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Kratom policy: The challenge of balancing therapeutic potential with public safety

Walter C. Prozialeck^{a,*}, Bonnie A. Avery^b, Edward W. Boyer^c, Oliver Grundmann^d, Jack E. Henningfield^e, Andrew C. Kruegel^f, Lance R. McMahon^g, Christopher R. McCurdy^d, Marc T. Swogger^h, Charles A. Veltriⁱ, Darshan Singh^j

^aDepartment of Pharmacology, Midwestern University, 555 31st Street, Downers Grove, IL 60515, USA

^bDepartment of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL 32610, USA

^cDepartment of Emergency Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

^dDepartment of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL 32610, USA

^eResearch, Health Policy and Abuse, Liability, Pinney Associates And Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 4800 Montgomery Lane, Suite 400, Bethesda, MD 20814, USA

^fDepartment of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA

^gDepartment of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, FL 32610, USA

^hDepartment of Psychiatry, University of Rochester Medical Center, 300 Crittenden Blvd., Rochester, NY 14682, USA

ⁱDepartment of Pharmaceutical Sciences, Midwestern University, 19555 N. 59th Avenue, Glendale, AZ 85308, USA

^jCentre for Drug Research, Universiti Sains Malaysia, Minden, Malaysia

Abstract

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*Corresponding author. wprozi@midwestern.edu (W.C. Prozialeck).

Authors' roles in writing manuscript

Drs. Walter Prozialeck and Darshan Singh conceived the manuscript and wrote the first draft. All of the authors provided significant input into the writing and editing of the manuscript. All authors have approved the final version of the manuscript.

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Drs. Prozialeck, Avery, McCurdy, McMahon, Grundmann and Singh have no potential conflicts of interest to disclose.

Dr. Edward Boyer is a Fulbright Scholar studying the effects of kratom.

Dr. Andrew Kruegel has served as a non-compensated consultant to the American Kratom Association and is a co-inventor on several kratom-related patent applications filed by Columbia University.

Dr. Jack E. Henningfield provides consulting support through Pinney Associates, on the development of abuse potential assessments and regulation of new medicines and formulations for the treatment of pain, addiction, epilepsy, and other central nervous system disorders. He has also served as a consultant for the American Kratom Association (see more at www.pinneyassociates.com).

Kratom (*Mitragyna speciosa*) is a tree-like plant indigenous to Southeast Asia. Its leaves, and the teas brewed from them have long been used by people in that region to stave off fatigue and to manage pain and opioid withdrawal. Evidence suggests kratom is being increasingly used by people in the United States and Europe for the self-management of opioid withdrawal and treatment of pain. Recent studies have confirmed that kratom and its chemical constituents have potentially useful pharmacological actions. However, there have also been increasing numbers of reports of adverse effects resulting from use of kratom products. In August 2016, the US Drug Enforcement Administration announced plans to classify kratom and its mitragynine constituents as Schedule I Controlled Substances, a move that triggered a massive response from pro-kratom advocates. The debate regarding the risks, and benefits and safety of kratom continues to intensify. Kratom proponents tout kratom as a safer and less addictive alternative to opioids for the management of pain and opioid addiction. The anti-kratom faction argues that kratom, itself, is a dangerous and addictive drug that ought to be banned. Given the widespread use of kratom and the extensive media attention it is receiving, it is important for physicians, scientists and policy makers to be knowledgeable about the subject. The purpose of this commentary is to update readers about recent developments and controversies in this rapidly evolving area. All of the authors are engaged in various aspects of kratom research and it is our intention to provide a fair and balanced overview that can form the basis for informed decisions on kratom policy. Our conclusions from these analyses are: (a) User reports and results of preclinical studies in animals strongly suggest that kratom and its main constituent alkaloid, mitragynine may have useful activity in alleviating pain and managing symptoms of opioid withdrawal, even though well-controlled clinical trials have yet to be done. (b) Even though kratom lacks many of the toxicities of classic opioids, there are legitimate concerns about the safety and lack of quality control of purported “kratom” products that are being sold in the US. (c) The issues regarding the safety and efficacy of kratom and its mitragynine constituent can only be resolved by additional research. Classification of the *Mitragyna* alkaloids as Schedule I controlled substances would substantially impede this important research on kratom.

