Kratom Science
Public Health Policy Implications

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For Wisconsin Department of Public Safety, Controlled Substances Board, Nov. 9, 2018

Through PinneyAssociates, I provide scientific and regulatory consulting to the American Kratom Association, as well as to the developers of a broad range of pharmaceutical products including opioid and other pain medicines, addiction treatment medicines, dietary supplements, cannabinoids, and noncombustible tobacco/nicotine products for FDA regulation.

Why I care. My lab's mantra was "Science in Service of Humanity" and it to guides me.

On March 28 I distributed the White House Science Letter to the College on Problems of Drug Dependence List

Response from Board Certified professor of psychiatry and addiction medicine specialist and vice chair of education at a major medical school:

"Thank you for doing this, Jack. This is of utmost importance and I hope it is impactful."

My Reply: "Thank you XXXX"

"FDA is wrong on the science and wrong on the policy but what drives me is that there are real people who are using kratom in place of opioids whether their opioid use was for pain or addiction. They are rightfully scared to death of a kratom ban. That would be like a reversal of sterile needle exchange programs."

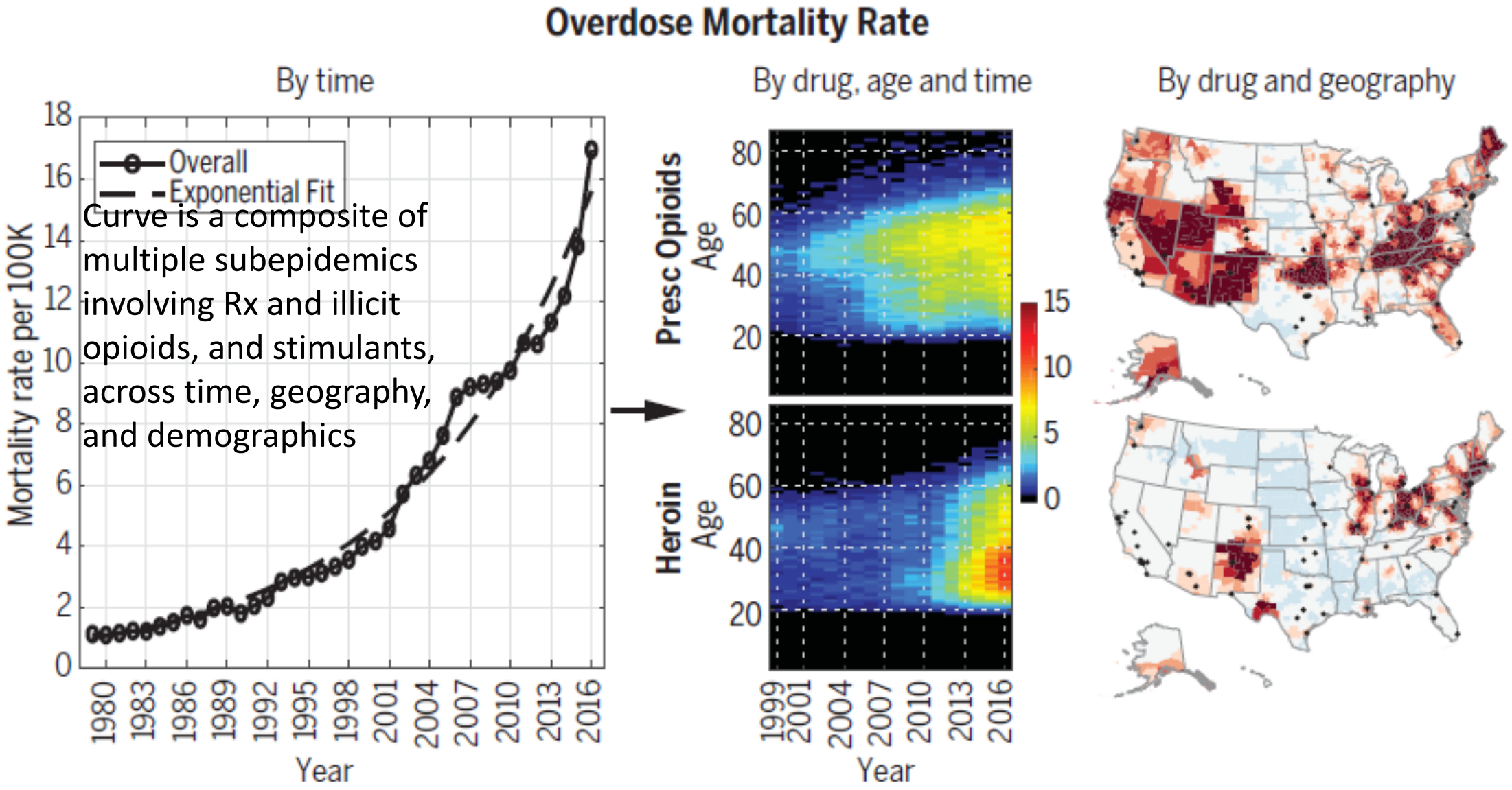
Her reply to me:

Jack: "Our 25-yo son is one of those people. He uses minimal doses of kratom to manage successfully his history of opioid dependence…. We are all gravely concerned as to what this scheduling might mean to him and our family."

