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WHAT IS KRATOM AND WHAT SHOULD WE DO ABOUT IT?

by James Craven
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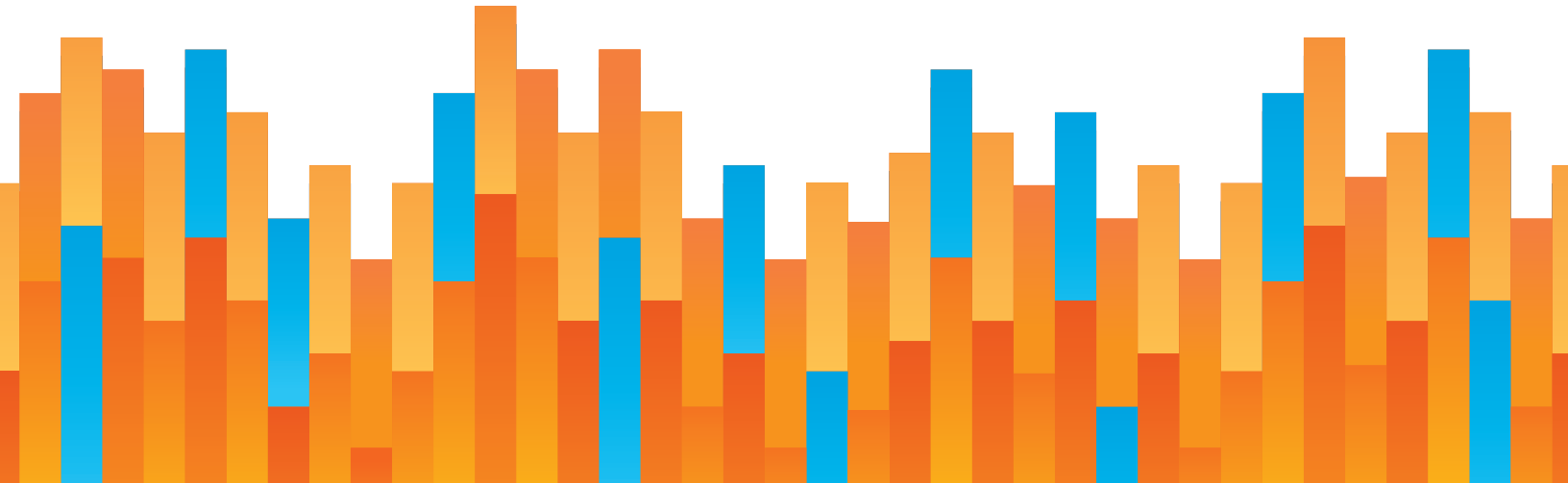

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PART 1

WHAT IS KRATOM?

Kratom is a plant native to Southeast Asia, where it has a long history of being used to combat fatigue. Related to coffee, kratom is a powerful painkiller that promotes alertness. It's difficult to estimate how many users it has attracted in the U.S., but a 2016 petition to keep kratom legal in the country found over 142,000 signees.[1] Various sources have claimed "industry experts" put the number of users between three and five million; two business owners interviewed around the time of writing estimate the number to be "over a million."[2]

1 P.M. "Please do not make Kratom a Schedule I Substance." *archives.gov*, We the People. 30 Aug. 2016. Web. <https://petitions.obamawhitehouse.archives.gov/petition/please-do-not-make-kratom-schedule-i-substance> Accessed 3 July 2018.

2 Botanical Education Alliance; American Kratom Association. "Groups: DEA Ban Of Natural Herb Kratom Could Cause Billions In Industry Losses, Harm More Than Three Million Americans." *prnewswire.com*, CISION PR Newswire. 29 Sept. 2016. Web. <https://www.prnewswire.com/news-releases/groups-dea-ban-of-natural-herb-kratom-could-cause-billions-in-industry-losses-harm-more-than-three-million-americans-300336610.html> Accessed 3 Jul. 2018; Scianno, Jim. Phone Interview. 03 July 2018.

Kratom contains two alkaloids known to possess psychoactive properties: mitragynine (MG), which makes up 60% of the plant, and 7-hydroxymitragynine (7-HMG), which makes up another 2%.[3] Both interplay with the brain's opioid receptors in a manner similar to morphine (binding to the mu-receptor), but MG's effects are far less potent. In contrast, 7-HMG is actually more potent than morphine, but its effects in kratom are muted by its limited presence.[4] The FDA decided this year to classify the drug as an opioid, a designation that casts doubt on its continued availability on American shores.[5]

[3] Prozialeck, Walter, Jateen Jivan, and Shridhar Andurkar. "Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects." *The Journal of the* American *Osteopath Association* 112:12 (2012) 792–799.

[4] Hemby, Scott, Scot Mcintosh, Francisco Leon, Stephen Cutler, and Christopher McCurdy. "Abuse Liability and the Therapeutic Potential of *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine." *Addiction Biology* 103:6 (2018) 1-12.

