ANNALS OF CLINICAL PSYCHIATRY 2020;32(4):275-280 doi: 10.12788/acp.0012

REVIEW ARTICLE

Kratom: A growing substance of abuse in the United States

Daniel Stephen Demick, MD
Taelor T. Lee, MD
Audrey T. Summers, MD
Rif S. El-Mallakh, MD

Department of Psychiatry and Behavioral Sciences
University of Louisville School of Medicine
Louisville, Kentucky, USA

CORRESPONDENCE
Rif S. El-Mallakh, MD
Department of Psychiatry and Behavioral Sciences
University of Louisville School of Medicine
501 E Broadway
Louisville, KY 40202 USA

E-MAIL
rselma01@louisville.edu

BACKGROUND: Use of kratom is increasing in the United States due to its perceived safety as a botanical product. This review provides salient information about kratom for the practicing clinician.

METHODS: We conducted a literature search of MedLine, UpToDate, and Google using the terms "kratom" and "*Mitragyna speciosa*" for articles published within the last 10 years.

RESULTS: We reviewed >500 articles. Kratom is derived from the *Mitragyna speciosa* plant of Southeast Asia. It has grown in popularity within the United States due to its dual effects of acting as a stimulant at low doses and acting as an opioid-like substance at higher dosages. The 2 major active ingredients in kratom, mitragynine and 7-OH mitragynine, act as partial agonists at the mu-opioid receptor. While adverse consequences are normally mild, there are several potentially serious adverse effects, including respiratory depression, especially with chronic, high-dose usage. Furthermore, in case reports, concomitant use of kratom with other substances has been linked to seizures. Unfortunately, an increasing number of deaths have been linked to kratom usage. Six states have made it illegal to possess or sell kratom.

CONCLUSIONS: Kratom is an emerging drug of abuse in the United States. Its use is increasing in individuals who may seek to experience an opioid-like "high" as well as to help reduce withdrawal effects from other opioids.

INTRODUCTION

The use of "botanical," "herbal," or "alternative" medical supplements is extremely common in the United States, with approximately 30% of adults having used or endorsed current use of herbal-based remedies.[1] This use persists despite a lack of appropriate studies documenting their potential utility. There is evidence that some of these remedies can have both therapeutic effects and deleterious effects. As such, it is necessary for physicians to stay abreast of commonly used herbal products and recreational substances that may impact their use.[2]

Kratom, a substance with opioid-like effects, is growing in popularity in the United States.[2,3] It is derived from the plant *Mitragyna speciosa*, which is indigenous to Thailand and Southeast Asia (**FIGURE 1**). Traditional uses of kratom include as a stimulant or for management of chronic pain, diarrhea, cough, and opioid withdrawal.[2,4] While kratom use in the United States is a relatively recent development, it is rising at a startling rate. Kratom exposures reported to US Poison Control Centers rose dramatically from 26 calls in 2010 to 263 in 2015 (a 10-fold increase).[5] Additionally, using the Google search engine, we found 5,970,000 results for kratom, which is an increase from the 2 million results produced by a similar Google search conducted by Prozialek et al in 2012. This likely indicates that the interest in kratom is increasing in the United States.

This article provides salient information about kratom for the practicing clinician. This includes descriptions of the background and chemistry of kratom; its pharmacology and epidemiology; clinical presentations associated with kratom use/exposure; and management considerations for patients who use kratom.

METHODS

A literature search was conducted using the terms "kratom" and "*Mitragyna speciosa*." These terms were first searched in the UpToDate database, with kratom yielding 6 results and *Mitragyna speciosa* also yielding 6 results. Medscape's Medline database yielded 358 and 294 results for kratom and *Mitragyna speciosa*, respectively. Our search was restricted to articles published within the last 10 years. Articles that did not include *Mitragyna speciosa* or kratom as a focus were excluded. We included articles with *in vivo* and *in vitro* data and excluded *in silico* information about the chemistry/pharmacology of kratom. Beyond these criteria, articles were chosen based on their relevance to the aims of this review. The Google search engine was utilized to quantify interest in kratom usage, and to compare this interest to previous levels reported in other articles.

