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Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic

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ABSTRACT

Background: Kratom, a Southeast Asian plant with opioid-receptor mediated effects, has emerged as a potential substance of abuse, with limited data on its use and effects. This study characterized kratom user demographics, use patterns, and perceived drug effects.

Methods: A cross-sectional, anonymous online survey was conducted between January and December 2017.

Results: 2,798 kratom users – mean age 40 (SD = 12); predominantly White (90 %), female (61 %), and located in the US (97 %) – completed the survey. Kratom was primarily taken orally in doses of 1 – 3 g (49 %), with daily use (59 %) being most common. Kratom was used for pain (91 %), anxiety (67 %), and depression (65 %), with high ratings of effectiveness. 1,144 (41 %) used kratom to stop or reduce prescription or illicit opioid use, citing decreased opioid withdrawal and craving related to kratom use, with 411 reporting > 1-year continuous abstinence from opioids attributed to kratom use. Roughly one-third of respondents reported adverse effects of kratom, largely rated as mild in severity and lasting ≤ 24 h. Seventeen participants (0.6 %) sought treatment for adverse effects. Fifty-six individuals (2 %) met DSM-5 criteria for a past-year moderate or severe kratom-related substance use disorder (SUD). When asked how troubled they felt regarding their kratom use, the mean (SD) rating was 3.2 (9.8) on a scale from 0 to 100.

Conclusion: Kratom is used among White, middle-aged Americans for symptoms of pain, anxiety, depression, and opioid withdrawal. Although regular use was typical, kratom-related SUD and serious adverse effects were uncommon. Additional research on kratom epidemiology and pharmacology is imperative in light of the present opioid epidemic.

1. Introduction

Kratom (*Mitragyna speciosa*) is an evergreen tree in the coffee (*Rubiaceae*) family native to Southeast Asia (SEA), where it has a long history of traditional use (Hassan et al., 2013; Singh et al., 2016). Kratom leaf or extract are typically ingested orally for treating pain and other medical conditions, and to aid in the performance of agricultural and manual labor (Hassan et al., 2013; Singh et al., 2016). Kratom and its alkaloids have been classified as atypical opioids because they are structurally and biologically distinct from classical opioids (e.g., morphine) that are derived from the poppy (*Papaveraceae*) family (Raffa et al., 2018). Kratom has emerged as a natural product available for purchase over the internet (Babu et al., 2008; Prozialeck, 2016), and has been identified as a Drug of Concern by the US Drug Enforcement Administration (DEA, 2017). Surveys and case studies suggest many Americans are using kratom to self-medicate a range of conditions including pain and opioid withdrawal (Boyer et al., 2007; Coe et al., 2019; Grundmann, 2017; Henningfield et al., 2018; Smith and Lawson, 2017; Swogger et al., 2015), although there are limited empirical data available to support a therapeutic benefit for such use.

Kratom contains more than three dozen unique indole alkaloids, including its primary alkaloid mitragynine, which makes up approximately 66 % of the total alkaloids in kratom leaves (Kruegel and Grundmann, 2018; Takayama, 2004). Preclinical studies of mitragynine suggest it may hold potential toward developing new and efficacious pain medications (Kruegel and Grundmann, 2018; Macko et al., 1972; Takayama, 2004). Mitragynine is a G-protein-biased partial agonist of the mu-opioid receptor that does not recruit the β-arrestin signaling

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pathway like classical opioids (Kruegel et al., 2016; Váradi et al., 2016). It is thus hypothesized to confer analgesic effects with lower risk of respiratory depression than classical opioids (Kruegel et al., 2016; Siuda et al., 2017; Váradi et al., 2016). Mitragynine and kratom extracts have shown robust antinociceptive effects in rats, mice, and dogs, suppressing nociceptive response to both mechanical and thermal noxious stimuli with minimal respiratory depression (Hassan et al., 2013; Macko et al., 1972; Matsumoto et al., 1996; Sabetghadam et al., 2010). Furthermore, these antinociceptive effects are blocked by the opioid antagonist naloxone, suggesting an opioid-receptor mediated mechanism of action (Matsumoto et al., 1996; Sabetghadam et al., 2010). Abuse liability testing of mitragynine in rats has shown that it reduces morphine self-administration but does not substitute for morphine, and it does not engender or maintain intravenous self-administration, suggesting low abuse liability (Hemby et al., 2018). In addition, pretreating rats with mitragynine has also been shown to reduce heroin self-administration though mitragynine itself is not self-administered (Yue et al., 2018). However, 7-hydroxymitragynine, a minor alkaloid present at low levels (~2 % of alkaloids) in kratom leaves (Ponglux et al., 1994) has shown mu-opioid receptor-mediated analgesic effects (Matsumoto et al., 2004), and has been found to substitute for morphine and engender and maintain intravenous self-administration in rats in a dose-dependent manner (Hemby et al., 2018).

Survey studies indicate kratom has been used as a substitute for opioids and to alleviate opioid withdrawal both in SEA (Vicknasingam et al., 2010) and the US (Boyer et al., 2008; Coe et al., 2019; Grundmann, 2017). Internet-based studies have found that in the US, kratom is predominantly being used by White, middle-aged, middle-income, college-educated individuals for treatment of pain, opioid withdrawal, and mental health conditions, with relatively minor (e.g. stomach upset), dose-dependent adverse effects (Grundmann, 2017; Henningfield et al., 2018; Swogger et al., 2015). Among a sample of 8,049 kratom users in the US, more than a quarter of respondents reported using kratom to reduce illicit (e.g. heroin; n = 539) or prescription (e.g. opioid medication; n = 1813) drug dependence or withdrawal (Grundmann, 2017).