[5] Gottlieb, Scott. "Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse." Food and Drug Administration. *fda.gov*. 6 Feb. 2018. Web. <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm595622.htm> 03 Jul. 2018. A word of caution on interpreting terms like "opioid" and "opioid receptors." Not

Psychoactives aside, no combination of juice, sugar, or cream will make kratom palatable. Keely Flow, a business owner who sells kratom drinks at a bar in North Carolina, says kratom's bitter taste will forever check its mainstream appeal. But customers keep coming anyway, and for a variety of reasons.[6]

everything that interacts with opioid receptors is an opioid—many common items like cheese and coffee affect these receptors. What is defined as an opioid is a matter of evolving human convention, based on which receptors are activated and how the interaction takes place. MG and 7-HMG are compared to morphine in potency because both are mu-receptor agonists and morphine is the prototypical mu-receptor agonist. Considerable differences exist in how these molecules interact with the mu-receptor and other parts of the brain.

6 Flow, Keely. Phone Interview. 03 April 2018.

PART 2

HOW KRATOM IS USED

2.1 AN OPIATE TREATMENT—OR SUBSTITUTE

Many of Flow's customers are part of an especially tight-knit community: they're recovering opioid addicts, struggling to break addictions to dangerous substances like heroin and fentanyl. These people have met at AA meetings, methadone clinics, and Flow's own bar. And it's no surprise to find them there.[7]

A survey in 2017 found 25.9% of roughly 7,000 respondents used kratom to help with withdrawal from prescription painkillers, and 7.9% used it to cope with withdrawal from illegal drugs like heroin.[8] Another study that examined a smaller population of kratom users enrolled in a drug recovery program found that 68.9% used the drug to reduce cravings for non-prescriptions opioids (NPOs) or heroin, and 64.1% used it as a substitute.[9]

Using an opioid or opioid-like substance to treat opioid addiction is nothing new. Methadone clinics nationwide provide recovering heroin and NPO users access to a

7 Ibid.

8 Grundmann, Oliver. "Patterns of Kratom use and health impact in the US – results from an online survey." *Drug and Alcohol Dependence* 176 (2017) 63–70.

9 Smith, Kirsten and Thomas Lawson. "Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program." *Drug and Alcohol Dependence* 180 (2017) 340-348.

controlled dose of opioids in the hope of weaning them off whatever more dangerous drug they're using. Kratom is being used in much the same way—but unlike Methadone, there are no hoops to jump through or paperwork to fill out, and users can control their own dose.

A recent study, the first to test whether or not kratom use encouraged or discouraged subjects to self-administer more potent opioids, found divergent results for kratom's two psychoactive compounds. The study divided 344 lab rats into two groups, which were first given a consistent supply of morphine and then moved to either MG or 7-HMG respectively. Both groups were then offered morphine again. Self-administration declined precipitously among rats that had used mitragynine, but increased among the 7-hydroxymitragynine receiving group. These results suggest that kratom's therapeutic potential warrants more investigation—but risks remain.[10]

2.2 RECREATIONAL USE

Kratom is also used recreationally. For those living in any state other than Arkansas, Alabama, Vermont, Indiana, Wisconsin, Rhode Island, Tennessee or Washington, D.C., a kratom business could be just a yelp search away.[11] It's also regularly sold in head shops and online.

The taboo surrounding recreational drug use complicates estimating how common kratom experimentation really is, but it's safe to say that not everyone who tries the chalk-like powder is struggling with an opioid addiction or self-treating for chronic pain. The 2017 survey did not attempt to quantify recreational use, perhaps due to an assumption of underreporting, but it did ask users to report on side effects and dosage. Those interested in trying kratom should be aware that users taking more than five grams were much more likely to report side effects such as nausea and constipation.[12] Both business owners

10 Hemby. "Abuse Liability and the Therapeutic Potential of *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine."

11 "AKA in Your State." American Kratom Association, 2018. Web. <https://www.americankratom.org/aka-in-your-state> 03 July 2018.

12 Grundmann. "Patterns of Kratom use and health impact in the US – results from an online survey."

interviewed for this article recommended trying doses of less than five grams on an empty stomach.[13]

As with any psychoactive substance, a good understanding of the risks is important. Tolerance builds quickly, and withdrawal symptoms such as flu-like symptoms, irritability and aggravation of chronic pain can occur days after use.[14]

[13] Flow; Scianno. Scianno shared that the kratom tea he regularly serves contains 3.5 grams of kratom. Flow also recommended long breaks between use.

[14] Flow; Singh, Darshan, Christian Müller and Balasingam Vicknasingam. "Kratom (Mitragyna speciosa) dependence, withdrawal symptoms, and craving in regular users." *Drug and Alcohol Dependence* 139 (2014) 132-137.

