



Kratom's Emergence and Persistence Within the US Polydrug Epidemic

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Abstract

Purpose of Review Use of “kratom” products, derived from the bioactive botanical *Mitragyna speciosa* have increased amidst US polydrug use epidemics. Kratom alkaloids interact with opioid, serotonergic, adrenergic, and other receptors and regular users have described experiencing a wide range of effects. Some with polydrug use histories have reported using kratom as a substitute for other drugs or to nonmedically self-manage substance use disorder (SUD) symptoms. Data describing this remain scarce and come from self-report. We review this literature describing kratom use as a drug substitute, or as a nonmedical “self-treatment” for attenuating dependence or SUD symptoms.

Recent Findings Kratom products have been documented as being used as a licit and illicit opioid substitute. Use to reduce alcohol or stimulant consumption is less well documented. Although prior and current polydrug use appear common among a some kratom users, it is unclear if co-use is contemporaneous or concomitant. Temporal order of use initiation is typically undocumented. Use for energy and recreation are also increasingly reported.

Summary Data on kratom consumption come primarily from self-report with significant limitations. Until controlled human laboratory studies have been conducted, we can presently only describe what is known about human kratom use based on self-report. Such data describe real-world kratom use, leaving unaddressed human abuse liability or therapeutic potential of kratom alkaloids. Clinicians should be mindful of use motivations among people with SUD histories, sensitively assessing use. The paucity of data highlights the urgent need to increase funding and research for understanding kratom's effects in humans.

Keywords Kratom · Opioids · Stimulants · Alcohol · Polydrug use · Harm-reduction

Introduction

Use of the psychoactive botanical *Mitragyna speciosa* (commonly referred to as “kratom”) in the USA is novel relative to use in Southeast Asia, where it is indigenous and has been used for at least centuries under varying legal conditions [1–4]. The novelty of kratom compared to Asian countries notwithstanding, kratom and kratom-derived products (which differ than fresh leaf preparations available

in Southeast Asia and should not be conflated with them) can no longer be considered “novel” in the USA. Although kratom may be considered obscure compared to traditional psychoactive substances, it has been increasingly used in the USA since 2006 [5, 6]. Its prevalence, while still poorly estimated, has grown over the past 15 years, with regular users numbering in at least the low millions but possibly more [7–10]. Presently, the kratom industry grows amidst an uncertain regulatory landscape and offers an increasing variety of branded kratom products beyond the whole leaf used traditionally in Asia [11, 12].

The initial uptake of kratom in the USA in the early 2000s is likely not coincidence, nor is the continued proliferation and diversification of kratom products surprising. The first documentation of kratom use in the USA occurred during a time when opioid prescribing and diversion was at its apex and coincided with changes in opioid prescribing guidelines, implementation of state prescription monitoring systems, and abuse-deterrent opioid formulations [13–18].

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It also coincided with increased availability of heroin and fentanyl [19–22]. Although some people supplemented or substituted prescribed opioids with heroin or switched to heroin once their prescription medications were decreased or discontinued, others, as we will discuss, turned to kratom as a substitute for prescription opioids and later, for another subset of users, as a substitute for heroin. It remains unclear, however, the extent to which kratom has been used as a substitute for stimulants and alcohol, or to decrease polydrug use that includes some combination of these commonly used drugs. It is critical to emphasize that what has been documented about kratom use in the USA, including reasons for use come nearly exclusively from self-report data.

Preclinical work shows that some kratom alkaloids can produce dose-dependent stimulatory and analgesic effects suggesting some alkaloids may have eventual therapeutic potential for targeting substance use disorders (SUDs) involving opioids, stimulants, or alcohol, even as there are signals that kratom can produce dose-dependent withdrawal [23–31]. Broader kratom use among people for addressing polydrug dependence or addiction, particularly to alcohol, amphetamines, or opioids, has been self-reported among people who use fresh kratom preparations in Asia [32–36].