Keywords

Kratom; Ketum; Mitragynine; Opioid use disorder (OUD); Pain management; Drug policy

Introduction and background

Kratom (also known as ketum in Malaysia) is a tree-like plant (*Mitragyna speciosa*, *Korth, Havi*) native to Thailand, Malaysia, Indonesia and other regions of Southeast Asia. When the plant's leaves are ingested in the form of teas or other extracts/decoctions, kratom leaves produce complex, dose-dependent stimulant and analgesic effects. For generations, indigenous people in Southeast Asia have used kratom to treat common health maladies (e.g. diarrhea, hypertension, cough, fever, etc.), enhance work performance, combat fatigue, alleviate pain, and manage opioid dependence (hereafter referred to as opioid use disorder (OUD)) (Adkins, Boyer, & McCurdy, 2011; Cinosi et al., 2015; Jansen & Prast, 1988; Vicknasingam, Narayanan, Beng, & Mansor, 2010). This suggests that traditional use of kratom has therapeutic potential, or at least that it is used by people seeking improved health and well-being. In considering the uses of kratom, in this commentary we distinguish

traditional use from “therapeutic use”, which in the United States (US) and many countries is defined by whether a substance or product has been officially approved by a regulatory authority such as the US Food and Drug Administration (FDA), typically with reliance upon randomized controlled clinical trials for new drugs. We recognize that kratom has not yet met standards for therapeutic use claims and has not been approved in the US for “therapeutic use”, despite the widespread and growing use of kratom as a self-treatment for a number of disorders, including pain, OUD, and depression or anxiety (Grundmann, 2017). Rather, it is currently marketed and regulated in the US as a food and/or dietary ingredient that is not subject to the same strict regulations that are used for approval of new drugs. Since kratom has not been approved for therapeutic use in the U.S, it cannot legally be advertised as a remedy for any medical condition.

Despite its long history of traditional use in Southeast Asia, kratom has only recently received significant attention as a plant-based remedy in the West. The emergence of kratom as a product of interest in the West, and particularly in the US, is evident from the results of several recent surveys, analyses of online user reports, and reviews of the scientific literature (Prozialeck, 2016, Adkins et al., 2011; Grundmann, 2017; Kruegel & Grundmann, 2018; Pain News Network, 2018; Prozialeck, Jivan, & Andurkar, 2012; Smith & Lawson, 2017; Swogger & Walsh, 2018; Swogger et al., 2015). Results of those analyses yield clear evidence that a large number of individuals in North America and Europe are using kratom products for the self-management of a number of medical conditions, including pain, OUD, anxiety, and depression (Grundmann, 2017). In the US, for example, current estimates from the American Kratom Association suggest that more than 1 million individuals in the USA may be using kratom (American Kratom Association, 2018a), although incidence of use has not been rigorously studied. At the same time, some unscrupulous marketers are promoting kratom as an opioid-like “legal high” (Babu, McCurdy, & Boyer, 2008; Griffin, Daniels, & Gardner, 2016; Rech, Donahey, Cappiello Dziedzic, Oh, & Greenhalgh, 2015; Schmidt, Sharma, Schifano, & Feinmann, 2011). The unregulated sale of kratom via the internet and deceitful marketing practices may have prompted some individuals to use kratom as a recreational drug. This poorly regulated market, wide distribution, and reported risks of toxicity associated with kratom use, are all likely to have encouraged regulatory agencies to suggest the removal of this product from the market.

In the West, a wide variety of kratom products—including raw leaves, capsules, tablets, and concentrated extracts—are available either from Internet-based suppliers or specialty stores commonly known as “head shops”, “vaping shops” or “smoke shops”. (Adkins et al., 2011; Boodman, 2016; Kroll, 2016; Prozialeck et al., 2012), unlike in traditional settings where kratom is usually sold as freshly-brewed teas and decoctions (Singh, Narayanan, & Vicknasingam, 2016). The growth of kratom use in the West parallels increasing concerns about the safety and abuse potential of kratom. The emerging controversies regarding kratom were highlighted in August of 2016, when the US Drug Enforcement Administration (DEA) announced plans to place the main active constituent of kratom, mitragynine, and a structurally related compound, 7-hydroxymitragynine, in Schedule I of the Controlled Substances Act (CSA), using its emergency scheduling authority (DEA, 2016b). This action would have restricted the use of kratom in the US and made it extremely difficult for researchers to investigate the medicinal potential of kratom (Prozialeck, 2016). The DEA’s

proposed action sparked an unprecedented public debate and protest, with thousands of kratom users filing comments in the Federal Register supporting the usefulness of kratom for the self-treatment of chronic pain or OUD without major abuse potential (DEA, 2016a). In response to the intense public outcry, the DEA withdrew its notice of intent to schedule kratom and has placed the final decision on indefinite hold pending an 8-factor analysis by the US FDA (DEA, 2016b, 2016c; Kroll, 2016; Prozialeck, 2016). As of this writing, kratom remains legal throughout most of the US, although a few states, including Alabama, Arkansas, Indiana, Vermont, and Wisconsin, have banned it. On October 17, 2017, the US Department of Health and Human Services asserted in a new letter to the DEA that mitragynine and 7-hydroxymitragynine should be classified as Schedule I controlled substance, a move that would severely restrict kratom use in the United States (Swetlitz, 2018). The details and timeframe for such a policy have yet to be worked out.

