued partnership in this critical work. Ms. Chapman asked that Nathan Dunn, MSA, Staff Liaison Designee, proceed with roll call.

The following members or designees were in attendance:
Shay Chapman, BSN, MBA, State Surgeon General Designee
Maggie Agerton for Ricky Dixon (Department of Corrections)
Melanie Brown-Woofter for Mark P. Fontaine (Governor Appointee: Substance Abuse Treatment, Florida Behavioral Health Association)
Jeffrey Cece, MS, CPM for Shevaun Harris (Department of Children and Families)
Elaina Cosentino for Representative Spencer Roach (Florida House of Representatives)
Aaron Gerson for Judge Steve Leifman (11th Judicial Circuit Court of Florida)
Mark Glass (Department of Law Enforcement)
Cindy Grant (Governor Appointee, Faith-Based Substance Abuse Treatment, HeartDance Foundation, Inc.)
Christina Harris for Ashley Moody (Office of the Attorney General)
Timothy Hay for Manny Diaz, Jr. (Department of Education)
Captain Jordan Jerris for Major General James Eifert (Department of Military Affairs)
St. George Pink for Senator Darryl Rouson (Florida Senate)
Captain Derrick Rahming for Terry Rhodes (Department of Highway Safety and Motor Vehicles)
Peggy Sapp (Governor Appointee: Substance Abuse Prevention, Informed Families)
Tracy Shelby for Eric Hall, Ed.D. (Department of Juvenile Justice)
Doug Simon for Chris Spencer (Governor's Office of Policy and Budget)

Guests and Staff:
Grace Boran, Florida State University
Nathan Dunn, MSA, Staff Liaison (Department of Health)
Jesseka Forbes, PharmD (Agency for Health Care Administration)
Robert Jacobson (Emergent BioSolutions)
John McClellan (Department of Law Enforcement)
Mary McClellan (Career Source)
Ashley Peterson (Agency for Health Care Administration)
Lori Reeves, MPH (Department of Health)
Keshia Reid, PhD (Department of Health)
Krista Riveron, PharmD, JD, MS (Boca Raton Regional Hospital)
Jasmani Riveron (Ardurra)
Stuart Waldo (Department of Health)
Ayesha Waters (Agency for Health Care Administration)
Lauren Whiteman, MPH, CPH (Department of Health)
Jennifer Williams (Department of Children and Families)

Opening Remarks
Ms. Chapman provided an overview of the meeting agenda and the presentations to follow.

Ms. Chapman reflected on the efforts within the Florida Department of Health (FDOH) related to DPAC's work to address substance use in the state of Florida. In the wake of Hurricane Ian, there was concern of increased substance use and overdose deaths due to the impact on individuals' mental health and the disruption of prescription medicine supply. It is critical that community partners continue to provide resources and innovative initiatives with cross-agency collaboration even during states of emergency.

Business

1. **Review and Approval of Meeting Minutes from July 19, 2022:**
   A motion was entered to approve the meeting minutes. Motion carried, all in favor. Minutes were approved with no opposition.

2. **Presentations:**
   Naloxone: Overcoming Pharmacy Barriers:
   A. **Naloxone Kits Before Hospital Discharge** – Lori Reeves, MPH, Maternal and Neonatal Opioid Prevention Coordinator, Florida Department of Health

   Ms. Reeves provided an overview of FDOH initiatives that support increased availability of naloxone in hospitals and issues related to maternal overdose and neonatal abstinence syndrome. FDOH has been working to engage hospitals in a standard group of practices that would increase the number of women screened and ensure they are prescribed naloxone when needed. The Florida Maternal Mortality Review Committee found that overdose was the leading cause of death for women during pregnancy and the year postpartum.

   B. **Florida Society of Health System Pharmacists** – Krista Riveron, PharmD, JD, MS, Medication Safety and Quality Coordinator, Pharmacy, Boca Raton Regional Hospital

   Dr. Riveron provided an overview of the Florida Society of Health System Pharmacists (FSHP), their goals related to the opioid epidemic, and who they serve. The FSHP strategic plan aims to work with key stakeholders to reduce opioid overdose deaths, promote free naloxone grant programs to Florida hospitals and discuss involvement in the drug epidemiology network throughout the state. At the 2022 FSHP Annual Meeting, attendees were offered, for the first-time, continuing education on addressing the opioid epidemic in addition to required bi-annual license renewal on controlled substances.

   One of FSHP's main goals is to obtain legislation to prescribe medication-assisted treatments (MAT). There is currently a federal bill, the Mainstreaming Addiction Treatment Act, in review. This legislation would eliminate barriers preventing pharmacists from prescribing and dispensing buprenorphine for MAT including modifications to X-waiver requirements.

   C. **Cross-Agency Partnerships to Support Naloxone at Hospitals** – Jeffrey Cece, MS, CPM, Florida Department of Children and Families

   Mr. Cece provided an overview of the Florida Department of Children and Families (DCF) initiative of using the Meds-to-Beds program as a model for dispensing inpatient naloxone nasal spray. A nationwide analysis of 148,966 emergency department visits for opioid overdose between August 2019 and April 2021, revealed that only 6.3 percent of individuals received a naloxone kit in hand or within 30 days of hospital discharge. In comparison, 45 percent of individuals who presented for anaphylactic shock or in need of a rescue medication, such as epinephrine (EpiPen), left the hospital with medication in hand or received within 30 days of hospital discharge. Researchers conducted a cross-sectional telephone audit of actively licensed community pharmacies, including 683 pharmacies in Florida, from May 2020 through April 2021, that revealed roughly 30 percent were not equipped to provide naloxone. Hospital-based naloxone

distribution utilizing new legislative authority to dispense will help to close the gap. DCF developed a plan to commit three million from opioid settlement dollars to purchase and distribute approximately 45,000 naloxone kits to hospitals, and these funds do not bear any restrictions to for-profit entities expanding the reach.

DCF's Overdose Prevention Program's current network has 306 organizations enrolled to distribute naloxone nasal spray kits. Since program initiation in 2016, approximately 372,958 naloxone kits have been distributed statewide.

3. **Discussion of 2022 Annual Report:**
Nathan Dunn, Staff Liaison Designee, addressed DPAC and provided an overview of the 2022 recommendations and requested input from DPAC to be added to the 2022 Annual Report. The content of the report is a compilation of information from the members of DPAC. DPAC recommendations were addressed, and discussion followed.

Recommendation #1
DPAC members had no additional edits for Recommendation #1.

Recommendation #2
DPAC members had no additional edits for Recommendation #2.

Recommendation #3
DPAC members recommended updating to substance use prevention strategies, as a plural, to incorporate multiple programs, cross-agency initiatives, and target various demographics. Suggestion of adding verbiage on utilizing the Red Ribbon Campaign as an umbrella and conduit to recognize and engage the public. DPAC members requested under section two of Recommendation #3 to remove language stating to increase screenings and address trauma-related issues among youth.

Recommendation #4
DPAC members recommended updating to encourage the use of evidence-based substance use prevention programs and the incorporation of parents, students, and residents, not only youth.

Recommendation #5
DPAC members had no additional edits for Recommendation #5.

Recommendation #6
DPAC members had no additional edits for Recommendation #6.

Recommendation #7
DPAC members had no additional edits for Recommendation #7.

Recommendation #8
DPAC members had no additional edits for Recommendation #8.

Recommendation #9
DPAC members recommended replacing the Agency for Health Care Administration (AHCA) with DCF and FDOH as they are more equipped to report on the protocols addressed within Recommendation #9.

Recommendation #10
DPAC members had no additional edits for Recommendation #10.

Recommendation #11
DPAC members had no additional edits for Recommendation #11.

Recommendation #12
DPAC members had no additional edits for Recommendation #12.

Recommendation #13
DPAC members had no additional edits for Recommendation #13.

Recommendation #14
DPAC members had no additional edits for Recommendation #14.

Recommendation #15
DPAC members recommended removal of condition to provide an annual report as it is not a requirement of Senate Bill 1120.

Recommendation #16
DPAC members had no additional edits for Recommendation #16.

Recommendation #17
DPAC members recommended removal of Recommendation #17 as it is complete as currently written.

4. **Agency and Member Updates:**

Doug Simon, Governor's Office of Policy and Budget
The Governor's Office of Policy and Budget had no additional updates for DPAC.

Christina Harris, Office of the Attorney General
The Office of the Attorney General had no additional updates for DPAC.