For people who have found kratom to be a lifeline away from opioids, banning kratom would be like taking the life-preservers from people who are struggling in the ocean because they were not Coast Guard approved- It is foreseeable that some will overdose and die

The US Drug Overdose is Shifting to Illicit Opioids –

in part due to reduced opioid prescribing, REMS, and Abuse Deterrent Opioids



Jalal et al., Science 361, 1218, 2018

Pain and Addiction Treatment Policy

- Pain and addiction management requires individualized attention with support for comprehensive interventions

- Strive to Surgeon General C. Everett Koop's goal to *"make addiction treatment as accessible as addicting drugs" – "For all the people."*

- Consider Henningfield test proposed at 2018 FDA Opioid Prescribing Workshop: *"For every recommendation and policy you consider, ask if it will help or hurt low income and minority persons who are already least likely to have their pain [and SUD] appropriately treated. Policies that fail this test should not be implemented."*

Safer Pain Management Must be Complemented by Expanded and Improved Addiction Treatment

- Disparities in OUD services parallel those in pain care with those hurting the most being hurt the most by some policies and cutbacks
- As summarized in 2017 White House Opioid Report & April 17 FDA NIDA Hearing: OUD treatment capacity is far short of demand & and for many people current treatments are ineffective or unacceptable
- Reduced opioid prescribing, REMS, & Abuse Deterrent formulations drive some to illicit drugs – Increased treatment access and harm reduction are vital complements to Rx opioid reduction efforts
- Unfortunately, harm reduction approaches are being blocked, under attack, or too expensive for many, e.g., supervised injection sites with identification testing, naloxone, kratom and other Complimentary and Alternative Medicine (CAM) approaches

THE MODEL: Surgeon General Koop put Personal Beliefs Aside & Supported Harm Reduction to Save Lives

To protect yourself from HIV AIDS:

1. Don't have sex other than with your monogamous partner – but if you do: use a condom

2. *Don't use intravenous drugs – LATER : What I say about any needle exchange is if it will contain the epidemic, you`ve got to be for it*

3. To JEH about 1996: *Addiction to nicotine gum is obviously preferred to addiction to cigarettes*

4. Make it as easy to get treatment as it is to get addictive drugs

Kratom Science: Deaths

Deaths: The science does not support FDA's position.

The nature or patterns kratom "associated deaths" is not the consistent pattern documented for any drug of abuse and is radically different from opioids which reliably and almost exclusively killed by respiratory depression.

About 49,000 deaths/year or 134/day in the US, likely approximately 1000 in 2017 (2017, CDC Wonder Data at NIDA)

3-5 million kratom users with a few potentially associated deaths per year – not clear if any are direct kratom overdose poisonings (consistent with South East Asia experience and National Institute on Drug Abuse Analysis -- 42 total?

Conclusion: The conclusion is not that kratom has no risk or has not contributed to any death. Rather, compared to opioids of abuse its risks are very low and use in place of opioids makes public health sense

This does not mean kratom with no rules and regulations – Kratom users want and public health would benefit from policies and regulations on product manufacture, standards and marketing

NIDA: Can a person overdose on Kratom?

In 2017, the Food and Drug Administration (FDA) began issuing a series of warnings about kratom and now identifies at least 44 deaths related to its use, with at least one case being investigated as possible use of pure kratom. Most kratom associated deaths appear to have resulted from adulterated products (other drugs mixed in with the kratom) or taking kratom along with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there have been some reports of kratom packaged as dietary supplements or dietary ingredients that were laced with other compounds that caused deaths.

National Institute on Drug Abuse Kratom Facts Website, Sept. 2018

4 Internet Kratom Surveys (20,025 respondents)

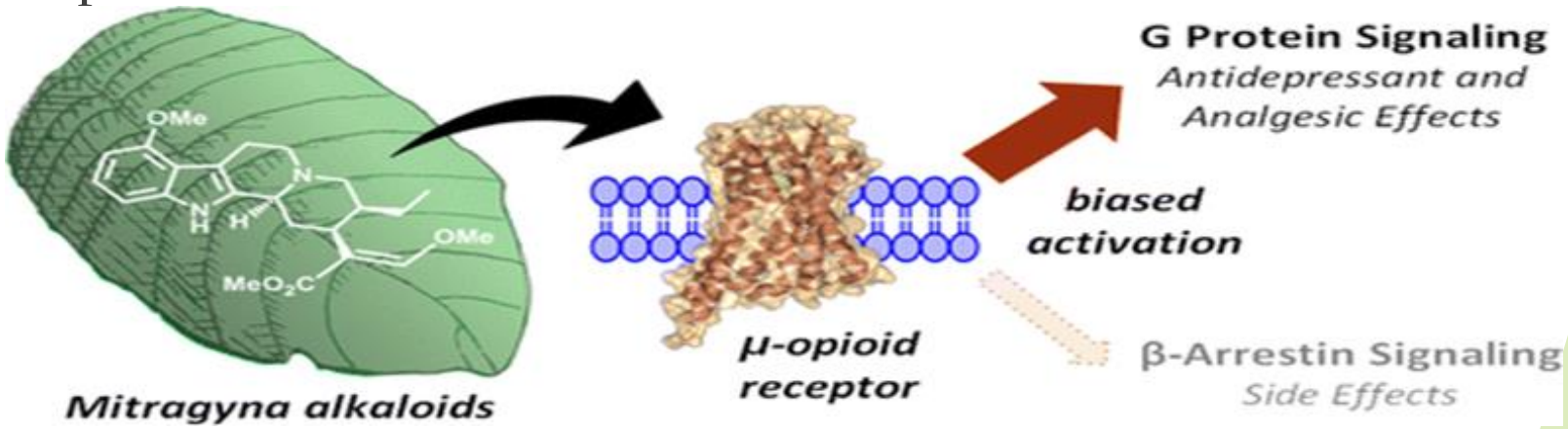
Author / Year	Sample Size	Reasons for Use
Grundmann (2017) Drug and Alcohol Dependence	Internet Survey N=8,049	Decreased pain, increased energy, decreased depressed or anxious mood, elevated mood, increased focus, "reduce or stop use of opioid painkillers"
Pain News Network Website (2016)	Internet Survey N=6,150	Chronic or acute pain, 51% (90% very effective); anxiety, 14%; opioid addiction treatment, 9%; depression, 9%; recreational use or curiosity, 2%
Pillitteri, Gerlach, Sembower, and Henningfield (ACNP, 2017)	Internet Survey N=3024	Pain, anxiety or depression, increase focus or energy, reduce or quit prescription pain medicine, relieve withdrawal, reduce or quit illegal drugs
Garcia-Romeu, Dunn, & Griffiths (2018 CPDD Poster)	Internet Survey N=2802	*Pain, Anxiety, Depression, Stop or reduce opioid use and manage withdrawal