With regard to international regulatory agencies, neither kratom, nor any of its alkaloids, are currently listed in the 1961 and 1971 Schedules of the United Nations Drug Conventions, although kratom has been criminalized in Thailand, Malaysia, Myanmar, and Australia, as well as several European nations. Notably, officials in Thailand have thrice considered ending their kratom ban since 2000, citing no known cases of overdose, death, or violence following at least 100 years of traditional use. Kratom-based drugs are currently classified as New Psychoactive Substances (NPS) by the United Nations Office on Drugs and Crime (UNODC), but do not appear on the agency's list of emerging drug threats (UNDOC, 2019). The European Union has taken a position that there is no approved use of kratom or its alkaloids in modern medicine (EMCDDA, 2015).

The legal uncertainty surrounding kratom appears to arise from two opposing narratives. The first is that kratom has potential therapeutic value as a substitute for classical opioids (e.g. morphine, oxycodone, heroin, etc.), providing safer pain management and a novel way for people who have OUD to wean themselves from the more dangerous opioids (Grundmann, Brown, Henningfield, Swogger, & Walsh, 2018; Henningfield, Fant, & Wang, 2018; Ward, Rosenbaum, HERNON, McCurdy, & Boyer, 2011). The second narrative is that kratom is a dangerous and addictive opioid, and therefore, should be classified in Schedule I of the US CSA (Gauvin & Zimmermann, 2018; HHS, 2018).

Given the widespread use of kratom and the extensive media attention it is receiving, physicians, scientists, and policy makers must be knowledgeable about the science of kratom. The purpose of this commentary is to provide an update about recent developments and controversies in this rapidly evolving area from the perspective of scientists who are actively engaged in various aspects of kratom research. In this commentary, we will address several key issues related to the opioid-like effects of kratom, uncertainties about its toxicities and addictive potential, as well as questions about its efficacy in the treatment of pain and OUD.

Should mitragynine and/or other kratom constituents be classified as opioids?

In describing their rationale for scheduling kratom (DEA, 2016b), the DEA emphasized that the mitragynine-type indole alkaloids can interact with opioid receptors and produce some opioid-like effects (Adkins et al., 2011; Kruegel & Grundmann, 2018; Matsumoto et al., 2006; Thongpradichote et al., 1998). In 2018, the FDA went further by publishing the results of its own molecular modeling study suggesting that there were more than 20 substances in kratom that could theoretically interact with opioid receptors (FDA, 2018c). A major short-coming of these molecular modeling studies is that the molecules were never tested to determine if they did, in fact, have opioid agonist activity in living cells or organisms (Grundmann et al., 2018). In considering the active compounds in kratom, it is important to note that the most well-documented pharmacological effects of kratom, namely analgesic activity and attenuation of opioid withdrawal symptoms, can be explained largely by the actions of mitragynine, the primary alkaloid and also the most studied (Kruegel & Grundmann, 2018; Takayama et al., 2002). Other alkaloids are either devoid of known pharmacological activity and/or, like 7-hydroxymitragynine, are present at such low levels as to not be considered factors in kratom effects or toxicity (Adkins et al., 2011; Kruegel & Grundmann, 2018; Takayama et al., 2002; Takayama, 2004). It is also important to note that mitragynine has other pharmacological actions that remain understudied. For example, in preclinical studies, mitragynine has been found to modulate central serotonergic and adrenergic transmission (Matsumoto et al., 1996) and inhibit prostaglandin production (Utar, Majid, Adenan, Jamil, & Lan, 2011). Furthermore, mitragynine has been shown to interact directly with other CNS drug targets, rendering it distinct from classical opioids (Boyer, Babu, Adkins, McCurdy, & Halpern, 2008; Kruegel & Grundmann, 2018). It is also important to note that the functional activity of mitragynine at these targets may vary from agonist to antagonist, but this is yet to be determined.

Most of the scientific evidence on kratom's opioid-like activity is derived from findings in cell and animal studies, where mitragynine has been found to bind to and activate opioid receptors, and induce opioid receptor-dependent analgesic effects (Adkins et al., 2011; Boyer et al., 2008; Kruegel & Grundmann, 2018; Prozialeck et al., 2012; Stolt et al., 2014; Yusoff et al., 2016). While no well-controlled trials of kratom in humans have been conducted, anecdotal reports and larger, carefully conducted surveys have shown that people have used kratom to successfully treat pain and OUD effects (Grundmann, 2017; Swogger & Walsh, 2018), consistent with actions at opioid receptors. In addition, anecdotal reports and commentaries indicate that some effects of kratom in humans, such as mild euphoria, may resemble those of opioid agonist drugs (Singh, Muller, Vicknasingam, & Mansor, 2015, 2016; Vicknasingam et al., 2010), but there is also strong evidence indicating that kratom's effects are distinct from those of classical opioids (Henningfield et al., 2018; Singh, Muller, & Vicknasingam, 2014, 2015, 2016; Vicknasingam et al., 2010). For example, at low to moderate doses, kratom has mild stimulant properties, unlike the sedating effects often exhibited by opioids. In addition, kratom does not seem to produce an intense high or euphoria at typical doses (Cinosi et al., 2015; Erowid, 2016; Prozialeck et al., 2012; speciosa.org, 2016; Wisdom, 2016). The most significant difference from opioids is that,

