Review of Eggleston et al. 2019 brief report, "Kratom Use and Toxicities in the United States"

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Summary: Eggleston et al. published a brief report summarizing selected findings from calls to the US National Poison Control Data System (NPDS) from January 1, 2011 to July 31, 2018.[1] The main focus of the report was on calls in which the callers reported only kratom exposure.

The brief report also summarized certain information "from a county medical examiner's office in New York State" that reported four "kratom-associated fatalities" during the same time period. The main conclusion of Eggleston et al.'s brief report was as follows:

> Kratom use is increasing and is associated with significant toxicities. Our findings suggest kratom is not reasonably expected to be safe and poses a public health threat due to its availability as an herbal supplement.

This conclusion is not supported by the information presented by Eggleston et al. due to limitations of the NPDS and severe shortcomings in the brief report. The report made no mention of what percent of the callers reported symptoms possibly associated with kratom, the severity of effects in those who did report symptoms, whether or not medical assistance was advised or sought, or whether any symptoms associated with kratom use could be attributed to their kratom exposure, let alone caused by kratom.

Similarly, from the information presented, it is not possible to determine whether kratom contributed to or was causative in any of the four deaths that were reported to have been associated with kratom use. Given the timing of the publication, it is surprising that the authors seemed unaware of limitations of relying on such medical examiner reports for establishing a causal relationship to kratom in such deaths, as were discussed in an April 12 2019 Morbidity and Mortality Weekly Report[2] and an earlier New England Journal of Medicine article, neither of which were cited.[3]

Conversely, the limitations do not mean that kratom is without risk or has never contributed to deaths. Kratom, like any substance should be assumed to carry some risks and unintended effects, which could be minimized by appropriate regulatory

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[1] Eggleston, W, Stoppacher, R, Suen, K, Marraffa, JM, and Nelson, LS, 2019. Kratom use and toxicities in the United States. Pharmacotherapy, 39: 775-777.

[2] Olsen, EO, O'Donnell, J, Mattson, CL, Schier, JG and Wilson, N, 2019. Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected - 27 States, July 2016-December 2017. MMWR Morb Mortal Wkly Rep 68:326-27.

[3] Gershman, K, Timm, K, Frank, M, Lampi, L, Melamed, J, Gerona, R and Monte, AA, 2019. Deaths in Colorado Attributed to Kratom. N Engl J Med 380:97-98.

oversight. Regulation, including standards for kratom product contents and labeling, and further research on kratom use, effects and safety, is needed, as has been concluded in every report on kratom contributed to by Henningfield.[4] Furthermore, as discussed elsewhere by Henningfield and others, kratom use must be considered in the context of an opioid crisis that is resulting in more than 1000 times more deaths each year (47,600 in 2017) compared with those deaths the Food and Drug Administration (FDA) concludes were associated with kratom in the past decade globally (44).[5] Evidence from four surveys of more than 20,000 kratom users and patients with opioid use disorder, and more than 23,000 comments to the Drug Enforcement Administration (DEA) indicates that kratom provides an alternative to opioids and a harm mitigation strategy for many opioid users, and is an important asset for the health and well-being of many of the millions of kratom users.[6] Thus, it is important to sustain consumer access to kratom, ideally FDA-regulated access, to avoid promoting relapse to opioids by these people.[7]

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[4] E.g., Henningfield, JE, Fant, RV, Wang, DW, 2018. The Abuse potential of kratom according the 8 factors of the Controlled Substances Act: implications for regulation and research. Psychopharmacology (Berl) 235:573-89.
Prozialeck, WC, Avery, BA, Boyer, EW, Grundmann, O, Henningfield, JE, Kruegel, AC, McMahon, LR, McCurdy, CR, Swogger, MT et al., 2019. Kratom Policy: The challenge of balancing therapeutic potential with public safety. Int J Drug Policy 70:70-77.

[5] Opioid overdose data from the Centers for Disease Control and Prevention, 2018. Drug overdose deaths, 2017 at https://www.cdc.gov/drugoverdose/data/statedeaths.html.
For FDA estimates of kratom associated deaths see 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 [Press release]. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm.
Note that the FDA estimate of 44 deaths includes an apparent duplication of ID No. 14449343 under ID No. 14254346, and that the all but one death appears to have involved other substances or probable causes (e.g., gunshot wound to the chest, suicide, injuries due to falling out of a building) except for one death that the FDA indicate it was investigating further. See Prozialeck et al. 2019; Grundmann et al. 2018.
Also see discussion of mortality risk and apparent causes by the National Institute on Drug Abuse at https://www.drugabuse.gov/publications/drugfacts/kratom.

[6] Coe, MA, Pillitteri, JL, Sembower, MA, Gerlach, K., and Henningfield, JE. 2018. Kratom as a substitute for opioids: Results from an online survey. Drug Alcohol Depend 202: 24-32.
Grundmann, O, 2017. Patterns of Kratom Use and Health Impact in the US-Results from an Online Survey. Drug Alcohol Depend 176:63-70
Smith, KE. and Lawson, T, 2017. Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. Drug Alcohol Depend 180:340-348.
Also see summary in Henningfield, J., Fant, R.V., Wang, D.W., 2018. The Abuse Potential of Kratom According the 8 Factors of the Controlled Substances Act: Implications for Regulation and Research.