PART 3

THE RISKS OF KRATOM

3.1 WITHDRAWAL

Readjusting from daily use of any psychoactive substance—even coffee—can be a painful experience. Kratom is related to coffee, and it contains a potent mu-agonist that produces significant withdrawal symptoms after long-term use. The first study on kratom withdrawal focused on a population in Malaysia, where kratom use is as popular as coffee in the U.S.

The study sampled nearly 300 men who regularly ingested kratom for six months or more. Upon quitting kratom cold turkey, 76% reported severe aches and muscle pain; 73% reported anger, tension, restlessness and depression the day after they stopped drinking kratom. But while painful, the duration of withdrawal was fairly short even for these chronic users: 64% reported symptoms ending within three days.[15]

U.S. poison control center records provide another good sample size. While this sample has severe limitations—likely being limited to the most severe cases and lacking critical information about dosage and duration—it does provide a good overview of possible withdrawal symptoms. Roughly a quarter of records indicated a rapid heart rate and

[15] Singh. "Kratom (Mitragyna speciosa) dependence, withdrawal symptoms, and craving in regular users."

irritability; drowsiness, nausea and high blood pressure were recorded in 10%-20% of cases.[16]

Both of these studies focus on severe use cases, and limiting dose and duration undoubtedly mitigate these effects a great deal.

3.2 ADDICTION

Lab studies show that tolerance develops to both MG and 7-HMG in mice after several days.[17] All of the regular kratom users in the Malaysia survey reported some degree of cravings, with 77% reporting a low craving and 23% reporting a high craving.[18] Systemic use of kratom to treat opioid withdrawal, combined with increased tolerance and mild to intense cravings, could lead to high intake among users. As volume increases, the likelihood of more-severe withdrawal symptoms also grows, which may aggravate addiction potential.

No remedy for kratom withdrawal and addiction is currently available, but as the symptoms include pain and hypertension, non-hypertensive painkillers such as aspirin are being explored. Kratom users recovering from heroin or NPO addiction may or may not find the less severe withdrawal symptoms of kratom to be a fair trade if it is alleviating the long-term difficulties of opioid withdrawal.

16 Anwar, Mehruba, Royal Law, and Josh Schier. "Notes from the field: Kratom (Mitragyna speciosa) exposures reported to poison centers - United States, 2010-2015." *Morbidity and Mortality Weekly Report* 65 (2016) 748-749.

17 Matsumoto, Kenjiro, Syunji Horie, Hiromitsu Takayama, Hayato Ishikawa, Norio Aimi, Dhavadee Ponglux, Toshihiko Murayama, and Kazuo Watanabe. "Antinociception, tolerance and withdrawal symptoms induced by 7-hydroxymitragynine, an alkaloid from the Thai medicinal herb Mitragyna speciosa." *Life Sciences* 78 (2005) 2–7; Matsumoto, Kenjiro, Hiromitsu Takayama, Minoru Narita, Atsushi Nakamura, Masami Suzuki, Tsutomo Suzuki, Toshihiko Murayama, Sumphan Wongseripipatana, Kaori Misawa, Mariko Kitajima, Kimihito Tashima, Syunji Horie. "MGM-9 [(E)-Methyl 2-(3-ethyl-7a,12a-(epoxyethanoxy)-9- fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxyindolo[2,3-a]quinolizin-2-yl)- 3-methoxyacrylate], a derivative of the indole alkaloid mitragynine: a novel dual-acting mu- and kappa-opioid agonist with potent antinociceptive and weak rewarding effects in mice." *Neuropharmacology* 55 (2008) 154–165.

18 Singh. "Kratom (Mitragyna speciosa) dependence, withdrawal symptoms, and craving in regular users."

PART 4

LIFE-SAVING POTENTIAL

Not long after designating kratom an opioid, the FDA claimed that it had caused over 44 deaths in half a decade. A closer examination of the report reveals that the vast majority of these deaths occurred in concert with other, more dangerous drugs.[19] Some have more obvious superseding causes: the FDA even included a homicide victim who was shot in the chest, just because the man was on kratom at the time. Only one of the reports describes a man who was only using kratom, and no details are provided on the cause of his death.[20] Likewise, the review of five years of poison control records noted only one death, which occurred in tandem with two other psychoactive compounds.[21]

Even if we take the FDA's report at face value, the numbers appear very favorable for kratom. An earlier report from the agency counted 36 deaths between the middle of 2011

19 "FDA Adverse Event Reporting System (FAERS)." Food and Drug Administration. 17 Dec. 2017. Web.<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/UCM595575.pdf> 03 July 2018.

20 Wing, Nick. "FDA Releases Kratom Death Data, Undermines Its Own Claims About Drug's Deadly Harms." *The Huffington Post*. 07 Feb. 2018. *huffingtonpost.com*. Web. <https://www.huffingtonpost.com/entry/kratom-deaths-fda_us_5a7a3549e4b07af4e81eda8b> 03 July 2018.

