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for the Life Sciences

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Michael J. Lewis
Office of Diversion Control
Drug Enforcement Administration
Attn: DEA Federal Register Representative
8701 Morrissette Drive
Springfield VA 22152-1080

Re: Docket No. DEA-442W

Dear Mr. Lewis:

I am writing to urge the Drug Enforcement Administration (DEA) to terminate efforts to schedule mitragynine (MG) and 7-hydroxymitragynine (7-OH-MG), constituents of the Kratom plant (*Mitragyna speciosa*), pursuant to either the emergency[1] or regular[2] scheduling provisions of the Controlled Substances Act (CSA)[3], pending definitive scientific analysis of the risks and more importantly the benefits of Kratom and its constituent alkaloids. It is my opinion that the benefits of Kratom vastly outweigh any risks.

The DEA initially proposed temporarily placing MG and 7-OH-MG under Schedule I of the CSA, along with such hallucinogenic substances as LSD, psilocybin, mescaline, and highly addictive opioids such as heroin, because it concluded that such action was "necessary to avoid an imminent hazard to the public safety"[4]. This conclusion was premature and appears to have been made based on contradictory opinions, incomplete knowledge of the most current scientific evidence and without input from the public on their experiences with Kratom[5]. I applaud the DEA for withdrawing its intent to temporarily place mitragynine and 7-hydroxymitragynine in Schedule I and instead

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[1] 21 U.S.C. §811(h).

[2] 21 U.S.C. §811(a)-(c).

[3] 21 U.S.C. §801et seq.

[4] 81 FR 59929, at 59929, col. 1.

[5] Gosa, "Kratom ban withdrawn by DEA. DEA admits conflicting information about Kratom," Albany Herald, Oct 27, 2016 (Quoting DEA spokesperson Melvin Patterson: "We received some conflicting information in regards to the effect of Kratom. We had a specialist and there was an outside specialist, but they had conflicting information on how Kratom affected the Mu receptors in the brain. So we decided to step back, take public comment and do this the right way, get as much information (as possible) before going forward.")

soliciting comments from the public.[6] I am confident that after considering the pertinent scientific facts, particularly recent evidence distinguishing MG and 7-OH-MG from scheduled opioids, and the overwhelmingly positive experiences of Kratom users as evidenced by more than 20,000 comments reflecting the views of current Kratom users, the DEA will conclude that scheduling these compounds is neither necessary nor in the public interest.

I trust that the DEA will objectively evaluate all the input and evidence presented herein, and by others, when reaching its decision, rather than repeat the mistake of rushing to judgment based on inappropriate generalizations and unsupported or hysterical tirades from those who may have ulterior motives for their opinions as the Centers for Disease Control (CDC) did when issuing opioid prescribing guidelines. The DEA's action on this issue can pave the way to a future in which the often conflicting interests of individuals with substance abuse disorders, mental illnesses, chronic and acute pain converge on solutions to the problems facing all members of our society, rather than pitting one group against the other. Based on the evidence available today, it is reasonable to conclude that Kratom may provide these solutions.

Eight-Factor Analysis under the CSA

Dr. Jack Henningfield of PineyAssociates has prepared an extensive evaluation of Kratom under the CSA[7], submitted as an attachment to the comments of the American Kratom Association[8]. I have reviewed and endorse these documents wholeheartedly. In the interest of avoiding duplication, Dr. Henningfield's analysis and the AKA Comments are incorporated herein by reference in their entirety.

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[6] 81 FR 70652,

[7] Henningfield, "Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation", November 28, 2016, pp. 1-128, submitted on Regulations.gov, Docket No. DEA-442W, on behalf of the American Kratom Association; see http://www.prnewswire.com/news-releases/american-Kratom-association-major-new-analysis-shows-no-basis-for-dea-to-restrict-herb-Kratom-300371521.html.

[8] Mehler & Fox, "Mitragynine and 7-Hydroxymitragynine, Constituents of the Kratom Plant, Should Not Be Scheduled under the Controlled Substances Act", November 30, 2016, pp. 1-17, submitted on Regulations.gov, Docket No. DEA-442W on behalf of the American Kratom Association; hereinafter "AKA Comments"; *see id.*

My further comments expand on specific issues that I believe are critical to a complete understanding of Kratom.

Kratom versus Mitragynine and 7-hydroxymitragynine

At the onset, it is important to distinguish the difference between Kratom (the plant, *Mitragyna speciosa*) and constituent alkaloid components MG and 7-OH-MG that make up only a small fraction of the dry weight of the plant leaves. A blanket ban on MG and 7-OH-MG (the compounds), would necessarily be a ban on Kratom (the plant material), while a ban on Kratom would not necessarily be a ban on MG and 7-OH-MG.