John McClellan, Florida Department of Law Enforcement
The Florida Department of Law Enforcement (FDLE) requested a presentation from the University of Florida College of Pharmacy on their two-year study on kratom and their findings. FDLE is continuing to work out the 14 benzodiazepine analogs to add to the controlled substance list to provide to the public and add to an emergency order with the Attorney General's office.

Jeffrey Cece, Department of Children and Families
DCF received federal approval for the State Opioid Response grant and is completing budget revisions with funders. The onboarding of Project Director, Project Coordinator, and Data Coordinator is now complete. Mr. Cece recommended a future presentation regarding the Florida Youth Substance Abuse Survey.

Maggie Agerton, Department of Corrections
The Department of Corrections is working with DCF to get naloxone in the hands of correction and probation officers to support distribution upon release. Collaborative effort is moving along and addressing challenges and barriers.

Tracy Shelby, Department of Juvenile Justice
The Department of Juvenile Justice is working to confirm that all detention centers, as well as residential programs, either have a supply of or access to naloxone at all sites.

Timothy Hay, Department of Education
The Department of Education convened the first meeting of School Safety Specialists and Mental Health Coordinators in October with a representative from each district in the state. Investment dollars put forth to support mental health awareness activities has increased from $75 million in 2019 to $140 million for 2023, demonstrating the importance of the prevention piece.

Captain Derrick Rahming, Department of Highway Safety and Motor Vehicles
The Department of Highway Safety and Motor Vehicles reported from January to June of 2022, 1,887 pounds of marijuana, 222 pounds of cocaine, 9 pounds of heroin, 48 pounds of meth, and 190 pounds of other drugs were removed from Florida's roadways, with contraband totaling $41 million.

Captain Jordan Jerris, Department of Military Affairs
The National Guard continues to provide drug prevention classes to students across the state, having reached 1,200 students to date this year. Additionally, the National Guard continues to support the Drug Take Back initiative to support prevention efforts.

Aaron Gerson, 11th Judicial Circuit Court of Florida
The Judicial Circuit Court had no additional updates for DPAC.

Peggy Sapp, Informed Families
Informed Families continues efforts in the currently active Red Ribbon Campaign week in Miami. The campaign theme of "Celebrate Life" was designed by students.

Melanie Brown-Woofter, Florida Behavioral Health Association
Melanie Brown-Woofter noted that the Florida Behavioral Health Association continues to partner with DCF on the State Opioid Response grant, focusing efforts on developing contracts with providers in order to provide MAT. Additionally, Ms. Brown-Woofer updated that residents on MAT, and residing in hurricane-affected areas, were able to continue to receive their medications through hurricane response efforts in collaboration with first responders.

Cindy Grant, HeartDance Foundation, Inc.
HeartDance Foundation, Inc. continues to collaborate and raise awareness on a local, regional, and statewide level. The Foundation recently completed the development of the 2022 Opioid Prevention Toolkit for Hillsborough County.

Jesseka Forbes, Agency for Health Care Administration
AHCA had no additional updates for DPAC.

5. **Public Comments/Open Discussion:**
Question was asked regarding the two gubernatorial appointment vacancies on the board. Submission of qualified candidates has been completed. What is needed to complete appointment of those persons? Ms. Chapman updated that FDOH is in regular contact and updating the Governor's appointment office and awaiting feedback.

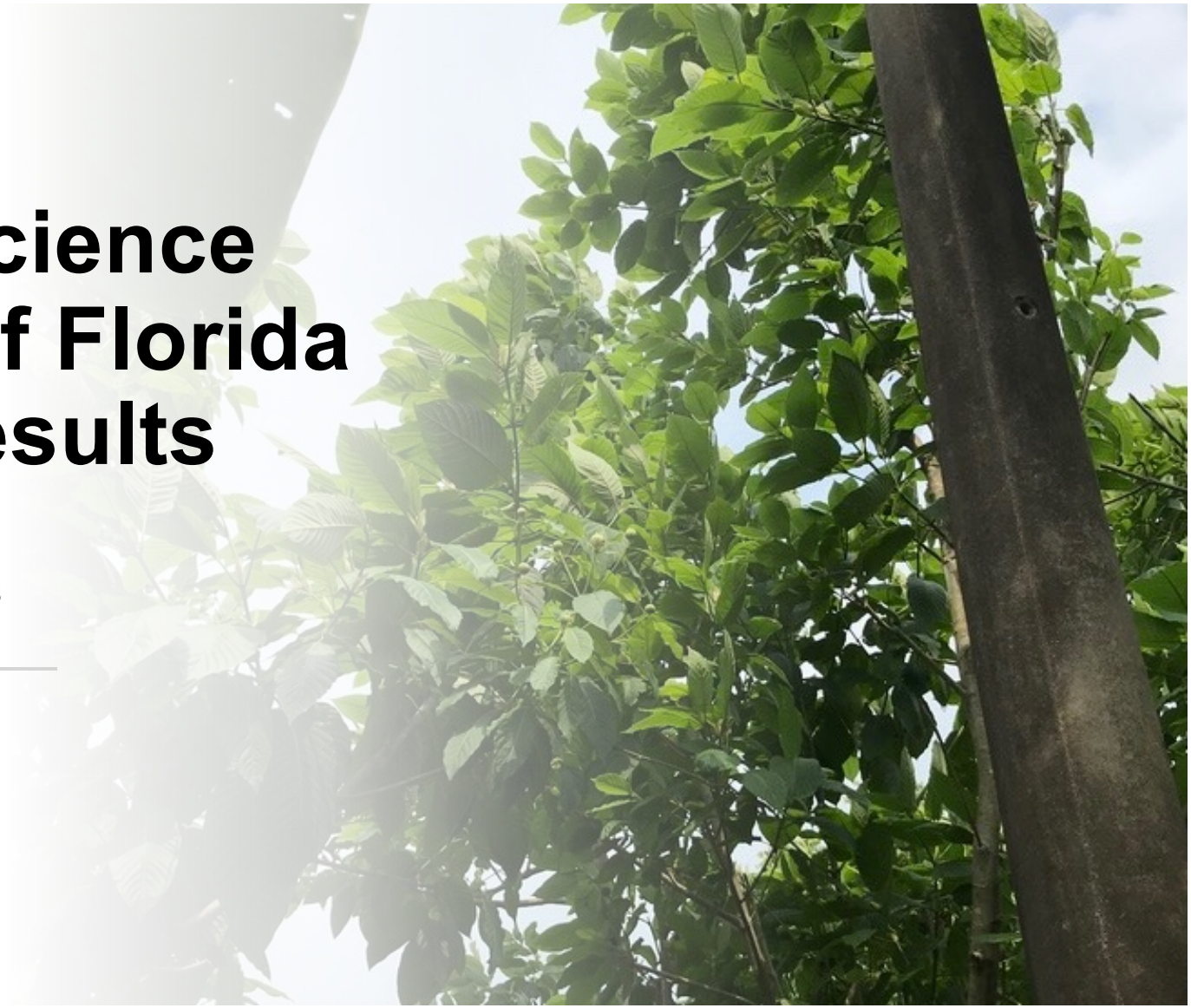
6. **Adjournment:**
For closing items, Ms. Chapman confirmed that edits would be incorporated into DPAC's 2022 Annual Report and submitted by the statutory deadline of December 1.

Proposal of DPAC meeting dates for 2023 were January 24, April 18, July 11, and October 3. Motion to approve dates was entered and carried with no opposition.

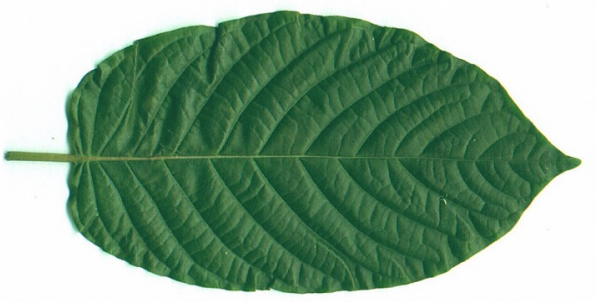
A motion was entered to adjourn. Motion carried with no opposition. Meeting was adjourned at 11:48 am.