even at very high doses, kratom is much less likely to depress respiration (to a fatal degree) than classical opioids (Singh, Narayanan et al., 2018, 2016; Varadi et al., 2016). Further, at the molecular level, mitragynine has a chemical structure that is quite different from classical opioids such as morphine, which are mostly derived from the alkaloids of the opium poppy (Adkins et al., 2011; Kruegel & Grundmann, 2018; Prozialeck et al., 2012; Takayama, 2004). Recent studies indicate that even though mitragynine acts on opioid receptors, its over-all molecular actions are quite different from those of classical opioids (Henningfield et al., 2018; Prozialeck et al., 2012). In two recent studies, Varadi et al. (2016) and Kruegel et al. (2016) demonstrated that mitragynine and several related compounds act as G protein-biased agonists at the mu-opioid receptor (MOR). In other words, although they activated G protein-mediated signaling pathways, much like classical opioids, they did not activate the β -arrestin-2 signaling pathway, which has been implicated as a mediator of some opioid-induced side effects, including respiratory depression (Raehal & Bohn, 2014; Schmid et al., 2017). Accordingly, the avoidance of β -arrestin-2 activation may in part explain the apparent respiratory safety of kratom, despite other opioid-like effects. These studies also showed mitragynine to be a partial agonist at MOR, as compared to most classical opioids, which are full agonists. Partial activity is also expected to attenuate the severity of side effects. For example, buprenorphine, a partial agonist at MOR, exhibits a dose ceiling for respiratory depression (Dahan et al., 2005).

Importantly, the improved side effect profile of mitragynine and related compounds has also been supported by preliminary animal studies. An early study with mitragynine demonstrated attenuated respiratory depression and constipation for this compound compared to the classical opioid morphine in several animal species (Macko, Weisbach, & Douglas, 1972). Further, the Varadi study (Varadi et al., 2016) demonstrated in mice that a mitragynine-derived compound, mitragynine pseudoindoxyl, induced marked analgesic effects, but with attenuated respiratory depression, slower development of tolerance, and lower rewarding effects than morphine. Accordingly, both the natural compounds in kratom (e.g. mitragynine) and synthetic derivatives thereof may represent a new class of opioid-acting drugs with an improved window between therapeutic effects and negative side effects.

As a result of its ability to interact with opioid receptors, mitragynine is often referred to as an “opioid”. On the other hand, a large volume of evidence indicates that mitragynine produces physiological, biochemical and behavioral effects that differ from those of classical opioids. Even though some effects of mitragynine may involve partial activation of MOR, mitragynine is able to interact with many other receptors that classical opioids do not bind (Boyer et al., 2008). In light of this evidence, mitragynine and its analogs can best be described as “atypical opioids” (Raffa, Pergolizzi, Taylor, Ossipov, & Group, 2018), and may actually represent a unique class of drugs.

Is kratom effective for the management of pain and/or OUD?

OUD continues to be a growing problem in the US, and the federal government has begun to address the challenge (Frieden & Houry, 2016; Harris, 2016; Nelson, Juurlink, & Perrone, 2015; NIDA, 2018b). Among actions taken by the federal government, the most significant has been the development of new guidelines by the Centers for Disease

Control and Prevention (CDC) for the prescribing of opioids, for non-cancer pain (Dowell, Haegerich, & Chou, 2016). In this environment, physicians are discouraged from prescribing opioids, especially for long-term usage, a strategy that has compelled patients with chronic pain conditions to seek alternatives to prescription opioid analgesics (Anson, 2016; Pain News Network, 2018; Smith & Lawson, 2017; Swogger et al., 2015). In addition, many patients receiving opioids for chronic pain seek alternatives that have fewer side effects and lower addiction potential than opioids (Anson, 2016; Pain News Network, 2018; Smith & Lawson, 2017; Swogger et al., 2015).