To date, the behavioral pharmacology and abuse liability of kratom have not been well-characterized in humans. One study conducted in Thailand that administered different doses of kratom tea to 10 chronic kratom-using males and evaluated blood and urine mitragynine levels found linear pharmacokinetics, time to maximum plasma concentration of roughly 1 h, and a terminal half-life of about one day (Trakulsrichai et al., 2015). Otherwise, no controlled laboratory research with kratom or its alkaloids has been conducted in humans. Given the lack of controlled human studies, it is important to understand more about kratom use patterns, users' motives, and outcomes following kratom exposure. This information can help inform prospective evaluations of kratom for different indications as well as regulatory decisions regarding scheduling. The present study collected demographic and self-report data from individuals who use kratom to extend the limited existing literature on contemporary kratom use.

2. Methods

2.1. Data collection

We conducted this cross-sectional, anonymous online survey to further characterize kratom user demographics, reasons for and patterns of kratom use, and perceived benefits of use. Self-reported adverse effects associated with kratom use were examined, including potential kratom withdrawal symptoms. Finally, indicators of abuse liability and problematic kratom use were assessed. All data were collected anonymously (no name or personally identifiable information recorded) using Qualtrics (Qualtrics, Provo, UT, USA). IP addresses were collected so the same person could not respond to the survey repeatedly, but were destroyed after data collection was completed. Between January 2017 and December 2017 participants were recruited using online advertisements and email announcements distributed via sites of interest to kratom users (e.g., American Kratom Association, Erowid, Reddit). Participants were required to be age 18 years or older, English language proficient, and have used kratom in the past year. Information about the purpose of the study was provided prior to beginning the survey, and by choosing to begin the survey respondents indicated their consent for voluntary participation. Participants who completed the initial pilot version of the survey through Amazon Mechanical Turk (n = 36) received $3.10 for completing the survey. Otherwise, no incentives were offered for study participation. Due to its confidential and anonymous nature, the Johns Hopkins University School of Medicine Institutional Review Board determined this did not qualify as human subjects research.

2.2. Measures

Participants provided demographic information (e.g., age, highest level of education, household income), location of residence, past-year use of licit (e.g., alcohol, nicotine), illicit (e.g., heroin, psychedelics), and prescription drugs (e.g., antidepressants, prescription opiates), and lifetime medical diagnoses. The 10-item Patient-Reported Outcomes Measurement Information System Global Health (PROMIS-GH) scale was used to assess general physical and mental health (Broderick et al., 2013). Chronic pain was assessed using the 15-item Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994).

Data regarding kratom use patterns, including age of kratom use initiation, frequency of use, typical dose of kratom, and route of administration were collected. Participants were asked to endorse whether they used kratom for specific conditions (e.g., pain, depression), if they would recommend kratom as a remedy for these conditions, and to rate how effective they considered kratom for these conditions using a visual analog scale (VAS) from 0 (not at all) to 100 (extremely). Participants were asked to report whether they had ever used kratom to help reduce or stop using heroin and/or licit or illicit use of pharmaceutical pain medications (e.g., Oxycontin, Percocet). Those who reported using kratom for this purpose then provided information on the perceived effectiveness of kratom to mitigate opioid use and ways in which kratom may have been useful in this capacity.

Incidence of self-reported adverse effects or side effects attributed to kratom was queried, and information on duration, severity, and medical treatment for adverse effects was collected. Similarly, potential kratom-related withdrawal was probed, with those endorsing possible kratom withdrawal completing the 16-item Subjective Opiate Withdrawal Scale (SOWS) to evaluate symptom severity (Handelsman et al., 1987). Participants rated typical subjective effects of kratom across 13 items from the Drug Effects Questionnaire (DEQ), assessing type, strength, and desirability of kratom effects associated with abuse liability (e.g., drug liking, euphoria, desire) using VAS from 0 (not at all) to 100 (extreme) (Morean et al., 2013). Additionally, participants were asked to rate how troubled or bothered they were by their kratom use using VAS from 0 (not at all) to 100 (extreme). Participants completed a DSM-5 substance use disorder (SUD) symptom checklist to assess whether past-year kratom use met diagnostic criteria for a kratom-related SUD (American Psychiatric Association, 2013; Hudziak et al., 1993).

2.3. Data analysis

Descriptive statistics were generated to determine the prevalence, means, and proportions of relevant variables. Chi-square (categorical variables) and Mann-Whitney U (continuous variables) tests were used to examine differences between those who used kratom to reduce opioid use and those who did not. To evaluate factors related to kratom use outcomes, we conducted four independent multivariate logistic regressions using Maximum Likelihood estimates for each of the

following outcomes: negative effect of kratom use ≥1 lifetime/never lifetime); experience withdrawal from kratom use (≥1 symptom/0 symptoms); ever sought treatment for kratom use (yes/no); and lifetime use of kratom to reduce opioid use (yes/no). Several demographic and drug use variables were entered into the models as predictors, including: age, sex, race, relationship status, education, employment status, income, geographic region, past 12-month alcohol use, past 12-month opioid use, diagnosis of bipolar disorder, diagnosis of depression, age of first kratom use, kratom use frequency, number of kratom-related SUD symptoms, SOWS total, pain severity, experienced opioid withdrawal, and the total number of different types of opioids used in past 12 months. Data were analyzed using IBM Microsoft SPSS version 25 (IBM®, 2017), and Prism version 7.0 (GraphPad, La Jolla, CA, USA).