In the USA, kratom's emergence is contextualized by the US opioid epidemic and the fact that this is but one of several ongoing drug epidemics. More accurately, we might characterize the US burden attributable to drugs, in terms of morbidities, mortalities, and lost productivity, as one resulting from a polydrug use epidemic and one that primarily (though not exclusively) involves opioids, stimulants, and alcohol [37–43]. Kratom has a place within this broader polydrug use epidemic, yet this may be overlooked by those unfamiliar with kratom or who have not encountered its use among patients in addiction practice [44•]. As kratom use persists, we must develop a better understanding of kratom's place among those with drug use histories. Our purpose here is to review the small but growing US literature documenting kratom use as an opioid, stimulant, or alcohol substitute, or as a nonmedical “self-treatment” for attenuating dependence or addiction symptoms associated with these drug classes. To be clear, when we say “substitution” we do not mean to imply drug discrimination studies have been conducted with kratom. They have not. We refer to substitution as those who use kratom have reported it on surveys in the behavioral economic sense of the word “substitute” wherein one commodity can serve as a substitute for a similar commodity. We also want to emphasize that the body of literature we review here is small and comprised entirely of self-report research, supported by some case reports. In these respects, it is limited on the overall picture it can provide. The implications of these limitations will be discussed in turn. We will also briefly review recreational kratom use, including conceptualization and use as a cognitive, mood,

or performance enhancement. We will then consider how kratom might be best provisionally characterized given the variability of kratom products, their effects, and the dearth of human studies. We conclude by providing recommendations for clinicians and researchers seeking to assess and study this complex plant and the variable products derived from it within a context that often includes other substance use.

Drug Substitution and Nonmedical “Self-Treatment” in the Context of Polydrug Use

Although some place kratom's US introduction contemporaneous to the Vietnam War (indeed one author, KES, has anecdotal information to this effect), it remains unsubstantiated and only plausible speculation [45]. The earliest documented account of kratom's use as a self-described substitute or nonmedical self-treatment was in 2007 among adults with chronic pain who self-treated with opioid analgesics purchased from an online pharmacy but who then began openly discussing kratom use to attenuate opioid withdrawal [6]. This was contemporaneous to a case report [46] of a chronic pain patient who had been intravenously using hydromorphone but who reported transitioning to kratom tea (used four times daily) to self-treat pain and opioid withdrawal symptoms while increasing “alertness.” This patient eventually co-administered kratom with modafinil, a psychostimulant with low abuse potential prescribed for sleep disorders. Upon cessation of kratom use, the patient reported mild withdrawal symptoms and was maintained on 16 mg daily buprenorphine. This case report is striking in that it is the first in the USA to document some self-reported effectiveness in using kratom to mitigate opioid withdrawal symptoms and also that kratom withdrawal symptoms upon cessation were deemed modest. Another UK-based report described a patient with a history of alcohol dependence and anxiety who ultimately became dependent on kratom and experienced mild kratom withdrawal of short duration managed by dihydrocodeine and lofexidine [47].

Since then, there have been numerous US-based cases documenting patient-reported kratom use motivations that included substituting or supplementing prescription opioids, attenuating acute opioid withdrawal, or otherwise “self-treating” dependence and addiction to licit and illicit opioids [4, 48–51]. As those case reports are reviewed elsewhere [52] we do not review them here. Kratom use motivations documented in some reports also describe kratom initiation as a means of reducing or substituting alcohol use [53, 54], but not clearly as a substitute for stimulants. This is interesting in that kratom's stimulant effects have been documented via survey and social media self-report. This was first recognized by [55] in a qualitative analysis of

Erowid data. Examining 198 reports made on the drug forum website by people with polydrug use histories, the authors found a range of self-reported kratom effects that included increased energy, analgesia, warmth, tingling, and sensory enhancement. They also found that kratom was used as a replacement, or substitute, for substances they considered problematic, including opioids (heroin and oxycodone), antidepressants, and benzodiazepines. Alcohol and stimulant substitution were not explicitly mentioned.