RESULTS

Background

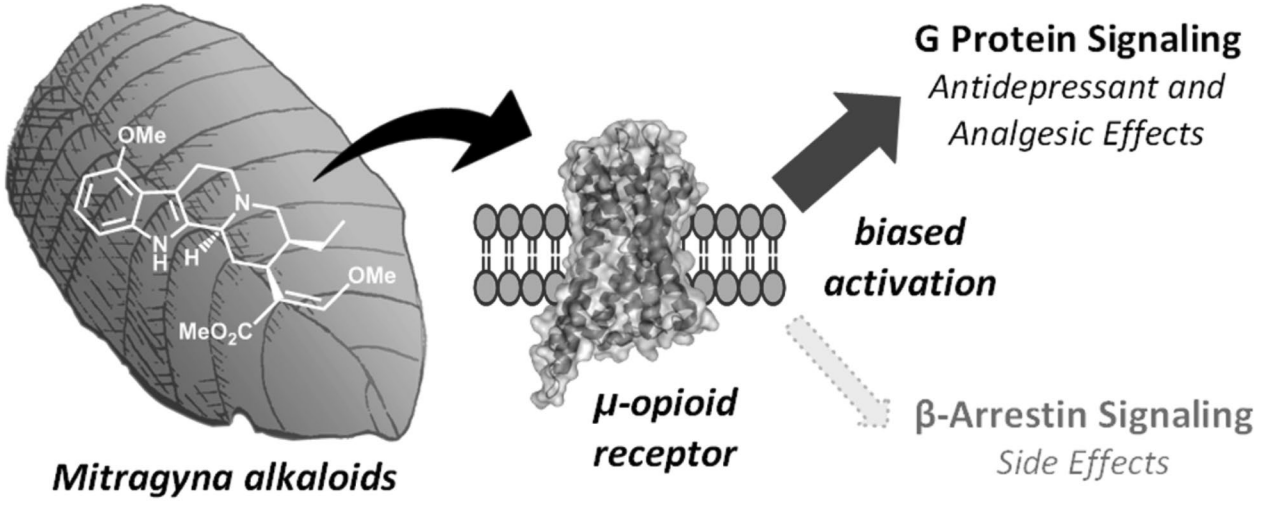
Mitragyna speciosa is a tropical evergreen tree of the coffee family. This plant is endemic to Thailand and Southeast Asia. It has been used in various countries in this area as traditional medicine since at least the 19th century.[4] Traditional uses of the plant have been for stimulant effects, pain management, appetite stimulation, and as a libido booster.[4] The leaves have been used as a local anesthetic, antitussive, and antidiarrheal agent.[4] Antidepressant and anxiolytic properties have also been attributed to kratom in traditional usage.[4] In addition to these traditional medical applications, kratom has been used recreationally and as a mood enhancer.[4] In the United States, kratom use for opioid withdrawal has also been reported.[5-7]

In the United States, kratom is available in many forms, including the natural kratom leaf and marketed kratom supplements, such as crushed or dried leaves, powder, preparations fortified with extracts from other leaves, extracts, resin, gum, tinctures, capsules filled with powdered kratom, and liquid formulations.[8] Kratom is available for sale to consumers via Internet vendors, gas stations, "head shops," and local dealer networks, as well as from illicit drug sellers. Despite this widespread availability, kratom is a relatively recent introduction to the United States. According to the Texas Poison Centers, there were no reported cases of kratom exposure from 1998 to 2008.[9]

Kratom use can be problematic. The Ohio Substance Abuse Monitoring Network (OSAMN) tracks the presence of kratom in its jurisdictions. In a report covering June 2017 to January 2018, the OSAMN stated that kratom was available from "heroin dealers" in the Cleveland and Akron-Canton regions.[10] Furthermore, from 2016 through 2018, the Ohio Department of Health identified 15 overdose deaths in which kratom was mentioned on the death certificate. Reports of problematic exposure to US Poison Control Centers increased from 25 in 2010 to 263 in 2015.[5] As of June 2020, the sale and possession

FIGURE 1
Mitragyna alkaloids

Mitragyna alkaloids are partial agonists at the mu-opioid receptor with a bias towards G protein signaling. This is correlated with the decreased rate of respiratory depression/adverse effects and the subjectively described milder withdrawal when compared to traditional opiates. This is thought to be due to differences in the binding motifs between the *Mitragyna speciosa* alkaloids and the traditional opiates.



Source: Reference 11. Reprinted with permission from *Journal of the American Chemical Society*.

of kratom was illegal in 6 states: Alabama, Arkansas, Indiana, Rhode Island, Vermont, and Wisconsin.