Much of the concern surrounding Kratom is based on the effects of isolated and purified MG and 7-OH-MG. Yet the DEA has provided no evidence that purified, pharmaceutical grade MG and/or 7-OH-MG is available to consumers; the only demonstrated uses of such purified compounds has been in the context of research and in extraordinary amounts. As isolated compounds, MG and 7-OH-MG have properties that hint at the effects of Kratom when consumed as a botanical supplement. Yet the compounds in isolation cannot approach the complexities of Kratom when consumed as a dietary supplement. While concerns surrounding the heterogeneity, variability and purity of Kratom are often cited as reasons for scheduling it, such concerns are not limited to Kratom and are more appropriately addressed by other provisions of the FDCA that protect consumers from adulterated, misbranded and contaminated food and dietary supplements.

Kratom is Not a "Drug" and is Neither "Abused" nor "Misused"

One indication of the DEA's past prejudicial evaluation of kratom is evidenced by the characterization of Kratom consumption as "abuse" and "misuse". These pejorative terms beg the question of whether the DEA had already resolved to schedule kratom based on a knee-jerk reaction to studies showing that MG and 7-OH-MG bind to opioid receptors. Such a reaction presumes that simply because the compounds bind opioid receptors they must inherently be addictive drugs, and since they have not been approved by the FDA under a New Drug Application (NDA) or a Biologics License

Application (BLA), they must be abused or misused rather than simply consumed as integral components of the herbal supplement, Kratom.

Under the Federal Food Drug and Cosmetic Act (FDCA)[9], a "drug" is not defined structurally, chemically or biologically, but by its recognized listing in one of a limited number of compendia or more often by its intended use.[10] Thus, a proteolytic preparation sold as a meat tenderizer is not a drug, but when sold as a treatment for epidural injection for treatment of degenerative disc disease, it is a drug.

While it has been suggested that Kratom is used for certain purposes, DEA has provided no proof that Kratom, MG and 7-OH-MG are marketed as drugs intended for use in the diagnosis cure, mitigation, treatment, or prevention of disease in man or other animals.

The Dietary Supplement Health and Education Act of 1994 (DSHEA)[11] contemplates the fact that dietary supplements may have physiological and pharmacological effects, but recognizes the autonomy of individuals to make choices regarding their own health based on their own studied evaluations of specific dietary supplements, including herbal products. At the time of enactment of the DSHEA, a majority of Americans reported consuming one or more dietary supplements, and Congress recognized the significance Americans place on having such products and accurate information on

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[9] United States Code, Title 21.

[10] 21 U.S.C. §321(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

[11] P.L. 103-417.

their effects available.[12] Such products then included substances that may have physiological and pharmacological properties, which did not then, and does not now render dietary supplements "drugs" under the FDCA.

"Abuse" is defined only once in the FDCA, as:

> (A) the illegal use or abuse of drugs, including substances listed in schedules I through V of section 812 of this title;
> (B) the abuse of inhalants; or
> (C) the use of alcohol, tobacco, or other related product as such use is prohibited by State or local law.[13]

Thus, only inhalants and ***illegal*** substances are appropriately deemed "abused" under the FDCA.

Kratom, MG and 7-OH-MG are banned or restricted in certain State and/or local jurisdictions, but are not illegal under federal law.[14] Therefore, characterization of use of Kratom by DEA as "abuse" is inappropriate and presumptive of a scheduling determination that has not yet been made.

Context of Proposed Scheduling – The Opioid Epidemic.

The proposal to schedule MG and 7-OH-MG comes on the heels of a crisis in opioid abuse and overdoses, characterized by CDC as an "epidemic"[15]. According to CDC, "the number of overdose deaths involving opioids (including prescription opioid pain relievers and heroin) nearly quadrupled" between 1999 and 2014[16]. Indeed, the numbers of deaths from opioids is quite high: in 2014 there were almost 19,000 deaths

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[12] Commission on Dietary Supplement Labels, Final Report Transmitted November 24, 1997, viewed at https://health.gov/dietsupp/default.htm.

[13] 21 U.S. Code § 1523

[14] *See* Henningfield, *infra*.

[15] *See e.g.*, "Understanding the Epidemic", http://www.cdc.gov/drugoverdose/epidemic/index.html, viewed December 1, 2016.

[16] *Id. citing* "CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov.

involving prescription opioids[17] and 10,500 deaths attributed to heroin[18]. According to the Substance Abuse and Mental Health Services Administration there are "an estimated 2.1 million people in the United States suffering from substance use disorders related to prescription opioid pain relievers in 2012 and an estimated 467,000 addicted to heroin."[19] Thus, roughly 2.5 million people are addicted to heroin and opioid pain relievers, resulting in roughly 30,000 deaths per year.

