Treatment of Kratom Withdrawal and Dependence With Buprenorphine/Naloxone: A Case Series and Systematic Literature Review

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Introduction: Some opioid use disorder (OUD) patients attempt to self-treat using herbal remedies such as kratom. However, kratom use itself can paradoxically cause physical dependence and OUD. Currently, there are no guidelines for treating patients with OUD stemming from kratom use. Our empirically-based hypothesis was that there would be a correlation between the amount of kratom used and the amount of buprenorphine-naloxone required for opioid agonist therapy.

Methods: This study includes a systematic review assessing treatment of kratom-dependent patients with buprenorphine-naloxone; a case series of our kratom-dependent patients; calculation of the correlation between the kratom dose and the buprenorphine-naloxone dose required to treat kratom-associated OUD; and our proposed starting doses for using buprenorphine-naloxone to treat kratom OUD.

Results: The OVID MEDLINE (1946-2020) database was searched using the terms ''kratom,'' ''buprenorphine,'' and ''case report.'' This search yielded 3 relevant cases of patients having kratom OUD who were treated with buprenorphine-naloxone with the amounts of all substances reported. Review of the bibliographies, citing articles, and Google Scholar turned up three additional cases, yielding 6 literature cases that were analyzed. We also analyzed 2 patients from our clinic, giving a total of 8 patients included in the Pearson correlation coefficient calculation. We found a strong correlation of 0.84 between these variables, consistent with our hypothesis.

Conclusions: Based on our analysis, patients using <20 g of kratom/d could be initiated on opioid agonist therapy with 4/1 mg-8/2 mg buprenorphine-naloxone/d, while patients using kratom doses >40 g/d could be initiated with 12/3 mg-16/4 mg of buprenorphine-naloxone/day.

Key Words: buprenorphine-naloxone, case series, kratom dependence, opioid agonist therapy

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Kratom (*Mitragyna speciosa)* is a tree native to Southeast Asia whose leaves are consumed for their stimulant and therapeutic effects.[1,2] The pharmacology of kratom is complex because kratom alkaloids bind to mu, delta, and kappa opioid receptors, serotonin receptors, and adrenergic receptors.[3] In Western countries, kratom is usually consumed orally by brewing it into a tea or adding the powdered leaves to a drink.[2] Recently, Western use of kratom has dramatically increased as it has been widely advertised on the internet as a safe, nonaddictive alternative method to treat pain and opioid use disorder (OUD) as well as for recreational use.[1]

According to the US Department of Health and Human Services, 2 million Americans had an OUD in 2018.[4] Given that access to Food and Drug Administration (FDA)-approved OUD treatment is not sufficient to meet all patient needs,[5] it is unsurprising that some OUD patients have used alternative therapies including kratom.[1] Unfortunately, kratom is not a risk-free panacea to treat OUD, as kratom use itself can cause physical dependence and OUD.[3,6–8] Although several addiction providers have anecdotally reported using buprenorphine to treat kratom dependence and withdrawal,[3,6,8–13] there are currently no standard treatment guidelines for treating patients with OUD stemming from the use of kratom.[8,10]

We have been caring for several patients who presented to our outpatient substance use disorder (SUD) clinic requesting treatment for kratom dependence, withdrawal symptoms, and OUD using buprenorphine-naloxone and weekly group therapy, with prevention of kratom-induced withdrawal symptoms and cravings as goals of therapy. This study reports a systematic literature review assessing treatment of kratom-dependent patients with buprenorphine-naloxone by other providers; a small case series of the treatment regimens of our kratom-dependent patients; and an analysis of the correlation between the patients' kratom dose and the buprenorphine-naloxone dose required to treat their OUD. Based on our anecdotal observations while treating kratom-dependent patients, we hypothesized that there is a correlation between the amount of kratom used by patients at presentation and the

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TABLE 1. Literature and Clinic Cases – Adults Using Known Amounts of Buprenorphine-Naloxone Opioid Agonist Therapy (OAT) to Treat Kratom Opioid Use Disorder With Known Amounts of Kratom Used