Comments to DEA & FDA (20,236+), Survey of People in Residential Opioid Treatment and Internet Drug Chatrooms

Author / Year	Sample Size	Reasons for Use
DEA Kratom docket (2016)	Testimonials submitted as comments to FDA/DEA N=23,236	Preferred kratom to Rx drugs due to lower side effects and/or better outcome for pain, PTSD, fibromyalgia, depression, addictions (to opioids, alcohol, and other substances)
Smith and Lawson (2017) Drug and Alcohol Dependence	12-Step SUD residential program clients Anonymous Survey of use and motivations	68.9% reported using to reduce or abstain from opioids, 64.1% as a substitute for NPOs or heroin, 18.4% for disability or chronic pain 1/3 reported kratom was "helpful" Kratom was "not preferred" to opioids and "indicated as having less appeal than NPO, heroin, amphetamines, and Suboxone
Bluelight & Erowid reports summarized in Swogger et al. 2015 and Henningfield et al. 2016, 2017	161 in Swogger et al. 2015 Also see summary in Henningfield et al. 2016, 2017	Thematically coded reports to Erowid summarized by Swogger et al. Henningfield et al. sampled experience reports by people with various drug use histories

Neuropharmacology of Kratom and its Mitragyines

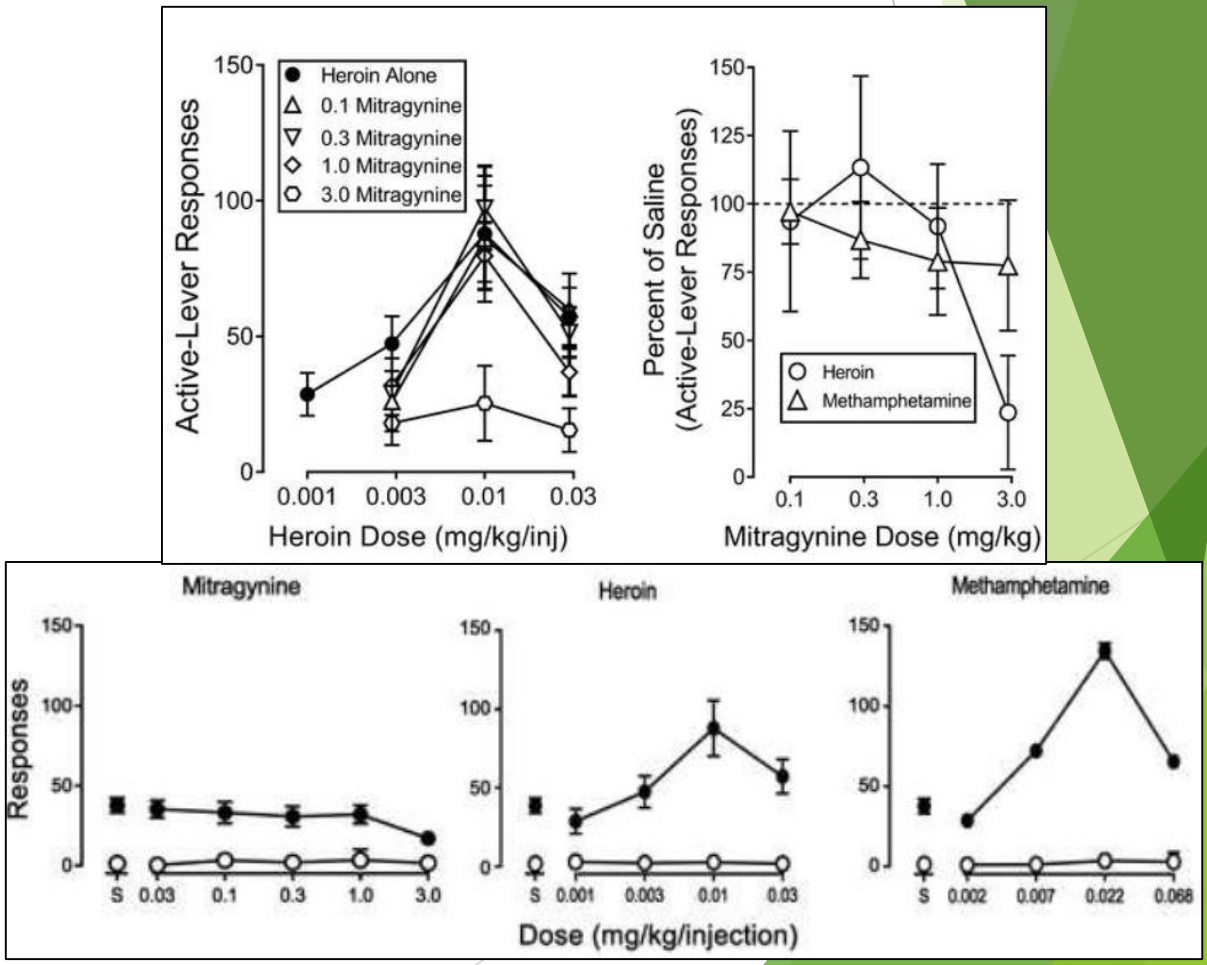
- Distinct from narcotic opioids in how it works (likely partial mu-agonist with biased G-protein low beta arrestin pathway) and what it does (increase energy/focus with low euphoria reinforcement and adverse addictive effects (kratom use more associated with social family and occupational benefits in distinct contrast to opioid abuse



- MG: partial agonist at human μ-opioid receptors, and competitive antagonist at human κ-opioid and δ-opioid receptors (Kruegel et al. 2016).
- Antinociceptive effects of MG and 7-OH-MG in several rodent models are inhibited by naloxone.