Pharmacology/chemistry

Mitragynine's systemic name is (alpha E,2S,3S,12bS)-3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy-alpha-(methoxymethylene)-indolo[2,3-a]quinolizine-2-acetic acid methyl ester. The systemic name for its more potent hydroxylated form, 7-OH mitragynine, is (alpha E,2S,3S,7aS,12bS)-3-ethyl-1,2,3,4,6,7,7a,12b-octahydro-7a-hydroxy-8-methoxy-alpha-(methoxymethylene)-indolo [2,3-a]quinolizine-2-acetic acid methyl ester. These are the most active alkaloids in kratom, and act as partial agonists at the mu-opioid receptor with a bias towards G protein signaling (**FIGURE 1**).[11] Pertinent chemical facts about the pair are listed in the **TABLE**. Other alkaloids with different effects on the opioid system—paynantheine, speciogynine, and speciociliatine—have also been identified, but occur at lower concentrations within the plant and consumed extracts. As with any plant-derived substance, concentrations of the alkaloids vary with growing conditions and different strains of mitragynine.[11,12]

G protein-coupled mu receptor activation by opioids has been linked with opioid-like effects, while beta-arrestin activation is associated with respiratory depression and other adverse effects of opioids. The mu-opioid receptor has 2 major downstream pathways: a G protein-coupled receptor and a beta-arrestin. Both of these pathways lead to separate downstream effects with the recruitment of different functional and signaling proteins.[13] The preferential activation of G protein coupled receptors relative to beta-arrestin by the mitragynine alkaloids in kratom (**FIGURE 1**) is thought to mediate its opioid-like effects with milder respiratory depression.[11] Mitragynine and 7-OH mitragynine activate the G protein system in humans, albeit at a fraction of the activation by enkephalin as a positive control (**FIGURE 2**), but there is no measurable beta-arrestin recruitment (**FIGURE 3**).[11] This is believed to account for the clinically observed phenomena that kratom is associated with less respiratory depression than traditional opioids.[14] It is unknown what mediates the stimulatory effects reported by individuals who used kratom at lower doses.

TABLE 1
Chemical characteristics of mitragynine and 7-OH mitragynine

Name	Chemical formula	Molecular weight	Melting point	Solubility
Mitragynine	$C_{23}H_{30}N_2O_4$	398.5 g/mol	102 to 106°C	Organic solvents, insoluble in water
7-OH mitragynine	$C_{23}H_{30}N_2O_5$	414.50 g/mol	102 to 106°C	Organic solvents, insoluble in water

Partial agonist activity at the mu receptor of kratom-derived alkaloids is important because it determines the ultimate magnitude of the opioid-like effects of kratom. The intrinsic activity, or partial activation, at the mu-opioid receptor of 7-OH mitragynine is approximately 60% of the full G-protein activation seen with the enkephalin DAMGO, whereas that of mitragynine is approximately 30% (**FIGURE 2**).[11,15] This partial agonist effect is reminiscent of buprenorphine, whose G-protein activation is in the range of 29% to 48%,[16,17] and has led some researchers to suggest that kratom or its purified alkaloids may have a potential future role in the therapeutic treatment of opioid use disorder. Furthermore, due to the negligible beta-arrestin activation of the *Mitragyna speciosa* alkaloids (**FIGURE 3**), they carry a milder adverse effect profile than conventional mu-opioid agonists. Additional research is required to fully characterize both the actual opioid-like effects and the potential therapeutic use of the kratom-derived chemicals for opioid use disorder.

Beyond mitragynine and 7-OH mitragynine, the 3 additional alkaloids derived from *Mitragyna speciosa*—paynantheine, speciogynine, and speciociliatine—have been found to exhibit some activity at opioid receptors. These alkaloids have been found to have varying effects at the mu-, kappa-, and delta-opioid receptors. Specifically, mitragynine and 7-OH mitragynine act as partial agonists, while paynantheine, speciogynine, and speciociliatine act as competitive antagonists.[11,12] Mitragynine acts as an antagonist at both kappa and delta opioid receptors, while the other major alkaloids do not exhibit any effects.