Kratom Science University of Florida Study Results

Christopher R. McCurdy, BSPh, PhD, FAAPS
Abhisheak Sharma, BPharm, MS, PhD
Jay P. McLaughlin, MS, PhD
Oliver Grundmann, MS, MEd, PhD
College of Pharmacy
University of Florida



Mitragyna Speciosa



- FAMILY: Rubiaceae
- GENIUS: Mitragyna
- SPECIES: speciosa
- Tree found in tropical Southeast Asia, particularly Thailand and Malaysia.
- Referred to as “Kratom” in Thailand and “Biak Biak or Ketum” in Malaysia.
- Contains over 40 alkaloids that have been isolated to date.[1]

[1] Adkins, J.E.; Boyer, E.W.; McCurdy, C.R. *Curr. Topics Med. Chem.*, **11**, 1165-75 (2011)

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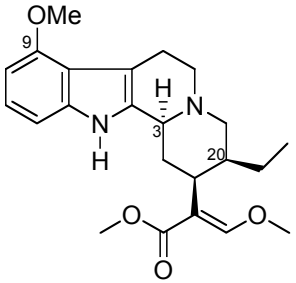
Kratom Use in Southeast Asia

- Kratom tea is used by field workers to relieve pain, as a stimulant to improve work capacity, and to reduce opioid withdrawal[1]
- Recently, polydrug users (METH) are using kratom to reduce use[2]
- The predominant active agent in Kratom is mitragynine (MG)



Mitragynine

[1] Jansen K.L.R., Prast C.J. *J. Ethnopharmacology*. **23**, 115-119 (1988)
[2] Singh, D. et al. *J. Ethnopharmacology.* **249**, 112462 (2020)

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Kratom Use in USA

- Widely available across the internet and smoke/vape shops
- June 2019*: American Kratom Association reported 1950 metric tons exported to US every month
- Typical dose 3-5g# suggesting >15 million users

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Kratom = Threat or Therapeutic

- Anecdotally used for chronic pain, mood elevation, opioid use disorder
- Adulterated or contaminated products reported
- Claims that kratom is severely addictive and deadly
- World Health Organization / US Food and Drug Administration
  - Ongoing talks regarding therapeutic vs. harm profiles

Kratom illegal in 6 states (Alabama, Arkansas, Indiana, Rhode Island, Vermont, Wisconsin)

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Therapeutic Potential of Kratom

- Opioid Detoxification: Kratom has potential to replace several medications used during detoxification (opioid, adrenergic, analgesic and anxiolytic). This would improve medication adherence and chances of completing detoxification.

- Medication Assisted Therapy: Kratom is informally used to reduce opioid use. Kratom withdrawal is mild (<9 on SOWS scale). Polydrug users report Kratom also reduces methamphetamine use.

- THE LACK OF A STANDARDIZED PRODUCT HAS PREVENTED RIGOROUS CLINICAL TRIALS TO EVALUATE THESE CLAIMS

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Mitragyna speciosa growing at the University of Florida MREC

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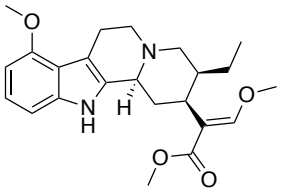
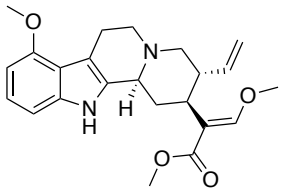
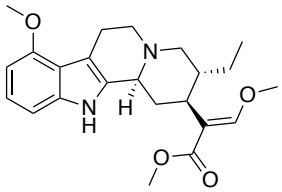
Isolation of kratom alkaloids



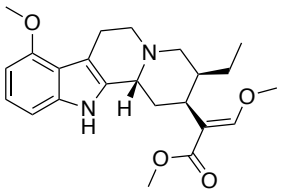
Mitragynine
66%



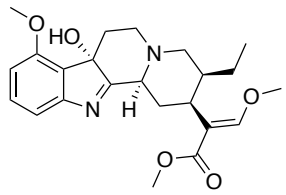
Paynantheine
9%



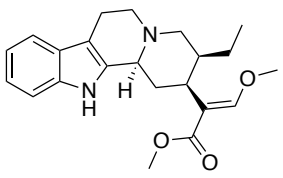
Speciogynine
7%



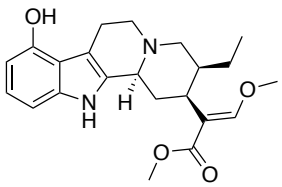
Speciociliatine
~1%



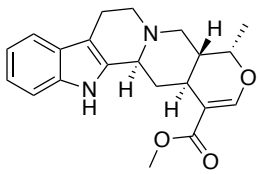
7α-hydroxymitragynine
~2%



Corynantheidine
<1%



9-Hydroxycorynantheidine
<1%



Ajmalicine
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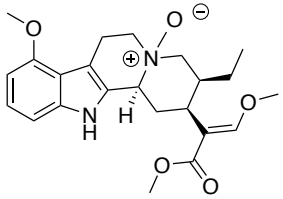
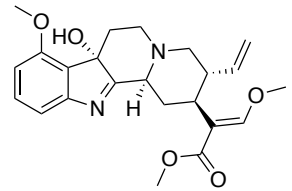
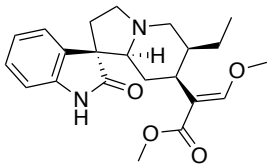


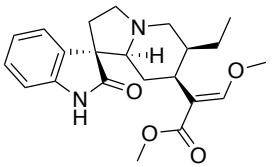
Mitragynine N-oxide
<1%



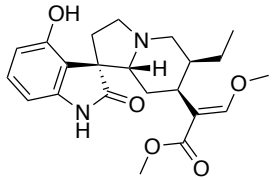
7α-hydroxypaynantheine



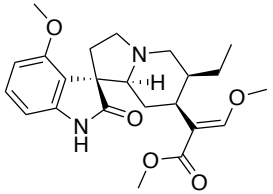
Corynoxine A
<1%



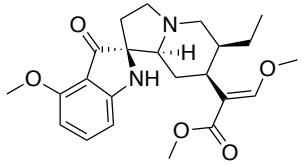
Corynoxine B
<1%



Isospeciofoline
<1%



Mitragynine oxindole B
<1%



Mitragynine pseudoindoxyl

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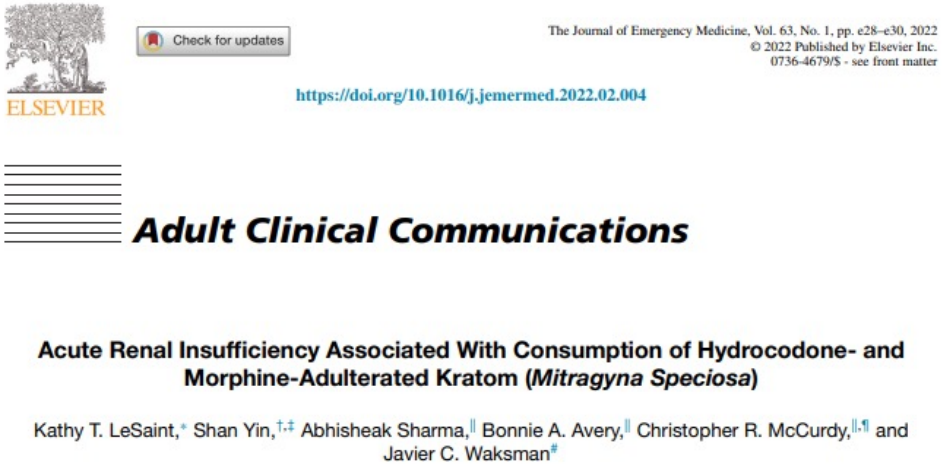
History of Adulteration of Kratom Products



ELSEVIER

Check for updates

The Journal of Emergency Medicine, Vol. 63, No. 1, pp. e28–e30, 2022

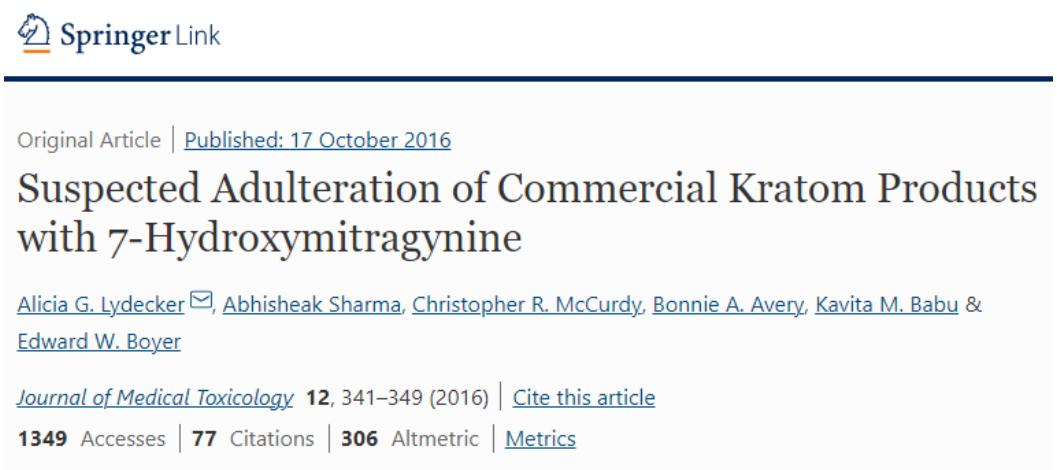
0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2022.02.004