Patient Source	Duration and Amount of Kratom Use	Concurrent Other Drug Use	Course of Opioid and Kratom Use	Onset of Withdrawal	Detoxification Protocol/Duration for Withdrawal	Other Meds Used/ Reasons	Buprenorphine-Naloxone Protocol for Kratom Dependence
SUD Clinic Patient #1: 36 y/o M w/ PMH anxiety, OCD, and depression	20 g/d × 1 yr, self-tapered to 4 g/d before presentation	Benzodiazepines, tobacco. PMH AUD, in recovery until he began withdrawing from kratom	Initial opioid use at age 17 (hydrocodone-APAP taken orally, last use 6 yrs ago). Used kratom daily before presentation, came to clinic because could not stop using kratom on his own. No prior OAT hx. Utox consistent.	Could not cut down below 4 g of kratom/d without going into withdrawal. Is now having same issue w/ buprenorphine.	Clonidine 0.05 mg TID, quetiapine, and 2/0.5 mg buprenorphine-naloxone	Sertraline 300 mg (depression and anxiety), clonidine 0.1 mg (insomnia)	Started OAT at 4/1 mg/d, now attempting to very slowly taper down with goal of discontinuing OAT. Decreased to 2.5/0.625 mg/d, currently taking 1.25/0.312 mg/d. Reports withdrawal sx at 0.5–0.75 mg buprenorphine/d.
SUD Clinic Patient #2: 37 y/o M w/ PMH anxiety and depression	7–14 g daily × 6 mo, had last used kratom 3–4 wk prior	Marijuana, buprenorphine-naloxone, had last used heroin one week prior, has intermittently used kratom and marijuana w/ OAT	Last snorted heroin one week before presentation. Prior SUD clinic patient who had declined OAT previously in favor of self-tx w/ kratom. UTox intermittently positive for mitragynine x2 and marijuana x5	N/A: was started on 8/2 mg buprenorphine-naloxone by another provider 1 wk before presenting to our clinic	8/2 mg/d buprenorphine-naloxone, clonidine 0.1 mg QHS	Sertraline 100 mg, trazodone 25–50 mg QHS (anxiety and depression)	Started OAT at 8/2 mg/d, decreased to 4/1 mg/d with the goal of discontinuing OAT via slow taper decreasing by 1/0.25 mg at a time. He reports ongoing craving for heroin and marijuana.
Buresh (2018)[9]: 60 y/o F w/ PMH chronic pain	Unknown time, 0.25 oz (∼7.1 g) q4 hours (1.5 oz/d ≈ 42.5 g)	Yes (was prescribed tramadol, used methadone and oxycodone-acetaminophen), yes (remote PMH EtOH)		Prescribed tramadol, also taking kratom and diverted opioids, had methadone OD, continued tramadol and endorsed stopping kratom, then was using kratom for withdrawal/pain, d/c kratom and tramadol, started buprenorphine-naloxone	17 h after last kratom use	outpatient OAT: buprenorphine-naloxone 4/1 mg QID (total 16/4 mg)	Tramadol, pregabalin, duloxetine for chronic pain
Buprenorphine/naloxone 4/1 mg QID (total 16/4 mg) and pregabalin							
Diep (2018):[10] 24 y/o male w/ PMH Asperger's and depression with suicidal ideation	Unknown time ×600 mg/d	No, yes (EtOH).	Unknown if previously had OAT or hx of other opioid use. UTox negative for all substances including opiates and oxycodone.	Unknown onset. Course complicated by severe delirium requiring intubation and rhabdomyolysis.	Inpatient: SM: Lorazepam, antibiotics, and levetiracetam for seizures, multiple medications for sedation and delirium	Hydroxyzine 50 mg, lorazepam 0.5 mg, sertraline 150 mg, zolpidem, trazodone 75 mg, gabapentin 300 mg (depression/anxiety)	Started buprenorphine 2 mg/d and increased to 4 mg BID (8 mg), switched to buprenorphine/naloxone 2/0.5 mg TID (6/1.5 mg/d), tapered off after 45 d

TABLE 1 (*Continued*)

