

Kratom: An Opioid-like Herbal Supplement Pediatricians Should Know About

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Abstract

Kratom is a legal, widely-available herbal supplement with opioid-like properties increasingly used by those with opioid dependence to self-treat opioid withdrawal. Kratom binds to opioid receptors and can induce withdrawal, dependence, and toxicity. Classification of Kratom as an opioid is controversial. The search for non-opioid alternatives for the treatment of opioid dependence has intensified in the current opioid epidemic. Kratom is heavily advertised as one such safe non-opiate alternative and has been used by pregnant women with chronic opioid use resulting in neonatal abstinence syndrome. Kratom cannot be detected on routine toxicology screening. As kratom use becomes more widespread, pediatric populations will likely be impacted and pediatricians should familiarize themselves with its pharmacology and adverse effects to appropriately counsel parents and care for kratom-exposed patients. This article reviews kratom's pharmacology, uses, potential benefits as a therapeutic, and risks for pediatric patients.

Background

Opioid use and enrollment in opioid treatment programs among pregnant women in the United States has spiked, resulting in more infants affected by neonatal abstinence syndrome (NAS)¹⁻³. NAS is the condition of neonatal withdrawal secondary to chronic in utero substance exposure. It is most frequently attributed to prescription and nonprescription maternal opioid use. Long-acting opioids, most commonly Methadone and Buprenorphine, are used to treat opioid addiction in pregnant women and can also cause neonates to withdrawal after birth⁴. A non-opioid treatment for opioid dependence would have perceived benefits for both mother and baby. The current epidemic has put increased pressure on the search for such alternatives. Kratom, an over-the-counter herbal supplement available as a tea, capsule or powder, is increasingly advertised on the internet as a safe, non-opiate alternative treatment for opioid dependence^{5,6}. Prevalence of kratom use in the United States is unknown but in 2016 revenue from sales of kratom exceeded \$1.13 billion from an estimated 10,000 kratom vendors operating across the US⁷. As kratom use becomes more widespread, pediatricians will likely encounter patients impacted by kratom. It cannot be detected by routine toxicology screening forcing medical providers to rely on history-taking to suspect its use. Therefore, pediatricians need to familiarize themselves with kratom's pharmacology and potential adverse effects to help guide their management of kratom-exposed patients.

Pharmacology

Kratom leaves are indigenous to Southeast Asia where they

have long been used recreationally and medicinally. At low doses kratom produces a stimulant effect and is used by some to increase productivity. At higher doses kratom induces analgesia and was historically used to treat opium withdrawal⁸⁻¹¹. More recently, kratom has been used increasingly by those with opioid dependence to alleviate opioid withdrawal^{5, 6, 12}. The pharmacological activities of kratom are primarily due to the indole alkaloids, mitragynine and 7-hydroxymitragynine¹³. These components act as partial agonists at μ -opioid receptors and competitive antagonists at κ -opioid and δ -opioid receptors¹⁴⁻¹⁸. Mitragynine and 7-hydroxymitragynine demonstrate biased-agonism at μ -opioid receptors, activating G-protein receptors without engaging β -arrestin, a signaling molecule linked to noxious opioid side effects such as constipation and respiratory depression¹⁴. Mitragynine is less potent than morphine while 7-hydroxymitragynine has a higher potency than morphine with less gastrointestinal effects. Although 7-hydroxymitragynine is structurally different than morphine, chronic exposure at μ -opioid receptors can result in dependence, tachyphylaxis, and cross-tolerance to morphine¹⁹⁻²¹. Ingestion of kratom primarily impacts the cardiovascular, central nervous, and gastrointestinal systems and has been associated with tachycardia, hypertension, central nervous system depression, altered mental status, abdominal pain, nausea, and cholestasis^{22, 23}. Unlike traditional opioids, kratom does not seem to be associated with respiratory depression which may be explained by its biased agonism at μ -opioid receptors, δ -opioid antagonism and its action at non-opioid receptors including α -2 adrenergic, serotonin and dopamine receptors^{5,11,14,17,18,24}.