Many individuals in the West have turned to kratom in the belief that it may provide an effective and safe alternative to prescription or illicit opioids, a view voiced by peers on psychoactive substance websites such as Erowid.org (Erowid, 2016), SageWisdom.org (Wisdom, 2016), speciosa.org (2016) and Reddit.com/r/kratom (Reddit, 2018). However, kratom has not been evaluated in the types of multi-center, controlled clinical trials that are required by regulatory authorities, such as the US FDA, to conclude that a drug is safe and effective for the treatment of OUD or other indications. Nonetheless, kratom has a long history of such use that is widely accepted in the general population in Southeast Asia, where it is commonly used as an affordable substitute for street heroin or other opioids (Vicknasingam et al., 2010). For example, a study conducted in northern Malaysia used convenience sampling to identify and survey 136 kratom users (99% male) in areas where heavy kratom use was reported (Vicknasingam et al., 2010). Results indicated that 90% of the subjects were using kratom as a substitute for illicit opioids and 84% reported that kratom helped to reduce their dependence on opioids and severity of withdrawal symptoms. Another Malaysian survey (Singh et al., 2015) used snowball sampling to enroll 293 adult males, most of whom were manual laborers who had used kratom for at least six months. Fifty percent indicated that they had used kratom to eliminate addictions to illicit substances, including opioids and cannabis, and/or to relieve withdrawal symptoms. Such use has increasingly been reported in the US through internet surveys of kratom users (Grundmann, 2017; Grundmann et al., 2018; Smith & Lawson, 2017), and in more than 23,000 comments to the DEA and FDA (DEA, 2016a; Henningfield et al., 2018). Thus, even though we do not make the claim that kratom should be viewed as a medically proven effective and safe therapy for OUD, we believe it is warranted to take seriously the extensive user reports and analytical surveillance indicating that many people are self-managing their OUD using kratom. Such information may be considered a form of Real-World Evidence that is taken seriously by users and many scientists and should not be ignored by the FDA which has stated that “Real world data (RWD) and real world evidence (RWE) are playing an increasing role in health care decisions” and is used to make “regulatory” decisions.

The situation is analogous with respect to the management of pain, where kratom has not been approved as an analgesic medicine, but relief of pain is among the more commonly reported uses (Grundmann, 2017; Henningfield et al., 2018; Pain News Network, 2018; Swogger et al., 2015). Caution is warranted in comparing results from these studies, as doing so requires accounting for potential cultural, demographic, and product-related moderators of effects and bias introduced due to research methodology. Nonetheless, the results of observational studies of kratom users in the US converge with case reports and descriptions of traditional kratom use in Southeast Asia to suggest that kratom does have utility as a

substitute for potentially more dangerous classical opioids in treating pain and OUD and should be studied in well-controlled clinical trials for such indications (Henningfield et al., 2018). It is also worth noting that the extensive anecdotal reports of analgesic activity in humans are consistent with the partial agonist activity of mitragynine at MOR and findings in animal models of pain, where mitragynine and kratom extracts exhibit analgesic activity.

With respect to the use of kratom for self-management of OUD, the statements by the US National Institute on Drug Abuse (NIDA) and the FDA are quite distinct. The FDA's position is that kratom use can cause deleterious health risks and that kratom users should turn to approved treatments (FDA, 2018c), despite the reality that many such users have commented to the DEA and FDA that such treatments were not available or acceptable, whereas kratom was accessible and helpful. In contrast, without discouraging or encouraging kratom use, NIDA simply states the facts on its website that kratom (1) is used by people to self-manage withdrawal and OUD and (2) that kratom has not been demonstrated to be safe and effective for pain treatment, in contrast to available opioid medications (NIDA, 2018b).

The many positive user comments on [Erowid.org](https://www.erowid.org) (Erowid, 2016), [SageWisdom.org](https://www.sagewisdom.org) (Wisdom, 2016), [Reddit.com/r/kratom](https://www.reddit.com/r/kratom) (Reddit, 2018) and [Speciosa.org](https://www.speciosa.org) (speciosa.org, 2016) comprise an extensive collection of anecdotal data documenting kratom use. Scientific analyses of such user reports clearly indicate that the therapeutic potential of kratom is too large to be ignored (Swogger et al., 2015). The 23,000+ comments submitted to the federal register in response to the DEA's proposed scheduling action also provide a vast collection of anecdotal data suggesting profound therapeutic benefits for kratom (DEA, 2016a). Another piece of evidence suggesting that kratom may have significant therapeutic potential is that US patents have been issued for companies and individuals who are interested in developing kratom-based drugs (Heyworth, 1964; Takayama, Kitajima, Matsumoto, & Horie, 2008). Together, these observations provide evidence that kratom may have potentially useful therapeutic effects, and that well-controlled clinical trials are urgently needed to evaluate the safety and efficacy of kratom and its principal alkaloid mitragynine.

Many kratom advocates have claimed that kratom is a safe and effective alternative to opioids for the treatment of OUD (Erowid, 2016; Singh et al., 2016; Toce, Chai, Burns, & Boyer, 2018). In this context, kratom is analogous to agents such as methadone and buprenorphine, which are widely used as replacement therapies in the treatment of OUD despite the fact that the treatment agents themselves may have significant potential for abuse (Eibl, Morin-Taus, & Marsh, 2016; HHS, 2016; Toce et al., 2018). Kratom (or compounds derived therefrom) may, in fact, have even greater therapeutic potential, especially in light of evidence suggesting that it lacks the severe overdose risk of classical opioid drugs, including methadone (Singh et al., 2014, 2015; Singh et al., 2016; Toce et al., 2018). In fact, more than 3,000 methadone-related fatalities were reported in the US in 2017 (NIDA, 2018a), suggesting that existing FDA-approved therapies for OUD have significant safety shortcomings that might be addressed in part by alternative kratom-based therapies.