Patient Source	Duration and Amount of Kratom Use	Concurrent Other Drug Use	Course of Opioid and Kratom Use	Onset of Withdrawal	Detoxification Protocol/Duration for Withdrawal	Other Meds Used/ Reasons	Buprenorphine-Naloxone Protocol for Kratom Dependence
Khazaeli (2018)[6]: 52 y/o F w/ PMH depression and chronic pain	9 mo × 1 tbsp (∼12.8 g) q4–6 h/d (∼51.2–76.8 g/d)	Yes (unknown)/no	"Addiction to [unspecified] opioid medications" ×9 yrs Utox positive for benzodiazepines (pt on clonazepam), repeat Utox positive for mitragynine x1	Day of admission (unknown # of hours)	inpatient OAT: buprenorphine/ naloxone 4/1 mg q2 hours (total of 4 doses = 16/4 mg)	Sertraline 100 mg, baclofen taper, gabapentin 900 mg, trazadone 100 mg, clonazepam 0.5 mg, lorazepam (anxiety)	Buprenorphine/naloxone 2/0.5 mg QID (total 8/2 mg/d) => 8/2 mg BID (16/4 mg)
Agapoff (2019):[11] 35 y/o M w/ PMH anxiety	3 yrs × 30 g/d (self-weaned to 5 g/d)	No/yes (nicotine lozenges 4 mg q2 hr, caffeine supplements 400 mg/d, EtOH)	Started w/ up to 10 g kratom/d for concentration => 30 g/d, self-referred for OAT, one UTox positive for cocaine/ amphetamines	Unknown, but occurred with decreased dose of 5 g/d	outpatient OAT: buprenorphine/ naloxone 4/1 mg BID (total 8/2 mg)	Sertraline and bupropion for anxiety	Buprenorphine/naloxone 4/1 mg BID (total 8/2 mg) => 12/3 mg/d (too sedated) => 3/0.75 mg BID (6/1.5 mg)
Schmuhl (2019)[12]: 20 y/o M w/ PMH ADHD	2 mo × 30 g/d (self-weaned to 10–15 g/d)	No/no	Started kratom (dose unknown) for anxiety and insomnia => max 30 g/d, UTox negative, one relapse	12 h	outpatient OAT: buprenorphine/ naloxone 4/1 mg daily	Dextroamphetamine for ADHD (stopped while on kratom due to palpitations)	Buprenorphine/naloxone 4/1 mg daily => 2/ 0.5 mg daily x4 days => 4/1 mg/d × 3 mo => 3/0.75 mg/d
Bowe (2020):[8] 47 y/o M w/ PMH OUD, anxiety, chronic pain, depression	1 yr × progressively ↑ dose => ∼100.8 g/ day at presentation	Unknown/yes (hydrocodone 5 mg TID => 10 mg QID), last use 1 yr previously	Peak hydrocodone use = 120 tabs/month, started kratom at 2 tsp (∼8.4 g) TID-QID (∼25.2–33.6 g/ d), ↑ to 2 tsp q2 hrs (24 tsp ≈ 100.8 g/d)	<2 hrs from previous dose	Outpatient OAT: buprenorphine/ naloxone 8/2 mg/d (helped pain) => 16/4 mg/d (helped withdrawal)	Escitalopram 20 mg, duloxetine 30 mg (depression, pain), alprazolam 0.25 mg TID, hydroxyzine (anxiety)	Buprenorphine/naloxone 8/2 mg daily (pain relief) => 12/3 mg daily => 16/4 mg daily (withdrawal and craving relief)

ADHD, attention deficit hyperactivity disorder; APAP, acetaminophen; AUD, alcohol use disorder; BID, twice per day; EtOH, ethanol; F, female; hx, history; M, male; MAT, medication-assisted therapy; mg, milligrams; N/A, not applicable; OAT, opioid agonist therapy; OCD, obsessive compulsive disorder; OD, overdose; PMH, past medical history; QID, four times per day; SM, supportive medications; SUD, substance use disorder; TID, three times per day; Utox, urine tox screen; w/, with; y/o, year old.

amount of buprenorphine-naloxone required for opioid agonist therapy (OAT) to treat them.

