

Treatment of Kratom Dependence With Buprenorphine-Naloxone Maintenance

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Introduction: Use of the unregulated herbal supplement kratom is on the rise in the United States. We present a case series of 2 patients who developed kratom dependence and withdrawal who were successfully transitioned to buprenorphine-naloxone maintenance.

Case Summary: Two patients using kratom to self-treat chronic pain after prescription opioids were discontinued presenting to our clinic with evidence of kratom dependence and withdrawal. On examination, both patients showed signs of mild opioid withdrawal. Both patients were successfully transitioned to buprenorphine-naloxone maintenance via home initiation with control of both their opioid withdrawal and chronic pain.

Conclusions: Kratom use is on the rise and with increasing evidence of developing opioid-type dependence due to chronic kratom use. This case series shows that buprenorphine can be used to treat kratom dependence and underlying chronic pain that drives its use.

Key Words: buprenorphine, chronic pain, kratom, mitragynine, opioid use disorder

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Since the early 2000s, use of kratom, an herbal drug with opioid-like properties, is on the rise in the West and receiving increasing media and Food and Drug Administration (FDA) attention, including seizure of 100 cases of kratom products in 2016 (Voelker, 2016). Used for centuries in Southeast Asia, kratom is obtained from the leaves of *Mitragyna speciosa* tree (Warner et al., 2016). It is largely obtained from internet and “legal high” shops as raw leaves, capsules, tablet, and concentrated extracts (Warner et al., 2016). It is marketed as a cheaper alternative to opioid replacement therapy without need for prescription or medical supervision (Cinosi et al., 2015; Warner et al., 2016).

Kratom contains over 40 structurally related alkaloids, the most common of which is mitragynine, which acts as a

weak mu-opioid agonist (Cinosi et al., 2015; Warner et al., 2016). A second key component is 7-hydroxymitragynine (2% of kratom by weight), a potent opioid mu-agonist which is 13-times more potent than morphine and 46-times more potent than mitragynine (Cinosi et al., 2015). Both compounds act as weak antagonists at the kappa- and delta-opioid receptors in vitro (Kruegel and Grundmann, 2017). Kratom has broad affinity for receptors including serotonergic, adrenergic, dopaminergic, and GABAergic pathways (Cinosi et al., 2015). It exhibits dose-dependent effects, acting as a mild stimulant at low doses (<5 g), opioid-like effects at 5 to 15 g, and sedation at doses >15 g (Chang-Chien et al., 2017). It reaches peak concentration at 0.83 hours with a half-life of 23 hours (Chang-Chien et al., 2017).

Due to growing number of poison control cases associated with kratom (Anwar et al., 2016), in February 2018, the FDA issued a warning on its addictive potential, citing novel computational model of kratom’s opioid properties (FDA, 2018).

The addictive potential of kratom remains debated. Dependence is common among persons who use kratom regularly in Southeast Asia; however, they generally maintain high levels of social functioning (Singh et al., 2016). There is a signal that patterns of use and supply of kratom in the United States may have higher level of toxicity due to adulterants from Internet shops and higher doses among persons who use kratom in the West (Singh et al., 2016). Here we present 2 cases of patients who developed kratom dependence and who were successfully transitioned to buprenorphine maintenance.

CASE SUMMARY

Patient 1

The first patient is a 60-year-old woman with remote history of alcohol dependence (in long-term remission), chronic pain due to fibromyalgia and osteoarthritis of knees treated with prescription opioids for several years. She initially presented after unintentional opioid overdose requiring admission to the intensive care unit after taking methadone purchased at a gas station, in addition to prescribed tramadol, oxycodone-acetaminophen, and kratom.

After hospital discharge, she transferred care to our practice where buprenorphine maintenance is offered as part of general primary care. She declined buprenorphine maintenance at the initial visit. She was continued on tramadol, pregabalin, and duloxetine for chronic pain and reported that she was no longer using kratom.

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After several months of follow-up, she admitted that she had been unable to stop using kratom due to rebound pain and withdrawal symptoms when she attempted to decrease her dose. The decision was made to discontinue tramadol and transition to buprenorphine via home initiation. At time of initiation, she was using 0.25 ounces kratom every 4 hours, purchased over Internet from supplier in the Philippines, as well as prescribed tramadol. On examination, she presented with mild opioid withdrawal (rhinorrhea, irritability). Urine toxicology was positive for tramadol and negative for opiates, oxycodone, methadone, buprenorphine and other illicit drugs.

She was transitioned to sublingual buprenorphine-naloxone from kratom using home induction. She waited 17 hours from last kratom and tramadol use and subjective withdrawal (rhinorrhea, irritability, and increased pain) before taking first dose of buprenorphine-naloxone (bup-nx). She took 4-1 mg bup-nx on first evening, then increased dose to 4-1 mg SL bup-nx 4 times daily. She reported resolution of her pain symptoms after transition to buprenorphine and follow-up urine drug testing has been negative for full-agonist opioids and positive for buprenorphine/norbuprenorphine. In 9 months of follow-up, she continues to have excellent pain control and is achieving her functional goals. She has also decreased her pregabalin dose from 300 mg PO bid to 200 mg PO bid.