In 2017, survey findings from two distinct populations provided further support for the possibility that kratom was being used as a drug substitute or address opioid dependence and opioid use disorder (OUD) symptoms. In a large national online convenience sample ($N=8049$), 1813 people reported using kratom because of a prescription opioid dependency and 539 reported using because of an illicit drug (heroin, cocaine, amphetamine, cannabis) dependency, with the former group slightly older on average and the latter slightly younger [56]. In another convenience sample ($N=500$) of residential drug treatment clients with polydrug use histories, 20.8% had ever tried kratom [57]. Of this group, 68.9% reported using kratom specifically to “cut back on or get off of heroin, opiates, prescription painkillers” and “reduce or stop using opiates or heroin” and 64.1% reported using kratom “as a substitute for opiates or heroin.” Although alcohol, stimulants (methamphetamine and cocaine), and prescription opioids were widely used and preferred by respondents, alcohol and stimulant substitution was not investigated. The extent of contemporaneous co-use of kratom with other substances is unclear in both surveys, yet past-year use of kratom and other substances was found among the clinical sample. Data from the 2020 National Survey on Drug Use and Health (NSDUH) indicate that among people who used stimulant drugs (i.e., cocaine, methamphetamine, MDMA, and prescription stimulants) in the past year, past-year kratom use was overrepresented relative to the US population (20.8% vs. 6.6%, $F(1, 50) = 10.62$, $p = 0.002$) [58]. Indeed, data from both surveys and case reports document lifetime, past-year, or past 30-day use of kratom and contemporaneous use of alcohol, opioids, and/or stimulants, but no causal or otherwise explanatory associations can be made with respect to polydrug use broadly or drug substitution or nonmedical management of SUD symptoms specifically [59–63]. These findings have not been detected among US adolescents (there, nicotine and cannabis displayed the strongest relationship) [64]. In other examinations of nationally representative samples, lifetime kratom use was associated with amphetamine use and higher burden of multiple SUDs, particularly OUD [9, 60].

Following initial convenience sample survey findings that documented that US adults were reporting using kratom as a drug substitute, more refined motivations for kratom use were examined among another online convenience sample

($N=3024$) with 2867 reporting current use [65]. Although similar reasons for use were found across current and former users, those who had used kratom previously, but not actively at the time of data collection, more often reported using kratom to relieve withdrawal symptoms (possibly indicating short- rather than long-term substitution). Over one-third of all respondents reported using to reduce or quit prescription analgesics; 18.0% of current and 11.5% of former users reported using to help reduce or quit alcohol; 14.5% and 27.4% of current and former users reported using to relieve withdrawal symptoms (drug types unspecified); and 12.1% and 9.5% of current and former users (respectively) reported using kratom to reduce or quit illicit drugs (drug classes unspecified). In another online convenience sample ($N=2798$) comprised of US adults with past-year kratom use (> 80% had used kratom within 24 h of survey completion), authors found that 52.9% had ever experienced opioid withdrawal or difficulty controlling opioid use, with 1144 (40.9%) using kratom specifically as an opioid reduction strategy [66]. Within both groups, rates of other past-year substance use were evident, though overall lower for respondents who did not use kratom for opioid reduction. Perhaps unsurprisingly, prescribed or illicit opioids were used at slightly higher rates by the kratom users seeking to reduce opioid use compared to those not using kratom for this purpose (48.1% vs. 22.5%). Among respondents who used kratom as a substitute and a way to reduce opioid use, a majority rated kratom as effective across the following opioid-related domains: withdrawal attenuation (87.3%); dysphoric mood relief (72.0%); addressing pain contributing to opioid use (86.1%); and craving reduction (79.6%). Nearly three quarters of this group had achieved ≥ 6 months of opioid abstinence that they attributed to kratom. Although past-year use of alcohol (47.4%) and cocaine (3.7%) among the sample were noted, respondents were not asked about kratom use motivations related to these substances, for substitution or potentiation.

These initial US surveys provided the first indication that some people using kratom were doing so specifically to manage features accompanying opioid dependence or OUD. However, there are significant limitations to this work. One is the possible self-selection bias of largely recruiting current or recent kratom users who may have overly favorable attitudes about kratom (compared to those who used intermittently or discontinued use due to unfavorable outcomes). Another is that the recruiting and data collection methods were similar across many larger studies. It may be that some of the same people participated in more than one survey, meaning that strength of the data might be inflated even though the studies were not seeking to reproduce prior findings per se. One online survey used Amazon Mechanical Turk (mTurk), a platform for crowdsourcing research, and possibly avoided some of the biases of earlier surveys in

that respondents were recruited as part of a larger survey regarding prescription medication misuse, not kratom [67]. Authors found that 112 out of 1842 respondents reported kratom use and, of these, many self-reported addiction to opioids (40.2%), alcohol (47.3%), or other substances (24.1%). Prior addiction treatment among kratom users was higher than for respondents not reporting kratom use (42.9% vs. 11.2%), and lifetime illicit drug use rates were high, including 74.5% and 71.4% of kratom users who reported methamphetamine and heroin use respectively. Motivations for kratom use were not reported. Furthermore, this and all other early surveys did not investigate temporal order of use initiation.