Potential Benefits of Kratom

Interest in kratom, particularly for self-treatment of opioid withdrawal has dramatically increased over the past decade. Those with histories of substance use disorders extol kratom's assistance in overcoming opioid dependence, alleviation of opioid withdrawal, mitigation of chronic pain, lower costs, legality, absence of detection on drug tests, and ease of availability as compared to prescription and illicit opioids^{5,6}. Kratom users perceive less severe withdrawal than with typical opioids²⁵. Kratom's multifactorial pharmacological action at both opioid receptors and non-opioid receptors (α -2 adrenergic, serotonin and dopamine receptors) producing opioid-like analgesia without opioid-associated adverse effects make it an attractive choice as a potential therapeutic for opioid dependence^{5,11,17,18,24}. Kratom's lack of respiratory depression is a substantial benefit over traditional opioids used in treatment programs such as methadone or suboxone. Many chronic users cite their ability to function despite developing dependence and some deny experiencing withdrawal symptoms from kratom⁹. All these characteristics make kratom an attractive

choice for those looking for an alternative treatment for opioid dependence perceived to be safer than traditional agents. The ability to self-treat without the intrusion of physician involvement, frequent appointments, drug testing, and counseling may be tempting to those with guilt or denial of their addiction. Opioid-dependent pregnant women's guilt is compounded by fear for their newborn's health, judgement from friends, family, medical providers and potential involvement of social services. Finding obstetricians comfortable managing women in treatment programs can be challenging²⁶. At a time when opioid use among pregnant women is increasing¹, an herbal, over-the-counter, safe "non-opiate" alternative would seem promising to this population.

Kratom Dependence, Withdrawal, Toxicity

Concerns regarding kratom's safety have been increasing. Regular users can develop dependence^{10, 27, 28}. Animal models have demonstrated high abuse potential for 7-hydroxymitragynine while interestingly establishing lower abuse potential for mitragynine^{29,30}. Although internet-based surveys of kratom users report less severe withdrawal from kratom compared to traditional opioids⁵, there is sufficient evidence to support a dose-dependent abstinence syndrome similar to opioid withdrawal: anxiety, depression, insomnia, abdominal pain, decreased appetite, weight loss, nausea, vomiting, sweating, fever, diarrhea, headaches, rhinorrhea, lacrimation, myalgias, sweating, and increased pain severity. Symptoms typically present 1-3 days after discontinuation^{10, 22,27,28,31,32}. Withdrawal has been treated with clonidine and opioids^{31,32}. Symptoms of kratom toxicity reported in adults include: Palpitations, tachycardia, hypertension, seizures, altered mental status, nausea, abdominal pain, syncope, myalgia, hepatotoxicity^{23,33}. Benzodiazepines have been used for treatment of toxicity²³. Other negative effects attributed to kratom include altered hormone levels in regular users^{34,35} and a recent salmonella outbreak has been linked to kratom-containing products³⁶.

Effects on Pregnant Women and Newborns

Pediatricians and neonatologists commonly engage in antenatal counseling of substance-dependent pregnant women, providing education of postnatal effects on their newborn. Kratom should be included in these discussions. Reports of kratom use among pregnant women are increasing, especially among women with histories of chronic opioid use^{22, 23, 37-41}. Pregnant women who have self-discontinued kratom have experienced symptoms of withdrawal^{37,39}. Similar to traditional opioid-dependence, these women have been managed with buprenorphine³⁷. Reports of NAS due to maternal kratom use are also increasing^{22,23,38-41}. Infants have exhibited withdrawal symptoms 1-2 days after birth^{22,23,39,41}. Mitragynine has an estimated terminal half-life of $\sim 24 \pm 16$ hours⁴².