3. Results

3.1. Sample characteristics

Of the 4,302 individuals who began the survey, 2,826 (66 %) met all study inclusion criteria and completed the entire survey. Of these, 28 were removed due to inconsistent responses or technical issues, resulting in a final sample of 2,798 kratom users. Fifty-three percent of the final sample learned about the survey through the American Kratom Association and 44.2 % found it through Facebook or other social media websites.

Table 1 displays the means and proportions for demographic and substance use items. Respondents were on average 40.2 years old (SD = 11.8) and majority female (60.7 %). Most were married or in a committed relationship (66.5 %), employed (68.4 %), and had some college education (83.9 %). The median annual household income was between $50,000-$59,000. The largest geographic residential concentration for respondents was the U.S. South (41.0 %). Alcohol was the most commonly reported substance used in the past year (47.4 %), followed by tobacco (42.2 %), cannabis (37.2 %), and opioids (33.0 %). Roughly half the sample (52.9 %) reported ever experiencing opioid withdrawal symptoms or difficulty controlling opioid use.

3.2. Physical and psychological health

A majority of the sample (n = 1,924; 68.8 %) reported experiencing chronic pain over the past 3 months. Among this group, the mean (SD) BPI pain severity score was 4.1 (1.8), and the mean pain interference score was 4.9 (SD = 2.9), with possible scores ranging from 0 to 10 and greater scores indicating more pain or pain interference in daily activities. Pain was most commonly reported in the lower (53.8 %) and upper back (34.6 %), shoulders (33.1 %), and knees (31.3 %). Among this chronic pain group, 39.4 % reported currently taking a prescribed medication to treat pain, and 87.6 % reported current kratom use for pain.

Among the entire sample, the most commonly reported lifetime medical diagnoses (Table 1) included back pain (72.5 %), depression (65.0 %), muscle pain (62.9 %), neck pain (55.0 %), joint pain (54.5 %), panic attacks (48.1 %), and arthritis (43.8 %). PROMIS-GH physical health mean (SD) scores were 13.7 (3.2), and mental health scores were 12.8 (3.5), which both convert to standardized PROMIS-GH T-scores of approximately 45, slightly below the US general population mean of 50 (Hays et al., 2009).

3.3. Reasons for kratom use and use patterns

Most respondents endorsed using kratom for pain relief (91.3 %), and/or to treat mood-related issues such as anxiety (67.2 %), and depression (64.5 %). Among these, the majority said they would recommend kratom for pain relief (98.7 %), and mood-related issues (96.7 %). Mean (SD) efficacy ratings of kratom for treating pain on a scale from 0 (not at all) to 100 (extremely) were 83.3 (18.5); for anxiety

Table 1
Demographic characteristics and comparisons of respondents who did and did not report using kratom to reduce opioid use.[a]