[7] Grundmann, O, Brown, PN, Henningfield, JE, Swogger, M, and Walsh, Z. The therapeutic potential of kratom. Addiction,113:1951–1954, 2018.
Henningfield, JE. Regulation of kratom to the benefit of public health. Keynote address at the Second International Symposium on Kratom February, 8-10, 2019, Orlando, Florida

Following is a summary of some of additional specific deficiencies of the Eggleston et al. brief report.

To help readers understand the limitations of conclusions drawn from NPDS call reports, the report should have included a brief summary of how NPDS works and what data are collected, and the limitations thereof, as discussed by the NPDS itself. For example, depending on the interviewer and the caller, the quality and completeness of the data can vary widely.

Furthermore, there is no way for the interviewer to tell what the actual cause of symptoms reported is or was. Thus, based on the data presented, and the limitations of the NPDS, it is impossible to conclude that no other substances, including medicines, were ingested, or to determine whether the kratom product actually was a pure and unadulterated product, or if the callers had medical conditions that may have accounted for their symptoms. In the absence of FDA regulation there is no simple way for consumers to know if the product they purchased can be assured of being pure, and not adulterated with other substances, or with added kratom alkaloids.[8]

Call numbers for any exposure need context for readers to understand the relative size and scope of the potential problem. For perspective, in 2015 there were 263 kratom-related calls to the NPDS, compared to 55,151 diphenhydramine-related calls, 18,470 aspirin-related calls, and 1,355 involving nicotine. Depending on the substance category, many if not most calls do not report symptoms related to the ingestion of the substance and of those that do, most do not require medical attention. For additional perspective, it is likely that there are at least 10 million and possibly as many as 16 million kratom users in the US,[9] indicating a very low rate of calls related to kratom. This is consistent with other studies indicating a very low risk of serious adverse events among kratom users.[10]

The brevity of the report left unexplained inconsistencies and factors that might have been relevant to the symptoms that were reported. Although the journal allows 2,000 words for its brief reports the authors used little over 1,000 words excluding the

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[8] The American Kratom Association (AKA) created a voluntary standards program mirroring FDA dietary supplement manufacturing standards for kratom vendors that provides kratom consumers with a list of vendors who have completed the process of qualifying for participation in this program and who have passed and continue to be subject to annual independent third-party audits. See https://www.americankratom.org/abou-aka/akagmpprogram.html

[9] The AKA surveyed export data from several Indonesian kratom grower's commercial export associations that document an average of 1,950 metric tons of kratom are exported on a monthly basis to the U.S. Based on the average amount of kratom used per day by consumers, there are approximately 15.6 million kratom consumers in the U.S. See http://www.americankratom.org/images/Kratom_Population_2019.pdf

[10] Grundmann, 2017; Prozialeck et al., 2018;
Singh D, Vicknasingam, BK and Mansor, SM, 2015. Social functioning of kratom (Mitragyna speciosa) users in Malaysia, J Psychoactive Drugs, 47:2, 125-131.
Swogger, MT and Walsh, Z. Kratom use and mental health: a systematic review. Drug Alcohol Depend 2018; 183: 134–40.

abstract. It is surprising that the reviewers or editors did not ask for clarification of inconsistent points. Perhaps the reviewers were unfamiliar with NPDS reporting categories and the limitations that are inherent in NPDS reports.

Eggleston et al. stated that all kratom single substance exposure cases "were reviewed for demographics and associated clinical effects." However, no fundamental demographic information was provided. Such information is vital to understanding determinants and correlates of risk. For example, were symptoms and potential adverse events more common in intentional or unintentional exposures (e.g., were these children who accidentally ingested kratom), and how many people had a serious medical condition? As large-scale surveys have found, many persons using kratom are doing so for serious medical conditions such as chronic pain, depression, anxiety, opioid use disorder, post-traumatic stress disorder, and fibromyalgia (see articles in footnote 4 and Prozialeck et al. 2019). Those with an opioid use disorder may have experienced adverse events associated with their underlying condition rather than kratom use.

The definitions of intentional misuse and abuse (accounting for 61.6% of all exposures reported to NPDS) were never explained in the brief report. They are below and were copied directly from the 2017 National Poison Data System Annual Report.[11]

- **Intentional misuse**: An exposure resulting from the intentional improper or incorrect use for reasons other than the pursuit of a psychotropic effect
- **Intentional abuse**: An exposure resulting from the intentional improper or incorrect use where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect

Kratom is not an illegal substance, nor is it regulated by FDA; therefore, it is unclear how it could be used improperly or incorrectly. Instead of misuse/abuse cases, it would have been more meaningful if the authors differentiated intentional vs. unintentional exposure cases. Further, the authors did not offer a potential explanation or comment on how the remaining 38.4% of exposures were categorized.

