Clinical Update:

WHAT DID MY PATIENT ACTUALLY TAKE? AN OVERVIEW OF KRATOM ALKALOIDS IN CLINICAL PRACTICE

Background

Kratom is a psychoactive plant derived from the leaves of the *Mitragyna speciosa* tree, which is indigenous to Southeast Asia.[1] While it has been used in this area for its mild stimulatory and analgesic effects for centuries, popularity in Western countries is more recent. Kratom use in the United States has increased markedly over the last two decades.[2] According to the *Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health*, an estimated 1.6 million Americans reported using kratom in 2023.[3]

Kratom contains over 50 alkaloids with mitragynine being the most abundant and primary active alkaloid.[4] Mitragynine is categorized as an indole alkaloid, also occasionally referred to as an *atypical opioid,* as it is structurally and pharmacologically distinct from traditional opioids.[5] It exhibits a multimodal mechanism of action via complex adrenergic, serotonergic, and opioid-like effects. Effects are proposed to be dose dependent with lower doses producing stimulant-like effects and higher doses producing opioid-like effects. Possible adverse effects from use include dry mouth, vomiting, anorexia, weight loss, constipation, nystagmus, tremors, seizures, and liver injury. Common formulations of kratom sold online and in-store include powders, capsules, resin extracts, crushed leaves, and tablets, although loose powder and prepared capsules have been reported to be the most frequently used formulations.[6,7]

New Variants: 7-hydroxymitragynine and Mitragynine pseudoindoxyl

In the last year, novel kratom variants have gained popularity within the United States. Many of these products contain high concentrations of 7-hydroxymitragynine (7-OH) and/or mitragynine pseudoindoxyl (MP).[8] 7-OH can exist as a metabolite of mitragynine or as a minor constituent of the plant, but only accounts for $\leq$ 2% of alkaloid content directly from the leaf. 7-OH is further metabolized in the body to produce MP. Although these metabolites occur naturally, they are now being synthetically produced in laboratories and incorporated into products with potencies 10 to 100 times greater than traditional kratom. These variants possess greater mu-opioid receptor affinity and potency than traditional mitragynine which is thought to drive analgesia and, at sufficient concentrations, respiratory depression. Product claims include: boosting energy, improving focus and mood, providing relaxation, relief from pain or discomfort, and stress or anxiety reduction. A recent analysis of 7-OH and MP products sold online found that 93% of these products were "mislabeled" or misleadingly marketed as traditional kratom, underscoring the risk of unintentional exposure to far more potent compounds.[9]

Dangers of Use

Although most kratom-associated fatalities involve polysubstance use, single-agent deaths have also been documented. While mitragynine alone may have a limited ceiling on respiratory depression in some preclinical models, 7-OH demonstrates potent respiratory depressive effects in animal studies and has been implicated in human toxicity. The rise in prevalence of highly concentrated or adulterated products may raise the risk to those exposed.[10] Co-ingestion with other CNS depressants also substantially increases risk of harm.

Between February and April 2025, the National Poison Data System documented 53 exposure cases involving 7-OH, most of which were associated with intentional abuse. While most cases resulted in minor or moderate outcomes, several were severe. Notably, fatalities involving 7-OH and MP tripled between 2023–2025 compared with 2019–2022, coinciding with increased availability of products and highlighting concerns regarding unpredictable potency.

Management of Cessation and Withdrawal

According to available literature, symptoms of traditional kratom withdrawal generally appear within 12 to 48 hours of stopping kratom use.[11] This data cannot be directly extrapolated to new variants as pharmacokinetic data on 7-OH and MP is limited. It is theorized that the half-life of 7-OH may increase relative to the dose administered. While parent mitragynine is thought to have a half-life of around 45 hours, the half-life of 7-OH may be as short as 5 hours.

Because 7-OH and MP are theorized to have shorter half-lives, clients may experience withdrawal symptoms as soon as 6 hours after the last dose. Withdrawal symptoms generally last 1 to 3 days from traditional kratom, though in some instances, individuals experienced withdrawal symptoms for up to a week.[12] Severity of withdrawal symptoms will vary depending on the frequency of use and potency of the product, with products containing higher amounts of 7-OH and MP producing a withdrawal similar to prescription opioids. Symptoms may include craving, low energy, fatigue, irritability, anxiety, depressed mood, restless legs, difficulty sleeping, gastrointestinal distress, cold/hot flashes, goosebumps, and muscle twitches. Regular use of kratom variants can produce physical dependence and withdrawal syndrome meeting DSM-5 substance use disorder criteria for some users.[13]

Given their opioid receptor activity, management principles for synthetic kratom withdrawal parallel those used in opioid use disorder. 7-OH and MP should respond to opioid reversal agents (naloxone) in cases of overdose or respiratory depression. Buprenorphine and buprenorphine-naloxone, both of which are FDA-approved for opioid use disorder and dependence, have been used off-label for kratom withdrawal.[14,15,16] It is hypothesized that these agents can effectively treat kratom withdrawal and dependence by alleviating withdrawal symptoms and reducing cravings. Buprenorphine, a high-affinity partial mu-opioid receptor agonist, is thought to prevent kratom alkaloids mitragynine and 7-hydroxymitragynine from binding to opioid receptors. There is no current data specific to its efficacy relative to MP. Several case reports have described potential efficacy of these agents in kratom withdrawal management, including symptom relief.[17-26]

Regulatory Restrictions and Detection

The FDA has issued warnings and stated no kratom products are approved as dietary ingredients or drugs. The DEA classifies kratom as a "drug and chemical of concern" but has not placed the leaf in a federal schedule.[27] Many states have opted to regulate kratom by enforcing minimum purchase age, testing requirements, and prohibiting synthetic products while other states have banned sale of kratom products entirely.[28] Clinicians should consult current state regulations, as policies differ substantially and continue to evolve.

Standard toxicology screens do not routinely detect kratom alkaloids and as such, specialized testing (LC-MS/MS) is required to identify kratom and its variants. Aegis' updated kratom testing includes mitragynine, 7-OH, and MP in urine, enabling comprehensive detection and harm reduction. Based on available pharmacokinetic data, kratom and its variants are thought to be detectable in urine for up to 5 days after use.[29] Testing in oral fluid includes mitragynine and 7-OH, with a period of detection of 48 hours or shorter in oral fluid.

Takeaways

The emergence of high-potency kratom variants containing 7-OH and MP represents a clinically significant shift from traditional kratom use. These compounds exhibit markedly greater mu-opioid receptor affinity and potency, resulting in increased risk for respiratory depression, dependence, and withdrawal severity comparable to conventional opioids. Limited pharmacokinetic data and the frequent mislabeling of products create diagnostic and treatment challenges for clinicians and care teams. Awareness of these differences is essential for accurate risk assessment, patient education, and effective management of toxicity or withdrawal. As synthetic kratom continues to evolve, collaboration among healthcare providers, toxicologists, and public health professionals will be critical to identifying, monitoring, and mitigating associated harms.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

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