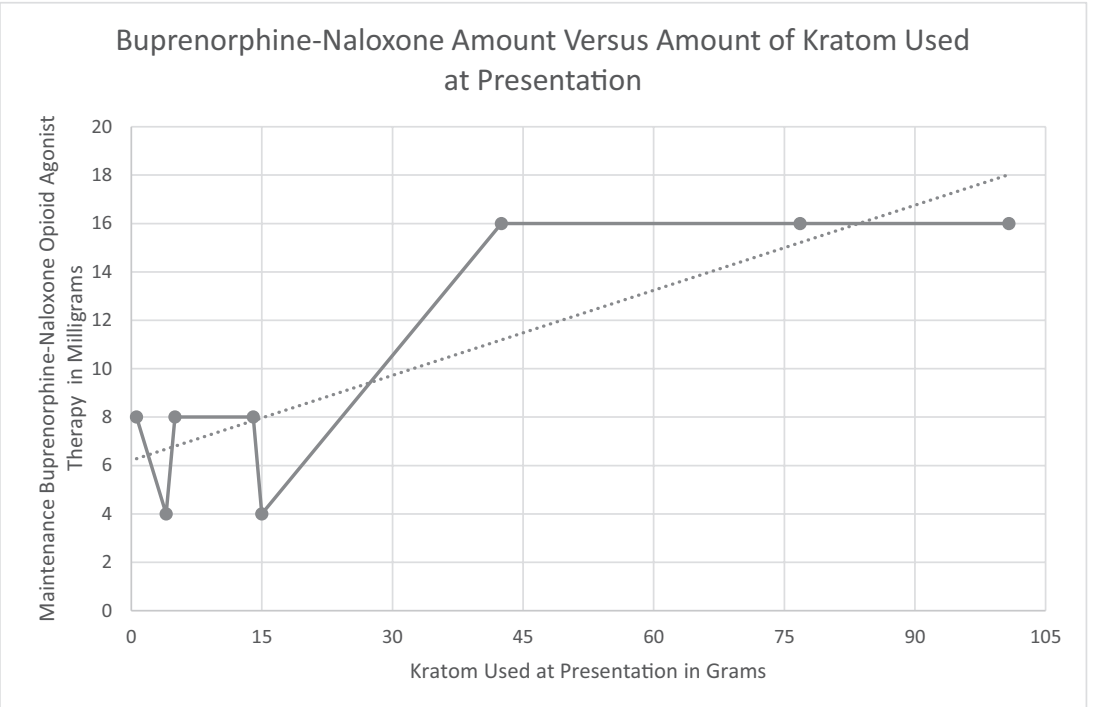
METHODS

The OVID MEDLINE (1946 to January 2020) and Google Scholar databases were searched using the terms ''kratom,'' ''buprenorphine,'' and ''case report'' to find case reports that described treatment of patients using kratom with buprenorphine or buprenorphine-naloxone OAT, and reported the amounts of all substances. The charts of 2 kratom-dependent patients from our clinic were also reviewed, and data from the literature and clinic cases were combined and used to calculate the correlation between the amount of kratom used at presentation for OUD treatment and the amount of buprenorphine-naloxone used in initiating OAT. The results of this analysis were then used to guide buprenorphine-naloxone dosing in kratom-dependent patients. A third clinic patient with variable kratom use is also briefly described. All 3 clinic patients provided written informed consent to include their data in our analysis and publish their cases. This study was approved by the Wake Forest University Institutional Review Board.

RESULTS

The cases of 3 patients from our SUD clinic are briefly described. Patient #1 is a 36-year-old male with a past medical history (PMH) of alcohol dependence, anxiety, and depression who attempted to self-treat these conditions with kratom. He presented to our clinic in kratom withdrawal with severe anxiety after self-tapering his kratom use from 20 g/d to 4 g/d, after which he was unable to taper any further due to intolerable withdrawal symptoms. He was started on buprenorphine-naloxone 4/1 mg/d and is currently slowly tapering his dose with the goal of discontinuing OAT. Patient #2 is a 37-year-old male with a PMH of anxiety and depression who presented to our clinic after being started on buprenorphine-naloxone 8/2 mg/d by another provider for kratom dependence stemming from his attempt to use 7 to 14 g of kratom daily to self-treat his heroin OUD. He was initially continued at this buprenorphine-naloxone dose and subsequently decreased to 4/1 mg/d at his request. He has used kratom once since beginning treatment at our clinic but remains abstinent from heroin. Patient #3 is a 42-year-old female with a PMH of chronic pain, anxiety, and depression who was intermittently taking variable amounts of kratom while on buprenorphine-naloxone 12/3 mg/d started by an inpatient addiction provider. We increased her buprenorphine-naloxone dose to 8/2 mg BID (total 16/4 mg/d), on which she is currently being maintained with no further kratom use for the past four months. See Table and Supplemental Table, http://links.lww.com/JAM/A208 for additional case details.

Our OVID MEDLINE literature search yielded 4 nonduplicate citations meeting criteria, of which 3 were considered relevant as unique case reports or case series describing patients who had used kratom and subsequently were treated with buprenorphine-naloxone OAT with the amounts of all



Dots represent each individual patient. The solid line shows the correlation (r = 0.84) between kratom dose used at presentation and dose of buprenorphine at OAT induction.