There is no question that opioid addiction and mortality is a problem, but the solution is less clear.

The zealots in the addiction treatment industry have apparently hypnotized otherwise intelligent individuals into believing that the only way to save victims of opioid addiction is to acquiesce to the fiction they espouse: that a life of pain for 100 million patients is more acceptable than the risk of addiction of perhaps 2.5% of those patients, and the otherwise inevitable overdose deaths of 1.2% of those addicts. They convinced the CDC to issue "voluntary guidelines" for "safer" opioid prescribing using data compiled and analyzed according to the "Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method."[20] The "Guideline" was widely criticized for providing strong recommendations based on weak evidence, supplemented with input from a secret panel of "experts" heavily biased toward addiction treatment (typically medication assisted treatment, which may be little more than medically-sanctioned addiction) and against opioids.[21] There is nothing safer

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[17] *See* http://www.cdc.gov/drugoverdose/data/analysis.html, viewed December 1, 2016.

[18] *See* http://www.cdc.gov/drugoverdose/data/heroin.html, viewed December 1, 2016.

[19] *See* https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse (viewed December 1, 2016), citing Substance Abuse and Mental Health Services Administration, *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.

[20] *See* http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm, viewed December 1, 2016.

[21] *See e.g.*, Letter from Jordan-Meadows-Cartwright-Connolly-to-Frieden-CDC-FACA, December 18, 2015-due-Jan.-5; Videocast and transcript from the Interagency Pain Research Coordinating Committee (IPRCC), December 5. 2015available at https://videocast.nih.gov/summary.asp?Live=17523&bhcp=1 (in which, *inter alia*, one member of the committee members describes the guidelines as an "embarrassment" to the government); Anson, "Congress Investigating CDC's Opioid Guidelines", Pain News Network, December 22, 2015,

about the CDC Guideline. It simply exchanges one harm for another, leading many chronic pain patients to choose between a life of pain, a life of crime purchasing pain medications on the black market and suicide.

They have gone so far as to suggest that we should no longer even ask patients about their level of pain.[22] Jayne Ballantyne's paper in the New England Journal of Medicine espouses a psycho-babble excuses for avoiding treatment of pain: "[s]uffering may be related as much to the meaning of pain as to its intensity"; over time "pain intensity becomes linked less with nociception and more with emotional and psychosocial factors'; and that a biopsychosocial approach to pain (in lieu of actual medical treatment) having a goal of "acceptance" "might make the intensity of pain less important to a person's functioning and quality of life."[23] I call this what it is – B.S. Anyone who has suffered actual physical pain will appreciate that no amount of consoling, distraction, discussion, reasoning, or counseling will lessen the absolute physical burden it imposes.

Yet this and similar arguments have been remarkably effective with those who merely want to ***gain the appearance of doing something***. For example, such arguments have convinced Medicaid to remove questions about pain from hospital satisfaction questionnaires given to patients.[24] Specifically, three questions are being dropped in 2017:

1. During this hospital stay, did you need medicine for pain?
2. During this hospital stay, how often was your pain well controlled?
3. During this hospital stay, how often did the hospital staff do everything they could to help you with your pain?

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https://www.painnewsnetwork.org/stories/2015/12/21/congress-investigating-cdcs-opioid-guidelines?rq=opioid%20guideline, and many others.

[22] Ballantyne & Sullivan, "Intensity of Chronic Pain — The Wrong Metric?", New England J. Med. 373:2098-2099, 2015

[23] *Id.*

[24] Anson, "Medicare Pain Questions Being Dropped in 2017", Pain News Network, November 3, 2016, viewed at https://www.painnewsnetwork.org/stories/2016/11/3/medicare-pain-questions-dropped-in-2017.

In making this change, the Centers for Medicare and Medicaid Services stated "[w]hile there is no empirical evidence of such an effect, we are finalizing the removal of the pain management dimension of the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) Survey…to eliminate any financial pressure clinicians may feel to overprescribe medications."[25] So the anti-pain lobby has not only suppressed pain treatment, but has actually wiped any discussion of pain treatment off the map, with a don't ask, don't tell mentality, as though pretending pain doesn't exist will make it go away.

The anti-pain, anti-opioid camp has further justified their rhetoric by exaggerating the infrequent side effect of opioid-induced hyperalgesia[26]. The CDC first concluded that there is no evidence that opioids are effective in chronic pain[27], but rather than recommend further study as the Agency for Healthcare Research and Quality (AHRQ) did[28], CDC recommended against opioid use by interpreting absence of evidence to be evidence of absence of efficacy. The perversion of the AHRQ report has become a mantra for the anti-pain lobby often stated as: "we now know that opioids are not effective for chronic pain…"

The zealots were wrong on all counts.