Respondent Group				
Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Age in years, Mean ± SD	40.2 ± 11.8	39.8 ± 10.5	40.5 ± 12.6	.449
Sex, No. (%)				
Female	1,699 (60.7)	696 (60.8)	1,003 (60.6)	.916
Race, No. (%)				
American Indian/ Native Hawaiian	40 (1.4)	25 (2.2)	15 (0.9)	.013
Asian	14 (0.5)	4 (0.3)	10 (0.6)	
Black/African American	11 (0.4)	2 (0.2)	9 (0.5)	
More than one race/ some other race	176 (6.3)	60 (5.2)	116 (7.0)	
White	2,513 (89.8)	1,035 (90.5)	1,478 (89.4)	
Prefer not to respond	44 (1.6)	18 (1.6)	26 (1.6)	
Relationship status, No. (%)				
Single, never married	530 (18.9)	206 (18.0)	324 (19.6)	.671
In committed relationship/ married	1,860 (66.5)	775 (67.8)	1,085 (65.6)	
Separated/divorced	362 (12.9)	144 (12.6)	218 (13.2)	
Widowed	46 (1.6)	19 (1.7)	27 (1.6)	
Education, No. (%)				
Did not complete High school	51 (1.8)	22 (1.9)	29 (1.8)	.006
High school graduate or equivalent	401 (14.3)	189 (16.5)	212 (12.8)	
Some college	998 (35.7)	424 (37.1)	574 (34.7)	
College degree (e.g., AA, BS)	921 (32.9)	362 (31.6)	559 (33.8)	
Some graduate school	150 (5.4)	55 (4.8)	95 (5.7)	
Advanced degree (e.g., Ph.D.)	277 (9.9)	92 (8.0)	185 (11.2)	
Employment status, No. (%)				
Employed	1,915 (68.4)	785 (68.6)	1,130 (68.3)	< .001
Unemployed	313 (11.2)	148 (12.9)	165 (10.0)	
Student	109 (3.9)	27 (2.4)	82 (5.0)	
Other (e.g., disabled, retired)	461 (16.5)	184 (16.1)	277 (16.7)	
Household income, No. (%)				
< $10,000–$29,999	716 (25.6)	305 (26.7)	411 (24.8)	.098
$30,000–$49,999	608 (21.7)	266 (23.3)	342 (20.7)	
$50,000–$62,999	459 (16.4)	192 (16.8)	267 (16.1)	
$70,000–$99,999	483 (17.3)	180 (15.7)	303 (18.3)	
≥$100,000	532 (19.0)	201 (17.6)	331 (20.0)	
Geographic region, No. (%)				
Northeast	417 (14.9)	163 (14.2)	254 (15.4)	.132
Midwest	540 (19.3)	223 (19.5)	317 (19.2)	
South	1,147 (41.0)	495 (43.3)	652 (39.4)	
West	612 (21.9)	237 (20.7)	375 (22.7)	
Outside U.S./Prefer not to say	82 (2.9)	26 (2.3)	56 (3.4)	
Past 12-month substance use, No. (%)				
Alcohol	1,327 (47.4)	489 (42.7)	838 (50.7)	< .001
Antidepressants	787 (28.1)	296 (25.9)	491 (29.7)	.028
Benzodiazepines	702 (25.1)	327 (28.6)	375 (22.7)	< .001
Cannabis	1,041 (37.2)	419 (36.6)	622 (37.6)	.278
Cocaine	103 (3.7)	57 (5.0)	46 (2.8)	.002
Hallucinogens	161 (5.8)	51 (4.5)	110 (6.7)	.014
Opioids (prescribed or illicit)	922 (33.0)	550 (48.1)	372 (22.5)	< .001
Tobacco	1,180 (42.2)	573 (50.1)	607 (36.7)	< .001
Lifetime medical diagnoses, No. (%)				
Arthritis	1,225 (43.8)	532 (46.5)	693 (41.9)	.016
Back pain	2,028 (72.5)	875 (76.5)	1,153 (69.7)	< .001
Depression	1,818 (65.0)	797 (69.7)	1,021 (61.7)	< .001
Herniated disc	792 (28.3)	413 (36.1)	379 (22.9)	< .001
Joint Pain	1,526 (54.5)	664 (58.0)	862 (52.1)	.002
Menopause	538 (19.2)	187 (16.3)	351 (21.2)	.001

(*continued on next page*)

Table 1 (*continued*)

Respondent Group				
Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Migraine/serious headaches	1,140 (40.7)	509 (44.5)	631 (38.1)	< .001
Muscle pain	1,760 (62.9)	774 (67.7)	986 (59.6)	< .001
Neck pain	1,540 (55.0)	669 (58.5)	871 (52.7)	.002
Ovarian cyst	550 (19.7)	261 (22.8)	289 (17.5)	< .001
Panic attacks	1,346 (48.1)	596 (52.1)	750 (45.3)	< .001
PTSD	711 (25.4)	327 (28.6)	384 (23.2)	.001
Restless leg syndrome	799 (28.6)	408 (35.7)	391 (23.6)	< .001
PROMIS-GH				
Physical health,[c] Mean ± SD	13.7 ± 3.2	13.8 ± 3.0	13.6 ± 3.3	.203
Mental health,[c] Mean ± SD	12.8 ± 3.5	13.0 ± 3.4	12.7 ± 3.5	.014

Abbreviation: No, number; SD, standard deviation; PTSD, Post-Trumatic Stress Disorder; PROMIS-GH, Patient-Reported Outcomes Measurement Information System Global Health scale.

[a] Opioid reduction users were classified as those who responded affirmatively to the question, "Have you ever used kratom to help you cut down or stop using heroin or prescription pain medications (such as Vicodin, Percocet, Oxycontin, etc.)?".

[b] P values calculated using chi-square and 2-tailed Mann-Whitney U tests.

[c] Range = 4–20. Greater values indicate better physical / mental health.

were 76.7 (24.3); and for depression were 76.5 (25.4). Subgroups also reported using kratom for post-traumatic stress (29.6 %) or bipolar mood (24.6 %), with mean (SD) efficacy ratings of 60.2 (38.2), and 51.4 (39.9), respectively.

The mean (SD) age for kratom use initiation was 38 (12.2) years (Table 2). The majority of respondents reported using kratom ≥100 times in their lifetime (76.2 %), and most had used kratom in the 24 h before completing the survey (80.7 %). The most commonly reported typical dose range per occasion was 1−3 grams (49.0 %), followed by 4−6 g (33.4 %). Daily use was reported by the majority of respondents (59.1 %), with a mean (SD) of 2.7 (1.3) doses used per day. Ingesting kratom orally in powder form was the most common method of administration (43.6 %) followed by drinking as a prepared beverage (e.g., tea, smoothie; 37.0 %).

