

Case Report

Is Kratom the New 'Legal High' on the Block?: The Case of an Emerging Opioid Receptor Agonist with Substance Abuse Potential

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Kratom is an unscheduled herbal extract that contains alkaloids with opioid receptor agonist activity. It is currently available in the form of dietary supplements and is used and abused by chronic pain patients on prescription opioids. Active alkaloids isolated from Kratom such as mitragynine and 7-hydroxymitragynine are thought to act on mu and delta opioid receptors as well as alpha 2 adrenergic and 5-HT2A receptors. Animal studies suggest that Kratom may be more potent than morphine. Consequently, Kratom consumption produces analgesic and euphoric feelings among users. Some chronic pain patients on opioids take Kratom to counteract the effects of opioid withdrawal. Although the Food and Drug Administration has banned its use as a dietary supplement, Kratom continues to be widely available and easily accessible on the internet at much lower prices than other opioid replacement therapies like buprenorphine. There are no Federal regulations monitoring the sale and distribution of this substance. Consumption of Kratom has been associated with hallucination, delusion, depression, myalgia, chill, nausea/vomiting, respiratory depression, hepatotoxicity, seizure, coma and death. A search of the pain literature shows past research has not described the use and potential deleterious effects of this extract. Many pain physicians are not familiar with Kratom. As providers who take care of high-risk chronic pain patients using prescribed opioids, knowledge of all current substances with opioid receptor agonists with abuse potential is of paramount importance. The goal of this article is to introduce Kratom to pain specialists and identify issues for further studies that will be required to help better understand the clinical and long-term effects of Kratom use among chronic pain patients.

Key words: Opioid receptor agonist, Kratom, Mitragynine, opioid overdose, chronic pain, substance abuse :

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Amidst growing concerns of an opioid-abuse epidemic in the United States (1), practicing pain physicians can now add a newcomer to their list of opioid receptor agonists with adverse effect profiles and substance abuse potential (2,3). Kratom, also known as *Mitragyna speciosa*, is extracted from the leaves of an evergreen deciduous tree native to Southeast-Asia and was originally described in 1839 by botanist Pieter Willem Korthals (3-5). For centuries, Kratom leaves were ground up to create an herbal tea consumed by laborers and blue collar workers in some parts of Asia for enhanced work productivity (5-

7). In addition to possessing stimulant effects at low doses (1-5 grams), Kratom powder and leaf extracts were considered powerful analgesics with opioid-like effects at high doses (5-15 grams) (8). Users reported feeling 'high' after ingesting Kratom and this helped to promote its utility as a recreational substance (9). Kratom is the chief ingredient in a popular local drink in Thailand, the '4x100' concoction is made with cola soft drink, and variable ingredients including marijuana, benzodiazepines, methamphetamines, and cough syrup containing codeine (10). Due to worsening abuse and side effects it was legally banned

Table 1. Dose dependent effects of Kratom.

Kratom use	Dose	Effects
Low to moderate	1-5 grams	Mild stimulant effects that enable workers to stave off fatigue.
Moderate to high	5-15 grams	Opioid-like effects including analgesia, treatment of diarrhea, opioid-withdrawal symptoms, and euphoria.
Very high	Greater than 15 grams	Sedating effects.

in Thailand in 1946 and other parts of Asia (11). Kratom made its way to the United States in the early 2000's, where it currently remains an unscheduled substance without strict regulations (12).

Purveyors of Kratom swear by its health benefits and suggest it can be brewed into morning tea, chewed, or smoked (12,13). Chewing Kratom leaves appears to produce the most immediate effect, with feelings of euphoria occurring within 5 to 10 minutes of consumption and lasting up to 1 hour (13). From a medical perspective, there have been increasing reports of emergency room visits and hospitalizations due to Kratom withdrawal. Patients typically present with symptoms of nausea, insomnia, irritability, restlessness, mood swings, diarrhea, rhinorrhea, myalgia, and arthralgia (14-16). Those who overdose on Kratom can experience seizures, psychosis, coma, hallucination, paranoia, severe emesis, respiratory depression and in the worst scenarios, death (13,16). Prolonged use of Kratom can result in drug cravings and eventual addiction, with resulting weight loss, anorexia, loss of libido, and hyper-pigmentation over the face and cheeks. These effects appear to be dose dependent, although toxicity levels are yet to be determined (13-16).