Abuse Liability of Mitragynine Assessed with a Self-Administration Procedure in Rats, Psychopharmacology, K. Yue1, T.A. Kopajtic and J.L. Katz

- Intramural Research Program, National Institute on Drug Abuse in collaboration with the Jianghan University, China
- CONCLUSIONS: "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."



Recommended Regulatory Actions

- Kratom is currently regulated by the FDA as a dietary ingredient/supplement. However, it is evident to me that the FDA's condemnation of kratom has stalled constructive regulation by its own Office of Dietary Supplements. Wisconsin could request that FDA to develop product performance and marketing standards for lawful vs. adulterated kratom products
- I recommend that the Wisconsin CSB act to de-schedule kratom and replace it with a ban on any adulterated kratom product. Standards for adulterated products could include maximum concentrations not to exceed the proportional content of the alkaloids present in the natural plant. This is about 60-70% for mitragynine (kratom's most abundant alkaloid that accounts for most of kratom's effects), and 2% for 7-hydroxy mitragynine that is a more potent alkaloid but which that that has not been demonstrated to contribute to kratom's effects at its naturally occurring levels.
- Alternatively, the Board might amend the schedule to apply to any product containing kratom alkaloids that exceed the proportional content of the alkaloids present in the natural plant.
- The Board could draft a statement to the Legislature asking them to change the law to de-schedule Kratom, or in the alternative, to amend the schedule to apply to any product containing kratom alkaloids that exceed the proportional content of the alkaloids present in the natural plant.
- The Board could stay neutral if the Legislature introduces legislation to de-schedule Kratom or change the scheduling to apply to any product containing kratom alkaloids that exceed the proportional content of the alkaloids present in the natural plant.

Protecting the Market with Reassuring and Safe Products

- Kratom leaf product (powder, encapsulated, etc.) should be processed, packaged, handled, stored, and distribute to ensure purity, and minimize contamination
- All manufactured products should aspire to the standards of potential foods, supplements, and new dietary ingredients as appropriate to the product
- Quantify, limit & label alkaloid content, e.g., upper limits for mitragynine might be no higher than typical tea brew in the US and South East Asia. Upper limits for 7 hydroxymitragynine might be no higher that the approximately 1.5-2% found in kratom leaves
- Only claims allowed by FDA should be made consistent with other foods and dietary products

Pinney Associates

Science. Strategy. Solutions.

May 18, 2018

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Via https://www.regulations.gov/

Re: FDA-2018-N-0987

Dear Food and Drug Administration

These comments are submitted in response to the April 17, 2018 Public Meeting on Patient-Focused Drug Development for Opioid Use Disorder (OUD).

I am Jack E. Henningfield, Vice President, Research and Health Policy at **Pinney**Associates, and Adjunct Professor of Behavioral Biology in the Department of Psychiatry and Behavioral Sciences at The Johns Hopkins University School of Medicine. Through **Pinney**Associates, I provide consultation to companies on issues including abuse potential assessments to support the development of safer medications for pain, addiction, and other disorders. We also provide advice to the dietary supplement industry, including to the American Kratom Association (see: www.pinneyassociates.com). No client had input into my comments or supported my attending this meeting.

Current treatments help, but increased capacity and diversity are needed

By way of additional disclosure, as well as the basis for some of my knowledge in this area, I have contributed to nearly every FDA approved treatment for OUD and other Substance Use Disorders (SUDs) through my research at NIDA and Johns Hopkins, and/or through my consulting work at **Pinney**Associates, which has helped bring many treatments through the FDA approval process and to market. I am proud of those efforts, and it was evident from the public hearing on April 17 where I gave a shorter version of these comments, that many people have benefitted from FDA approved treatments.

But it was also evident at that meeting that we have a long way to go with respect to the capacity of our treatment infrastructure, the accessibility and acceptability of our treatments, and the effectiveness of treatments. Some people reported being unable to get treatment when and where they needed it. Some did not like the side effects of offered treatments or found that a treatment that was helpful at one stage of recovery was not helpful or was not acceptable at another stage, putting them at risk of relapse. Some found benefits from approaches that are not FDA approved drugs and may never be. None of this was a surprise, and, indeed, awareness of such issues is part of the reason that FDA and NIDA convened the hearing and are to be commended for doing so.

Near-term help AND long-term MAT development are needed

This meeting gave people with OUD the opportunity to share their thinking with the two federal agencies that can help address many of their concerns and needs – hopefully in the near-term as well as the longer term. In the longer term we need new medicines and more, but with an average time of 10 years and a cost of 2.7 billion dollars per medicine, that path is not an answer for them now, so we must also be making every effort we can to do everything to help them in the near-term.

One of my mentors was Former Surgeon General C. Everett Koop. He was dedicated to advancing addiction science and making treatment as easy to access as are addicting drugs. I think he would have been pleased that the White House Opioid Report acknowledged the need to address shortcomings of our OUD treatment capacity, and its recommendations for research to "improve the range of medications to assist in treating OUD" to match the diversity of our treatment-related needs. However, he would also have been very frustrated at the slow pace of implementation and funding plans to more rapidly ramp up our nation's treatment services.

Treatment needs to be more flexible including embracing harm reduction

We must also keep in mind that people with diagnosed OUD are just the tip of the iceberg of the opioid epidemic. Many people who are at risk and some who die of overdose do not have OUD but might also be helped by more flexible treatment approaches and programs to reduce the risk of transition from occasional use to addiction, as Dr. Thomas McLellan has long fought for (see bibliography).

