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Deaths in Colorado Attributed to Kratom

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TO THE EDITOR:

Kratom (*Mitragyna speciosa*) is an herbal drug identified by the Food and Drug Administration (FDA) as an opioid for which there is “no evidence of safety or effectiveness for any medical use.”¹ The drug is derived from a tropical tree native to Southeast Asia whose leaves have been used traditionally to increase energy among laborers and to treat pain and illness. At higher doses, kratom has opioid-like effects.² Kratom use has become popular as an alternative medicine for the treatment of pain, mood disorders, and opioid withdrawal.³ Mitragynine is the most abundant of the many alkaloids in kratom and is responsible for its clinical and psychoactive effects. Activity occurs through agonism at mu receptors and antagonism at delta receptors, which may explain the apparently reduced risk of respiratory depression associated with kratom as compared with pure mu agonists, such as heroin and oxycodone.⁴

It has been asserted that no deaths solely attributable to mitragynine have been documented,² although the scope of use is unknown, in part because routine drug testing does not detect mitragynine. The FDA issued a warning on February 6, 2018,¹ stating that three-dimensional computational modeling of mitragynine reveals a structural similarity to

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opioids, with binding to mu-opioid receptors. In the warning, the FDA reported 44 deaths associated with kratom use, including 1 that was associated with mitragynine only. These findings have prompted the FDA to issue warning letters to numerous businesses that sell kratom illegally.⁵

We reviewed Colorado death certificates for any mention of kratom or mitragynine from 1999 through 2017 and identified 15 kratom-related deaths (see the Supplementary Appendix, available with the full text of this letter at [NEJM.org](https://www.nejm.org)). Autopsy reports were reviewed for all 15 deaths, which included 13 men and 2 women, with a median age of 28 years (range, 24 to 53). On the basis of toxicology testing, 11 cases involved multidrug ingestion (two to six drugs), and 8 persons had positive test results for other opioids. Four deaths were reported to involve mitragynine only, and coroners attributed each to mitragynine toxicity.

We further investigated the 4 deaths that appeared to be due to mitragynine only, reviewing police investigation records for all 4 and performing comprehensive toxicology screening with high-performance liquid chromatography with tandem mass spectrometry for the 3 cases for which residual blood was available (Table 1). In our investigation of all 15 kratom-related deaths, we determined that 14 deaths clearly involved multiple drugs. Mitragynine levels varied widely, from 16 to 4800 ng per milliliter. Residual blood was not available for confirmatory testing in the remaining kratom-related death.

It is likely that mitragynine increases the risk of adverse events, especially when ingested with opioids or psychoactive drugs. Careful examination of deaths apparently due to kratom only must include comprehensive toxicology screening. Further study is needed to assess the safety and potential effectiveness of kratom as an herbal drug.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

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Table 1. Reported Cases of Death Due to Mitragynine Only in Colorado, 1999–2017.*

Year of Death	Medical History	Whole-Blood Mitragynine Concentration	Additional Drugs Identified (Whole-Blood Concentration)	Comments
2013–2016	NA	NA	No residual blood available for comprehensive toxicology screening (NA)	Apparent seizure leading to cardiorespiratory arrest after ingestion of kratom
2013–2016	Opioid and benzodiazepine abuse; recent history of seizures associated with benzodiazepine withdrawal	16 ng/ml	5-MeO-AMT, psychedelic tryptamine (56.19 ng/ml) Etizolam, benzodiazepine (1.3 ng/ml) Acetaminophen, analgesic (NA) Gabapentin, anticonvulsant (NA) Caffeine, stimulant (NA) Ethanol (18 mg/dl)	Multiple medications affecting central nervous system; psychoactive prescription medications; evidence of etizolam use on scene
2017	NA	170 ng/ml	1,3-dimethylamylamine, methylhexanamine — also known as geranium extract, an illegal dietary supplement with stimulant effects (157 ng/ml) Selegiline, antidepressant (NA)	Packing slip fortianeptine; bottles of pills and dietary supplements; empty packets of selegiline found on scene
2017	NA	48 ng/ml	Trimethoxyamphetamine — a synthetic alkaloid amphetamine; analogue of phenethylamine cactus alkaloid mescaline (2.83 ng/ml) Inhaled hydrocarbons (NA)	History of inhalant abuse (including recent use); aerosol cans found on scene

* All persons were male. 5-MeO-AMT denotes 5-methoxy-a-methyltryptamine, a potent psychedelic tryptamine. NA denotes not available.