Adult Clinical Communications

Acute Renal Insufficiency Associated With Consumption of Hydrocodone- and Morphine-Adulterated Kratom (*Mitragyna Speciosa*)

Kathy T. LeSaint,* Shan Yin,†,‡ Abhisheak Sharma,‖ Bonnie A. Avery,‖ Christopher R. McCurdy,‖,¶ and Javier C. Waksman#



Springer Link

Original Article | Published: 17 October 2016

Suspected Adulteration of Commercial Kratom Products with 7-Hydroxymitragynine

Alicia G. Lydecker, Abhisheak Sharma, Christopher R. McCurdy, Bonnie A. Avery, Kavita M. Babu & Edward W. Boyer

Journal of Medical Toxicology **12**, 341–349 (2016) | Cite this article

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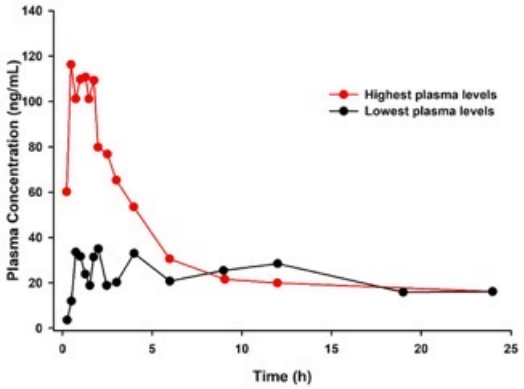
Recent Analysis of Commercially Available Kratom Products

- **211** kratom products provided by the volunteers of NIDA-Kratom Ecological Momentary Assessment (KEMA) clinical study were tested.
- No illicit substance was detected during the qualitative analysis for 35 illicit substances/drugs.
- 7-Hydroxymitragynine contents were similar to found those found in raw kratom leaves

Clinical Pharmacokinetics of Mitragynine (Thailand Study)



Parameters	Mean ± SD
T_{max}(h)	0.8 ± 0.4
Terminal $t_{1/2}$ (h)	23.2 ± 16.1
V_d/F (L/kg)	38.0 ± 24.3
CL/F (L/h kg)	98.1 ± 51.3

Forensic Analysis in the United States

Case I: The measured mitragynine plasma concentration in a deceased individual from Florida was found to be 1,800 ng/mL

Case II: The measured mitragynine plasma concentration in a deceased Tupper Lake police Sgt was found to be 3,500 ng/mL

Satariya Trakulsrichai *et al*., *Drug Des Devel Ther*. 2015; **9**: 2421.
Chrostowski L. Report of diagnosis and autopsy of Christopher Waldron. Medical Examiner Department. Hillsborough County, FL, USA [22 August 2017]
http://speciosa.org/analysis-of-two-deaths-reportedly-associated-with-kratom/

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Measured mitragynine plasma concentration in the deceased Americans were found to be 17.1- to 189-times higher than the peak plasma concentrations (C_{max}) (18.5 – 105.0 ng/mL) measured in regular kratom users.

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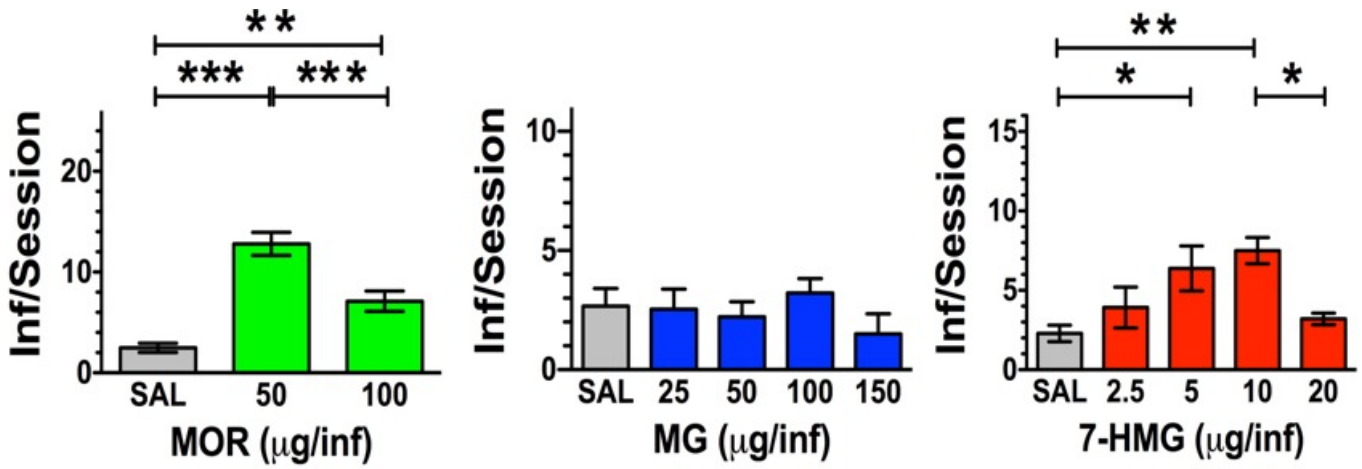
Substitution of MG and 7-HMG for morphine



Hemby SE, et al. *Addict Biol*. 2018 June 27.

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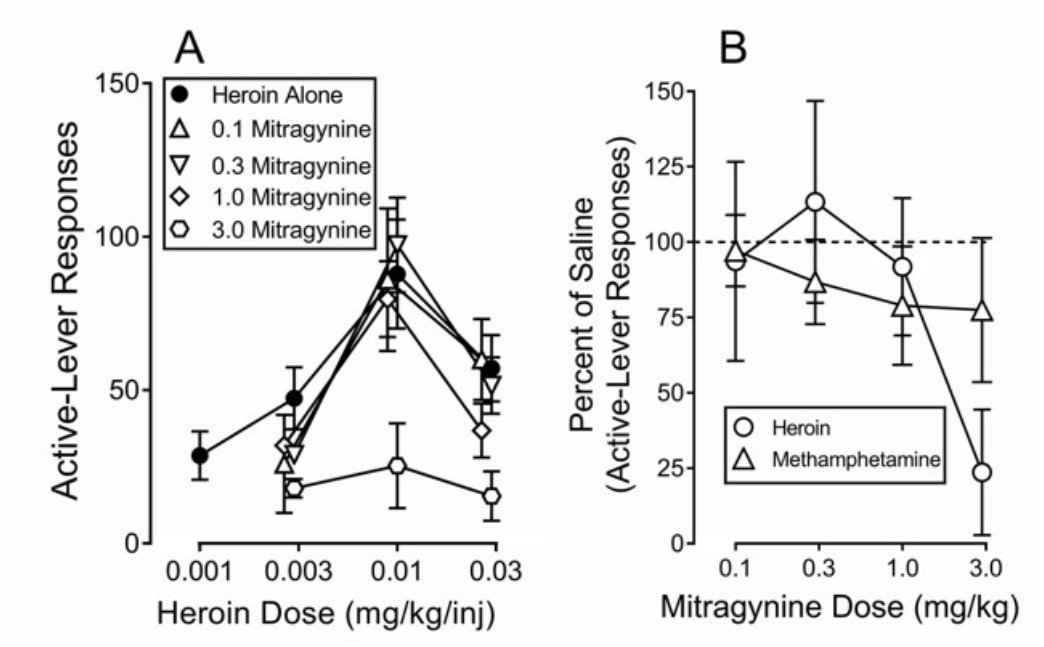
MG administration *reduced* heroin self-administration



Yue K, Kopajtic TA, Katz JL. *Psychopharmacology* (Berl) 2018 Oct; 235(10):2823-2829

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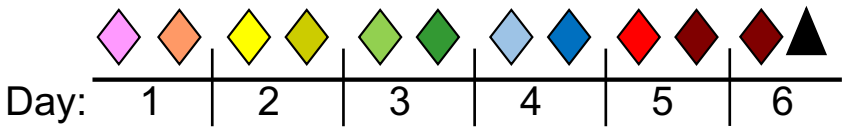
Assessing opioid physical dependence with naloxone precipitation: Less withdrawal by repeated treatment with lyophilized Kratom tea



