JPPT | Invited Commentary

Kratom's Use and Impact on Pediatric Populations

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ABBREVIATIONS DEA, Drug Enforcement Administration; FDA, US Food and Drug Administration; IRL, interim reference level SUD, substance use disorder; WCBP, women of childbearing potential

KEYWORDS botanical; kratom; mitragynine; opioid use disorder; pain; pediatrics; 7-hydroxymitragynine

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Introduction

Kratom is derived from the leaves of the *Mitragyna speciosa* tree in Southeast Asia.[1] According to the National Survey on Drug Use and Health, kratom has been used by approximately 4.9 million Americans including 45,000 children aged 12 to 17 years and 913,000 people aged 18 to 25 years.[2] Kratom is sold in gas stations, convenience stores, smoke shops, and over the internet. It is currently not classified as a drug or a dietary supplement by the US Food and Drug Administration (FDA) but attempts by the Drug Enforcement Administration (DEA) to make kratom a Schedule I substance failed.[3]

Pharmacology of Kratom and Noted Adverse Events

Mitragynine (66%) and 4 corynanthe-type monoterpenoids (speciociliatine, speciogynine, paynantheine, corynantheidine) (20%) comprise the vast majority of the total alkaloids in kratom.[1] Mitragynine binds to the peripheral and central μ-opioid receptor as a partial agonist, is a weak competitive antagonist at κ- and δ-opioid receptors, and stimulates serotonin and adrenergic receptors. The corynanthe-type monoterpenoids have varied effects including mild opioid receptor partial agonism or opioid receptor antagonism, and agonism at serotonin or alpha-adrenergic receptors.[1] One metabolite of mitragynine, 7-hydroxymitragynine, has 9-fold higher affinity for the μ-opioid receptor than mitragynine.[4] In animal models, mitragynine and 7-hydroxymitragynine provide traditional opioid effects such as analgesia and constipation.[1,4,5] Mitragynine is unlikely to induce respiratory depression, but the reason is not entirely clear. Some possibilities include mitragynine's inability to recruit beta-arrestin with μ-opioid receptor–like traditional opioids, because mitragynine is a weak partial agonist that blocks the respiratory depressant effects of its bioconverted 7-hydroxymitragynine, or because mitragynine has mild stimulant instead of sedative effects. Naloxone and naltrexone reverse opioid receptor effects of mitragynine and 7-hydroxymitragynine. Animal studies demonstrate that opioid-like tolerance and withdrawal occur when chronic mitragynine or 7-hydroxymitragynine is withheld.[6] However, mitragynine shows a low abuse potential when compared with 7-hydroxymitragynine or substances with reinforcing effects (traditional opioids or methamphetamine).[1,4–6]

These pharmacologic effects are temporally related to kratom adverse events.[5,6] According to US poison control centers, from 2011 to 2017 there were 1807 reports of kratom exposure and 10.2% were for children younger than 20 years.[7] Forty-eight children were younger than 13 years (42 used kratom only) and 137 children were 13 to 19 years of age (80 used kratom only). Overall, 14.3%, 21.3%, and 27.0% of people younger than 13 years, 13 to 19 years of age, and ≥20 years of age were admitted to a health care facility after kratom monotherapy, respectively. Figure 1 displays the level of care that these people received once admitted. Kratom-only exposures (Figure 1A) were less severe than multiple substance exposures (Figure 1B). The percentage of people in different age groups reporting adverse events after kratom monotherapy is presented in the Table.[7] The kratom adverse event profile includes opioid-related issues such as confusion, drowsiness, vomiting, and nausea.[1,5,7] Respiratory depression, a serious risk with regular opioids, was only rarely noted.[5,7] Other adverse events were related to kratom's stimulant (serotonin and adrenergic) effects including agitation, seizures, tremor, tachycardia, hypertension, chest pain, and tachypnea.[1,5,7] The cardiac rhythm disturbances could be due to kratom's stimulant effects or its IKr potassium channel–blocking properties.[5,7] Like loperamide and methadone, the IKr potassium channel–blocking effects can prolong the QTc interval.[5,8] The reasons for hepatic injury are not well understood but could be due to heavy metal or microbial contamination of the products.[5]

The Global Kratom Coalition presented data on adults from US poison control centers for select