We could also save more lives with broader acceptance and support of harm reduction approaches that reduce the risks for occasional nonmedical opioid users as well as for people with advanced OUDs. This is another area in which Dr. Koop was a leader. He embraced harm reduction for addictions to opioids, tobacco, and other substances, as well as for HIV AIDS. Regarding AIDS, whereas he made clear his moral and faith-based opposition to sex out of wedlock, he was a powerful advocate for the use of condoms when sex occurred outside of "monogamous" relationships. He put life and good health for All the People (the theme of his 90th birthday celebration) first and included access to addiction treatment in that concept (Koop, 2006).

Disparities in treatment of OUD and pain are interrelated and must be addressed

I am certain that Dr. Koop would have found it unconscionable that low income and minority people continue to face the greatest disparities in treatment of both pain and addiction—and that gap has actually been growing. He might have asked "Where is the outrage?" as he was wont to do faced with such inequities. I mention pain and addiction because these are frequently interrelated problems: inadequate treatment of pain can lead to illicit drug use, and concerns about addiction can contribute to inadequate treatment of pain in the people who are least likely to abuse opioids, namely properly diagnosed and monitored pain patients.

As evidenced by the April 17th hearing, we have great need for more diverse, affordable, acceptable, and accessible treatments; and, we need to address barriers to treatment access and reimbursement that hurt most those who are already hurting the most. At FDA's January opioid prescribing meeting, I proposed a simple test for every policy pertaining to prescribing and opioid pain medicine access: Ask if it will help or hurt low

income and minority persons with pain. I suggest including this test for substance abuse policy ideas as well as ensuring that representatives of low income communities, minorities, youth, elderly, physically and mentally disabled, and other populations whose voices are too often left out be included in the evaluation of SUD treatment policies and approaches.

Substance use problems are complex and will not be solved by simple solutions

Many people on opioids have poly-drug use problems and/or other mental health disorders. Let's keep in mind HL Mencken's aphorism that "for every complex human problem there is a simple solution that is neat, plausible, and wrong." The opioid epidemic is not just an opioid problem; it did not have a simple cause and it certainly does not have a simple solution. OUDs typically involve multiple drugs, psychiatric disorders, social factors, and economic factors. Drug development must recognize that; treatment programs must recognize that; the reimbursement system must recognize that; and governmental policies and actions must recognize that from the local to federal levels. The science shows that both pain and SUDs have better outcomes when treatment approaches are comprehensive. Unfortunately, most pain management programs provide prescriptions with little by way of individually tailored multi-modal programs, and medication-assisted treatment programs for SUDs often provide little of the comprehensive behavioral treatment with which the medication was intended to work because there is inadequate funding for multi-modal behavioral support.

Kratom is an in-hand asset: will its potential be realized or will this asset be unfathomably rejected?

Some of the research and development efforts under discussion, including vaccines, are important to pursue but are far from emerging as assets in the near-term. It was pointed out that that we do have assets that are not being utilized and some that are threatened. I will comment only on kratom in this regard. Kratom is presently being used by an estimated 3-5 million Americans to improve their health and well-being, and by many people as a preferred alternative to conventional medicines for various disorders including OUDs.

Kratom is a tree in the coffee family and so it is not surprising that its leaves provide some of the alerting and focusing effects of caffeine that are reported by many consumers to be their main reason for using kratom. Many others report use to relieve symptoms of anxiety, depression, pain, and to reduce or eliminate opioid use whether their use was for pain or addiction. These effects and reasons for use have been known for a century or more in South East Asia and were recently well-documented by four US-focused internet surveys that together included more than 20,000 respondents and more than 20,000 comments to FDA, as well as in global review of the mental health effects of kratom (see reports below).

With respect to the opioid epidemic and people with OUDs, kratom is an in-hand asset, and for many people it is their life line because FDA-approved treatments were either not accessible, not effective, or were not acceptable to them due to side effects and other reasons. This was commented on in the April 17th public hearing. Some kratom users report that methadone or buprenorphine helped break their addiction cycle but that at some point in their recovery, those drugs were not acceptable, and they found that kratom was more helpful and tolerable. Telling them they should go back to methadone or buprenorphine because kratom has not been proven effective to FDA's standards

rings hollow: for them kratom is working and has helped give their lives back to themselves, their families, friends, and co-workers.

Though the science is at an early stage, it supports the conclusion that kratom is far less harmful and addictive than narcotic-like opioids and does not support claims to the contrary

As compared to narcotic-like opioids such as morphine, fentanyl, and heroin, kratom is far less harmful, and its main ingredient, mitragynine, is far less addicting and with little of the signature respiratory-depressing effects of morphine-like opioids that kill more than 115 people every day. This has been demonstrated in laboratory studies for decades, including more recent studies to support the safety of kratom and guide its regulation by FDA's Office of Dietary Supplements. Also, in contrast to opioids, is the absence of documented deaths—in South East Asia or the US—due to kratom-caused respiratory depression. This does not mean there has never been an actual kratom-caused death or serious respiratory depression or that kratom is without risks, but it supports the conclusion that the harmfulness of kratom is far lower than that of narcotic-like opioids. Nor is there is evidence that kratom is feeding the opioid epidemic. Rather, thousands of comments to DEA and FDA and the 4 surveys I mentioned earlier make clear that kratom is a path away from opioids for many people.