Days 1-5: Treatments (a.m. and p.m.):

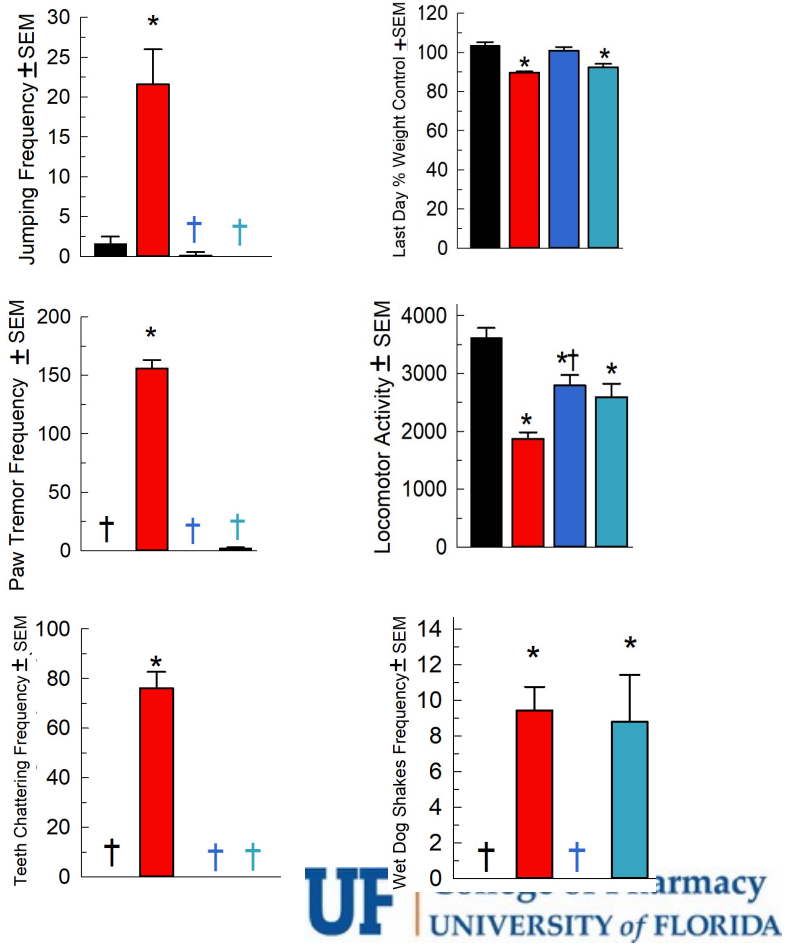
Group 1: Saline, p.o. x2/d

Group 2: Morphine, i.p. x2/d:
- Day 1: 20 mg/kg, i.p., x2
- Day 2: 40 mg/kg, i.p., x2
- Day 3: 60 mg/kg, i.p., x2
- Day 4: 80 mg/kg, i.p., x2
- Day 5: 100 mg/kg, i.p., x2

Group 3: Kratom (1 g/kg, p.o.) x2/d

Group 4: Kratom (2 g/kg, p.o.) x2/d

Day 6: (a.m.): repeat high dose of day 5,
(2 h later): Naloxone (10 mg/kg, s.c.)
Opioid withdrawal testing, 15 min



Wilson LL et al.; Drug and Alcohol Dependence, 2020; ***216:****108310-108318.*

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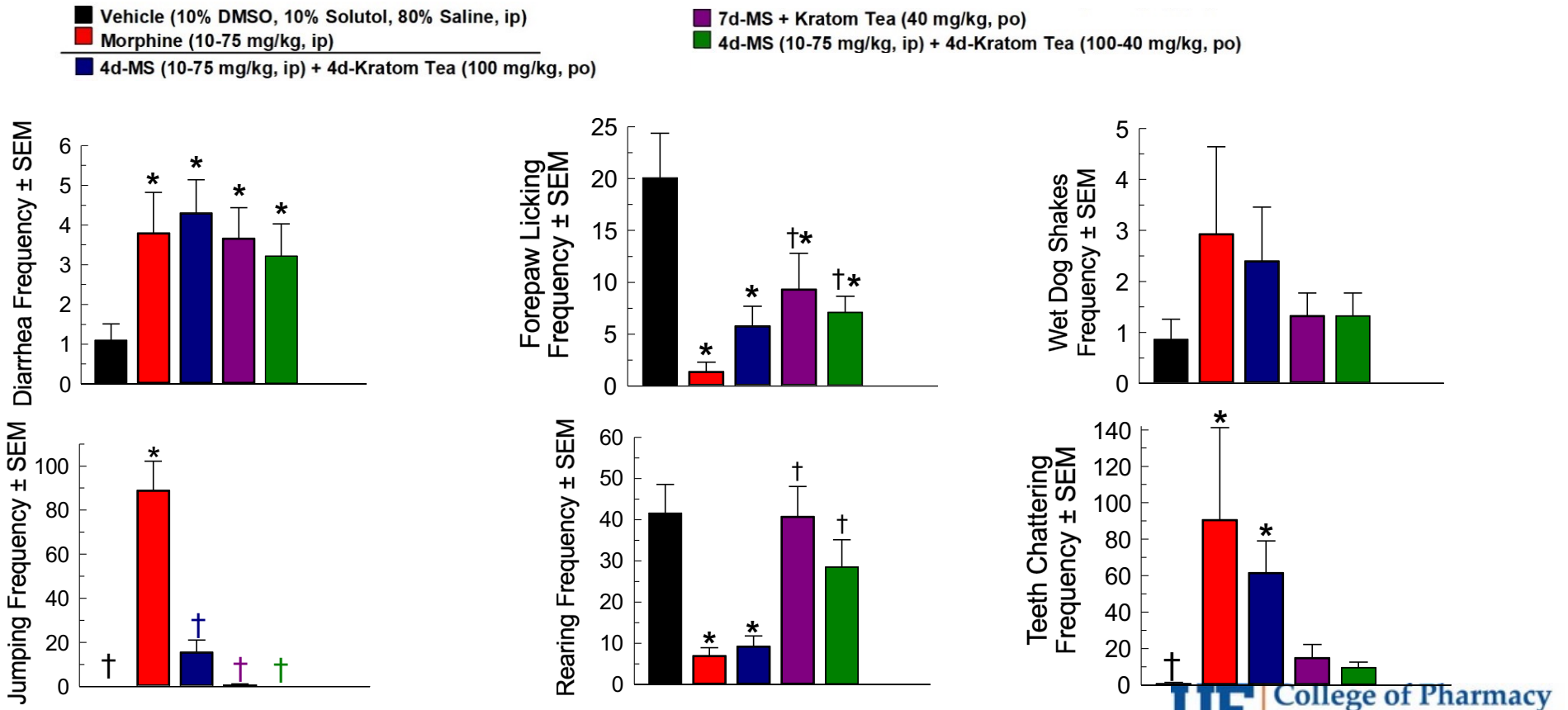
Substitution of lyophilized Kratom tea ameliorates *some* naloxone-precipitated withdrawal symptoms in morphine-dependent mice



*Wilson LL et al.; Drug and Alcohol Dependence, 2020; **216:**108310-108318.*

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Assessing opioid physical dependence with naloxone precipitation: Less withdrawal after repeated mitragynine treatment (5 days)

Measure:	Saline	Treatment (twice/d for 4 d +1) Morphine	Mitragynine	Statistical analysis: (One-way ANOVA)
Forepaw Tremor	20.2 ± 8.0	9.8 ± 3.7	29.2 ± 10.1	$F_{(2,27)}$ =1.56, p=0.23
Wet dog shakes	0.8 ± 0.51	1.0 ± 0.45	0.6 ± 0.22	$F_{(2,27)}$ =0.24, p=0.79
Straightening	5.7 ± 2.33	3.7 ± 1.22	2.7 ± 1.65	$F_{(2,27)}$ =0.72, p=0.49
Stool consistency	1.1 ± 0.41	3.8 ± 1.02	2.4 ± 0.78	$F_{(2,27)}$ =3.02, p=0.07
Jumping Frequency	0.0 ± 0.0	89 ± 13.3	2.4 ± 2.29	$F_{(2,27)}$ =42.6, p<0.0001
Rearing Frequency	55.4 ± 6.59	4.2 ± 0.94	57.8 ± 14.5	$F_{(2,27)}$ =10.8, p=0.0004
Forepaw Licking Frequency	15.1 ± 3.27	0.2 ± 0.2	14.7 ± 3.12	$F_{(2,27)}$ =10.6, p=0.0004
Teeth Chattering Frequency	0.4 ± 0.27	37.1 ± 11.0	10.9 ± 5.31	$F_{(2,27)}$ =7.22, p=0.003