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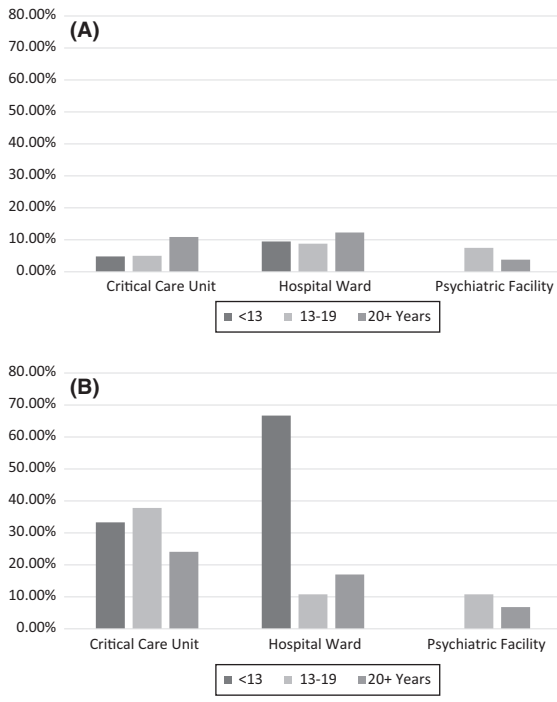
Figure 1. Treatment level required for adverse events in people calling poison control centers according to age.



Each bar corresponds to an age category of people who used kratom and were linked to a poison control center call. Data shown are (A) after single use exposure and (B) after multi-use exposure. Data obtained from Post et al.[7]

Table. Adverse Events Reported to Poison Control Centers According to Age After Kratom-Only Substance Exposure*

	<13 yr	13–19 yr	≥20 yr
Neurological			
Seizures	0.0%	11.3%	9.9%
Hallucinations	0.0%	5.0%	5.5%
Agitation	9.5%	16.3%	23.9%
Confusion	2.4%	13.8%	10.9%
Drowsiness	9.5%	18.8%	14.3%
Cardiovascular			
Syncope	0.0%	7.5%	1.6%
Rhythm abnormality	0.0%	1.3%	3.1%
Chest pain	0.0%	1.3%	2.9%
Tachycardia	2.4%	20.0%	22.5%
Hypertension	0.0%	8.8%	10.8%
Gastrointestinal			
Vomiting	9.5%	20.0%	12.9%
Nausea	0.0%	18.8%	14.7%
Hepatic			
AST or ALT >100 u/L	0.0%	2.5%	5.5%
Bilirubin increased	0.0%	1.3%	2.8%
Respiratory			
Tachypnea	2.4%	1.3%	1.8%
Respiratory Depression	0.0%	1.3%	3.9%

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase

* Age categories reflect the age of people using kratom who were associated with a call to a poison control center. Data obtained from Post et al.[7]

substances from 2017 to 2022.[9] Antidepressants and benzodiazepines had 140 to 310 calls per 100,000 users a year; traditional opioids had 40 to 60 calls per 100,000 users a year; tobacco and cannabis products had 15 to 35 calls per 100,000 users a year; and kratom, kava, and energy drinks had fewer than 10 calls per 100,000 users a year. Traditional opioids were associated with 1790 deaths over these years as compared with 262 antidepressant deaths, 83 benzodiazepine deaths, 23 cannabis deaths, 18 kratom deaths, 15 tobacco deaths, 3 energy drink deaths, and zero kava deaths.[9]

The Global Kratom Coalition also presented data on the comparative percentage of adults taking a substance who met criteria for a substance use disorder (SUD).[9] Heroin (86%), methamphetamine (68%), and cannabis (59%) users were more likely to have a use disorder than kratom (29%) and cocaine (27%) users. In the subset of patients with an SUD, cannabis had the highest percentage of people with a mild SUD (55%) followed by kratom (47%), cocaine (39%), methamphetamine (30%), and heroin (20%). Importantly, 24% and 29% of people reported a moderate or severe kratom use disorder, respectively.[9] Additionally, kratom withdrawal was demonstrated in a case series of 6 neonates who experienced symptoms 24 hours after birth.[10] The neonates experienced jitteriness, irritability, excessive sneezing and sucking, vomiting, reduced oral intake, and excessive crying. They were treated with morphine or buprenorphine therapy, tapered off over time to manage their symptoms.[10]

Most of the kratom products are derived from pulverizing dried kratom leaves for teas, capsules, or tablets.[11] More recently, products have appeared on the market that contain high doses of synthetic 7-hydroxymitragynine (500% higher doses than can be obtained naturally), which based on the known pharmacologic effects, could be much more like traditional opioids in its euphoric effects and risk profile.[1,5,12]

Heavy Metals and Microbial Contamination of Kratom Products

In a systematic assessment of laboratory studies, Caroti et al[11] noted many of the 68 assessed kratom products studied were found to contain excessive amounts of heavy metals. Excessive heavy metals can impair brain, liver, kidney, and bone functioning in adults and in children.[11] The interim reference level (IRL), defined as the total amount of lead that could be