Epidemiology of kratom use

Exact measures of kratom use in the United States are not available. Interest in kratom is high and increasing, as reflected by the number of Internet pages that a Google search of *Mitragyna speciosa* or kratom (>5 million) produces. Alternatively, calls to US Poison Control Centers can be a proxy of use. There were 1,807 kratom-related calls to US Poison Control Centers from 2011 to 2017.[15] These numbers rose from 13 in 2011 to 682 in 2017—a >5,000% increase.[15] Furthermore, >65% of these calls occurred in 2016 and 2017, meaning that kratom use is continuing to increase.[15]

Clinical presentation

There are a number of different ways to ingest kratom. Traditionally, kratom has been chewed, smoked, or brewed as a tea.[18] In the United States, kratom is commonly taken in pill form and consumed in powder form, which can be used to form various drinks.[5,18,19] The clinical presentation of a person who uses kratom is contingent upon the dosage ingested.

At low doses (1 to 5 g), kratom is suggested to have a mild stimulant-like effect.[11] This effect is generally described to be less intense than typical stimulants, but sufficient to cause an increase in energy and productivity. In fact, many kratom manufacturers tout these effects in their advertisements.[20]

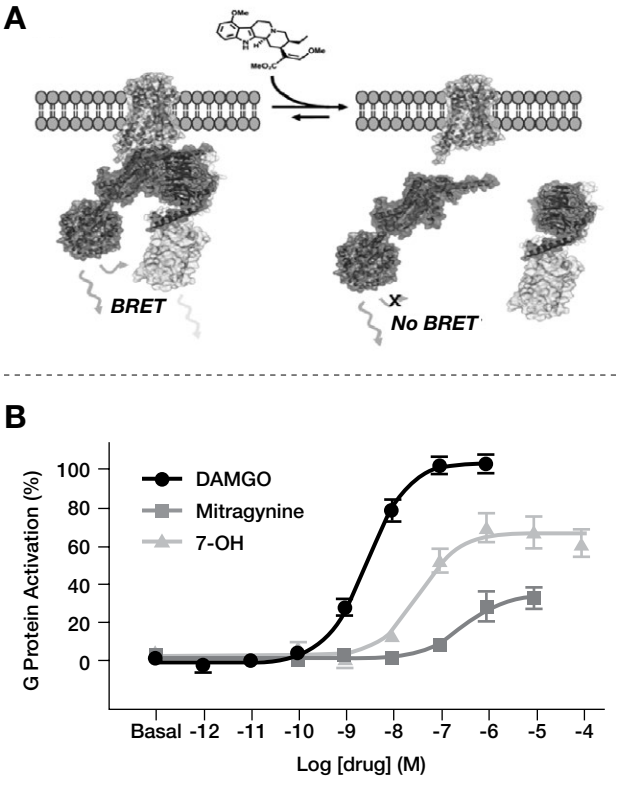
At higher doses (5 to 15 g), kratom has been described to have more opioid-like effects, due to the partial agonist properties previously described at the mu-opioid receptor.[11] As a result, kratom is often used at these higher doses.

Acute undesirable consequences of kratom include anxiety, irritability/increased aggression, sedation, nausea, constipation, pruritus, and respiratory depression.[21] Chronic, heavy use of kratom can be associated with withdrawal potential, hyperpigmentation of the cheeks, tremor, anorexia nervosa with weight loss, psychosis, and seizures (especially with comorbid modafinil use).[21] Individuals with chronic, heavy use are at risk for respiratory depression. Seizures have been documented in multiple case reports; these invariably occurred in the presence of comorbid conditions or substance use, and it is thought that seizures associated with kratom use are rare.[21]

FIGURE 2

Activity of mitragynine and 7-OH mitragynine at the human mu-opioid receptor (hMOR)

(A) Conceptual representation of the G protein BRET assay employing atomistic cartoons derived from available X-ray crystal structures. To measure G protein activation, hMOR37 was co-expressed with GαoB 38 fused to RLuc839, beta138, and mVenus40 fused to γ238.
(B) Agonist activity at hMOR; positive control = [D-Ala2, N-Me-Phe4, Gly-ol5]-enkephalin (DAMGO); curves represent the average of n ≥ 3, with error bars representing ± SEM.