How serious are the abuse and addiction potentials of kratom?

Regular use of kratom, particularly at higher doses, can lead to tolerance and dependence (Galbis-Reig, 2016; Singh et al., 2014; Swogger & Walsh, 2018; Yusoff et al., 2016). However, available human reports suggest that abstinence from kratom is typically associated with milder symptomatology than abstinence from classical opioids (Erowid, 2016; Singh, Narayanan et al., 2018, 2014; Singh et al., 2016). At the same time, although these reports indicate that the effects of kratom can, in some ways, resemble those of opioids, many individuals report that the subjective effects of kratom are quite different from those of opioids. As noted previously, low to moderate doses of kratom tend to be somewhat stimulating, rather than sedating, and do not produce the “high” or strong euphoric effects associated with opioids, although some users have reported intoxication and euphoria after using higher doses (Erowid, 2016; Singh et al., 2016; speciosa.org, 2016; Swogger et al., 2015; Wisdom, 2016). This distinct spectrum of effects, including attenuated euphoria and abuse potential, is supported by two recent preclinical studies, which found that mitragynine is not self-administered by rats (Hemby, McIntosh, Leon, Cutler, & McCurdy, 2018; Yue, Kopajtic, & Katz, 2018). Further, even at high doses, kratom does not appear to severely depress respiration as do classical opioids (Singh et al., 2014, 2016). Thus, even though kratom has some potential for abuse and dependence, several investigators have concluded that kratom has both less abuse liability and much lower risk of fatal overdose than traditional opioids and that the potential benefits of kratom in the treatment of OUD may outweigh these risks (Henningfield et al., 2018; Singh et al., 2014, 2015; Singh et al., 2016; Swogger et al., 2015). This does not mean that kratom is not sometimes used by people to get high and/or intoxicated because such use has been documented (Swogger et al., 2015). Such findings were also considered by Henningfield et al. (2018), who concluded that the overall assessment of kratom did not warrant it being listed as a controlled substance. They noted that many substances, including over-the-counter drugs (for cough and cold symptoms) and dietary ingredients, are also sometimes misused and abused for the purposes of causing intoxication and to get high, yet overall, seem appropriately left unscheduled.

Are kratom products safe?

In recent years, kratom use has been associated with increasing reports of adverse health effects, including death in rare cases (Anwar, Law, & Schier, 2016; Forrester, 2013; Ulbricht et al., 2013; Warner, Kaufman, & Grundmann, 2016). These increases in adverse events were cited as a major rationale for the DEA’s proposal to ban kratom (DEA, 2016b). However, there is no concrete evidence to prove that kratom was the main culprit in all 44 total fatalities reported worldwide by the FDA as of 2018 (FDA, 2018c). At low to moderate doses of 5 g of raw leaves or less, the adverse effects vary markedly from one individual to another, but generally appear to be mild (Anwar et al., 2016; Prozialeck et al., 2012; Singh et al., 2014, 2016). The most common adverse effects are anxiety, irritability, nausea and vomiting (Anwar et al., 2016; Prozialeck et al., 2012; Singh et al., 2014; Swogger et al., 2015). More troubling have been occasional reports of more serious toxicities, often associated with high dose usage or usage of concentrated extracts in the West. Some of the reported adverse effects include tachycardia, liver damage, and seizures (Dorman, Wong, & Khan, 2015; Kapp, Maurer, Auwarter, Winkelmann, & Hermanns-Clausen, 2011; Lu et

al., 2014; Nelsen, Lapoint, Hodgman, & Aldous, 2010; Pantano et al., 2016). In addition, several deaths have been attributed to the use of “kratom” products (Anwar et al., 2016; DEA, 2016b; FDA, 2018c; Gershman et al., 2019; Karinen, Fosen, Rogde, & Vindenes, 2014; McIntyre, Trochta, Stolberg, & Campman, 2015; Neerman, Frost, & Deking, 2013; Warner et al., 2016; Wing, 2018), although in many such cases causality was not clearly linked given that little is known about lethal dose levels of kratom in humans (Gershman et al., 2019; Wing, 2018). Further, in some cases, severe adverse events may stem from the use of adulterated “kratom” products contaminated with other substances (including potent synthetic opioids) or where the content of the principal alkaloids mitragynine and 7-hydroxymitragynine is enriched compared to natural leaf material (Kronstrand, Roman, Thelander, & Eriksson, 2011; Lydecker et al., 2016). In contrast, when used in its traditional context, pure kratom leaf is unlikely to produce serious adverse effects in the vast majority of users (Trakulsrichai et al., 2013). In fact, there have been no reported deaths attributed to kratom in Southeast Asia when used in the traditional setting as unadulterated, pure kratom leaf.