Restriction of opioids **has not** had the effect of lowering opioid deaths, as evidenced by a recent report from the Massachusetts Department of Public Health indicating that opioid deaths have ***increased substantially*** since the release of the CDC Guidelines, attributable to opioids previously characterized as "prescription drugs", but now

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[25] *Id.*

[26] Opioid induced hyperalgesia is the paradoxical effect of increasing pain with increasing opioids. OIH is distinguish from tolerance in that in tolerance pain can be overcome by an increase in opioid dose, while an in opioid dose increases pain in OIH; see e.g. Tompkins & Campbell, "Opioid-Induced Hyperalgesia: Clinically Relevant or Extraneous Research Phenomenon?" Curr Pain Headache Rep. 15: 129-136,.

[27] *See* http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm, viewed December 1, 2016.

[28] Chou *et al.* "The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain" AHRQ Publication No. 14-E005-EF, September 29, 2014, viewed at *https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1988.*

recognized as counterfeit fentanyl and analogs thereof.[29] Indeed, the DEA's own reports support this observation.[30] Of even greater concern is the fact that even more dangerous counterfeit opioids have been appearing in the illicit drug supply, including carfentanil, a drug that the DEA describes as "10,000 times more potent than morphine and 100 times more potent than fentanyl".[31] There's nothing safer about the current government approach to opioids. While the supply of pharmaceutical opioids manufactured under GMP conditions available for diversion may have diminished, much more dangerous counterfeit replacements have followed in lock-step.

Increasingly, physicians and others are speaking out against the heavy-handed, supply side approach advocated by the anti-opioid lobby, and calling out the CDC for relying on "faulty data and [failing] to address the changing nature of opioid abuse when it released its opioid prescribing guidelines in March [2016]. Since then, many pain patients have reported their opioid doses have been lowered or discontinued, while some have been discharged by their physicians and forced to seek treatment elsewhere."[32] According to Stefan Kertesz, MD, an associate professor at the University of Alabama at Birmingham School of Medicine "[r]educing opioid prescribing is not going to save many lives at this point, even though it gives many officials ***a chance to look like they are doing something.***"[33]

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[29] *See* Massachusetts Department of Public Health, "Data Brief: Opioid-related Overdose Deaths Among Massachusetts Residents," November 2016, viewed at http://www.mass.gov/eohhs/docs/dph/stop-addiction/current-statistics/data-brief-overdose-deaths-nov-2016-ma-residents.pdf.

[30] "Counterfeit Prescription Pills Containing Fentanyls: A Global Threat", DEA-DCT-DIB-021-16, July 2016, viewed at https://www.dea.gov/docs/Counterfeit%20Prescription%20Pills.pdf.

[31] "DEA Issues Carfentanil Warning to Police and Public", September 22, 2016, viewed at https://www.dea.gov/divisions/hq/2016/hq092216.shtml;Healy, "Drug Linked to Ohio Overdoses Can Kill in Doses Smaller than a Snowflake," New York Times, September 5, 2016 viewed at http://www.nytimes.com/2016/09/06/us/ohio-cincinnati-overdoses-carfentanil-heroin.html?_r=0; Mettler, "This is unprecedented': 174 heroin overdoses in 6 days in Cincinnati," Washington Post, August 29, 2016, viewed at https://www.washingtonpost.com/news/morning-mix/wp/2016/08/29/this-is-unprecedented-174-heroin-overdoses-in-6-days-in-cincinnati/?utm_term=.4aca1c0a9dfb.

[32] Anson, "Fentanyl & Heroin Changing U.S. Opioid Epidemic, Pain News Network, November 19, 2016 viewed at https://www.painnewsnetwork.org/stories/2016/11/19/fentanyl-heroin-changing-us-opioid-epidemic;

[33] *Id.* (emphasis added).

Indeed, pain patients have been abandoned by their physicians, abruptly cut off from pain medications, and left to their own devices for relief. Some have committed suicide. Those that are still able to obtain pain treatment are subjected to inconvenience of visiting their physicians at least monthly, involuntary titration of their medication, humiliation, accusations of addiction and drug-seeking behavior, restrictive and derogatory pain contracts, urine drug screening, pill counts and more.

Those that are able to find pain treatment are funneled into the offices of an increasingly small number of pain clinics and physicians. Those practitioners brave enough to continue prescribing opioid pain medication in the face of increasing scrutiny by medical boards, local law enforcement and particularly the DEA, are operating at maximum capacity, and seeing increasing numbers of patients as the availability of care dwindles. Rather than support these highly trained professionals operating under stressful conditions, the DEA targets them because they are now prescribing above-average numbers of opioids.

Under these circumstances, why would a pain patient not seek relief outside of conventional medical care that has obviously lost its way? I would.