Some limitations from survey methodology have been addressed by examining social media data. In a small sub-survey pertaining to kratom use during the Covid-19 pandemic conducted as part of a larger international survey, 70 respondents provided survey data specific to use during the pandemic [68]. Of these, 19.5% reported using kratom to “mitigate, enhance, or reduce” effects of concomitant drug misuse (e.g., heroin, cocaine, amphetamine, marijuana) and 32.5% reported using kratom to “mitigate, enhance, or reduce” effects of prescription analgesic drug dependency or as a replacement to medications for opioid use disorder (MOUD; e.g., buprenorphine, methadone). Just over a quarter reported using kratom in combination with other substances. Social media posts examined in the same study ($N=379$) pertaining to kratom use during the pandemic collected for the same period as survey data found that polydrug use was mentioned in posts at a high rate ($n=132$). Another 62 posts explicitly noted kratom was used as a substitute for another drug and 26 reported using kratom due to pandemic-related restrictions for receiving MOUD. More extensive polydrug use involving kratom was also found in social media data analyses focused on tianeptine [69]. Evidence of polydrug use involving kratom and kratom as a drug substitute or SUD nonmedical “self-treatment” were further evidenced in a separate analysis of Reddit data [70•]. Among the 280 posts coded, polydrug use, defined as contemporaneous or concomitant use of kratom with other licit or illicit substances or supplements, was found across 155 posts. Kratom was also widely described as being used as a self-treatment for opioid withdrawal in 133 posts and as self-treatment for other drug withdrawal in 17 posts; descriptions of kratom use for long-term opioid substitution were found in 38 posts.

That vivid descriptions of kratom use for the purposes of reducing problematic substance use were found in social media posts independent from survey findings provides some validation to initial survey self-report. This is most evident with opioid substitution or OUD self-treatment, but also for alcohol. Some social media findings were the first non-survey data to clearly identify kratom being used to quit

or reduce alcohol consumption [70•]. In a follow-up to this paper, Smith et al. (data not yet published) found additional evidence of kratom substitution for alcohol, stimulants, and/or opioids and for self-treatment of symptoms related to dependence or use disorder(s), but also found that some people were professing kratom addiction to extract formulations. Although social media platforms are also self-selecting, the kratom-related data derived from social media provide a more nuanced and complicated picture of kratom compared to survey findings. This includes well-articulated positive, even “life-saving” attributions to kratom but also greater specificity on adverse kratom effects, such as dependence, and unsuccessful quit attempts.

More recently, a large ($N=5152$) international online survey of kratom-using adults (primarily from the USA) found that 8.3% of respondents had ever been diagnosed with any SUD, and they most frequently reported receiving prior treatment for opioids or benzodiazepines [71]. Over a quarter reported using kratom due to illicit drug dependency and had used kratom in combination with another substance. Of those who had used kratom concomitantly with another substance, the most frequently co-used substances included cannabis, cannabidiol, benzodiazepines, kava, and amphetamines (for further discussion on kava and kratom co-use and methamphetamine use see [72, 73]). This is in keeping with preliminary findings from an online survey ($N=1670$) unrelated to kratom that found similar relationships for lifetime kratom use and use of cannabis, cannabidiol, nonprescribed opioids, MOUD, and psychedelics [74]. Kratom users in this sample were also more likely to have ever participated in MOUD treatment. Complete survey data from this crowdsourced study (see [62]) included 2615 responses with 11.1% reporting lifetime kratom use. From this sample, 129 kratom-using respondents were re-recruited for follow-up [5•]. While polydrug use was endemic in this smaller sample, it was also highly varied. Average age of kratom use initiation (29.9 years) was older than for most other substances except for those also relatively novel or previously not widely available in the USA (e.g., tianeptine, cannabidiol, medical cannabis). Average age of initiation for prescribed buprenorphine was closest to kratom (28.1). For comparison, average age of heroin use initiation was 24.8 years, and for prescribed opioids and nonmedical prescription opioids ages 20.4 and 19.9 years, respectively. Unlike prior work [57], kratom was reported as more preferred among those who had tried it compared with other substances. Kratom ranked third among respondents’ top 5 preferred substances, below cannabis and caffeine.