3.4. Kratom adverse effects

Approximately 19 % of participants reported adverse effects from kratom use (Table 2), with an additional 12.8 % reporting possible kratom-related adverse effects. Among those reporting definite or possible adverse effects, only 1 % (n = 9) indicated serious to extreme severity, and 1.9 % (n = 17) reported seeking medical treatment for adverse effects. Most adverse effects were rated mild in severity (63.2 %) and lasted ≤1 day (86.1 %). Kratom-related withdrawal symptoms were reported by 9.5 % of respondents with another 17.5 % reporting possible kratom-related withdrawal. The overall logistic regression model fit was significantly improved by including the abovementioned predictor variables (χ^2 = 580.73, $p < .001$). Logistic regression revealed that adverse effects of kratom use were significantly associated with younger age (aOR > 1.20 for people 65 years or younger; 95 % CI: 0.18, 13.42)[1], male sex (female aOR = 0.75; 95 % CI: 0.59, 0.95), having less education (aOR > 0.90 for people without a graduate/professional degree; 95 % CI: 0.35, 2.07), and lower income (aOR > 1.20 for people earning < $250k annually; 95 % CI: 0.44, 6.14), as well as past 12-month alcohol use (aOR = 0.61 for no alcohol in past 12 months; 95 % CI: 0.48, 0.76), past 12-month opioid use (aOR = 0.59 for no opioid use in past 12 months; 95 % CI: 0.45, 0.76), kratom-related withdrawal (i.e., SOWS total; aOR < 0.01 for SOWS total < 50; 95 % CI: 0.00, 1.21 × 10^{10}), and the number of opioids used in the past 12-months (aOR > 2.45 for people whose used 8+ different types of opioids; 95 % CI: 0.00, 1.44 × 10^{13}). Self-reported depression (aOR = 0.68 for no depression; 95 % CI: 0.54, 0.87), pain severity (χ^2 = 9240.28, $p < .001$), and kratom-related DSM-5 SUD symptoms (χ^2 = 149.93, $p < .001$) were also related to kratom adverse effects.

3.5. Symptoms of withdrawal following kratom abstinence

The mean (SD) SOWS score among these individuals was 8.8 (8.4), indicating mild opiate withdrawal symptoms (i.e., SOWS score < 11). Most respondents (87.7 %) did not meet diagnostic criteria for a past-year kratom-related substance use disorder (SUD) based on the DSM-5 symptom checklist. Less than 3 % met diagnostic criteria for moderate and severe kratom-related SUD. When asked how troubled or bothered they were by their kratom use on a scale from 0 (not at all) to 100 (extremely), the mean (SD) response across the entire study sample was 3.2 (9.8). The most highly rated subjective effects of kratom on a 0–100 VAS (Table 2) included 'good effects' (M = 86.4; SD = 23.0) and 'drug liking' (M = 85.7; SD = 23.7), followed by 'alert' (M = 49.8; SD = 30.9) and 'stimulated' (M = 41.3; SD = 28.6), with lower ratings of 'euphoric' (M = 25.1; SD = 27.1) and 'high' (M = 12.0; SD = 20.1), suggesting potential differences in subjective effects profiles of kratom from classic opioids (Walsh et al., 2008). The overall logistic regression model fit was significantly improved by including the abovementioned predictor variables (χ^2 = 4015.85, $p < .001$). Logistic regression analyses revealed that experiencing kratom withdrawal was significantly predicted by the number of kratom-related DSM-5 SUD symptoms (χ^2 = 3301.90, $p < .001$), sex (female aOR = 0.21; 95 % CI: 0.09, 0.47), total SOWS score (χ^2 = 77.25, $p < .001$), and having experienced opioid withdrawal (aOR = 0.14 for never experiencing opioid withdrawal; 95 % CI: 0.05, 0.36). Seeking treatment for kratom use was also significantly predicted by the number of kratom-related DSM-5 SUD symptoms (all aOR < 0.01 for < 9 DSM-5 SUD symptoms; 95 % CI: 0.00, < 0.01) and SOWS total (all aOR < 0.01 for SOWS total < 50; 95 % CI: 0.00, < 0.01).

3.6. Kratom for opioid use reduction

A subsample of 1,144 individuals (40.9 %) reported using kratom to reduce or stop opioid use, including prescription opioid medications and heroin. Kratom was endorsed by this group as effectively treating their opioid withdrawal symptoms (87.3 %; n = 999), addressing underlying pain related to opioid use (86.1 %; n = 985), reducing opioid cravings (79.6 %; n = 911), and improving mood while tapering off opioids (72.0 %; n = 824). Kratom was widely reported to reduce opioid withdrawal symptoms among this group, including anxiety (86.5 %; n = 989), body aches (86.5 %; n = 989), restlessness (86.4 %; n = 988), and insomnia (79.5 %; n = 910).

Among these respondents, Percocet (33.2 %; n = 380) and Vicodin (32.3 %; n = 369) were the most commonly used opioids in the past year, and heroin exhibited the least past-year use (5.8 %; n = 66). Among this group 122 (10.7 %) reported past-year Suboxone use, 89 (7.8 %) reported past-year methadone use, and 411 (35.9 %) reported no past-year opioid use. Most of these respondents (74.2 %; n = 849) reported achieving ≥6 months of abstinence from opioids attributed to kratom use. The large majority of these participants (99.2 %; n = 1,135) said they would recommend kratom as an opioid withdrawal treatment. The overall logistic regression model fit was significantly

[1] Adjusted odds ratios (aOR) are included where data showed a significant monotonic relationship. χ^2 values are included where the predictor variable had a significant non-linear relationship to the dependent variable. Where multiple categories exist for a variable, the 95% CI shows the range of minimum-to-maximum for all catgeories.