While the foregoing summary indicates why the FDA’s and DEA’s concerns about the safety of kratom are reasonable, several factors require consideration in evaluating whether the FDA’s and DEA’s proposed bans are justified. First are the relative statistics. In announcing their decision to ban kratom, the DEA emphasized that between January 2010 and December 2015 there had been 600 calls to poison control centers regarding adverse reactions to kratom products (DEA, 2016b). More recently, the FDA has reported 44 total deaths associated with use of kratom products worldwide (FDA, 2018c). While these might seem on their face to be alarming numbers, they are actually rather small compared to the 49,000+ opioid overdose *deaths* in 2017 alone (NIDA, 2018a). In addition, the extent to which kratom played a role in the available lethal case reports is uncertain. In the majority of these case reports associating kratom with lethal outcomes, patients have had confounding health conditions, have been using other drugs along with kratom, or both (Galbis-Reig, 2016; Gershman et al., 2019; Prozialeck et al., 2012; Singh et al., 2015, 2016; Wing, 2018). Moreover, in the absence of evidence for a defined mechanism by which kratom would lead to death (e.g. respiratory depression), these anecdotal reports involve considerable speculation and do little to establish a scientific backing for the proposition that kratom is potentially deadly.

One of the major problems in evaluating the potential uses and safety of an herbal agent such as kratom is the lack of understanding of how mitragynine and other substances in kratom may interact with each other, prescription medications, drugs of abuse, or even herbal supplements (Prozialeck et al., 2012; Ulbricht et al., 2013). Recent findings show that kratom and its alkaloids are direct inhibitors and/or transcriptional inducers of a number of cytochrome P450 enzymes and P-glycoprotein, suggesting a significant potential for kratom to cause complex herb-drug interactions that require further study (Hanapi, Ismail, & Mansor, 2013; Kong et al., 2011; Lim et al., 2013; Manda et al., 2014, 2017). These issues are compounded by a lack of regulations and standardization related to the production and sale of “kratom” products. Further, an increasing body of evidence supports the hypothesis that many unscrupulous purveyors of “kratom” are adulterating their products with potentially toxic drugs (Chittrakarn, Penjamras, & Keawpradub, 2012; Griffin et al.,

2016; Lydecker et al., 2016; Scott, Yeakel, & Logan, 2014). Probably the most notorious example of such adulteration involved a product known as “Krypton”, which was touted as a very potent form of kratom. It was sold mainly in Europe and was found to be a factor in at least 9 deaths (Kronstrand et al., 2011; Nelsen et al., 2010). Detailed forensic analyses, however, revealed that Krypton was adulterated with large amounts of the synthetic opioid *O*-desmethyltramadol, which has potent opioid and neuromodulator activity (Kronstrand et al., 2011). Even though mitragynine was also detected in the products, it was not determined how the two substances may have interacted to cause death. In another study, several purported kratom products were found to contain 7-hydroxymitragynine (a more potent opioid alkaloid) at concentrations significantly higher than those found in plain leaf products (Lydecker et al., 2016). The source of the high levels of 7-hydroxymitragynine reported in that study remains unclear. More recently, the FDA has raised concerns about the contamination of kratom products with *Salmonella* (FDA, 2018a) and toxic metals (FDA, 2018b). These reports of contamination of some kratom products highlight the need for quality control policies in the production and sale of kratom.

Without standardization, use of good manufacturing practices, and strict quality control measures by manufacturers and distributors, individuals who ingest “kratom” products cannot be sure what they are taking. This problem suggests that systematic and cautious regulation of kratom products is likely to improve their safety. Such regulation and standardization is certainly needed, but it is unclear how such quality control programs can be developed and administered. One possible approach might be to use typical concentrations of mitragynine and 7-hydroxymitragynine found in kratom leaf as ceilings for alkaloid content of all products. It would also be essential that the products be tested to show that they have not been fortified or contaminated with other substances, particularly opioid derivatives. The American Kratom Association has recently announced plans to address many of these issues by adopting a set of “Good Manufacturing” standards for the kratom industry (American Kratom Association, 2018b).

Despite the quality control issues with kratom products in the West, a large number of scientists have stated that in its traditionally used form (kratom leaf decoction or powdered leaf form), kratom appears to be relatively benign, especially in comparison to classical opioids such as hydrocodone, oxycodone, or heroin (Singh et al., 2015, 2016; Trakulsrichai et al., 2013). In writing these comments, we wish to emphasize that we, too, have concerns about the safety of so-called “kratom” products. Moreover, since kratom contains pharmacologically active compounds (which it clearly does), it certainly has potential toxicities. Nevertheless, the scientific literature supports the conclusion that, in pure herbal form and in moderate doses of less than 5 g, pure leaf kratom appears far less dangerous than classical opioids. Recent kratom studies from Southeast Asia show that long-term kratom use does not appear to alter hematological and biochemical parameters (Singh, Muller et al., 2018) or interfere with users’ abilities to function in society (Singh et al., 2015). So far, no serious health incidents associated with kratom use have been reported among regular users in traditional settings.