In this same survey, some common kratom use motivations were unrelated to drug substitution or self-treatment. However, among the reasons that were, they included use as a short-term substitute/replacement for opioids, endorsed by 24.8% of respondents and use as a short-term alcohol

substitute/replacement (18.6%), both more common than use as a long-term opioid substitute/replacement (16.3%). With respect to using kratom for alleviating withdrawal symptoms, nonprescribed opioids (19.4%) was most commonly reported, followed by medically prescribed opioids (15.5%), multiple drugs (10.9%), alcohol (6.2%), nonprescribed and prescribed buprenorphine (3.1%, 5.4%), nonprescribed and prescribed methadone (4.7%), and nootropics (3.1%). When asked to rank kratom's effectiveness for each motivation using visual analogue scales (0–100, with 100 meaning "extremely effective") respondents rated kratom as at least moderately effective (average ratings ranging from approximately 60–80). The authors found a specific motivation for some users was that healthcare providers would not prescribe needed medications (18.6%). Among the 20.9% of respondents who reported ever experiencing difficulties accessing SUD treatment, 59.3% cited this as a reason for trying kratom.

Pleasure and Productivity

The findings noted earlier [55] were among the first to document the unique energy-enhancing effects of kratom self-reported by adults not based exclusively in Asia, where that phenomenon has been well characterized [1, 35, 36]. Although kratom use as a substitute for stimulants was not explicitly mentioned in the Swogger et al. (2015) findings, reported stimulatory effects from lower kratom doses obliquely indicated that respondents were seeking energy enhancing, stimulant-like effects from their kratom. This finding of increased activity/hyperactivity, energy, work, and desire to be active in the context of kratom's use as a stimulant is striking in that, as the authors noted, the effect "...paradoxically coincided with relaxation." In subsequent social media analyses, [68, 70•] effects people wrote that they wanted from kratom included enhancing energy, increasing cognitive (attention, focus, alertness) or physical performance, and maximizing productivity. In some cases, kratom use was reported as being used to reduce attentional deficits attributed to attention deficit hyperactivity disorder (ADHD). This latter finding of nonmedically managing ADHD symptoms has also been found in survey self-report [5•, 66, 71, 75] as has more general enhancement of focus and energy [65]. In one sample, kratom use to address occasional feelings of sleepiness or low energy was endorsed by a majority of respondents and was perceived as effective [5•]. Likewise, kratom use to "boost energy, stamina and/or for endurance" during work or exercise was endorsed by 48.1% of respondents. Elsewhere, kratom was not positively associated with exercise despite the increasing marketing around kratom as an exercise or energy supplement [76]. More broadly, 54.4% of respondents who routinely experienced

acute kratom effects reported those effects to be both compatible with and an aid in helping meet daily obligations, with another 29.1% reporting effects as compatible with meeting daily roles and obligations, though not necessarily helpful [77].

Of course, the motivations to use kratom for increasing energy or enhancing productivity are not mutually exclusive with other motivations, including use as a drug substitute, nor are they mutually exclusive with respect to use or polydrug use to achieve recreational pleasure or enjoyment. Use for the purpose of achieving pleasant psychoactive and somatic states that include euphoria or a "high" are well-represented in the literature [5•, 55, 65, 70•] and should not be overshadowed by the initial emergence of kratom in the USA primarily as self-reported form of opioid substitution or SUD symptom management [73, 78]. Regardless of whether pleasant, pleasurable, or mood enhancing states (i.e., positive reinforcement) and not merely relief from unpleasant states through analgesia, antidepressant, or antinociceptive effects (i.e., negative reinforcement) were sought out explicitly or manifested as part of a larger effect profile is unknown. Yet evidence suggests that kratom is capable of producing more than one type of effect and that many are using it for more than one purpose [5•].

Can We Characterize Kratom Despite Its Variability?