Wilson LL et al., Cellular and Molecular Neurobiology. 2021 July; ***41(5):****1131-1143*

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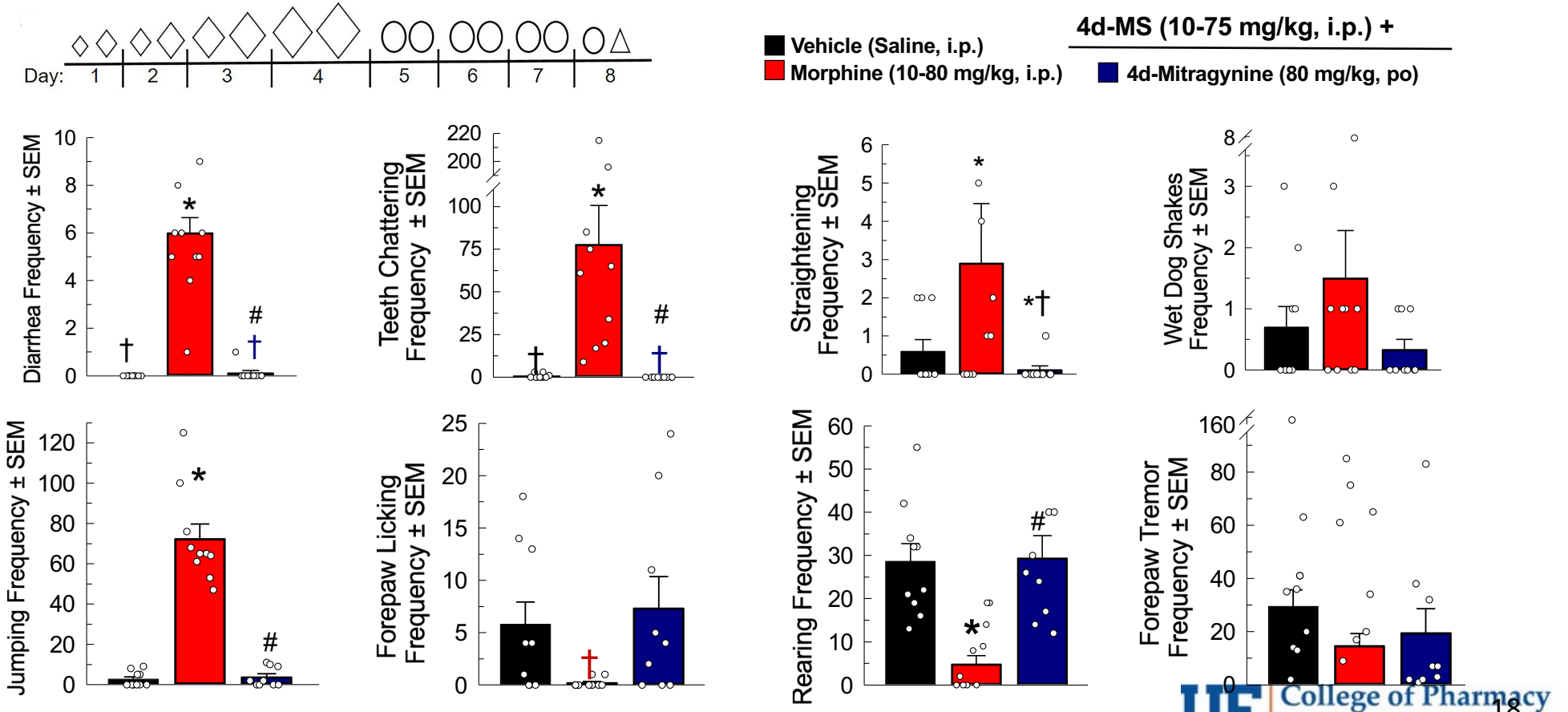
Substitution of mitragynine ameliorates opioid withdrawal symptoms in morphine-dependent mice



*Wilson LL et al., Cellular and Molecular Neurobiology. 2021 July; **41(5):**1131-1143*

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Conclusions of opioid dependence testing in mice

- Kratom Tea and mitragynine alone displayed little-to-no physical dependence
- Substitution of Kratom Tea or mitragynine for morphine in physically-dependent mice ameliorated some effects of opioid withdrawal

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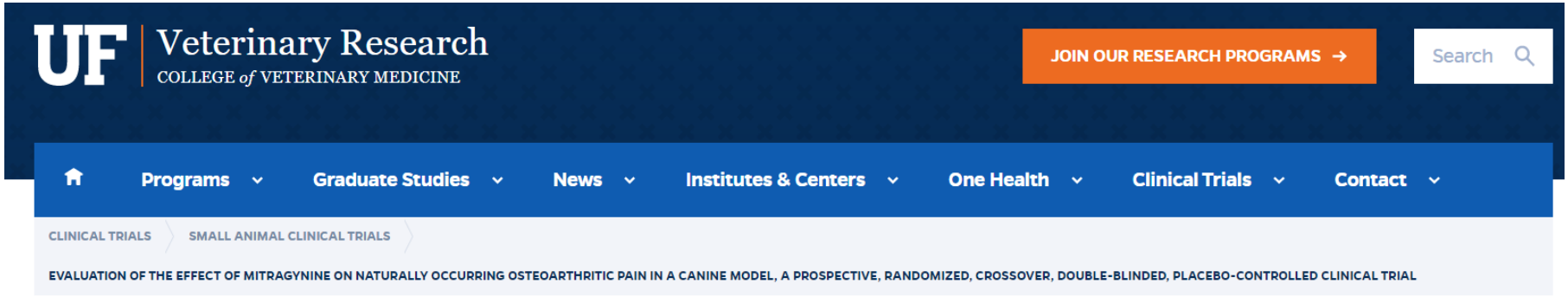
Clinical Trial in Dogs



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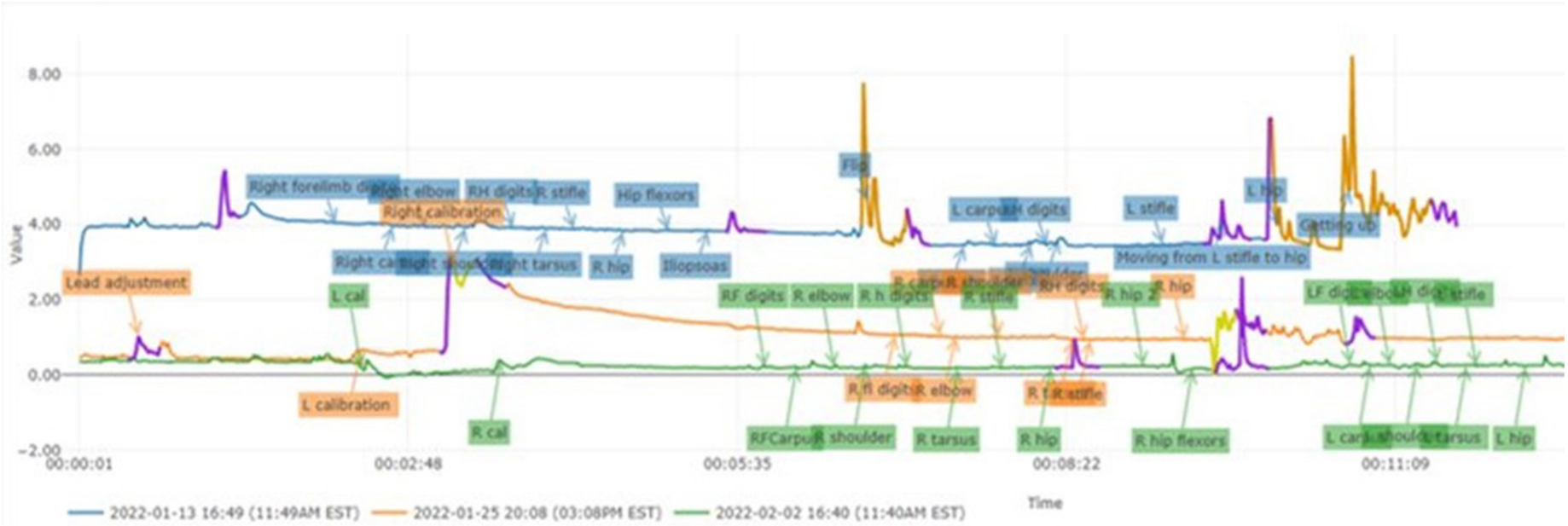
Clinical Trial in Dogs



- PainTrace of Dog 1 after dose and frequency escalation, demonstrating a decline in baseline pain measures (Baseline Delta -0.66 > -0.3 >-0.02 > 0.11), denoting summative pain during exam improved.