Table 2
Kratom use patterns and comparisons of respondents who did and did not report using kratom to reduce opioid use.[a]

Respondent Group				
Kratom Use Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Reasons for kratom use,[c] No. (%)				
Treatment of mood-related or psychiatric symptoms	1,975 (70.6)	873 (76.3)	1,102 (66.7)	< .001
Anxiety	1,881 (67.2)	827 (72.3)	1,054 (63.7)	< .001
Depression	1,804 (64.5)	814 (71.2)	990 (59.9)	< .001
Bipolar Mood	687 (24.6)	340 (29.7)	347 (21.0)	< .001
Post-traumatic Stress Disorder (PTSD)	829 (29.6)	402 (35.1)	427 (25.8)	< .001
For treatment of pain	2,554 (91.3)	1,078 (94.2)	1,476 (89.2)	< .001
To reduce or stop using prescription or illicit opioids	1,144 (40.9)	1,144 (100.0)	0 (0)	< .001
Age of kratom use initiation, Mean ± SD	38.0 ± 12.2	37.3 ± 11.0	38.4 ± 12.9	.107
Has used kratom ≥100 times, No. (%)	2,133 (76.2)	939 (82.1)	1,194 (72.2)	< .001
Last time of kratom consumption, No. (%)				
Past 24 h	2,258 (80.7)	990 (86.5)	1,268 (76.7)	< .001
Past week	300 (10.7)	88 (7.7)	212 (12.8)	
Past month	129 (4.6)	33 (2.9)	96 (5.8)	
Past Year	111 (4.0)	33 (2.9)	78 (4.7)	
Typical dose in grams, No. (%)				
< 1	242 (8.6)	60 (5.2)	182 (11.0)	< .001
1–3	1,372 (49.0)	542 (47.4)	828 (50.1)	
4–6	935 (33.4)	424 (37.1)	509 (30.8)	
7 or more	249 (8.9)	118 (10.3)	135 (8.2)	
Number of doses per day, Mean ± SD	2.7 ± 1.3	3.1 ± 1.3	2.4 ± 1.3	< .001
Past-year frequency of use, No. (%)				
≤1 time per month	109 (3.9)	26 (2.3)	83 (5.1)	< .001
2–4 times per month	152 (5.4)	27 (2.4)	125 (7.6)	
2–3 times per week	375 (13.4)	99 (8.7)	276 (16.7)	
4–6 times per week	508 (18.2)	197 (17.2)	311 (18.8)	
Daily	1,654 (59.1)	795 (69.5)	859 (51.9)	
Route of administration, No. (%)				
Capsule/pill	530 (18.9)	214 (18.7)	316 (19.1)	< .001
Prepared as tea/beverage	1,035 (37.0)	373 (32.6)	662 (40.0)	
Ingested powder	1,221 (43.6)	550 (48.1)	671 (40.6)	
Other (e.g., smoked, IV/SC, consumed as extract)	12 (0.4)	7 (0.6)	5 (0.3)	
Experienced adverse effects from kratom, No. (%)				
Yes	540 (19.3)	198 (17.3)	342 (20.7)	.045
Maybe	357 (12.8)	140 (12.2)	217 (13.1)	
No	1,901 (67.9)	806 (70.5)	1,095 (66.2)	
Adverse effect severity, No. (%)				
Not at all	274 (9.8)	95 (8.3)	179 (10.8)	.589
Mild	567 (20.3)	219 (19.1)	348 (21.0)	
Moderate	47 (1.7)	20 (1.7)	27 (1.6)	
Serious to Extreme	9 (0.3)	4 (0.3)	5 (0.3)	
Sought medical treatment due to adverse effects	17 (0.6)	9 (0.8)	8 (0.5)	.311
Duration of adverse effects, No. (%)				
≤1 day	772 (27.6)	288 (25.2)	484 (29.3)	.476
2–6 days	76 (2.7)	28 (2.4)	48 (2.9)	
1–12 weeks	30 (1.1)	14 (1.2)	16 (1.0)	
4–11 months	6 (0.2)	4 (0.3)	2 (0.1)	
≥1 year	13 (0.5)	4 (0.3)	9 (0.5)	
Has experienced kratom-related withdrawal symptoms, No. (%)				
Yes	267 (9.5)	140 (12.2)	127 (7.7)	< .001
Maybe	491 (17.5)	251 (21.9)	240 (14.5)	
No	2,040 (72.9)	753 (65.8)	1,287 (77.8)	
SOWS Score,[d] Mean ± SD	8.8 ± 8.4	9.2 ± 8.4	8.3 ± 8.5	.017
Past-year DSM-5 kratom-related SUD criteria, No. (%)				
No criteria met	2,454 (87.7)	981 (85.8)	1,473 (89.1)	.043
Mild	276 (9.9)	131 (11.5)	145 (8.8)	
Moderate	51 (1.8)	26 (2.3)	25 (1.5)	
Severe	17 (0.6)	6 (0.5)	11 (0.7)	
How troubled or bothered by kratom use?[e] Mean ± SD	3.2 ± 9.8	3.4 ± 9.9	3.1 ± 9.8	.034
Ratings of typical kratom effects,[e] Mean ± SD				
Drug Effect	27.3 ± 29.8	25.9 ± 29.3	28.2 ± 30.1	.061
Drug Liking	85.7 ± 23.7	87.3 ± 22.5	84.6 ± 24.4	< .001
High	12.0 ± 20.1	11.1 ± 18.9	12.6 ± 20.8	.265
Good Effects	86.4 ± 23.0	86.7 ± 23.5	86.2 ± 22.6	.009
Bad Effects	11.5 ± 15.7	10.8 ± 15.5	12.0 ± 15.9	.036
Desire	30.1 ± 28.9	33.3 ± 29.3	27.9 ± 28.4	< .001
Stimulated	41.3 ± 28.6	42.5 ± 27.9	40.6 ± 29.0	.066
Euphoric	25.1 ± 27.1	24.7 ± 26.6	25.4 ± 27.4	.981
Sick	6.2 ± 12.3	5.8 ± 11.8	6.5 ± 12.6	.094

