A Systematic Review with Case Series Kratom Withdrawal: A Systematic Review with Case Series

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Kratom Withdrawal: A Systematic Review with Case Series

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ABSTRACT
Recent years have seen a widespread increase in kratom use, not just for the purpose of easing opioid withdrawal, but also for management of emotional and mental health concerns by individuals without histories of opioid use. Chronic use can lead to dependence, tolerance, and withdrawal on cessation, and clinicians are seeing an increasing number of presentations involving the latter. Although there is literature discussing the use of kratom to assist in opioid withdrawal, this article comprehensively examines independent withdrawal from kratom. We systematically review existing evidence and provide our own clinical cases. Clinicians need to be aware of the withdrawal symptomatology and implement a similar approach as for opioid withdrawal with long-term maintenance to prevent relapse.

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KEYWORDS
7-hydroxymitragynine; kratom; Mitragyna speciosa; mitragynine

Introduction

Mitragyna speciosa or “kratom” is a deciduous tree part of the Rubicaceae (coffee) family found in the southeastern regions of Asia. Historically, leaves were chewed or brewed as a tea by heavy laborers to help them cope with the demands of hard labor. When ingested in small amounts, stimulant properties emerge, such as increased alertness and stamina. In larger doses, it confers opioid-like sedative effects—sedation, euphoria, and a “dream-like” state. With years of regular use, weight loss, insomnia, skin hyperpigmentation, constipation, frequent urination, delusions, hallucinations, and extreme fatigue can emerge. Severe side-effects include respiratory depression, hepatotoxicity, seizures, coma, and death.

To date, over 40 compounds have been isolated from the leaves and the major alkaloid found within the crude extract, mitragynine, has been evaluated in several pharmacological studies and deemed to have opioid-like actions (Adkins, Boyer, and McCurdy 2011). In recent years, the Western markets have seen an increased introduction of these compounds in various preparations, leaving regulatory agencies with uncertain regulations. M. speciosa kratom has had the most interest in use as an opium substitute to combat opioid withdrawal symptoms. Other species are used to combat pain and general mood disorders (Brown, Lund, and Murch 2017). Users are mainly 31–50 years of age, in middle socioeconomic classes, who seek relief from pain and emotional and mental conditions (Grundmann 2017).