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Prevalence of Kratom use

- Current estimates vary widely
  - 0.7% past-year kratom use was associated with higher odds of opioid use disorder (Palamar, *Am J Prev Med*, 2021)
  - 1.3% lifetime prevalence of kratom use from 2019 NSDUH with 18-fold increase among opioid use disorder patients (Xu et al., *Prim Care Companion CNS Disord*, 2021)
  - 6.1% lifetime prevalence for kratom use in survey with up to 48% reporting diagnosed addiction (Covvey et al., *J Addict Dis*, 2020)
  - 0.8% past-year and 1.3% lifetime prevalence of kratom use from NMURx program survey, higher use of illicit and prescription drugs for non-medical reasons (Schimmel et al., *Addiction*, 2021)
- Caveat: Cause and Effect of Kratom use in regards to substance use has not been determined ("chicken and egg dilemma")

The common Kratom user

- Kratom user surveys repeatedly confirmed demographics of average user (Grundmann, 2017; Garcia-Romeu et al., 2020, Covvey et al., 2020):
  - Middle-aged user, approximately 60/40 male/female
  - Mostly Caucasian (85-95%)
  - Most married or partnered (55-65%)
  - Middle-class income ($35K-$60K)
  - Employed with health insurance (55-70%)
  - Majority Higher Education (AA, BS, or advanced degree)
- Estimated number of active kratom users based on imported kratom ranges from 2-20 million in the US (Henningfield et al., *Prev Med*, 2019)

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The dose and the effect

- Oral doses of Kratom exert distinct effects
  - Doses ranging from 1-5 g mainly cause mild stimulant effects, but may also cause muscle relaxation
  - Doses from 5g up to 15g are usually taken for analgesic effects and may also cause constipation, tachycardia, hypotension, dizziness, etc.
  - No indication of other routes of administration (although smoking has been occasionally reported)
- To date, no case of fatal Kratom-only exposure from respiratory depression

Table 1 Pharmacological effects of kratom

	Low dose (1–5 g)	High dose (5–15 g)
Stimulant effects	Increased alertness Physical energy Talkativeness Sociable behavior	Tachycardia
Sedative/opioid-like effects	Loss of muscle coordination	Constipation Dizziness Hypotension
Adverse effects	Itching Nausea Loss of appetite Increased urination	Dry mouth Sweating

Source(s): Int J Legal Med. 2016 Jan;130(1):127-38

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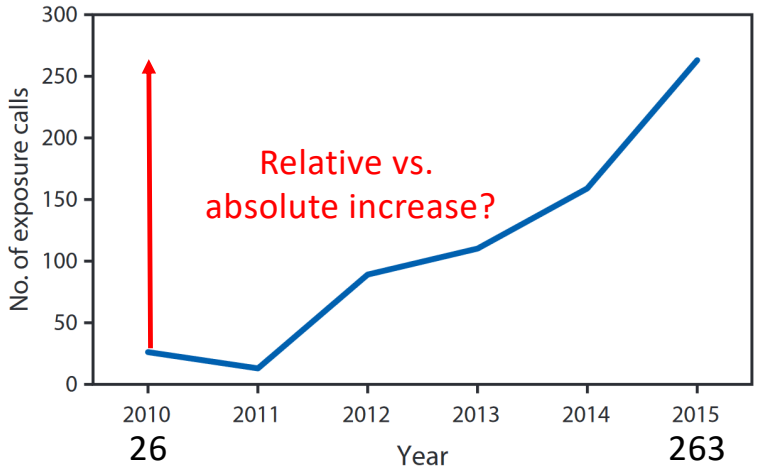
Toxicity of Kratom

- Traditional uses are not associated with major toxicity, even with chronic use
  - Often used orally for hard labor to gain stimulant effects by chewing on fresh leaves
  - Treatment of acute pain and diarrhea with tea preparations of dried leaves
  - Observations of mild dependence if used over long periods of time
- Kratom use in opioid withdrawal
  - Initial data indicate that self-treatment of opioid withdrawal symptoms with Kratom products in Southeast Asia is widely practiced
  - Increasing use in US for self-treatment of opioid use disorder (heroin & prescription opioid) and withdrawal symptoms
  - Case reports indicate organ toxicity (primarily liver) with high chronic doses and in users with prior liver damage
  - Fatalities associated with Kratom use are almost exclusively poly-drug exposures

Regulatory status of Kratom

- Currently NOT regulated as an herbal supplement BUT
  - FDA considers Kratom as a new dietary ingredient and hence can enforce stricter regulations on its import, resulting in seizure of various Kratom shipments in recent years
  - DEA has filed an intention to place Kratom and its alkaloids in schedule I in October 2016 without public comment due to concerns of immediate threats to public health, withdrawal of intent
  - Based on publication by CDC that has shown an increase in Kratom-related cases reported to poison control centers between 2010 and 2015

FIGURE. Number of reported exposure calls to poison centers related to kratom use, by year — National Poison Data System, United States and Puerto Rico, January 2010–December 2015



Source(s): MMWR Morb Mortal Wkly Rep. 2016 Jul 29;65(29):748-9.

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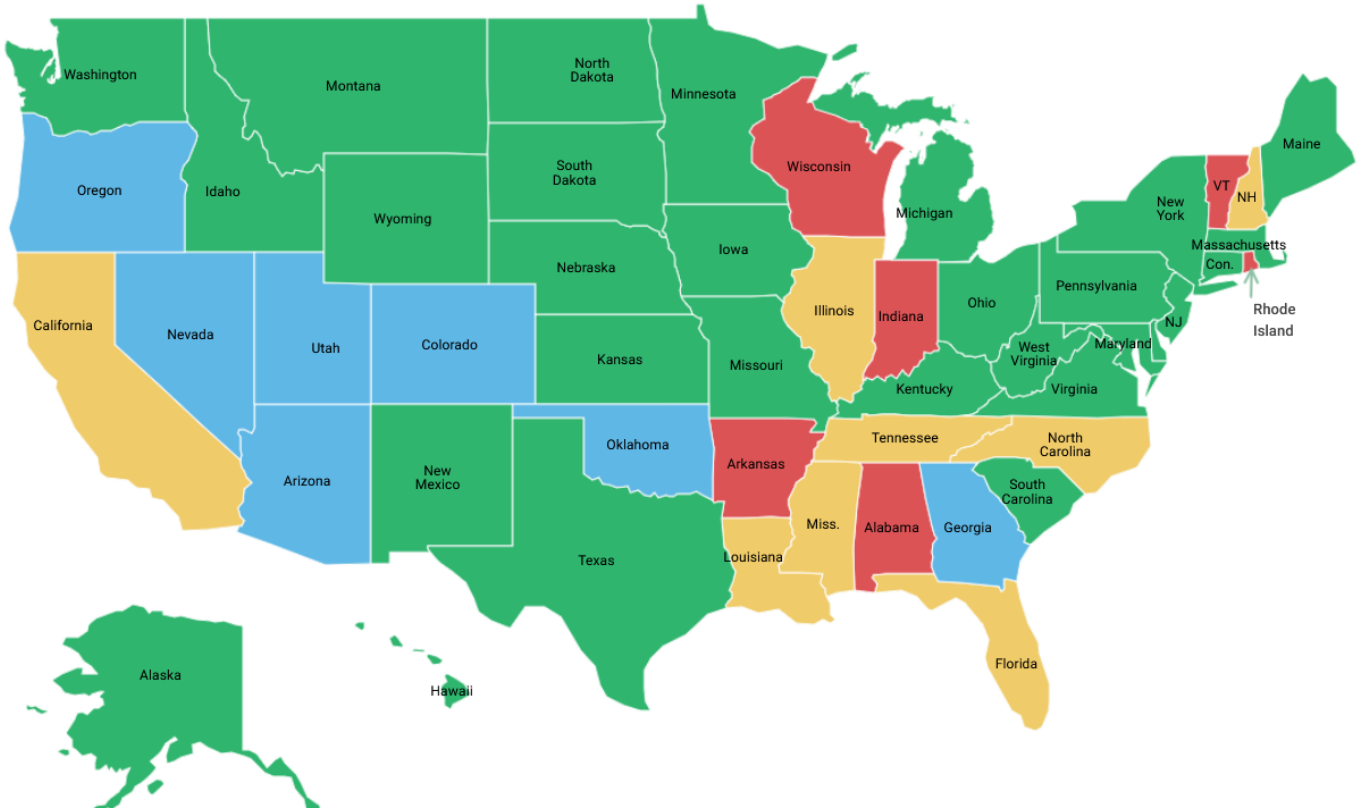
Regulatory status of Kratom in the US