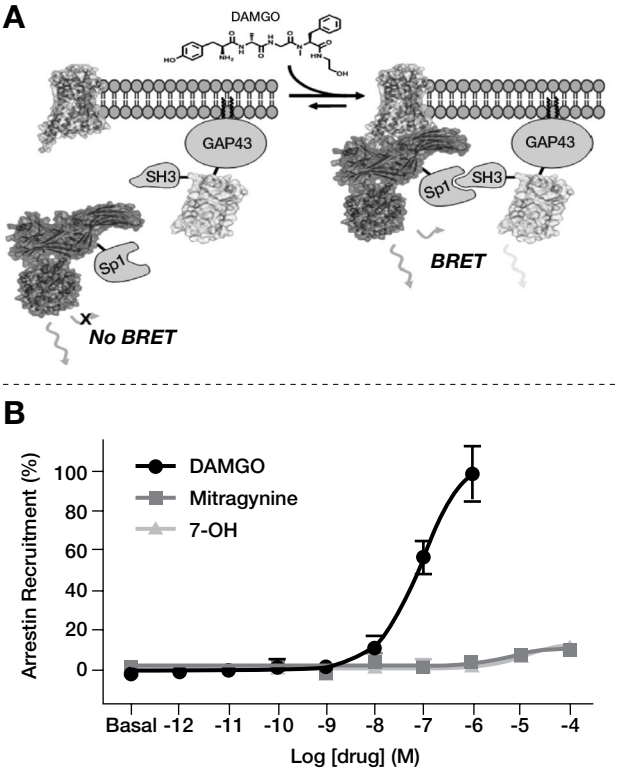
BRET: bioluminescence resonance energy transfer.

Source: Reference 11. Reprinted with permission from *Journal of the American Chemical Society*.

FIGURE 3

Mitragynine and 7-OH mitragynine do not recruit beta-arrestin

(A) Conceptual representation of the beta-arrestin BRET assay employing atomistic cartoons derived from available X-ray crystal structures. To measure beta-arrestin recruitment, hMOR37 was co-expressed with beta-arrestin-250 fused to RLuc839 and Sp1, GAP43 fused to citrine40 and SH3, and G protein-coupled receptor kinase 2 (GRK2). On beta-arrestin recruitment, association of the Sp1 and SH3 domains results in an increase in the BRET signal between RLuc8 and citrine.
(B) Beta-arrestin recruitment at hMOR, positive control = DAMGO; curves represent the average of n ≥ 3, with error bars representing ± SEM.



BRET: bioluminescence resonance energy transfer; hMOR: human mu-opioid receptor.

Source: Reference 11. Reprinted with permission from *Journal of the American Chemical Society*.

Management

The clinical management of kratom intoxication is generally supportive. Withdrawal symptoms, while unpleasant, are normally milder with kratom than in traditional opioids, although often longer-lasting, and rarely require more than supportive care.[6] Withdrawal symptoms include rhinorrhea, insomnia, poor concentration, constricted affect, and myalgias.

Currently, there are no specific recommended medical treatments for kratom intoxication or withdrawal. In several case reports, suboxone has been used for both withdrawal symptoms and relapse prevention.[22,23] Similarly, withdrawal or intoxication seizures appear to be responsive to traditional anti-seizure treatments such as lorazepam and phenytoin.[15,16] While respiratory depression is milder than that seen with traditional opioids, naloxone is an

appropriate measure for patients who display worrying respiratory symptoms.

CONCLUSIONS

Kratom is a substance derived from the *Mitragyna speciosa* plant in Southeast Asia. It has grown in popularity in the United States due to its dual effects of acting as a stimulant at low doses and as an opioid-like substance at higher doses. Psychoactive effects are mediated by 2 potent alkaloids, mitragynine and 7-OH mitragynine, which act as partial agonists at the mu-opioid receptor. Severe adverse consequences associated with chronic, high-dose usage include respiratory depression, and seizures. There are also an increasing number of deaths related to kratom use. Currently, it is illegal to sell or possess kratom in 6 states. ■

DISCLOSURES: Dr. El-Mallakh receives grant/research support from Janssen Pharmaceuticals and Sage Pharmaceuticals, and is a speaker for Allergan, Indivior, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Takeda, and Teva. The other authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