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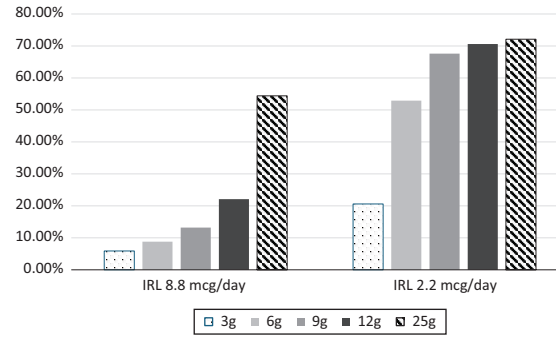
consumed through all food, drugs, and supplements consumed daily, is 12.5 mcg/day in adults, 8.8 mcg/day in women of childbearing potential (WCBP), and 2.2 mcg/day in children.[13] The lower IRL values for lead reflect the risk of damaging children's cognitive function.[13] Using an adult IRL of 12.5 mcg, 1.5% and 33.8% of kratom products had excessive lead amounts at 3-g and 25-g daily doses. In Figure 2, we used our source data from our original publication to calculate the percentage of products that would exceed the IRL for WCBP and children.[11] For WCBP, 5.9% and 54.4% of kratom products would exceed the IRL at 3-g and 25-g doses, while for children, 20.6% and 72.1% of kratom products would exceed the IRL at these doses. Other heavy metals were also noted in excessive amounts. When assessing the permissible daily exposure levels—the maximum amount that the FDA specifies a drug or dietary supplement can provide each day—0% and 20.6% of products had excessive nickel (200 mcg/day) and 3.1% and 9.4% had excessive arsenic (15 mcg/day) at doses of 3 g and 25 g, respectively.[11] It is difficult for consumers to know which products have acceptable concentrations of heavy metals because there is no requirement for testing, testing frequency, or the quality of the testing. Some companies provide certificates of analysis on their website, specifying what the laboratory testing allegedly found, but sometimes these data reflect a snapshot in time evaluation where greater care is taken to achieve a passing result or the product being tested is not actually the one being sold to consumers. Kratom products, like other minimally processed botanical products, can be contaminated with microbes.[14] In one particular outbreak from January 11, 2017, to May 8, 2018, a total of 199 cases of *Salmonella* poisoning were detected from 41 states and 54 patients were hospitalized.[15] Multiple serotypes of *Salmonella* were detected in products and several companies issued recalls as a result.[15] It is important to note that some products had high heavy metal amounts, whereas others had virtually none; and while several kratom products had microbial contamination, others did not, suggesting good manufacturing practices and proper quality control could eliminate this issue.[11,14,15] While consumers could look at posted microbiologic testing on a product's website, it is unclear whether these results reflect the quality of the product at the time of consumer purchasing or whether the results were manipulated (such as running and re-running tests until passing results are found).

Why People (Including Children) Use Kratom

In a survey of 8049 people regardless of age, kratom was used to self-treat opioid withdrawal; as an opioid substitute therapy; or to treat pain, anxiety, depression, and tiredness or lethargy.[1,5] Specifically in children, kratom has been termed *a smart drug*—a stimulant students use to pull "all-nighters" or to enhance their

Figure 2. Percentage of kratom products exceeding the lead IRL for women of childbearing potential (8.8 mcg/day) and children (2.2 mcg/day).



IRL, interim reference level.

The dose categories are the daily dose of kratom consumed. Data obtained from Caroti et al[11] and reanalyzed with pediatric- and women of childbearing potential–specific IRLs.

academic focus.[5] It has been used by athletes to deaden pain and increase stamina. Importantly, there are no placebo or active controlled clinical trials demonstrating relief of any disease or disorder with kratom.[1,5]

The best trial to date assessing kratom for pain management is the randomized, placebo-controlled, double-blind study by Vicknasingam et al.[15] These authors assessed the cold pressor pain response (measured as the time between pain onset and hand withdrawal from an ice bath). Participants (26 males, 24.3 ± 3.4 years, 6.1 ± 3.2 years of chronic kratom exposure) kept their arm in an ice bath for a mean of 11.2 ± 6.7 seconds before using kratom and 24.9 ± 39.4 seconds 1 hour after using kratom ($p = 0.02$), while participants' retention time lasted 15.0 ± 19.0 seconds before using placebo and 12.0 ± 8.1 seconds afterwards ($p = 0.40$). While this suggests kratom can diminish acute pain, it indirectly suggests that kratom use can cause hyperalgesia. The baseline arm retention time in both groups is lower than in other studies with non-opioid users.[1,15] Previous studies show non-opioid users can retain their arms in an ice bath for considerably longer periods than opioid users, but after opioid detoxification the arm retention in the ice bath increases back toward normal.[1]