Legal kratom states that have passed the KCPA are in Blue

Legal kratom states are in Green

States with some known local bans are in yellow

States with kratom bans are in Red

States with proposed bans are purple

Source(s): https://www.americankratom.org/aka-in-your-state

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Self-reported uses of Kratom

- Kratom user surveys repeatedly indicate several self-treatment indications for kratom use:
  - 70-90%: Psychiatric conditions are most common (depression, anxiety, PTSD, ADHD)
  - 65-85%: Acute and chronic pain (arthritic conditions, fibromyalgia, back pain)
  - 30-45%: Mitigation of prescription medicine withdrawal symptoms
  - 7-25%: Mitigation of illicit drug withdrawal symptoms
- Most kratom users have chronic health conditions and add kratom on top of existing medication regimens: potential for DDIs!

Kratom & co-use of drugs

- Only 5.2% still co-using other substance with kratom, 94.8% last took other substance >6 months ago
- Highest prior or concomitant use with cannabis, CBD, BZDs, kava, and amphetamines
- If substance use disorder treatment was sought, primarily for synthetic opioids, medications to treat OUD, BZDs, or heroin
- 32% increased regular dose of kratom over time

		Have you taken/Are you taking Kratom in combination with other drugs/substances?											
		18–20 years		21–30 years		31–40 years		41–50 years		51–60 years		61 years and older	
Substance(s)	Frequency (%)	Yes (0.61%)	No (0.61%)	Yes (4.05%)	No (8.72%)	Yes (6.38%)	No (21.76%)	Yes (5.67%)	No (18.62%)	Yes (4.88%)	No (13.52%)	Yes (3.91%)	No (10.36%)
Cannabis (marijuana, hashish)	643 (12.5)	3.57%		24.03%		29.87%		18.67%		15.26%		8.60%	
CBD (Cannabidiol) oil	594 (11.5)	2.28%		16.99%		29.60%		22.24%		15.59%		13.31%	
Others	465 (9.0)	1.56%		14.00%		22.67%		22.22%		20.00%		19.56%	
Benzodiazepines	259 (5.0)	1.61%		21.77%		27.42%		23.79%		15.32%		10.08%	
Kava	156 (3.0)	4.61%		24.34%		36.84%		17.76%		11.18%		5.26%	
Amphetamine	99 (1.9)	4.21%		37.89%		32.63%		16.84%		7.37%		1.05%	
Fentanyl or other synthetic opioids	84 (1.6)	2.47%		3.70%		18.52%		24.69%		25.93%		24.69%	
Hallucinogenic mushrooms	58 (1.1)	7.14%		37.50%		37.50%		16.07%		1.79%		0.00%	
Tryptamines	33 (0.6)	13.79%		41.38%		17.24%		17.24%		6.90%		3.45%	
Cocaine	30 (0.6)	3.33%		50.00%		33.33%		0.00%		10.00%		3.33%	

Source(s): Am J Drug Alcohol Abuse. 2022 Apr 7;1-12.

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First Human Clinical Pharmacokinetics Study in the USA Published March 11, 2022

pharmaceutics

MDPI

Article

Clinical Pharmacokinetic Assessment of Kratom (*Mitragyna speciosa*), a Botanical Product with Opioid-like Effects, in Healthy Adult Participants

Rakshit S. Tanna [1], James T. Nguyen [1], Deena L. Hadi [1,2], Preston K. Manwill [3], Laura Flores-Bocanegra [3], Matthew E. Layton [4], John R. White [5], Nadja B. Cech [2,3], Nicholas H. Oberlies [2,3], Allan E. Rettie [2,6], Kenneth E. Thummel [2,7] and Mary F. Paine [1,2,*]

- Single 2 gram dose given as “tea” (8 patients screened, 7 enrolled, 6 completed)
- Provides a good foundation for more research

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Planned Human Clinical Trials

- FDA trial contract has been awarded to Altasciences and planning is underway for those trials
  - Safety and tolerability with single doses at multiple dose levels
  - Human abuse potential study
- Nutrasource is carrying out a “Kratom Plant Study” in Canada to assess the safety and effectiveness as well as potential impact on cognitive performance.

I am Christopher McCurdy, Ph.D., Professor of Medicinal Chemistry and Director of the Translational Drug Development Core at the University of Florida. I am also a past president of the American Association of Pharmaceutical Scientists. I have been studying the science of kratom (*Mitragyna speciosa*) for over 15 years. I am recognized as one of the foremost international experts of this species. I began to study this plant and its chemistry based on the extensive use in SE Asian ethnomedicine. For centuries kratom has been used to increase mood, stamina, energy, and decrease anxiety and pain. The historical use of kratom to prevent withdrawal and ween users from opioids is of great relevance to the current global opioid crisis. As kratom use has steadily increased in the United States (US), reports of adverse events have risen. It is estimated that >15 million US individuals consume kratom products. Poison control center calls mentioning kratom totaled 682 in 2017. This number of kratom incidents is small when put in context with other analgesics, sedatives, and antidepressants which resulted in 334,729 calls in 2019. Nonetheless, there has been increased scrutiny around the opioid nature of kratom. From our conducted studies, supported by two (2) large grants from the National Institute on Drug Abuse (totaling $11,535,437), we conclude that kratom has low abuse liability when it is utilized in its pure leaf/plant material form. We believe issues arise from concentrated extracts and other formulations that utilize dried or cured leaf materials. The abuse liability in these products is most likely due to the varying concentrations of one alkaloid, 7-hydroxymitragynine (7OHMG). *We have <u>not</u> detected this alkaloid in freshly harvested leaf material or freshly prepared traditional teas in SE Asia*. As part of our research, we monitor products in the US marketplace and over the past decade, the presence of 7OHMG has been decreasing to low or non-detectable levels in many products. This is a result of the published science around 7OHMG from our team as well as other kratom researchers. 7OHMG is a potent mu opioid receptor agonist with abuse potential. It is a metabolite or decomposition product of the major alkaloid, mitragynine (MG). We, and others, have shown that MG has no abuse potential and has a unique pharmacology involving several neurotransmitter systems. In fact, alkaloids in kratom interact with the adrenergic and serotonergic systems to a greater extent than opioid systems. This polypharmacology renders kratom unique from other opioids and to label kratom an opioid is scientifically and factually incorrect. MG and lyophilized kratom tea can reduce opioid withdrawal symptoms in opioid dependent subjects. Two reports in the literature demonstrate the ability of MG to block self-administration of opioids in animals. We have reconfirmed through a more extensive study that is not yet published. It seems clear that more studies on kratom are warranted before any decision is made to ban this substance. In 2016, the US determined further research was needed before a ban. That research has exponentially increased to the point of FDA sanctioned human clinical trials where results are pending.

All four of us are faculty in the College of Pharmacy at the University of Florida and listed in order of presentations.

Chris McCurdy, PhD, is a Professor of Medicinal Chemistry and Director of the UF Translational Drug Development Core. He is a pharmacist and a pharmaceutical scientist with expertise in drug design and development, with primary focus on pain, anxiety and substance use disorders.

Abhisheak Sharma, PhD, is an Assistant Professor of Pharmaceutics and Assistant Director of the UF Translational Drug Development Core. He is a pharmacist and a pharmaceutical scientist with expertise in pharmacokinetics, drug metabolism, and drug development.

Jay McLaughlin, PhD, is a Professor of Pharmacodynamics at the University of Florida. He is a neuroscientist and opioid pharmacologist, with expertise in drug discovery, including the development of new treatments for opioid use disorder.

Oliver Grundmann, PhD, is a Clinical Professor of Medicinal Chemistry. He is a pharmacist, forensic scientist, and pharmaceutical scientist focused on new treatment options from natural products for nervous system and gastrointestinal disorders.

Kratom selected Scientific Literature

Expert evaluations of kratom policy, 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.

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Kratom abuse potential and assessment for treatment of dependence and withdrawal

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. 2020;215:108235.

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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. 2019;24(5):874-85.

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