Summary and perspective

Kratom is widely used in the West and Southeast Asia as a relatively safe herbal supplement (traditional medicine) for the self-treatment of medical disorders, including pain and OUD. Extensive reports from kratom users, considered alongside limited basic science and clinical research studies, suggest that kratom and its constituent compounds (especially mitragynine) may in fact have beneficial pharmacological and therapeutic properties. Unfortunately, no well-controlled clinical trials have been performed to date to determine the true risks and benefits of kratom use in humans. The high monetary costs of such clinical trials greatly complicate this issue, given that sufficient intellectual property protection to justify the large capital investments necessary for formal drug approval is often challenging to obtain for natural products like kratom. In response to the growing concerns about safety and abuse/addiction potential, it appears that the DEA is planning to classify kratom, mitragynine, and 7-hydroxymitragynine as Schedule I controlled substances, despite the preponderance of preclinical and anecdotal human evidence indicating that kratom is less harmful than prescription opioid analgesics or illicit opioids.

We believe that actions by the FDA and DEA to classify mitragynine as a Schedule I controlled substance could have several unintended consequences. First, such a classification would likely foster a significant “black market” for kratom products. Many thousands of individuals in the US have been using kratom as a means of avoiding use of more dangerous classical opioids and are terrified of losing what they view as a life-line to sobriety (Anson, 2016; DEA, 2016c; FDA, 2018c; Henningfield et al., 2018). It is reasonable to conclude that under Schedule I restrictions, a subset of kratom users would turn to or return to prescription or illicit opioids, resulting in an increase in unintended negative public health consequences, including higher incidence of OUD, incarceration, and overdose death. A second potential problem is that a move of kratom or its constituents to Schedule I will make it much more difficult for researchers to conduct necessary research exploring kratom’s medicinal potential (Chen, 2016). In this regard, the legal milieu surrounding kratom is comparable to what has happened with “medical marijuana” and psychedelic-assisted therapies, where federal policies, including classification as a Schedule I substance, have impeded hypothesis-driven research investigations (Belouin & Henningfield, 2018; Stith & Vigil, 2016). Many institutions and government agencies are reluctant to fund research on Schedule I substances because such work involves infrastructure and resources that many institutions lack (Belouin & Henningfield, 2018).

Even in the absence of cumbersome controlled substance regulation, many practical issues complicate research on herbal products such as kratom. For example, what type of kratom products (extracts or leaf materials) should be evaluated? How would products be “standardized” for activity? Since kratom contains a mixture of active compounds, this would be an extremely complex problem to resolve. One solution might involve focusing on specific chemical constituents, such as mitragynine. However, in studying single molecular entities, researchers might miss important contributions of other active constituents in kratom. This would require additional studies on the interactions of mixtures of compounds from kratom. Another major challenge is presented by the correlation of human consumption practices with laboratory animal models. Clearly, more scientific

research is needed to address these issues, which would be much more challenging under Schedule I regulatory policies.

Kratom/ketum has been traditionally used in Southeast Asia for at least the last century for its medicinal properties. This traditional use of unadulterated, natural kratom leaf has not resulted in large-scale abuse and toxicity. Further, significant evidence of the benefits of kratom gleaned from this traditional use certainly warrants further study. We conclude that well-designed, controlled human clinical trials are needed to more thoroughly investigate the therapeutic and addictive potential of kratom; to establish safety and toxicology limits; and also, to evaluate pharmacological responses among various populations who might consume kratom. The effects of kratom in the general population are poorly described, while data on special populations, such as children, elderly, pregnant females and the developing fetus, and patients with confounding health conditions, are essentially non-existent. Finally, almost nothing is known about how kratom might interact with other drugs or herbal agents that subjects may be using. Unfortunately, future control as a Schedule I substance would erect substantial barriers to this necessary research. Furthermore, the source of funding for such work is unclear, given the limited commercial opportunity provided by unpatentable natural products. One possible approach to begin funding research might be for kratom trade organizations and/or vendors to provide research grants to members of the scientific community. Also, kratom provides avenues for entrepreneurial-driven research, much like what is now happening in the burgeoning marijuana industry. Despite these significant challenges, clinical trials into the safety and efficacy of kratom and mitragynine can and should be done. It is our sincere hope, as kratom researchers, that this commentary will facilitate an informed discussion about kratom and foster the necessary research to resolve the scientific and regulatory issues presented here.

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While this manuscript was under review, one of our co-authors, Dr. Bonnie Avery, passed away after a courageous battle with cancer. Dr. Avery was a leader in kratom research, an outstanding colleague and a wonderful person. We hereby dedicate the paper to Dr. Avery. She will be missed, but not forgotten.

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