Scientific studies are beginning to unravel how kratom's main active ingredient, mitragynine, actually works, and why it is so much lower in the addictive euphoria and deadly respiratory depressing effects than morphine-like opioids. The science and epidemiology indicate that it makes no more sense to place kratom in the same categorical bucket as narcotic-like opioids as it would to place caffeine in the same category with crack cocaine, even though caffeine can cause physical dependence, withdrawal, addiction, mood alteration, is sometimes abused, and sometimes contributes to death. In fact, analogs of mitragynine, as opposed to analogs of opioids, may be among the safer pain relievers and OUD treatments of the future. This is being investigated by several laboratories in the US, though any such medicines are likely many years and many billions of dollars away. These researchers are concerned about efforts to put kratom in Schedule I of the Controlled Substances Act because that would grind their research to a halt.

More importantly for the near-term efforts to address the opioid epidemic and help people with OUDs, kratom is an in-hand asset that is helping many people. These people and their families are rightfully terrified of the possibility that legal sale and possession would be banned by scheduling kratom. Banning kratom would be like taking life preservers away from people struggling in the ocean because they were not Coast Guard approved.

Kratom is helping now, but could help more, and with even less risk if appropriately regulated by FDA: FDA's Office of Dietary Supplements should be encouraged and supported to expedite reviews and work with stakeholders

The public would be far better served by FDA using its broad and flexible regulatory tools to resume the course that its Office of Dietary Supplements had been on (at least through last November) to work with kratom product suppliers, marketers, and makers to set standards for kratom and regulate it to the same standards of other dietary supplements and foods. FDA could set the standards desired by consumers and responsible manufactures alike for product purity, packaging, labeling, claims, and even

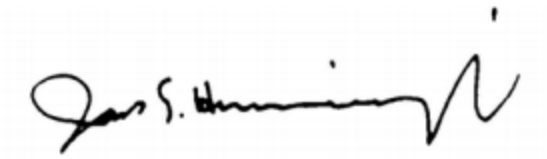
maximum allowable levels of mitragynine and other constituents. It can warn and even ban irresponsible marketers. With registered products, it could more quickly track and trace those brands and batches that are problematic. Those actions will serve kratom users and public health. But there can be no such consumer or public health protections if the lawful kratom market is banned. Instead, more serious problems and less controllable problems would be created by such a ban, as the lawful and regulatable market would be quickly replaced by the truly deadly black market.

Kratom use has been increasing since its introduction to the US by about the 1980s. Many of us in addiction science and medicine and many with OUDs are thankful that we have it as a valuable asset for combatting the surging opioid epidemic. Rather than killing this asset and putting its users at resumed risk of opioid use, and/or black market kratom, I hope that FDA will bring relevant stakeholders (including consumers, kratom vendors, other natural products organizations, scientists and addiction treatment professionals, and NIDA representatives) together to preserve and develop consumer and public health serving regulations while we continue to explore additional longer-term solutions that are supported by appropriate research and surveillance. That approach would be in the interest of people with OUDs and public health.

We appreciate the Food and Drug Administration's effort to organize this public meeting. Thank you very much for the opportunity to provide these comments. Please contact me at **Pinney**Associates at jhenning@pinneyassociates.com or 301-718-8440 if you have any questions or need further information.

Oral Comment for April 17, 2018 At: https://www.regulations.gov/document?D=FDA-2018-N-0987-0001

Sincerely,



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Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University School of Medicine

For additional information on kratom safety, how it works, and its potential in the opioid epidemic see:

Babin, J. (2018). The FDA Kratom Death Data: Exaggerated Claims, Discredited Research, and Distorted Data Fail to Meet the Evidentiary Standard for Placing Kratom as a Schedule I Controlled Substance. *American Kratom Association Policy Report, 1.*

Brown, P.N., Lund, J.A., and Murch, S.J. (2017). A botanical, phytochemical and ethnomedicinal review of the genus Mitragyna korth: Implications for products sold as kratom. *Journal of Ethnopharmacology, 202*, 302-325.

Grundmann, O. (2017). Patterns of Kratom use and health impact in the US-Results from an online survey. *Drug and Alcohol Dependence, 176*, 63-70.

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 (Berlin), 235*(2), 573-589. Note that this includes a summary of the 4 US focused internet surveys mentioned above see Factor 5, section 1.5.2)

Kruegel, A.C., Gassaway, M.M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Javitch, J.A., and Sames, D. (2016). Synthetic and receptor signaling explorations of the mitragyna alkaloids: Mitragynine as an atypical molecular framework for opioid receptor modulators. *Journal of the American Chemical Society, 138*(21), 6754-64.

Kruegel, A.C. and Grundmann, O. (2017). The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology*, [Epub ahead of print].

Swogger, M.T. and Walsh, Z. (2018). Kratom use and mental health: A systematic review. *Drug and Alcohol Dependence, 183,* 134-140.

Warner, M.L., Kaufman, N.C., and Grundmann, O. (2016). The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. *The International Journal of Legal Medicine, 130*(1), 127-38.

For additional information on some of the general addiction research and treatment issues mentioned in this comment see the National Institute on Drug Abuse Website at www.drugabuse.gov and the following:

Henningfield, J.E. (2017). Comment on Docket No. FDA-2017-N-2903.

Koop, C. E. (2006). Health and Health Care for the 21st Century: For All the People. *American Journal of Public Health, 96*, 290-292.

McLellan, A.T., Lewis, D.C., O'Brien, C.P., and Kleber, H.D. (2000). Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA, 284*(13), 1689-95.

Vallerand, A.H., Cosler, P., Henningfield, J.E., and Galassini, P. (2015). Pain management strategies and lessons from the military: A narrative review. *Pain Research & Management, 20*(5), 261-8.

Volkow, N.D. and McLellan, A.T. (2016) Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. *New England Journal of Medicine, 374*(13), 1253-63.

Volkow, N.D, Koob, G.F., and McLellan, A.T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine, 374*, 363-371.