A turning point for me was when I read recommendations from the American Pain Society seeking the next step ***beyond*** the CDC Guideline for Chronic Pain, by suggesting that epidural anesthesia was appropriate for major thoracic surgery (e.g., thoracotomy). I visualized my daughter, who has had three open heart surgeries (at ages 3 months, 18 months and 10 years), screaming as she watched the cardiovascular surgeon approach with a rib-spreader. While this may not be what was intended, at what point do we as a reasonable American public tell the government that ***merely looking like it is doing something***, whether it is the right thing to do or not, is simply not acceptable?

I CALL ON THE CDC TO GO BEYOND

MERELY LOOKING LIKE IT IS DOING SOMETHING:

IT IS TIME TO DO THE RIGHT THING!

Why is Kratom Important?

Kratom may be a better way; perhaps the best way available in the current medical reality.

The tens of thousands of Kratom users who have commented on Regulations.gov attest to the safety and efficacy of Kratom in addressing analgesia, depression and opioid addiction. The sheer volume of comments from living, breathing adults clearly indicates that Kratom is less harmful than either scheduled or illicit opioids. The overwhelming majority of the now 20,000+ comments (and I have read a substantial number of them) are from Kratom users who oppose scheduling. If the rate of deaths amongst just these Kratom users alone was the same as those that abuse scheduled and illicit opioids, there should be 240 deaths per year among them[34]. If there are, as the American Kratom Association estimates, between 2 and 5 million regular kratom users, and all of these are "abusers" of a "drug" as dangerous as heroin and prescription opioids (as the DEA suggests), then we would expect on the order of 24,000 to 60,000 deaths per year. Even if only 2.5% were "addicts" (as is the percentage of opioid users who are addicts, according to the CDC), there would be hundreds or thousands of deaths per year instead of the one (1) that could not be accounted for by polypharmacy in five years.

The few that have experienced negative side effects ***while coincidentally*** using Kratom (not because of using Kratom), have generally used unimaginably excessive amounts of Kratom or have co-ingested other harmful substances. [35]

For example, the individual reported by Boyer et al. in 2008[36] was spending $15,000 a year on Kratom. He didn't experience adverse effects for 3.5 years before have a seizure

[34] 30,000 deaths per 2,500,000 opioid and heroin addicts = 12 per thousand.

[35] Henningfield, "Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation", November 28, 2016, pp. 1-128, submitted on Regulations.gov, Docket No. DEA-442W, on behalf of the American Kratom Association; *see* http://www.prnewswire.com/news-releases/american-kratom-association-major-new-analysis-shows-no-basis-for-dea-to-restrict-herb-kratom-300371521.html (hereinafter "Henningfield").

[36] "Self-treatment of opioid withdrawal using kratom (Mitragyna speciosa korth)" Addiction. (2008) 103: 1048–1050,

when he added modafinil to promote alertness. In a previous report from 2007[37] Boyer et al. estimated the cost of kratom to be $10-40 per ounce, which means this patient had been consuming on average about 1 to 4 ounces of Kratom per day for 3.5 years – all without negative effects. At 28.35g per ounce, that's an average of between 29.13 to 116.51 grams of Kratom per day, for several years – all without incident. The DEA's 3 factor analysis[38] indicates that 9 grams of Kratom is a high dose (FN 14, pg 13). At the low end of the average estimated dose range, this patient was taking a "high" dose 3 times a day for 3.5 years without any problem.

Among the strikingly few deaths attributed to Kratom, the individual discussed on pages 24-25 of DEA's 3 factor was a 45-year old male who died in 2015 in San Diego, CA, with a level of mitragynine in his liver 200 times that in McIntyre[39] of 0.43 mg/kg. This man's liver had 86 mg/kg (~129 mg of mitragynine for an average 1.5 kg human liver). At 9 mg mitragynine/gram kratom[40], this individual had MG equivalent to *over14 grams of kratom leaf in his liver alone*! He either consumed an enormous amount of Kratom or had an underlying disease that prevented elimination.

The skeptics and agenda-pushing anti-pain pundits may argue that "of course the commentors want Kratom to remain unscheduled – they are using it to get high." I think not. This is exactly the attitude the commentors have experienced daily from a medical establishment so brainwashed against pain treatment that they cannot distinguish fiction from reality. Their cries for help are dismissed as drug-seeking behavior, doctor shopping or worse when making an appointment with a physician for pain, seeking treatment for dependence, filling a prescription at their pharmacy, or even when being treated in an Emergency Department for obvious trauma.