Kratom has high abuse liability and patients who are on prescription opioids are at the highest risk for co-dependence (16). Ease of availability and access to Kratom via online stores and websites have led to a surge in demand for this product (15). Together, these observations ought to engender a note of caution among all pain physicians prescribing opioid analgesics for their patients. Many opioid abusers now turn to Kratom to ameliorate opioid withdrawal for two reasons: 1) Procurement is as easy as a mouse click away and needs no prescription, and 2) It is a less expensive than other opioid replacement therapies such as buprenorphine (13).

While many pain physicians comply with the imperative to appropriately screen patients for opioid abuse and high-risk behaviors, it is equally important for them

to continue to discuss and address dangers of using untested and unregulated herbal remedies and supplements (15). Kratom is available as a dietary supplement and it would be instructive when reviewing patients' medication lists to inquire about non-prescribed supplements (15-16). Pain experts would do well to expand the traditional focus beyond illicit drugs to query the use of other legal but unendorsed substances such as Kratom, which is not yet criminalized in the United States (11,13). Due to its titular benefit as a stimulant at low doses and its incipient rise on the drug market, there are no formalized systems for monitoring Kratom sale and distribution (13). Public use lags any regulatory policies by the Drug Enforcement Agency (DEA) or Food and Drug Administration (FDA). The DEA, stated in 2013, "There is no legitimate medical use for kratom in the United States." In 2014, the FDA abolished its inclusion in dietary supplements (17,18). In the fall of 2016, the DEA has announced plans to add the psychoactive compounds in kratom to the list of schedule I drugs banned under the Controlled Substances Act. This act was subsequently placed on hold as the DEA is waiting for input from the FDA (19-20). Although there are no tests currently available to detect Kratom itself, its metabolites may be detected by specialized spectrometry tests (11). Due to increasing popularity of Kratom, some drug testing systems offer detection of these metabolites yet these are not universally available (21).

Over 25 alkaloids have been identified in Kratom extract, possessing antinociceptive, anti-inflammatory, anti-depressant, and muscle relaxant properties (22). Although they have activity at the opioid receptors, the active ingredients in Kratom are not opioid compounds. Mitragynine, the primary active alkaloid isolated from Kratom, has been identified as a partial opioid receptor agonist with similar effects to morphine (13,17). In addition, 7-hydroxymitragynine, a minor alkaloid of Kratom is considered to be more potent than morphine although dose levels producing analgesia remains undefined (9,13,17). Mechanistically, these alkaloids are thought to activate supraspinal mu and delta opioid receptors (9,11,13). This explains the analgesia and euphoria derived from Kratom and why abusers use it to counteract the effects of opioid withdrawal, and successful self-medication to treat opioid addiction (11,16-17). Animal studies suggest that mitragynine may be involved in noradrenergic and serotonergic pathways and stimulate post-synaptic alpha 2 adrenergic receptors, but inhibit 5-HT_{2A} receptors (8,13).

Safety profile has not been ascertained and the jury

is still out in regards to its analgesic and opioid antidote efficacy (8-10,16-18). In the context of Kratom overdose, animal studies have yielded conflicting findings regarding which opioid antagonists can reverse the effects of Kratom (8,23). Naloxone, which has proven effective in various community opioid overdose treatment programs and which is now the mandated intervention by national guidelines, appears to be prime candidate for consideration (13). Mortality from Kratom is on the rise and although the exact numbers remain uncertain, one thing is clear: pain physicians are well advised to be cognizant of the perils of this new 'legal high' (12,13,16,24).

It is often said that ignorance is bliss, but in as much as pain prescribers remain ignorant of Kratom, opioid overdose treatment outcomes may be less than blissful if Kratom abuse continues unabated. Given the dearth of studies in the pain literature, the authors hope this article sheds light on this important but under-recog-

Table 2. *Pharmacokinetics of Kratom.*

Pharmacokinetics	Time
Time to reach maximum plasma concentration	0.83 ± 0.35 hour
Terminal half-life	23.24 ± 16.07 hours
Volume of distribution	38.04 ± 24.32 L/kg

nized consumption of under-regulated substances like Kratom. As pain specialists continue to seek ways to help curb the opioid overdose epidemic through various programs (1,25), further studies on the clinical and long-term effects of Kratom are required. Indeed, time and research may demonstrate that the active substances in Kratom may be harnessed to treat pain, or opioid addiction. Pain management specialists should be apprised of the ongoing medical and legal developments regarding this controversial substance.

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