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Statement to the State of Wisconsin Department of Safety and Professional Services, Controlled Substances Board

November 9, 2018

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Vice President, Research, Health Policy, and Abuse Liability
and
Professor, Adjunct, Behavioral Biology
Department of Psychiatry and Behavioral Sciences
The Johns Hopkins University of Medicine

Disclosure

Through PinneyAssociates, I provide scientific and regulatory consulting to the American Kratom Association, as well as to the developers of a broad range of pharmaceutical products including opioid and other pain medicines, addiction treatment medicines, dietary supplements, cannabinoids, and noncombustible tobacco/nicotine products for FDA regulation.

On August 14, 2015, I commented on kratom science and regulation at the meeting of the State of Wisconsin Department of Safety and Professional Services, Controlled Substances Board when the state was considering the potential placement of Kratom in Schedule I of the Wisconsin Uniform Controlled Substances Act. I commented that the science concerning kratom's pharmacology, its risks, primary reasons for use and patterns of use, and public health effects did not warrant scheduling. Furthermore, I expressed my opinion that scheduling kratom could have an adverse public health impact by driving many lawful kratom consumers to illicit sources of kratom that were more likely to be of poor quality and adulterated, and/or back to opioids for those who were using kratom to cease opioid use whether their opioid use had been for pain or addiction.

Since 2015, the science of kratom has advanced considerably. The attached articles and summaries for US congressional leadership describe the following areas of advances in greater detail.

Surveys on reasons for and patterns of use and effects: We have extensive survey data better documenting that most kratom use is largely for a variety of health and well-being related effects including use in place of coffee for alertness and focusing effects, improving mood in people with depressed symptoms, pain relief, and use in place of opioids for pain and to achieve opioid abstinence. Whereas these uses and patterns have been well-documented in South East Asia, we now have four Internet surveys of more than 20,000 US kratom consumers, in addition to more than 23,000 comments to the Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA), internet chat room monitoring, and a survey of people with opioid use disorder. Especially important in the context of the opioid epidemic is that many of the estimated 5 million or more US kratom consumers are using kratom to stay off opioids whether their opioid use was for pain or addiction.

Many of these people expressed great concern about the possibility of a national kratom ban in addition to existing challenges to access in states where kratom already has been banned.

Neuropharmacology and abuse potential. We now understand that kratom's most abundant alkaloid, mitragynine, which primarily accounts for kratom's effects, is a biased G-protein partial mu opioid receptor agonist, which helps explain its low abuse potential and low respiratory depressant risk. This is under exploration as a potential model for analogs that may eventually lead to safer medicines for pain and other disorders, though that is a $2-3 billion path taking a decade or more.

Mitragynine, currently placed in Schedule I of the Wisconsin Uniform Controlled Substances Act, has also been evaluated in two independent series of rodent intravenous self-administration studies to evaluate its abuse potential, including one at the NIDA Intramural Research Program (Yue, Kopajtic, and Katz, 2018). These studies showed intravenous mitragynine looked more like saline than morphine, heroin or methamphetamine in the self-administration comparison. However, mitragynine pretreatment produced direct dose-related decreases in self-administration of morphine and heroin.

These data are consistent with human reports suggesting that use of kratom is generally related to some functional beneficial effect, including as an aid to abstain from opioids, as opposed to "getting high". The NIDA researchers included the following conclusions: "The present study suggests that mitragynine has limited abuse liability from the perspective of self-administration procedures.... it appears at present that mitragynine is deserving of more extensive exploration for the development of a therapeutic use for treating opioid abuse." (Yue et al., 2018, page 2828). I would concur but would remind the Wisconsin CSB that development of mitragynine or an analog may be a $2-3 billion path taking a decade or more, and that neither I nor NIDA has suggested taking the naturally occurring form off the market while waiting for a pharmaceutical product to be available – especially given the tragic fact that on current course an opioid overdose death is occurring at an average of every 10-15 minutes nationwide and every few hours in Wisconsin, with no signs of imminent abatement (Jalal et al. 2018).

As I told a leading addiction medicine professional, banning kratom would be analogous to rescinding sterile syringe exchange programs (see my attached slides for my comment and her very sobering response).

On the other hand, 7-hydroxymitragynine (also listed in the Wisconsin Uniform Controlled Substances Act) serves as a reinforcer for rodents. Product monitoring and chemistry studies, however, indicate that its typical concentrations in natural products and many manufactured products range from undetectable to about 1.5%. There is no evidence that these levels contribute meaningfully to the effects of kratom as used in the US or South East Asia. Nonetheless, some manufactured products have been found to contain substantially higher levels, suggesting adulteration.

Toxicology and overdose risk. The September summary by NIDA is consistent with the South East Asian experience reported at NIDA's international kratom symposium in a satellite meeting to the June 2018 College on Problems of Drug Dependence. The symposium conclusion was as follows: *"There are no known reported severe toxicity or fatality incidents in Malaysia or Thailand where there are large populations of long-term, daily users or kratom."*

NIDA's summary on its Kratom Facts Page (attached) is as follows (italic added):
Can a person overdose on kratom? *In 2017, the Food and Drug Administration (FDA) began issuing a series of warnings about kratom and now identifies at least 44 deaths related to its use, with at least one case being investigated as possible use of pure kratom. Most kratom associated deaths appear to have resulted from adulterated products (other drugs mixed in with the kratom) or taking kratom along with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there have been some reports of kratom packaged as dietary supplements or dietary ingredients that were laced with other compounds that caused deaths.*

My conclusion has been and continues to be consistent with NIDA's conclusion. Moreover, the absence of overdose deaths directly and solely attributable to kratom does not mean that kratom carries no mortality risk and has not contributed to deaths in which the primary factor may have been preexisting disease and/or other substance intake, however, the risks of kratom and, by extension, its mitragynines, appears much lower than for opioids and many common over the counter substances. It also supports a regulatory approach that could be taken by Wisconsin, and hopefully, at some point, nationally by the FDA, that would define adulterated kratom products. This could include products in which the concentrations of alkaloids exceed the proportional content of the alkaloids present in the natural plant.