FIGURE 1. Amount of Buprenorphine-Naloxone Used for Opioid Agonist Therapy (OAT) Versus Amount of Kratom Used at Presentation.

substances used reported. Review of the bibliographies and citing articles and Google Scholar turned up three additional case reports that included the necessary drug amount information, giving a total of 6 literature cases that were included in the analysis.[6,9–12] See Supplemental Figure for PRISMA diagram, http://links.lww.com/JAM/A209.

The data from these 6 published cases and our first 2 clinic patients were included in the Pearson correlation coefficient calculation between the amount of kratom used at presentation for OUD treatment and the amount of buprenorphine-naloxone used in initiating OAT, giving a total of 8 patients who were included in the analysis. We found a strong correlation of 0.84 between these variables, consistent with our hypothesis (see Supplemental Fig. http://links.lww.com/JAM/A209). A summary of patient characteristics for all eight patients is given in the Table 1. The third clinic patient and the 4 literature patients whose daily kratom use could not be determined and analyzed[3,9,13] are summarized in the Supplemental Table, http://links.lww.com/JAM/A208.

DISCUSSION

This study resulted from our efforts to treat a subpopulation of kratom-dependent patients meeting *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5) criteria for OUD with buprenorphine-naloxone OAT in a systematic and consistent way. OUD is defined in DSM-5 according to 11 mostly behavioral criteria.[14] These include taking more opioids than intended, an inability to cut down opioid use, cravings for opioids, and continued opioid use despite negative physical, personal and social consequences such as legal difficulties, health problems, or interference with life responsibilities and other activities, as well as physical dependence including the development of tolerance and withdrawal.[14] Although kratom-induced OUD is not specifically recognized in the DSM-5, there are multiple examples of kratom-dependent patients meeting DSM-5 criteria for OUD from our clinic and in the literature.[2,7,8,11]

Despite the existence of numerous literature examples of addiction providers using buprenorphine-based OAT to treat kratom OUD,[3,6,9–13] no formal guidelines for doing so have been published. This may be in part because kratom-induced OUD is still relatively unrecognized by addiction and primary care providers.[15] In addition, there is some debate regarding whether kratom alkaloids are opioids, although the FDA has concluded that some kratom alkaloids, including mitragynine and 7-hydroxymitragynine, have opioid-like pharmacological properties, bind to the mu opioid receptors, and have potential to be addictive opioid-like drugs.[16]

A review of the literature is notable for the wide variety of strategies used to treat kratom-dependent and kratom OUD patients, including symptomatic control during detoxification that does not include short-term OAT[7,10,17]; brief OAT (primarily using morphine or buprenorphine) for detoxification due to physical dependence on kratom with[6,8,9,11,18,19] or without[20] long-term OAT; and buprenorphine-based[3,6,8–11] or other[18,19] OAT that is primarily intended for long-term OUD treatment.

As the Figure indicates, our analysis of literature patients and our own patients suggests that people who use kratom can be divided into two groups based on the amount of kratom they report using at presentation (Fig. 1). We hypothesize that the opioid withdrawal symptoms and cravings of patients using doses of kratom <20 g/d may be controlled with relatively low doses of buprenorphine-naloxone in the range of 4/1 mg to 8/2 mg/d. In contrast, patients who are using doses of kratom >40 g/d may require higher buprenorphine-naloxone doses in the range of 12/3 mg to 16/4 mg/d. Interestingly, we did not have any clinic patients or find any published literature patients whose presenting kratom dosage fell in the intermediate use range between 20 and 40 g/d. However, our analysis suggests that a reasonable starting buprenorphine-naloxone dose for these patients might be on the order of 8/2 mg to 12/3 mg/d.

Limitations of this study include the small number of observations with inability to adjust for confounders and the nonexperimental design with no comparison group. In addition, these patients may not represent the spectrum of kratom use. Finally, patient reports of their amount of kratom use may not be reliable.

CONCLUSIONS

We propose that OUD patients using <20 g of kratom per day be initiated on buprenorphine-naloxone OAT with 4/1 mg to 8/2 mg of buprenorphine-naloxone per day, while patients using kratom doses >40 g/d be initiated with doses of buprenorphine-naloxone in the range of 12/3 mg to 16/4 mg of buprenorphine-naloxone per day. Some patients may require adjustment of their initiating OAT dose depending on their use of other drugs along with kratom, as well as whether patients are able to self-taper their kratom use before starting buprenorphine-naloxone OAT. The empirical finding that buprenorphine dose appears to correlate with self-reported kratom dose requires further research to confirm the existence of this relationship.

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