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[37] "Self-treatment of opioid withdrawal with a dietary supplement, Kratom." American J. Addictions / American Academy of Psychiatrists in Alcoholism and Addictions 16:352–356, 2007.
[38] Viewed at https://www.regulations.gov/document?D=DEA-2016-0015-000.
[39] McIntyre et al., "Mitragynine 'Kratom' related fatality: a case report with postmortem concentrations. Journal of Analytical Toxicology 39:152–155, 2014.
[40] *See* Henningfield.

The Downside of Opioids and a Paradigm Shift

At the heart of the debate over pain medication (particularly opioids), treatment of pain (particularly chronic pain), and opioid addiction, is the risk of injury to users.

Among the risks or side effects of opioids reported by the CDC are[41]:

Addiction
Physical dependence
Overdose
Tolerance
Increased sensitivity to pain (i.e., OIH)
Confusion
Sleepiness and dizziness
Constipation
Nausea, vomiting, and dry mouth
Depression
Low levels of testosterone (can result in lower sex drive, energy, strength)
Itching and sweating

If the DEA takes Kratom users at their word, as the agency must if it is to survive a critical evaluation of its validity, Kratom use avoids or minimizes most if not all these side effect. Without such side effects, there is no need to fear, ban or schedule Kratom. The published reports support and are consistent with the user comments if corrected for realistic dosages likely to be consumed by ordinary Kratom users.

Biased Agonism of MG is Consistent with Kratom User Reports

Among the dismal outlook for the state of pain treatment in the U.S., the one thing I have found hopeful and indeed exciting is that the emerging science can ***explain the mechanisms*** by which Kratom alkaloids MG and 7-OH-MG promote analgesia and well-being, without tolerance, addiction, and OIH.

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[41] *See* "Safer, More Effective Pain Management" viewed at http://www.cdc.gov/drugoverdose/prescribing/patients.html.

Key findings which were not considered by the CDC are described in Kruegel et al.[42]. Rather than simply measure the binding affinity of mitragynine to opioid receptors, as previously reported and apparently relied upon by the CDC, Kruegel et al. investigated what MG actually does once it binds. In an elegant series of experiments, the investigators determined that MG acts as a partial agonist (similar to buprenorphine) of the G-protein mediated signal transduction at mu opioid receptors (MOR), but acts as a competitive antagonist of kappa opioid (KOR) receptors and a weak antagonist of delta opioid receptors (DOR).

As summarized in Table 1 of Stein[43] (reproduced below), MOR agonism is responsible for analgesic effect of opioids, and is believed to the primary analgesic mechanism of most commonly prescribed opiods.

[42] "Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators", J.Am. Chem Soc. 138, 6754–6764, 2016 (hereinafter "Kruegel").

[43] "Opioid Receptors", Ann. Rev. Med., 67:433–51, 2016.

Table 1 Opioid receptors and ligands (adapted from [illegible] with permission)

Receptor	Site of Action	Effects	Agonist[a]	Antagonist
Mu	Systemic	Analgesia, euphoria, constipation, respiratory depression	DAMGO, morphine, fentanyl, endomorphins, beta-endorphin	CTOP, naloxone
	Peripheral	Analgesia, constipation, reduced inflammation	DiPOA, HS731/AS006, loperamide, frakefamide, DALDA, morphine-6-glucuronide, IQMF-4, SS620	Alvimopan, naloxone methiodide, methylnaltrexone
Delta	Systemic	Analgesia, convulsions, anxiolysis	DPDPE, SNC 80, enkephalins, deltorphin, beta-endorphin	Naltrindole; ICI 174,864; naloxone
	Peripheral	Analgesia, constipation	UK-321,130; ADL5747; ADL5859; JNJ-20788560	Naloxone methiodide
Kappa	Systemic	Analgesia, diuresis, dysphoria	U-69593; U50,488; bremazocine; dynorphin	Norbinaltorphimine, naloxone
	Peripheral	Analgesia, reduced inflammation	Asimadoline, FE200665/CR845, ADL10-0101, CJC-1008, ICI204448	Naloxone methiodide

[a]DAMGO, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin; DALDA, Tyr-Arg-Phe-Lys-NH2; DiPOA, [8-(3,3-diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]-acetic acid; HS-731/AS006, 2-[(4,5alpha-epoxy-3-hydroxy-14beta-methoxy-17-methylmorphinan-6beta-yl)amino]acetic acid, SNC 80, 4-(alpha-(4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide; FE200665/CR845, H-D-Phe-D-Phe-D-Nle-D-Arg-NH-4-picolyl; ADL5747, N,N-diethyl-3-hydroxy-4-(spiro[chromene-2,4'-piperidine]-4-yl)benzamide; ADL5859, N,N-diethyl-4-(5-hydroxyspiro[chromene-2,4'-piperidine]-4-yl) benzamide, JNJ-20788560, [9-(8-azabicyclo[3.2.1]oct-3-ylidene)-9H-xanthene-3-carboxylic acid diethylamide]; ICI204448, (R,S)-N-[2-(N-methyl-3,4-dichlorophenylacetamido)-2-(3-carboxyphenyl)-ethyl]pyrrolidine hydrochloride.
All others are proprietary names.