REFERENCES

1. Barnes PM, Bloom B, Nahin RL, et al. Complementary and alternative medicine use among adults and children: United States, 2007. Natl Health Stat Report. 2008;12:1-23.
2. Denneky CE, Tsourounis C. Dietary supplements & herbal medications. In: Katzung B, Masters S, Trevor A, eds. Basic and clinical pharmacology, 12th ed. New York, NY: McGraw Hill; 2011:1125-1137.
3. Gershman K, Timm K, Frank M, et al. Deaths in Colorado attributed to kratom. N Engl J Med. 2019; 380:97-98.
4. Singh D, Narayanan S, Muller C. Motives for using kratom (Mitragyna speciosa Korth.) among regular users in Malaysia. J Ethnopharmacol. 2019;233:34-40.
5. Bergen-Cico D, MacClurg K. Kratom (Mitragyna speciosa): use, addiction potential, and legal status. In: Preedy VR, ed. Neuropathology of drug addictions and substance misuse: general processes and mechanisms, prescription medications, caffeine and areca, polydrug misuse, emerging addictions and non-drug addictions, Volume 3. Amsterdam, Netherlands: Elsevier; 2016: 903-911.
6. Boyer EW, Babu KM, Adkins JE, et al. Self-treatment of opioid withdrawal using kratom (Mitragynia speciosa Korth). Addiction. 2008;103:1048-1050.
7. Saingam D, Assanangkornchai S, Geater A. OR03-1. Effect of krathom (Mitragyna speciosa Korth.) use among traditional users in Southern Thailand. Alcohol Alcoholism. 2014;49(suppl 1):I40.
8. Lovrecic B, Lovrecic M, Gabrovec B, et al. Non-medical use of novel synthetic opioids: a new challenge to public health. Int J Environ Res Pub Health. 2019;16:177. doi: 10.3390/ijerph16020177.
9. Forrester MB. Kratom exposures reported to Texas Poison Centers. J Addict Dis. 2013;32:396-400.
10. Controlled Substance Scheduling – Kratom. Columbus, OH: The Common Sense Initiative - Ohio; 2019. https://www.americankratom.org/images/CSI.BIA.Ohio.pdf. Accessed June 30, 2020.
11. Kruegel AC, Gassaway MM, Kapoor A, et al. Synthetic and receptor signaling explorations of the mitragyna alkaloids: Mitragynine as an atypical molecular framework for opioid receptor modulators. J Am Chem Soc. 2016;138:6754-6764.
12. Calvey TN, Williams NE. Principles and practice of pharmacology for anaesthetists, 5th ed. Malden, MA: Blackwell Publications; 2008.
13. Kang J, Shi Y, Xiang B, et al. A nuclear function of beta-arrestin1 in GPCR signaling: regulation of histone acetylation and gene transcription. Cell. 2006;124: 833-847.
14. Saref A, Suraya S, Singh D, et al. Self-reported prevalence and severity of opioid and kratom (Mitragyna speciosa korth.) side effects. J Ethnopharmacol. 2019; 238:111876. doi: 10.1016/j.jep.2019.111876.
15. Post S, Spiller HA, Chounthirath T, et al. Kratom exposures reported to United States poison control centers: 2011-2017. Clin Toxicol (Phila). 2019;57:847-854.
16. Saidak Z, Blake-Palmer K, Hay DL, et al. Differential activation of G-proteins by mu-opioid receptor agonists. Br J Pharmacol. 2006;147:671-680.
17. Sutcliffe KJ, Henderson G, Kelly E, et al. Drug binding poses relate structure with efficacy in the μ opioid receptor. J Mol Biol. 2017;429:1840-1851.
18. Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J Am Osteopath Assoc. 2012;112:792-799.
19. Anwar M, Law R, Schier J. Notes from the field: kratom (Mitragyna speciosa) exposures reported to poison centers - United States, 2010-2015. MMWR Morbid Mortal Weekly Rep. 2016;65:748-749.
20. Karp JF, Butters MA, Begley AE, et al. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. J Clin Psychiatry. 2014;75:e785-e793.
21. Saref A, Suraya S, Singh D, et al. Self-reported prevalence and severity of opioid and kratom (Mitragyna speciosa Korth.) side effects. J Ethnopharmacol. 2019; 238:111876. doi: 10.1016/j.jep.2019.111876.
22. Khazaeli A, Jerry JM, Vazirian M. Treatment of kratom withdrawal and addiction with buprenorphine. J Addiction Med. 2018;12:493-495.
23. Bowe A, Kerr PL. A complex case of kratom dependence, depression, and chronic pain in opioid use disorder: effects of buprenorphine in clinical management [published online June 17, 2020]. J Psychoactive Drugs. 2020:1-6. doi: 10.1080/02791072.2020.1773586.