Patient 2

The second patient is a 57-year-old man with chronic low back pain, anxiety, and depression who was initially prescribed oxycodone for chronic pain several years prior which was discontinued by providers after he developed medical misuse of opioids. He transitioned from oxycodone to kratom approximately 1-year before presenting to our clinic to treat his pain. He quickly developed a tolerance to kratom, with escalating use and inability to stop using, and was spending approximately \$2500 per month on kratom purchased online. He reported withdrawal (anxiety, edginess, and leg shaking) when without kratom and had used diazepam to self-treat withdrawal. At time of presentation, he was using kratom to “feel normal” and for energy. Given his ongoing compulsive use, he sought treatment for his kratom addiction and was referred by his primary care doctor to the clinic’s buprenorphine practice. At time of buprenorphine initiation, he had last used kratom 14 hours prior and oxycodone-acetaminophen for a tooth extraction and reported mild withdrawal symptoms (rhinorrhea and irritability). Baseline urine toxicology was positive for codeine/morphine and negative for all other substances. He successfully underwent home initiation of bup-nx 8-2 mg SL films with control of withdrawal symptoms and chronic pain. Over first month of follow-up, his buprenorphine dose was increased to 24 mg daily (dosed 6 mg 4 times daily) to treat his pain. Seven months later, he remains on bup-nx with follow-up urine toxicology positive for buprenorphine/norbuprenorphine and negative for other opiates.

DISCUSSION

Kratom is a growing and under-recognized drug of misuse. Previous case reports document use of kratom for self-treatment of opioid withdrawal (Boyer et al., 2007;

Galbis-Reig, 2016). Kratom dependence and withdrawal is common in persons who use kratom regularly in Southeast Asia (Singh et al., 2014). Most clinical information that we have about the clinical effects of kratom in the West are limited to self-report data and poison control series.

Persons who use kratom report beneficial effects of relaxation, pain relief, increased energy, and decrease in depression (Swogger et al., 2015; Grundmann, 2017). Common side effects reported by users include stomach upset, vomiting, itching and mild sedation (Swogger et al., 2015) and tachycardia, agitation/irritability, drowsiness, nausea, and hypertension in Poison Control calls (Anwar et al., 2016).

Among case series of 12 patients from poison control centers, the main clinical effects were seizures (25%), altered mental status, agitation, central nervous system depression and tachycardia (Cumpston et al., 2018). Reported fatalities after kratom use have been in the setting of polysubstance use (Neerman et al., 2013; McIntyre et al., 2015). Kratom is not detected by conventional drug screening tests; it requires advanced test like liquid chromatography-tandem or ion-mass spectrometry (Cinosi et al., 2015).

In an online survey of people who use kratom in the United States, participants were predominantly male, age 21 to 50, white, employed, and had some college education (Grundmann, 2017). Similar to the cases presented here, many reported use of kratom for self-treatment of pain (Grundmann, 2017). In a survey of online forums, motivations for use included opioid holidays, economic alternative to opioids analgesics, and as opioid replacement therapy (Boyer et al., 2007). Other reasons for use included self-treatment of anxiety, depression and post-traumatic stress disorder (Grundmann, 2017). The antidepressant effects of kratom may be due to its kappa-opioid antagonism (Lalanne et al., 2014; Kruegel and Grundmann, 2017). Of note, depressive symptoms also improved on buprenorphine, a mu-agonist/kappa-antagonist. In a study of persons in substance use treatment, kratom was primarily used to replace heroin and prescription opioids, but rarely the drug of choice (Smith and Lawson, 2017).

Given the increased use for self-treatment and lack of regulation of kratom, there is need for more safety studies and evidence on addictive potential of kratom to educate the general public. At this time, there are no systematic human studies on the addictive potential of kratom. However, in mouse studies, mitragynine showed similar addictive potential to morphine and methamphetamine with impairments in memory and learning (Yusoff et al., 2016).

The legal status of kratom remains in flux. The Drug Enforcement Agency attempted to make it Schedule I in 2016; however, they withdrew this request after significant backlash (Prozialeck, 2016). It remains on the Drug Enforcement Agency’s Drugs of Concern list and sale and possession has been banned in 6 states (Prozialeck, 2016).

Although some debate whether kratom is a true opioid or not, this case series shows that opioid agonist treatment with buprenorphine-naloxone is effective for some patients with kratom dependence and demonstrates 2 safe home initiations of buprenorphine. This is first case series in the literature to report use of buprenorphine for treatment of

kratom dependence, and demonstrates that while kratom has polypharmacologic effects, the predominant opioid-like effect can be effectively treated with opioid agonist therapy. Further research is needed on addictive potential of kratom and treatment for kratom dependence.

Statement of Consent

Written consent obtained from participants. Consent forms available on request.

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