Currently, kratom is readily available for purchase in a leaf, tablet, or extract/powder form as a “dietary supplement” in health stores or through the World Wide Web, or even sold in local head shops as “incense.” It can also include formulations such as topical creams, balms, or tinctures. Although the Drug Enforcement Agency (DEA) does not control it as a scheduled substance and there are no federal regulations monitoring the sale and distribution, the Food and Drug Administration (FDA) has put out several advisory warnings concerning the safety of products containing kratom. While it is not scheduled by the DEA, it is on their list of substances of concern, and it was close to being scheduled one year ago. Several states have also classified it as a Schedule 1 narcotic by the State Controlled Substances Board. Epidemiological studies have seen an increased number of individuals presenting with various symptoms emerging upon abrupt cessation of consumption. It is reminiscent of the standard presentation noted with opioid withdrawal. This is
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patient</th>
<th>Duration of use</th>
<th>Amount used</th>
<th>Concurrent drug use/Experience with opioids</th>
<th>Onset of withdrawal</th>
<th>Setting</th>
<th>Detox protocol</th>
<th>Detox duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galbis-Reig (2016)</td>
<td>37 yo F</td>
<td>2 years total, noticed withdrawal after 6 months of use when attempting to stop</td>
<td>unknown</td>
<td>no/no</td>
<td>~12 hr after last use</td>
<td>inpatient; she failed 1.5 y of outpatient attempts at detox</td>
<td>symptom-triggered clonidine therapy and scheduled hydroxyzine</td>
<td>4 days</td>
<td>started on effexor for anxiety at discharge</td>
</tr>
<tr>
<td>McWhitter and Morris (2010)</td>
<td>44 yo M</td>
<td>3 years of everyday use</td>
<td>40 g total daily dose in 4 divided doses</td>
<td>no/no</td>
<td>12 hr after last use</td>
<td>inpatient</td>
<td>dihydrocodeine 60 mg 4 times daily and lofexidine 0.2 mg twice daily, titrated against the severity of his withdrawal symptoms</td>
<td>4 days</td>
<td>started on naltrexone 50 mg 7 days after discharge for relapse prevention</td>
</tr>
<tr>
<td>Stanciu et al., current report</td>
<td>26 yo F</td>
<td>1.5 years of everyday use</td>
<td>10 g in the morning, 20–30 g in the evening</td>
<td>no/no</td>
<td>12 hr after last use</td>
<td>inpatient</td>
<td>symptom triggered clonidine 0.1 mg every 2 hours as needed and on scheduled gabapentin 300 mg three times daily</td>
<td>4 days</td>
<td>individual with underlying anxiety</td>
</tr>
<tr>
<td>Stanciu et al., current report</td>
<td>27 yo M</td>
<td>3 years of everyday use</td>
<td>5 g daily yes/yes</td>
<td>16 hr after last use</td>
<td>inpatient</td>
<td>symptom triggered clonidine 0.1 mg three times daily as needed and scheduled neurontin 100 mg three times daily</td>
<td>5 days</td>
<td>individual with underlying psychotic condition; detoxification complicated by benzodiazepine detoxification (diazepam taper)</td>
<td></td>
</tr>
<tr>
<td>Mackay and Abrahams (2018)</td>
<td>29 yo F and infant delivered at 37 w and 5 days</td>
<td>2+ years of everyday use with several failed attempts after 2 continuous years</td>
<td>18–20 g three times daily no/yes, past history</td>
<td>4–6 hr after last use</td>
<td>inpatient for the patient; she failed several outpatient detox attempts; baby was transitioned to NICU</td>
<td>morphine taper with decreasing doses of kratom for the patient; infant initially placed on IV morphine, was stepped down to PO and off all postpartum day 7</td>
<td>4 weeks for the patient, 5 days for the infant</td>
<td>infant experienced feeding intolerance, jitteriness, irritability, and vomiting postpartum day 2, requiring NICU</td>
<td></td>
</tr>
</tbody>
</table>
a new area, and since the exact mechanism of action is not fully understood, many physicians are unfamiliar with the withdrawal phenomenon and best practices when it comes to management.

**Methodology**

A Medline literature search (1975–2018) was conducted with keywords “Kratom AND Withdrawal,” “Kratom AND Cessation,” “Kratom AND COWS,” “Kratom AND Detox*,” “Mitragyna AND Withdrawal,” “Mitragyna AND Cessation,” “Mitragyna AND COWS,” “Mitragyna AND Detox*.” Results were supplemented by references gleaned from recent reports and credible online sources (Figure 1). Following a review of the initial returns, the authors judged each entity based on title and abstract. As part of the inclusion criteria, primary focus was on English literature, 1975 and recent, preferably pertaining to withdrawal in humans. However, studies discussing animal models were also considered. Any type of publication was considered. Our main interest was in primary kratom withdrawal, as there is abundant literature on kratom use to taper off opioids. A total of 23 papers met such criteria for use in the review.

**Withdrawal**

In recent years, emergency departments across the country have begun seeing more and more individuals presenting with symptoms secondary to abrupt discontinuation after long-term kratom use. These individuals, unaware of the addictive nature of the substance, experienced symptoms mimicking opioid withdrawal (Singh, Müller, and Vicknasingam 2014; Trakulsrichai et al. 2013).

According to reports filed with the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), symptoms are first noted 12–24 hours from last use and can last up to seven days (Manda et al. 2014). Symptoms can include physiological elements such as mydriasis, nausea, sweating and chills,
muscle and body aches, tremors and twitches, diarrhea, rhinorrhea, and lacrimation, as well as psychological elements such as insomnia, restlessness, irritability/hostility, fatigue, anxiety and mood disturbances, and sometimes hallucinations. Cravings for the substance also develop (Singh, Müller, and Vicknasingam 2014; Trakulsrichai et al. 2013). Withdrawal intensity has been positivity correlated to the daily amount consumed, as well as the duration and frequency of use (Saingam et al. 2016; Singh, Müller, and Vicknasingam 2014).