The preclinical and self-report literature on kratom indicate a diversity of effects both among the whole plant matter and isolated alkaloids that will require extensive continued research to evaluate and understand. For the type of real-world kratom use reviewed here, based entirely on self-report, the undertaking is fraught due to the variability of the kratom leaf, additional variability in alkaloid content that can arise between harvesting and commodification within an unregulated market, and biases inherent in all forms of self-report [79–81]. In the USA, "kratom" indicates many things. Although products containing only the isolated alkaloids for Mitragynine (which metabolizes to 7-hydroxymitragynine) may, based on self-report, be expected to produce stronger analgesia compared to the whole plant matter, Mitragynine and other alkaloids may also (even simultaneously) produce increased energy or stimulant-like effects. That remains to be scientifically demonstrated. Regarding drug substitution or SUD nonmedical "self-treatment": although kratom trends toward opioid substitution in the self-report literature (more than stimulants or alcohol), the reasons for taking kratom for the purposes of energy enhancement, focus, and productivity are increasingly evident. In one small survey, kratom use for addressing symptoms of chronic fatigue was reported by 19.4% of respondents [5•]. Even among those using kratom

to substitute opioids or self-treat OUD symptoms (or for pain-management), the possible desirability of kratom's reported energy-enhancing effects are somewhat intuitive given the lethargy and/or hypersomnolence associated with early OUD remission and chronic pain, and the fact that low-doses of opioids can produce stimulatory effects. For those with histories of opioid and stimulant use, kratom may hold a particular appeal.

The abundance of alkaloids in kratom and the unknown ways in which they interact, coupled with self-report literature that portrays kratom as having both stimulatory and "opioid-like" effects, means we should be cautious in attempting to fit kratom or its alkaloids into a pharmacological box, particularly with respect to human effects. To date, there exist at least two small pharmacokinetic studies [82, 83] of whole plant kratom with no larger scale pharmacokinetic/pharmacodynamic (PK/PD) study data published. Although the PK properties of Mitragynine, administered as either an oral solution or a salt form of the alkaloid, have been more thoroughly studied, evidence of Mitragynine's pharmacodynamic profile in humans is still severely limited [84, 85]. Findings from lab-based studies using commercially available products are not yet published.

The literature on self-reported kratom effects, even with the limitations of retrospective responding, may contain hints about the pharmacologic properties kratom could be hypothesized to possess. These remain indicators requiring systematic study. As much of the evidence for kratom's stimulatory effects relies on self-reported experiences of increased energy, alertness, and/or focus, it may be worth noting that kratom's anxiolytic properties purportedly work via κ -opioid action [86], for which kratom alkaloids have demonstrated modulation [87•]. Complaints of difficulty with memory and concentrating, amotivation, and restlessness are all shared features of anxiety and depressive symptom presentation [88]. Although psychological symptom measures have indicated elevated anxious and depressive experiences among kratom using samples [56, 63, 89•], it may be that people who experience greater symptom severity or particular symptom presentations are more likely to appraise their cognition as improved when using kratom.

Conclusion: A Holding Pattern

The central take-away from this review is that kratom has a role in the US polydrug epidemic and, relatedly, the chronic pain and psychiatric health epidemics, but that it remains premature to make strident or unequivocal claims about kratom or kratom-derived products even though they have evolved in US markets for over a decade and the self-report, while limited, consistently trends in the same direction. Presently, we are in a holding pattern with respect to

our understanding of kratom. The findings reviewed here indicate that we can characterize human kratom use only insofar as we understand its effects in humans. To date, we do not understand these. The most prudent claim that can be made about kratom is that people with polydrug use histories are using it and, oftentimes, the motivations for use are to substitute other drugs or reduce problematic drug use. Although self-reports of motivations for kratom use may not be the most rigorous form of data, self-reports are the highest strength of data currently available. There is no reason to assume that these reports, which are consistent across platforms, are inaccurate. If we exclude the possibility of mendacity on the part of those self-reporting that they have used kratom successfully as a drug substitute and to attenuate SUD symptoms, then that leaves us with a still very weak type of information, but a source of information, nonetheless. When we weigh the value of evidence as weak, and when premises based on the evidence have not yet been strengthened by data derived from rigorous controlled experimental designs then it suggests that significantly more work is needed. Indeed, kratom alkaloids have not been studied for therapeutic efficacy for any human condition, nor have they been evaluated for human abuse potential or toxicity. Rather, and in the absence of scientific study, millions of people are "self-experimenting." This is an indictment of the state of kratom human research. A more rigorous or even systematic review of the self-report literature on kratom is not presently tenable given the overall paucity of research. As more self-report literature is amassed, systematic literature reviews will be warranted.