(*continued on next page*)

Table 2 (*continued*)

Respondent Group				
Kratom Use Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Dizzy	4.8 ± 10.9	4.9 ± 11.4	4.7 ± 10.5	.703
Alert	49.8 ± 30.9	52.5 ± 30.7	47.9 ± 30.8	< .001
Anxious	3.9 ± 9.6	3.8 ± 8.6	4.0 ± 10.3	.385
Sleepy	22.3 ± 23.6	20.4 ± 22.0	23.6 ± 24.7	.009

Abbreviation: No, number; SD, standard deviation; SOWS, Subjective Opioid Withdrawal Scale; SUD, Substance Use Disorder.

[a] Opioid reduction users were classified as those who responded affirmatively to the question, "Have you ever used kratom to help you cut down or stop using heroin or prescription pain medications (such as Vicodin, Percocet, Oxycontin, etc.)?".

[b] P values calculated using chi-square and 2-tailed Mann-Whitney U tests comparing Opioid reduction users (n = 1,144) and Other users of kratom (n = 1,654).

[c] Respondents could identify multiple reasons for use.

[d] SOWS scores can range from 0 to 64, with scores 0–10 = mild, 11–20 = moderate, > 20 = severe.

[e] Possible scores range 0 (not at all) to 100 (extremely).

improved by including the abovementioned predictor variables (χ^2 = 2988.20, $p < .001$). Kratom use for opioid use reduction was significantly associated with age of first kratom use (aOR > 8.87×10^4 for starting use at age 65 or younger; 95 % CI: 0.00, 12.92×10^6), lifetime kratom use on < 100 occasions (aOR = 0.26; 95 % CI: 0.13, 0.52), frequency of current kratom use (χ^2 = 10.64, $p = .031$), never having experienced opioid withdrawal (aOR < 0.01; 95 % CI: 0.00, < 0.01), greater number of opioids used in the past 12-months (χ^2 =644.46, $p < .001$), and past 12-month opioid use (aOR = 5.89; 95 % CI: 3.35, 10.39).

3.7. Comparison of kratom users by motivation for use

Tables 1 and 2 show between-groups comparisons of individuals who reported using kratom to reduce opioid use (n = 1,144), and those who reported using kratom for other reasons such as pain or depression (n = 1,654). These groups were similar in many respects including age, sex, relationship status, and geographic location (Table 1). However, groups differed significantly in education and employment status, with those using kratom for opioid use reduction showing lower rates of college or advanced degrees, fewer current students, and greater unemployment.

Those who used kratom to reduce opioid use were less likely to have used alcohol ($p < .001$), antidepressants ($p = .028$), and hallucinogens ($p = .014$), but more likely to have used tobacco ($p < .001$), opioids ($p < .001$), benzodiazepines ($p < .001$), and cocaine ($p = .002$) in the past year (Table 1). Individuals who used kratom to reduce opioid use reported significantly greater lifetime prevalence across a variety of medical diagnoses including back pain, depression, and panic attacks, with menopause being the only diagnosis more common among those using kratom for purposes other than opioid use reduction. Respondents who used kratom to reduce their opioid use also showed significantly higher rates of endorsing kratom use for anxiety, depression, post-traumatic stress, bipolar mood, and pain.

Those who reported using kratom for opioid use reduction exhibited greater likelihood of having used kratom in the 24 h prior to completing the survey, higher dose used per occasion, more doses used per day, greater frequency of use, and higher prevalence of kratom-related withdrawal symptoms (Table 2). Between-group differences in typical subjective effects of kratom were also observed, with opioid reduction users reporting significantly greater drug liking, good effects, alertness, and desire for kratom, and significantly less sleepiness. Those who reported using kratom for opioid reduction were slightly more likely to meet DSM-5 criteria for mild or moderate kratom-related SUD in the past year.

4. Discussion

The current study collected data on kratom user demographics, use patterns, and perceived therapeutic and adverse effects. Participants in the present study were predominantly White, middle-aged, female, with some college education, in a committed relationship, and employed. Physical and psychological health in the current sample was on average slightly below US general population means (Hays et al., 2009), though lifetime pain and depression diagnoses were highly prevalent among respondents. These findings are congruent with observed comorbidity between opioid use disorder, pain, and psychiatric conditions such as depression (Conway et al., 2006; Fischer et al., 2012). Interestingly, respondents who reported using kratom for opioid use reduction had a higher life-time prevalence of depression, but were less likely to use antidepressants than other respondents. It is possible that these individuals use kratom as an alternative to antidepressant medications, though this might also be related to lack of access to medical care, which was not explicitly probed in this survey and should be examined in future studies. Consistent with other recent research (Boyer et al., 2007; Coe et al., 2019; Grundmann, 2017; Henningfield et al., 2018; Smith and Lawson, 2017; Swogger et al., 2015), these data suggest individuals in the US are using kratom to self-treat medical conditions such as pain, depression, anxiety, and opioid withdrawal symptoms, and reporting robust effectiveness for these indications.