Opioid epidemic science. There is no evidence that kratom is contributing to the opioid epidemic either as a path (i.e., "gateway") to opioid use, or as a factor, let alone a single death, in the approximately 49,000 opioid deaths in 2017, an average 134 opioid deaths per day (CDC WONDER, Revised August 2018: accessed at https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates) which likely includes approximately 1,000 deaths in the state of Wisconsin. These deaths are fueled by increasing availability of illicit fentanyl and heroin (see Jalal et al in Science, 2018), an enormous shortfall of opioid use disorder treatment access, and the fact that FDA approved and other treatments are often ineffective or unacceptable, as well as inaccessible to those who seek help to abstain from opioids as documented in the 2017 White House Opioid Report (see also attached Henningfield comment to FDA/NIDA).

In this context, I along with many other addiction experts ask, why, with the documentation that many opioid users are staying off of opioids by self-use of kratom (as has been documented for decades in South East Asia), why would we ban it. The evidence shows that for some fraction of opioid users kratom is a helpful and acceptable path away not path to opioids.

I agree with NIDA's factual statement, however, which neither promotes nor discourage such use but simply states the facts as follows: *"Does kratom have value as a medicine? In recent years, some people have used kratom as an herbal alternative to medical treatment in attempts to control withdrawal symptoms and cravings caused by addiction to opioids or to other addictive substances such as alcohol. There is no scientific evidence that kratom is effective or safe for this purpose; further research is needed."*

By the standard of multi-center controlled clinical trials relied upon by FDA and NIDA to define "effective and safe" drugs, NIDA is correct and I agree. I also do not promote kratom for such use, but I am attending this meeting to urge you to take actions to ensure that kratom products are legally available to those who choose to use them, but ideally with some basic regulatory parameters, as advocated by the American Kratom Association, and which include no unapproved medical claims, and that products are not adulterated. In addition, though use by youth has not emerged as a problem in national surveys, it would seem reasonable to support minimum age of purchase such as 18 years old as is the case for nicotine gum and tobacco products.

Summary of my specific regulatory recommendations:

1. Kratom is currently regulated by the FDA as a dietary ingredient/supplement. However, it is evident to me that the FDA's condemnation of kratom has stalled constructive regulation by its own Office of Dietary Supplements. Wisconsin could request that FDA develop product performance and marketing standards for lawful vs. adulterated kratom products

2. I recommend that the Wisconsin CSB act to de-schedule kratom and replace it with a ban on any *adulterated* kratom product. Standards for adulterated products could include maximum concentrations not to exceed the proportional content of the alkaloids present in the natural plant. This is about 60-70% for mitragynine (kratom's most abundant alkaloid that accounts for most of kratom's effects), and 2% for 7-hydroxy mitragynine that is a more potent alkaloid but which that that has not been demonstrated to contribute to kratom's effects at its naturally occurring levels.

3. Alternatively, the Board might amend the schedule to apply to any product containing kratom alkaloids that exceed the proportional content of the alkaloids present in the natural plant.

4. The Board could draft a statement to the Legislature asking them to change the law to de-schedule kratom, or in the alternative, to amend the schedule to apply to any product containing kratom alkaloids that exceed the proportional content of the alkaloids present in the natural plant.

5. The Board could stay neutral if the Legislature introduces legislation to de-schedule Kratom or change the scheduling to apply to any product containing kratom alkaloids that exceed the proportional content of the alkaloids present in the natural plant.

Supporting attachments. I attach documents that I hope will be useful to you. These are as follows:

November 9, 2018 printed slide-deck summary of my comments to the Wisconsin Controlled Substances Board

May 18, 2018 Henningfield Comment to FDA and NIDA on the place of kratom in the opioid epidemic

June 21, 2018 Letter from 9 leading kratom scientist to US Congressional Leadership on kratom science and policy

June 14, 2018 American Society for Pharmacology and Experimental Therapeutics (ASPET) letter to DEA opposing kratom scheduling

September, 2018 National Institute on Drug Abuse (NIDA) Kratom Drug Facts web page

2018 Review in Psychopharmacology by Henningfield et al on The Abuse Potential of Kratom According to the 8 Factors of the Controlled Substances Act

2018 Peer-reviewed letter to Addiction on The Therapeutic Potential of Kratom by Grundmann, Brown, Henningfield, Swogger, and Walsh

2017 Report in Drug and Alcohol Dependence on Patterns of Kratom Use and Health Impact in the US-Results from an Online Survey in Drug by Grundmann

2018 Poster presented at the College on Problems of Drug Dependence, Annual Meeting on Kratom and its Mitragynines in the Opioid Crisis: A Path to or Away From Opioids by Henningfield, Raffa, Garcia-Romeu, and Doshi

2017 Review in Neuropharmacology on The Medicinal Chemistry and Neuropharmacology of Kratom: A Preliminary Discussion of a Promising Medicinal Plant and Analysis of its Potential for Abuse by Kruegel and Grundmann

2018 Report in Science on Changing Dynamics of the Drug Overdose Epidemic in the United States from 1979 through 2016 by Jalal, Buchanich, Roberts, Balmert, Zhang, and Burke

2018 Report for the American Kratom Association on The Kratom Death Data: Exagerated Claims, Discredited Research, and Distorted Data Fail to Meet the Evidentiary Standard for Placing Kratom as a Schedule I Controlled Substance, by Babin

2018 Comment to FDA/NIDA Dockett on kratom use among people with opioid use disorder and the importance of keep kratom accessible and risks of a kratom ban by Smith