Related to the medical examiner reports, in addition to the limitations summarized above, the authors should have discussed what was reported about the manner of death which led to the conclusion that kratom was a contributing or causative factor. For example, opioid overdoses cause death by severe respiratory depression and arrest in a majority of cases. This has not been documented for kratom in animals or humans. The kinds of considerations discussed in footnotes 1 and 2 should be included. This includes what substances were actually tested for given that the limited testing routinely ordered by medical examiners is likely to miss many drugs, including substances of abuse and prescription medicines that may have been the major if not primary causes of death. The lack of any detail about these decedents including potential preexisting

[11] American Association of Poison Control Centers, National Poison Data System Annual Reports, at https://www.aapcc.org/annual-reports.

conditions, substance use histories, and other factors, makes it impossible to draw conclusions about the potential role, if any, of kratom, in the deaths.

The likelihood that kratom is more likely associated with a far greater public health benefit than a threat, as suggested by four surveys of more than 20,000 kratom users and more than 23,000 comments to the DEA, was not discussed.

The few mentions related to kratom's alkaloids and pharmacology are superficial and incorrect. For example:

Paragraph 2 leads with the statement: "Hydroxymitragynine, a minor component of kratom, also has opioid activity and is thought to be more potent than morphine." Presumably the authors were referring to 7-hydroxymitragyine but such an error is not trivial.

Furthermore, numerous studies and publications over the past few years have elucidated that mitragynine and 7-hydroxymitragyine have a complex pharmacology that should not simply be described as having "opioid activity".[12] Opioids of course are diverse depending on whether they are full or partial agonists or antagonists, and which opioid receptors they primarily bind to and the degree to which they produce biased G-protein signaling effects. Thus, scientific articles are generally more specific than to simply characterize a substance as an "opioid". Nonetheless, when people simply use the term "opioids" it is generally presumed that what is meant is a "narcotic", "morphine", or "heroin-" like opioid. In kratom products that are pure and unadulterated, the primary active alkaloid is mitragynine. Mitragynine does produce some of the pain-relieving, constipating and nauseating effects of morphine-like opioids, but only limited respiratory-depressing and brain rewarding effects which are the signature effects of morphine-like opioids that account for their high overdose and addiction risk, respectively.[13] This is a critical distinction and thus it is surprising that the peer-review and editorial process allowed publication with discussion in this section so inaccurate and outdated.

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[12] Eggleston et al. 2019, first page.

[13] Kruegel, A.C., Grundmann, O., 2018. The Medicinal Chemistry and Neuropharmacology of Kratom: A Preliminary Discussion of a Promising Medicinal Plant and Analysis of its Potential for Abuse. Neuropharmacology 134:108-20. 10.1016/j.neuropharm.2017.08.026
Kruegel, A.C., Gassaway, M.M., Kapoor, A., Varadi, A., Majumdar, S., Filizola, M., Javitch, J.A., Sames, D., 2016. Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. J Am Chem Soc 138:6754-64.
Prozialeck, W.C., Avery, B.A., Boyer, E.W., Grundmann, O., Henningfield, J.E., Kruegel, A.C., McMahon, L.R., McCurdy, C.R., Swogger, M.T., et al., 2019. Kratom Policy: The Challenge of Balancing Therapeutic Potential with Public Safety. Int J Drug Policy 70:70-77.
Varadi, A., Marrone, G.F., Palmer, T.C., Narayan, A., Szabo, M.R., Le Rouzic, V., Grinnell, S.G., Subrath, J.J., Warner, E., et al., 2016. Mitragynine/Corynantheidine Pseudoindoxyls as Opioid Analgesics with Mu Agonism and Delta Antagonism, Which Do Not Recruit beta-Arrestin-2. J Med Chem 59:8381-97.

In addition, the sentence “The addition of synthetic 7-hydroxymitragynine to kratom as an adulterant is thought to produce a product with more profound opioid effects.[7]” misrepresents the article it cites. Nowhere in the referenced article did Lydecker et al.[14] refer to “synthetic 7-hydroxymitragynine” as the possible adulterant. This is simply poor scholarship and it should have been accurately addressed as “adulterated” or perhaps “artificially elevated”.

Conclusions: The brief report by Eggleston et al., lacks the scientific rigor to support its conclusions and to meaningfully address the potential risk of kratom products for the public. The peer-review process appears to have failed, in this case, to ensure that the article met the standards of the Journal. The authors should have provided further information on demographics and further details on the severity of exposures. A lack of reporting leaves many questions unanswered and undermines the strength of the report and findings. Hence, few if any conclusions can be drawn from the report that would otherwise benefit researchers, healthcare providers, and the public at large to make kratom safe – either by regulating it or banning it.

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[14] Lydecker AG, Sharma A, McCurdy CR, Avery BA, Babu KM, Boyer EW. Suspected adulteration of commercial kratom products with 7-hydroxymitragynine. J Med Toxicol 2016;12 (4):341–9.