Pharmacology

Kratom leaves have been analyzed and over 25 indole alkaloids were found possessing antinociceptive, anti-inflammatory, antidepressant, and muscle relaxant properties (Suhaimi et al. 2016). The predominant active constituents are mitragynine and 7-hydroxymitragynine. There are well-documented agonists at the opioid receptors both in vivo and in vitro (Takayama 2004; Takayama et al. 2002). A competitive binding study demonstrated mitragynine’s highest affinity at kappa receptors, followed by mu and delta (Apryani et al. 2009). At the mu receptors, they act as partial agonists just like buprenorphine, while at the kappa receptors they are antagonists with much greater affinity. Animal studies suggest that potency might exceed that of morphine (Chien, Odonkor, and Amorapanth 2017). Some animal studies also show that mitragynine may be involved in noradrenergic and serotonergic pathways, and stimulate post-synaptic alpha-2 adrenergic receptors and inhibit 5-H2A receptors (Babu, McCurdy, and Boyer 2008; Matsumoto et al. 2004).

At low doses (1–5 grams), a stimulant effect is noted; however, at higher doses (5–15 grams), a powerful opioid analgesic effect is noted (Matsumoto et al. 2004). 7-hydroxymitragynine is the more potent opioid receptor agonist, with in vivo studies displaying tolerance, cross-tolerance to morphine, and a precipitated withdrawal when naloxone is administered (Matsumoto et al. 2004). Some animal studies have found some agonistic activity of mitragynine at the alpha-2 adrenergic receptors (Boyer et al. 2008, 2007). Both of these properties have led to some individuals using kratom as a way to taper off opioids. At the same time, withdrawal from kratom itself tends to exert the same signs and symptoms as opioid withdrawal, hinting that a management similar to that for opioid withdrawal is warranted. The half-life of mitragynine has not yet been determined, but is deemed to be relatively short (Apryani et al. 2009). Individuals typically dose every 6–12 hours (Boyer et al. 2007). Withdrawal symptoms begin 12 hours after last use in most of the case reports (Boyer et al. 2008; Galbis-Reig 2016; Mackay and Abrahams 2018; Manda et al. 2014; McWhirter and Morris 2010). The duration of withdrawal is less than four days in all case reports.

Withdrawal management

There are no concrete guidelines on management of kratom withdrawal; however, based on previous case reports (Galbis-Reig 2016; McWhirter and Morris 2010) and current case series, the best approach follows that of opioid withdrawal with symptomatic management of a hyper adrenergic state (Table 1). High doses of alpha-2 agonism combined with other comfort agents provide relief from both physiological and psychological symptoms experienced in withdrawal. The duration is consistent with that of opioid withdrawal.

Cases

Case 1

A 26-year-old Caucasian female with no history of formal mental health diagnoses presented to the emergency department of a rural hospital very tearful, endorsing symptoms of restlessness, generalized body aches, overwhelming anxiety, and thoughts of suicide with no particular plan. On presentation, vital signs showed tachycardia of 102 beats per minute, hypotension of 158/100, and a body temperature of 107°F with normal pulse oximetry. Skin was clammy. A thorough organic workup for clearance that included electrocardiogram, urinalysis, urine toxicology, complete blood count, comprehensive metabolic panel, and thyroid stimulating hormone revealed only mild hypokalemia of 3.3 mEq/L. While awaiting psychiatric evaluation, she received lorazepam 0.5 mg PO on two occasions, 30 minutes apart, with little resolution of anxiety symptoms. She revealed to the examining psychiatric physician a two-year history of kratom use that was abruptly stopped the previous day when she lost her job at the head shop from which she was obtaining it. She reported that, during the prior two years, she had never gone without using for more than 12 hours.

She initially began experimenting with kratom as a “natural” energy supplement, taking half or even a full amount of the powder typically found in a standard capsule and ingesting it orally in the mornings. This would provide her with energy and stamina for the entire morning, and sometimes even into the noon hours. Each capsule contained 10 grams. In time, she learned that she could also take two to three
Case 2

A 27-year-old unmarried male was referred to a rural psychiatric hospital following presentation to an emergency department (ED) at a general hospital with complaint of suicidal ideation and feelings of hopelessness and helplessness. He reported an adult lifelong history of chronic mental disorder variously diagnosed as bipolar disorder and schizophrenia. He had been lost to formal psychiatric treatment for several years, but had been buying clonazepam that he took daily at 3 to 4 mg per day. He reported hearing mumbling auditory hallucinations, the content of which he could not specify.