When an agonist such as morphine or DAMGO binds to MOR[44] on the surface of a cell, it triggers conformational change in the receptor that elicits an intracellular signal transduction cascade, which is illustrated in Figure 1 of Stein (reproduced below). G-protein mediated signal transduction at MOR leads to analgesic effects, as well as respiratory depression, euphoria and constipation. Partial agonism as demonstrated by MG[45] may be reflected in less analgesia, but also less respiratory depression, euphoria and constipation.

[44] MOR, DOR and KOR are cell surface G-protein coupled receptors having 7 transmembrane domains and are often referred to as 7-TM GPCRs.

[45] *See* Kruegel.

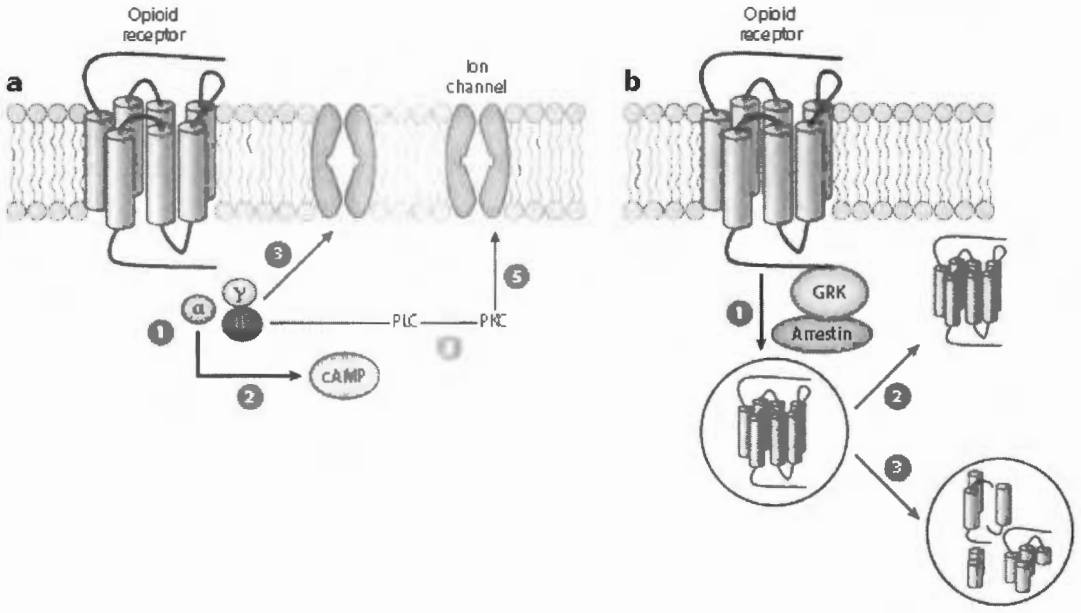


Figure 1

Opioid receptor signaling and recycling (adapted from Reference 9 with permission). (*a*) Opioid receptor ligands induce a conformational change at the receptor that allows coupling of G proteins to the receptor. The heterotrimeric G protein dissociates into active G_{α} and $G_{\beta\gamma}$ subunits ❶, which can inhibit adenylyl cyclase and reduce cAMP ❷, decrease the conductance of voltage-gated Ca^{2+} channels, or open rectifying K^{+} channels ❸. In addition, the phospholipase C/phospholkinase C pathways can be activated ❹ to modulate Ca^{2+} channel activity in the plasma membrane ❺. (*b*) Opioid receptor desensitization and trafficking is activated by G protein–coupled receptor kinase (GRK). After arrestin binding, the receptor is in a desensitized state at the plasma membrane ❶. Arrestin-bound receptors can then be internalized via a clathrin-dependent pathway and either be recycled to the cell surface ❷ or degraded in lysosomes ❸.

Among the additional effects of typical GPCR agonism is recruitment of arrestins, such β-arrestin 2. Recruitment of β-arrestin 2 by MOR leads to desensitization and results in internalization of MOR within the cell. β-arrestin 2 mediated process are believed to be a mechanism for opioid tolerance, which can be understood by considering that when fewer MOR molecules are available on the cell surface for binding to opioid, an increased amount of opioid would be needed to obtain an identical analgesic, G-protein mediated effect. β-arrestin 2 knock-out mice (mice in which the gene β-arrestin 2 has been eliminated) demonstrate the role β-arrestin 2 in analgesia and tolerance: such experimental animal show increased morphine analgesia without the development of

tolerance[46]. Thus, elimination of β-arrestin 2 recruitment is a mechanism that has long been sought for reducing tolerance as well as other side effects of opioids.