Cases of NAS suspected to be due to kratom have been managed with morphine, clonidine, and benzodiazepines^{23,38-41}. The effectiveness of opioids and α -2 agonists may be explained by mitragynine's and 7-hydroxymitragynine's compound actions at opioid and non-opioid sites. Length of pharmacological treatment for NAS due to kratom has been reported from 5 days to 2 months^{38,39,41}. Although there are no formal studies of kratom transmission through breastmilk, The American Kratom Association (<https://www.amerikanatom.org/science>) recommends against use among pregnant or breastfeeding women. However, alleviation of withdrawal symptoms has been reported with breastfeeding³⁹. Exact dosage of kratom ingested by reported mothers of infants with NAS is mostly unknown or not mentioned, however one case reports 18-20 g of powder three times daily³⁹. The maternal frequency of kratom use in several cases is not specified, but for the most part, is cited as daily^{23,38-41}.

Other Pediatric Issues

In addition to newborn issues, pediatricians may encounter use among adolescents. Consumption of kratom cocktail or "4 x100" is increasing among youth in Asia and is named for its four components: kratom, soft drink, codeine- or diphenhydramine-containing cough syrup, and a variable ingredient- anxiolytics, antidepressants, analgesics, household products and non-prescription illicit substances have all been reported^{12,43,44}. The cocktail induces euphoria and can be fatal⁴³. There has also been a case of driving under the influence linked to kratom use⁴⁵.

Screening for Kratom

Kratom cannot be detected by routine toxicology screening. Definitive testing requires Liquid Chromatography or Tandem Mass Spectrometry, although qualitative immunologic-based tests are in development⁴⁶. Levels of mitragynine and 7-hydroxymitragynine in pregnant women using kratom have been found to be 61 and 980 ng/dl respectively using these methods³⁷. It is unclear for what duration kratom can be detected in urine, however, one case reports the detection of kratom 48 days after last use⁴⁷. Urine can be sent out for testing and may take 1-2 weeks to return³⁷, well after withdrawal symptoms are likely to occur. Without readily available testing, medical providers must heavily rely on history-taking. To provide optimal care for pediatric patients; obstetricians, neonatologists and pediatricians must remember to ask about kratom use in those with histories of opioid dependence. Despite obstacles to urine testing, some recommend screening for Kratom in all women with histories of opioid use³⁷.

Legal Debate

Classification of kratom as an opioid and the need

for regulation is debated. Its action at opioid receptors without respiratory depression and its perceived ability to assist in addiction and withdrawal for opioid-dependent users make it a strong therapeutic candidate under controlled conditions⁴⁸⁻⁵¹. However significant morbidity has been reported to warrant careful consideration of the appropriateness of its use. As kratom is not regulated, commercial products have the potential to be adulterated to increase potency or mixed with potentially dangerous contaminants such as a recent kratom-linked Salmonella outbreak^{36,52}. In February 2018 the US Food and Drug Administration released a statement classifying compounds found in kratom as opioids based on a review of scientific literature and computational modeling of kratom binding⁵³. The Drug Enforcement Administration considered federally policing kratom, however, advocates of kratom argued successfully for its benefits for opioid users. Kratom is illegal in several Asian countries as well as several US states and cities but remains legal, unregulated and widely-available in most of the United States⁴⁴. Further research is needed to fully understand kratom's risks and possible benefits, however banning kratom completely may severely limit researchers' ability to study its therapeutic potential⁴⁸.

Conclusions

Kratom use in the United States is increasing, especially among those with histories of opioid dependence to alleviate opioid withdrawal. Physicians caring for those with histories of opioid dependence will likely encounter kratom users and kratom-related morbidity. Providers need to familiarize themselves with the substance and its consequences for adult and pediatric patients- dependence, withdrawal, toxicity. Currently, physicians are limited to history-taking to make the diagnosis of kratom use as it is not detected on routine toxicology screening. Patients should disclose kratom use to their medical providers as they would other legal substances such as alcohol or tobacco and in turn, medical providers have an obligation to counsel patients on the risks of kratom use. Further research is needed to educate the general public about kratom's risks and to help guide medical providers in the optimal management of kratom-related complications.

Abbreviations: Neonatal Abstinence Syndrome (NAS)

Contributors' Statement Page

Dr. Eldridge drafted the initial manuscript and reviewed and revised the manuscript.

The author has approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

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