21 Anwar. "Notes from the field."

and the middle of 2017.[22] Comparing opiate deaths from 2012 to 2016 alone reveals 152,196 opioid-related deaths.[23] This means kratom was involved in less than .00024% of opioid deaths.[24] When we consider the number of users who report to be substituting kratom for other opioids, kratom may be saving lives just by keeping people away from other, more dangerous drugs.[25] Compared to heroin and NPOs, kratom appears to be remarkably safe.

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[22] Gottlieb, Scott. "Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom." Food and Drug Administration. fda.gov. 4 Nov. 2017. Web. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm> 03 July 2018.

[23] "Opioid Overdose Deaths and Opioid Overdose Deaths as a Percent of All Drug Overdose Deaths." Kaiser Family Foundation, 2018. Web. <https://www.kff.org/other/state-indicator/opioid-overdose-deaths> 3 July 2018.

[24] This calculation is performed by taking 36, the number of deaths reported by the FDA where kratom was identified in the deceased between mid 2011 and mid 2017, and dividing it by 152,196, the total number of deaths caused by opioids according to the Kaiser Family Foundation (KFF). Because the data are not available for the number of deaths caused by opioids for part of 2011 or 2017, a narrower range is used for the total. It is also worth noting that the KFF range only includes death specifically *caused by opioid overdose*, while the FDA's range includes any death where kratom was merely present (in addition to the homicide, the FDA also included, for instance, a man who threw himself out a window while also on other drugs and a teenager who hanged himself while also on other drugs). Both of these limitations suggest this result is actually much stronger than reported. The researcher concedes that there may be more people who have died incidentally to kratom use that the FDA has not yet found, but does not expect that this would significantly alter the result.

[25] Even without knowing the number of kratom users, these results are strong enough that they would hold if even 2% of the *sample size subsection* in the Grundmann study that confirmed use of kratom to help alleviate withdrawal from prescription opioids or illegal drugs were successful in their efforts. These results could be controverted by substantial evidence that kratom use *causes and leads to a significant increase in the usage of opioids leading to fatal overdose*. The researcher is not aware of any research finding that kratom is a "gateway drug" to opioid use. Evidence exists, and is cited here, that administering 7-HMG after morphine leads to increased self-administration of morphine after 7-HMG is cut off. This result is mitigated by three factors. First, the competing effect of MG shown in the same study to decrease self-administration of morphine. Second, that relapse after kratom use would in no way be dispositive of kratom *causing* relapse. Lastly, the proximate cause of "relapse" in the mice was the removal of access to 7-HMG followed by the immediate provision of morphine. Humans cannot be subjected to these conditions by researchers.

Kratom has two known properties that likely contribute to its safety, the first of which is simply its low overall potency relative to heroin and many NPOs such as fentanyl. The second is more unique: kratom does not appear to have a substantial risk of respiratory depression, a major catalyst in opioid-related deaths.[26]

[26] Kruegel, Andrew, Madalee Gassaway, Abhijeet Kapoor, András Váradi, Susruta Majumdar, Marta Filizola, Jonathan A. Javitch, and Dalibor Sames. "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 (2016) 6754–6764.

PART 5

RECOMMENDATIONS

Kratom has life-saving potential as an opioid substitute, demonstrates promise as a therapy for opioid withdrawal, and has been shown to be remarkably safe even among heavy users. Banning kratom could potentially cut off a lifeline for many people struggling with opioid addiction, and would complicate research into a potential remedy for opioid addicts at a time when such research is desperately needed.

While kratom is an intoxicant, with the inherent risks of all intoxicants, it appears to have low to no mortality. Kratom has clear psychoactive properties, can trigger days of painful withdrawal symptoms, and has addiction potential, but none of these conditions is severe enough to amount to a substantial risk. The risks of banning kratom may be higher: it may result in kratom users reaching for other, more dangerous opioids. Concern about kratom's limited risks is likely best resolved by public information rather than prohibition.

Much is still unknown about kratom, and new research could call for these conclusions to be reevaluated. For now, the sale of kratom appears to provide a valuable service to many at minimal risk to the general public.

ABOUT THE AUTHOR

James Craven is a Senior Fellow at Reason Foundation. His work includes a policy brief and presentation on driver's license suspension reform in Michigan, task force participation assessing mandatory minimum sentences in North Carolina, and a study of forgiveness remedies for marijuana crimes nationwide. Craven is committed to helping states achieve cost-efficient solutions that maximize opportunity for their citizens.

Prior to his time at Reason, Craven worked as a defense attorney representing private and indigent clients throughout North Carolina's Piedmont Triad area. He graduated from Georgetown University Law Center in 2013.