He reported the use of heroin by injection, beginning at age 13, leading to several past facility stays in his early twenties. He entered methadone maintenance at age 24, and reported that he never returned to the use of opioids. However, after leaving the methadone maintenance program three years prior to admission, he began to use kratom leaves that he prepared as a tea. He reported that he used about 5 grams of kratom leaves per day. He described that the use of kratom had decreased his craving for opioids. Upon admission, he noted that his last use was the day prior to his ED presentation. He came to the facility with a large paper bag filled with kratom leaves. He requested to continue to use them during his hospitalization. Since the inpatient pharmacy would not permit the dispensing of kratom, he had no access to it during his stay.

During the first five days of hospitalization, his mood improved and hallucinations were absent in response to use of quetiapine, 100 mg at bedtime. A diazepam taper over five days was used to assist with benzodiazepine withdrawal, supplemented later in the hospitalization with neurontin, 100 mg, three times daily. Daily COWS was administered and the patient was offered clonidine 0.1 mg three times daily as needed for perceived symptoms of opioid withdrawal. No COWS score exceeded 8 and the patient received a total of six doses of clonidine. At the time of discharge, his depressive symptoms were in remission, there were no psychotic symptoms, and the patient reported no residual craving for opioids.

User withdrawal and detoxification experiences

User-driven forums contain self-reports of individuals experiencing issues with withdrawal symptomatology upon abrupt cessation of kratom (Erowid Kratom Reports). Although exact amount is not specified by users, all have had exposure for several years, dosing anywhere from two to four times daily with no interruptions prior to cessation. Initially, symptoms experienced include those of myalgias, restlessness, excessive panic, and sweating, and these seem to transform for most into a protracted withdrawal with anxiety, irritability, and insomnia lasting for weeks. “Severe” cravings are acknowledged. Persistence of symptoms results in relapse.

Discussion

In this section, we review the current literature describing withdrawal from long-term kratom use. Given the mechanism of action, as expected, the same protocol as for opioid detoxification is successful. Standard urine drug screens do not detect kratom. Special confirmatory testing is needed, such as gas chromatography coupled with mass spectroscopy (GC-MS) (Kaewklum et al. 2005), liquid chromatography with linear ion-trap mass spectroscopy, or with electrospray tandem mass spectroscopy (Lu et al. 2014).

Currently, very few reports of buprenorphine- or methadone-assisted detoxification exist. These have not been explored much due to the medico-legal hindrance from the classification of kratom as a non-opioid until recently. With kratom’s active constituents being declared opioid analogues, we are likely to see these agonist therapy modalities being used. Previously, use of antagonism (naltrexone) was the only “safe” treatment, and even this has not been explored extensively. There is also no evidence of how to handle long-term maintenance of sobriety. There are reports that cravings do exist (Singh, Müller, and Vicknasingam 2014; Singh et al. 2015). Whether the same protocol as for opioid withdrawal should be used, with
medication-assisted treatment and psychosocial intervention, remains to be explored. Study limitations include the heterogeneity of the cases and management protocols used. Certain aspects, such as the pharmacological basis, were gleaned from animal models or in vitro. The user experiences incorporated here aim to bridge the gap between the clinical world and real-life experiences.

The two case reports illustrated earlier are clinical examples of the initial symptomatic management of withdrawal; however, one of the limitations is the lack of long-term follow-up. It is important to note that although detoxification was completed within a few days, kratom dependence is quite severe and withdrawal is long-lasting, with a high tendency to relapse due to distressing withdrawal symptoms, particularly body aches. A long-term management and relapse prevention plan is thus warranted. More individuals are relying on kratom not just to aid in opioid withdrawal, but also to manage pain, to manage low mood states or anxiety symptoms, and to improve stamina. One of its psychoactive effects is exerted at the opioid receptors, and dependence, tolerance, and withdrawal are possible. Clinicians need to be familiar with this agent and comfortable in managing withdrawal. In this article, we introduce the notion of withdrawal and cover the current literature in an attempt to introduce it to clinicians, create a consensus when it comes to management, and exert interest in researching potential abstinence maintenance strategies.

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References