Kruegel demonstrated that MG effects G-protein mediated signal transduction, but does not recruit β-arrestin 2. Taken together, these results are consistent with a pharmacological profile for MG that exhibits less respiratory depression and low or no tolerance, while providing analgesia – exactly the effects reported by Kratom users.

In peripheral neurons, such biased agonism may explain the reduced or absent opioid induced hyperalgesia similarly reported by Kratom users. In an impressive series of experiments, Rowan et al.[47] investigated the effects of the peripherally acting G-protein biased MOR agonist, herkinorin[48]. The involvement of the Transient Receptor Potential Vanilloid Type 1 (TRPV1, a calcium channel) has been implicated in OIH by a mechanism that also involves β-arrestin 2. In this case, the association of β-arrestin 2 with TRPV1 maintains the channel in a de-sensitized state, while dissociation of β-arrestin 2 sensitizes the channel, thereby producing a pain signal. The investigators found that MOR agonism with DAMGO or morphine recruits β-arrestin 2 away from TRPV1 and induces OIH, but the effects could be reduced by reducing expression of β-arrestin 2 with an anti-sense siRNA. In contrast, herkinorin, a MOR agonist that does not recruit β-arrestin 2, did not sensitize TRPV1 and did not induce OIH in mouse models. These results are consistent with users reports that Kratom is useful for neuropathic pain and do not induce hyperalgesia when used for extended periods of up to many years.

Furthermore, the effects of KOR antagonism are consistent the role as anti-depressants reported by Kratom users. Agonism at KOR induces dysphoria, while KOR antagonists are implicated in treating depression and dysphoric conditions.[49] They may also be

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[46] *See e.g.*, Bohn, et al. "Enhanced Morphine Analgesia in Mice Lacking β-Arrestin 2" Science 286:2495-2498, 1999.

[47] "Activation of Mu Opioid Receptors Sensitizes Transient Receptor Potential Vanilloid Type 1 (TRPV1) via b-Arrestin-2-Mediated Cross-Talk", PLOS-One 9: e93688, 2014.

[48] Herkinorin does not cross the blood-brain barrier and has limited solubility, and therefore has not proven to be a good pharmacological candidate.

[49] Lalanne et al., "The kappa opioid receptor:from addiction to depression,and back" Frontiers in Psychiatry 5:1-17, 2014.

useful in combating addiction. Thus the antagonistic effect of MG on KOR may further explain the effects reported by Kratom users.

Breakthrough Pharmacology

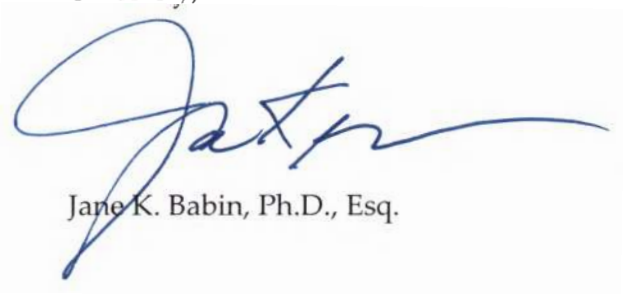
Trevena, Inc. has a developed an analgesic (Oliceridine) that has reduced β-arrestin 2 recruitment, which is currently in phase III clinical trials for i.v. use in post-operative pain[50]. The compound effects analgesia with reduced respiratory depression, and has been awarded "breakthrough status" by the FDA.[51] However, it may be years before this product is available and even longer before an oral formulation that can replace Vicodin or Oxycodone hits the market.

KRATOM IS HERE TODAY.

While we may not understand all the secrets Kratom has yet reveal about pain and analgesia, Kratom has centuries of use demonstrating significantly improved safety over scheduled opioids, and what we do understand increasingly substantiates user experiences. As an herbal supplement, its consumption is self limiting, while offering safe, non-sedating, non-depressant analgesia and a path out of addiction.

There is no reason for DEA to schedule Kratom, and it would be criminal to leave millions of Kratom with no alternatives to pain and suffering, other than a return to increased use of prescription opioids or resorting to illegal purchase on the black market.

Sincerely,



Jane K. Babin, Ph.D., Esq.

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[50] *See* http://www.trevena.com/trevena-pipeline.php.

[51] Crist, "Paradigm Shift: Oliceridine Found Effective for Pain Relief" PainMedicine News, October 16, 2016, viewed at http://www.painmedicinenews.com/Science-Technology/Article/10-16/Paradigm-Shift-Oliceridine-Found-Effective-for-Pain-Relief/38006/ses=ogst?enl=true