This study supports the results of previous studies (Coe et al., 2019; Grundmann, 2017; Smith and Lawson, 2017; Swogger et al., 2015) by suggesting that kratom has a relatively benign risk profile compared to typical opioids, with only a minority of respondents endorsing kratom-related adverse effects, withdrawal symptoms, or problematic use. Adverse effects reported here were most commonly rated as mild and lasted ≤1 day, and less than 1 % of the total sample found the effects of kratom to be severe enough to seek medical treatment. Adverse effects of kratom use were related to a number of demographic, health, and drug use variables including age, sex, education, income, depression, pain severity, and past 12-month alcohol and opioid use. Therefore, younger individuals or people with depression or more severe pain may experience more kratom-related adverse effects, potentially related to co-use with alcohol or other opioids. However, daily kratom users among the current sample were unlikely to meet criteria for a kratom-related SUD, or report substantial problems or concerns related to their kratom use. Logistic regression models additionally found that greater kratom-related SUD symptoms predicted negative effects of kratom use, kratom withdrawal, and seeking treatment for kratom use, but not kratom use for the purposes of opioid reduction. Thus, kratom may differ in important respects from typical opioids, and may have significant therapeutic potential in light of the present opioid crisis (Henningfield et al., 2018; Raffa et al., 2018).

The major limitation of this and other internet-based surveys of kratom users is the self-selected convenience sample queried. Because data were collected online, and recruitment was conducted through websites of interest to kratom users, the sample likely exhibits selection bias towards individuals who are younger, more affluent, and more

positively inclined towards kratom. Therefore, these results may underrepresent individuals from lower socio-economic status backgrounds, older and less technologically-fluent people, and those with negative experiences using kratom (e.g., who discontinued use due to adverse effects and are no longer part of the kratom-using online community). Thus, adverse effects may be underestimated, and benefits overestimated. It was also impossible to distinguish medically prescribed from illicit use of opioid medications in the current dataset, representing another significant limitation of the present study.

Kratom is currently unscheduled in the US, although the US Drug Enforcement Administration and Food and Drug Administration have raised the possibility of Schedule I classification of kratom and its alkaloids, which would strongly deter research and pose a significant public health risk for individuals currently using kratom in place of other opioids (DEA, 2017; Henningfield et al., 2018; Prozialeck, 2016). The rationale for Schedule I classification includes 44 possible kratom-related deaths worldwide over the past decade, most of which are known to involve other substances and/or preexisting medical conditions (Henningfield et al., 2018). The current scope of kratom use in the US remains unknown, and only one controlled human laboratory study of kratom has been conducted to date (Trakulsrichai et al., 2015), highlighting a notable lack of empirical information about the epidemiology and pharmacological effects of kratom in humans. Nationally-representative epidemiological research is needed, along with controlled studies of the potential risks, benefits, medication interactions, and abuse liability of kratom in humans prior to any Scheduling action that may confer unintended, but deleterious, public health consequences. There is a high likelihood that banning kratom or its constituents would compel individuals who are presently using kratom for pain relief or opioid use reduction to return to using prescription or illicit opioids with a known risk of dependence and possible lethal overdose.

With nearly 49,000 opioid-related overdose deaths in the US in 2017, the current opioid epidemic has reached unprecedented levels (Ahmad et al., 2018). Prescription opioid use has increased more than 4-fold since 1999 (Frenk et al., 2015), comprising 245 million prescriptions for opioid medications in 2014 (Levy et al., 2015; Rudd et al., 2016), and contributing to almost half of current US opioid overdose deaths (Ahmad et al., 2018; Rudd et al., 2016). The majority of pharmaceutical opioids are prescribed for the management of acute pain. However, prescription opioid misuse, diversion, and use disorder represent rapidly growing public health concerns (Vowles et al., 2015), highlighting an urgent need for novel pain management options that are safer, and less addictive than current medications (Volkow and McLellan, 2016). If controlled research in humans finds that kratom exhibits analgesic effects with minimal abuse liability and risk of respiratory depression, this could provide a much-needed avenue towards the development of novel medications for pain management and potentially OUD. Thus, additional investigation of kratom and its alkaloids is both timely and promising, and may have critical public health ramifications in the midst of the current opioid crisis.

Contributors

Dr. Garcia-Romeu made substantial contributions to the conception and design of the study, the acquisition, analysis, and interpretation of the data, and the drafting of the manuscript. Dr. Cox made substantial contributions to the analysis of the data, and made critical revisions to the manuscript. Dr. Smith made substantial contributions to the design of the study, the analysis of the data, and made critical revisions to the manuscript. Dr. Dunn made substantial contributions to the conception and design of the study, the acquisition and interpretation of the data, and made critical revisions to the manuscript. Dr. Griffiths made substantial contributions to the conception and design of the study and made critical revisions to the manuscript. All authors read and approved the final version of this manuscript, and agree to be accountable for all aspects of the work.

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Declaration of Competing Interest

The authors have no conflicts of interest to report.

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