Until more work is done, the best source of published data, despite its limitations, for drawing preliminary conclusions about kratom's effects in humans is presently self-report data, as we cannot extrapolate to humans kratom dose-related findings in other species [89•]. This is a starting point, and may be helpful in developing some subjective endpoints in controlled human laboratory studies, but it is an unsatisfactory and unacceptable place to scientifically remain. Controlled human laboratory studies are desperately required. In addition to PK/PD studies using whole plant matter preparations and isolated alkaloids, drug-discrimination studies and clinical trials evaluating the efficacy of kratom alkaloids and alkaloid combinations for OUD and other use disorders are critically needed.

Until more is known about kratom's risks or what constitutes toxicity in humans, prescribing clinicians should be cautious as there are likely unknown drug-drug interactions with kratom alkaloids and given doses. It is critical that clinicians become more aware of kratom and assess for use, particularly among patients with SUD or chronic pain histories, but in a manner that does not further stigmatize the use of substances, especially those being used to manage already-stigmatized conditions like SUD and chronic pain; see [44•]

for greater discussion. Although some may feel comfortable disclosing use to healthcare practitioners, others may not. Failure to assess kratom use history, dosage, product type, or potential kratom use disorder will leave clinicians without documented information critical for their clinical record [90]. With respect to patients with SUD histories using kratom as an opioid, stimulant, and/or alcohol substitute, we make no moral judgment nor strong clinical recommendations apart from thorough and sensitive assessment and caution regarding coingestants. The seeming harm-reduction practices adopted by a subset of the kratom-using community are evident. When coupled with the relatively low rates of kratom-related morbidities and mortalities (see 52), it seems prudent, based on limited epidemiological data, to provisionally conceptualize real-world kratom use as being less lethal than the use of non-medical opioids (e.g., heroin, fentanyl).

Kratom is also not without risks, many of which remain unknown. Yet, in a context where polydrug-related and fentanyl-related fatalities are at record highs, it may be pragmatic to listen to those most qualified to speak about kratom's effects (those regularly using it) until controlled trials and mechanistic understanding is developed. Clinicians have noted that use of kratom for therapeutic purposes is not “real medicine.” They are correct. Kratom alkaloids may or may not eventually be developed into pharmaceutical formulations regulated by the US Food and Drug Administration. That kratom products are not FDA-approved pharmacological intervention has no bearing on the fact that people still nonmedically use them for medical conditions. The stark and perhaps, for some, unwelcome reality is that people are using kratom to nonmedically “self-treat” myriad conditions, including SUDs, and that the limited self-report data we have indicates that these unregulated products appear to be helping some reduce the use of substances to which they developed dependence on or addiction to. In the era in which > 100,000 people in the USA die each year of drug overdoses, this is information we cannot afford to ignore as scientists and public health officials.

For clinicians, particular care is indicated in assessing kratom use among those who may be reluctant to quit and who do not tolerate nor wish to take MOUD, which are known to be largely effective and lifesaving for OUD but have not been scientifically evaluated as therapeutically appropriate or effective for treating SUD for kratom. While clinical engagement with a patient taking kratom to “self-treat” SUD symptoms may not be ideal, it is the encounter that some clinicians will experience. As such, the engagement should be conducted with the curiosity and objectivity of a scientist and the sensitivity and humility of a clinician dedicated to providing care, even when they do not fully understand the patient's motivations for certain behaviors. Until scientific principles can be brought to bear on engaging patients who use kratom and other drugs, the principle of charity should be extended.

Clinicians should remain open to documenting the full history of substance use and develop an understanding for why kratom use was initiated, particularly among people with SUD histories. It may be that these conversations serve as opportunities for improving patient interaction and orienting patients to established and possibly beneficial medical care.

Author Contribution KES conceptualized the manuscript and wrote as primary author. JMR and JDF helped write, edit, and format the manuscript and assisted in curating and reviewing the literature.

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Declarations

Ethics Approval The Section Editors for the topical collection Kratom are Oliver Grundmann and Kirsten Smith. Please note that Dr. Smith was not involved in the editorial process of this article as she is a co-author.

Research Involving Human Participants and Informed Consent All studies reviewed here were approved by the appropriate ethics committee for the study's respective institution. For those involving human subjects research, informed consent was either undertaken as part of study enrollment or the need to obtain informed consent was waived by the Institutional Review Board of the institution where the study was conducted.

Competing Interests The authors declare no competing interests.

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