Unfortunately, some manufacturers are now creating kratom products that focus solely on delivering high doses of 7-hydroxymitragynine. Preclinical studies and anecdotal experiences suggest these products provide a euphoric effect reminiscent of morphine, which is being used increasingly as a recreational product.[16–18] Some products are using dosage forms and packaging that would be attractive to children seeking a recreational product, such as "OHMZ Conez" in which

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the dosage form looks like a waffle cone and the "ice cream" portion is strawberry flavored.[19]

Protecting Children From Kratom

Making kratom a Schedule I substance will deter children from accessing the products legally in the United States, but will it reduce use? Other substances that are illegal, such as synthetic cannabinoids and synthetic cathinones, are still used by children.[2] According to the National Survey on Drug Use and Health, synthetic cannabinoids are used by 159,000 children 12 to 17 years and 788,000 adults 18 to 25 years of age, while synthetic cathinones are used by 52,000 children 12 to 17 years and 73,000 adults 18 to 25 years of age.[2] When substances are illegal there is no leverage that regulators have over manufacturers to enhance manufacturing quality to protect children from accessing the products.[20] This was underscored by the detection of the rat poison brodifacoum in synthetic cannabinoid products whereby more than 150 people in Illinois started bleeding uncontrollably between March and April 2018. By July 2021, these same adulterated products were still being sold in 10 states and the District of Columbia, resulting in hundreds of additional severe bleeds and several deaths.[21]

Regardless of the lack of trials substantiating the benefit of kratom vs methadone or buprenorphine, there are only 2 opioid-related substances legally accessible without a prescription: kratom and megadose loperamide.[5,8] The loss of kratom could push people back to using illicit opioids with all the associated risks.[20] The outpouring of constituent support to maintain kratom's legality to manage opioid use disorder compelled many congress people to ask the DEA not to make kratom a Schedule I substance.[5] If kratom were assigned as a Schedule II or III substance, it would be banned for non-prescription use, real clinical trials would be needed to substantiate the benefits and risks, and there would eventually be control over the patient use by prescribers and pharmacists. There are distinct benefits to this approach. However, there would be no legal access while the trials were being conducted (if they are ever conducted) and prescription status would decrease access and impair affordability. In the interim, there would undoubtedly be a market for illicit kratom, with enhanced risks of poor-quality manufacturing and intentional adulteration with substances like fentanyl. Consumers could also revert back to using illicit opioids like heroin with increases in risky behaviors such as intravenous injection. This is a tradeoff that public health officials need to consider as they attempt to tease out the net benefit vs the net risk to society.

Some states are entertaining legislation to maintain kratom's legality but to enhance transparency and safety in the marketplace.[22] California has proposed legislation requiring manufacturers to properly label products, specify suggested doses, alert consumers about addiction products and risks to fetuses, and prevent sales to minors. Manufacturers would register their products in California and test their products for heavy metal and microbial contamination. The state can buy products off the store shelves and test them at the manufacturer's expense with substandard products barred from sale. This is a positive step consistent with how many states currently deal with tobacco, alcohol, and cannabis products.[22] However, it would still not tackle the creation of products with product names, color schemes, dosage forms, and flavorings or scents that appeal to children.[19]

Children and their parents should be warned by pharmacists that while kratom is legal, it has no proof of effectiveness for any reason in clinical trials.[5] Kratom is a risky pain reliever because it may work in the short term but lead to more pain over time.[1] Kratom can be addictive, and you may not be able to stop it if you wanted to.[5] 7-Hydroxymitragynine products can be used recreationally and may be as addictive as morphine.[16–18] Kratom use can also lead to child harm including seizures, hallucinations, agitation, arrhythmias, liver damage, and vomiting.[7] While the opioid receptor–stimulating harms can be ameliorated with naloxone, others including Torsade de Pointes and seizures, cannot.[1,5]

I fully support national regulations, or state regulations, that reduce many of the vulnerabilities that consumers face when using kratom products: registration of products, age restrictions, clear labeling, product warnings, proof-of-quality manufacturing, avoiding high-dose isolate products with an unknown safety profile, and control over the advertising and the look, smell, and taste of the product to ensure they are not appealing to children.

Article Information

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