DrugTalk: Kratom, the "Old" New Kid

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Just when you thought there was enough to worry about regarding the opioid crisis, a relatively new player from the plant world enters the game. Clinicians, toxicologists, and the public at large have little to no familiarity with this plant or its effects on humans. To compound the problem, the use of this plant is increasing in popularity in the United States despite minimal information about its pharmacology and toxicology.

Kratom (pronounced KRAY-tom or KRAH-tom), or its scientific name, *Mitragyna speciosa*, is an evergreen tree native to Southeast Asia.[1–7,9] The plant has a lengthy history of medicinal use for conditions ranging from minor ailments such as diarrhea, cough, and fatigue to more serious conditions like diabetes, hypertension, and depression. Higher doses have analgesic properties that support its use for pain relief, and euphoric effects that encourage its use recreationally. Historically, in Southeast Asia, resident laborers (farmers, fishermen, and rubber-tappers) knew of the stimulant effects resulting from the consumption of kratom as a beverage and would prepare a brewed tea containing kratom leaves to combat fatigue and maintain or increase productivity.

Today, there is a wide variety of kratom preparations available to the consumer via the internet, herbal stores, and head/vaping shops. Kratom's use and availability is controlled to some degree in many parts of the world, and it has been identified as a novel psychoactive substance (NPS) with the potential for abuse. It is being marketed as an alternative medicine or supplement for boosting energy, enhancing mood, sedation, and as a "legal opioid" for relieving pain and treating opioid withdrawal symptoms. Street names of kratom include Biak, Kakuam, Ketum, Ithang, and Thom.[4,7,9] Typically, products derived from kratom consist of chopped leaves that can be chewed, smoked, or brewed for tea. Kratom can also be ingested by mixing the powder form with food (e.g., yogurt, cookies, beverages, etc.) to reduce bitterness. Small capsules, pellets, and paper 'bombs' filled with kratom powder are also available for oral ingestion. Liquid products from kratom extracts (tinctures) have been used in vaporizers as well as via intravenous injection, a practice strongly discouraged by health professionals.[2–7,9]

Kratom leaves contain over 25 alkaloid compounds and unknown quantities of other substances.[1,3,5,9] An in-depth review of its pharmacological and toxicological properties is beyond the scope of this publication. Briefly, however, kratom's pharmacological effects are believed to be the result of the actions of two primary psychoactive components, mitragynine (MG) and 7-hydroxymitragynine (7-OHMG). Research has shown that both of these compounds affect opioid and nonopioid receptors in the brain. The effects of kratom are dose-dependent (i.e., they increase with increasing dose).[1,2,4,5,9] 7-OHMG is the stronger central nervous system agonist with 46 times the potency of MG and 13 times the potency of morphine in producing opioid-like effects.[2,4]

MG is primarily metabolized in humans by the cytochrome P450 family of enzymes in the liver. Specifically, the CYP3A4, CYP2D6, CYP1A2, and CYP2C9 enzyme isoforms appear to be involved.[1,4,9] MG is converted to 7-OHMG via this metabolic process, thus leading to the hypothesis that the significantly more potent metabolite is responsible for kratom's psychoactive effects. In addition, these enzyme isoforms are heavily involved in the metabolism of multiple drugs. The question of serious drug-drug interactions with concurrently used medications, resulting in potentially toxic effects, must be considered. Following oral consumption, half-lives of 3.5 and 2.5 h for MG and 7-OHMG, respectively, have been reported. Not all studies have been consistent, however, as some have reported a

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much longer half-life of 23 h. Both substances are eliminated primarily in the urine.[2,4,5,8,9]

As kratom use increases, reports of adverse effects are emerging. Reports have included nausea, vomiting, seizures, and death. Toxicity of the liver, thyroid, and respiratory system have also been reported.[2,4] Between 2011 and 2017, there was a 58-fold increase in calls to U.S. Poison Control Centers for adverse events from kratom.[4] In 2018 and 2019, warnings were issued by the U.S. Food and Drug Administration (FDA) regarding impurities, including heavy metals, in kratom products and a reported 44 fatalities associated with kratom use.[1] Controlled studies are lacking to formally evaluate its efficacy and safety.

Of particular concern to aviators and Federal Aviation Administration (FAA) policy-makers are increasing reports of kratom abuse and the potential for pilot performance impairment that would be detrimental to aviation safety. Both stimulant effects at low doses (1–5 g) and opioid-like effects at higher doses (5–15 g) suggest a potential for kratom to have serious deleterious effects on safety sensitive tasks. It has also been reported that subjects given higher doses (over 15 g) demonstrated central nervous system depression with increased sedative effects suggestive of intoxication and impairment.[2,5,9] These individuals were also shown to be less sensitive to emotional or physical pain. They appeared calm, with a general feeling of euphoria, including reports of a dreamlike mental state. Additional side effects may mimic opioid-like effects such as stupor, dizziness, sweating, nausea, and dysphoria. Chronic users have had instances of seizures, tremors, psychosis, anorexia, and weight loss. Case reports show that individuals chronically using kratom develop tolerance to the drug, cross-tolerance to both kratom and opioids, and display physical dependence, addiction, and drug withdrawal symptoms.[1,2,9] These dose-dependent side effects may dramatically impair psychomotor performance in individuals executing specialized tasks that require sustained awareness such as operating an aircraft, driving a vehicle, or executing critical safety functions.

In conclusion, as more has been learned about kratom from the limited studies done, it is clear this herbal pharmaceutical has a complex pharmacological profile. A comprehensive portfolio of chemical properties and physiological effects, including potential uses and safety issues, has not been elucidated by well-controlled scientific investigational studies. As a result, the use of kratom should be of significant concern to aviators. The effects of kratom include dose dependent sedation (drowsiness) and cognitive impairment, particularly from chronic use, which may seriously degrade psychomotor performance. Users should exercise extreme caution before getting into the cockpit of an airplane. Finally, aviators, and consumers in general, are to be cautioned that kratom-containing products are not regulated and may contain unknown quantities of the primary active alkaloids MG and 7-OHMG, not to mention the other alkaloids, heavy metals, and other impurities. There are significant risks with this "old" new kid that warrant further scientific research and user restraint.

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