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Patterns of Kratom use and health impact in the US—Results from an online survey

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ABSTRACT

Background: Kratom preparations have raised concerns of public health and safety in the US. Investigation into the demographics, perceived beneficial and detrimental effects of Kratom as well as common doses and purposes of its use are important to properly evaluate its potential health impact.

Methods: An anonymous cross-sectional online survey was conducted in October 2016 of 10,000 current Kratom users through available social media and online resources from the American Kratom Association. A total of 8049 respondents completed the survey.

Results: Kratom is primarily used by a middle-aged (31–50 years), middle-income ($35,000 and above) population for purposes of self-treating pain (68%) and emotional or mental conditions (66%). Kratom preparations present with a dose-dependent effect with negative effects, which were primarily gastrointestinal related including nausea and constipation, mainly presenting at high (5 g or more/dose) and more frequent (22 or more doses/week) dosing.

Conclusions: Kratom shows a dose-dependent opioid-like effect providing self-reported perceived beneficial effects in alleviating pain and relieving mood disorders. Kratom was primarily used for self-treatment of pain, mood disorders, and withdrawal symptoms associated with prescription opioid use.

1. Introduction

Kratom preparations are extracts of the leaves of a tree (*Mitragyna speciosa* Korth., Rubiaceae) native to Southeast Asia (Shellard, 1989; Tanguay, 2011). The leaves are traditionally chewed in fresh or dried form to alleviate pain, decrease fatigue, and elevate mood (Warner et al., 2016). It has also been used to alleviate opioid withdrawal symptoms in opioid misuse or abuse such as heroin or morphine (Boyer et al., 2008; Hassan et al., 2013). Kratom extracts available in the US are primarily powders that can be dissolved in fluid or consumed with food. Most commercially available powdered Kratom products in the US are recommended in doses of 2–6 g depending on the Mitragyna strain used and the intended use. In most cases, users will titrate themselves starting with lower doses until they reach the desired effect.

Although Kratom has been available in the US for at least the past ten years as a dietary supplement, public attention has recently increased with a report by the Centers for Disease Control and Prevention (CDC) stating a significant increase in Kratom-related calls to poison control centers between 2011 and 2015 (Anwar et al., 2016). Among the 660 reported calls, 49 (7.4%) were classified as major, life-threatening with some residual disability.

Based on the CDC report, the Drug Enforcement Administration (DEA) issued the intent to place Kratom and its opioid-like active constituents mitragynine and 7-hydroxymitragynine in schedule I of the controlled substances act (DEA, 2016). This intent has since been withdrawn awaiting a final decision after a public commenting period that expired on December 1st 2016. An eight-factor analysis of Kratom as mandated by the FDA has been made available by Drs. Henningfield and Fant leading up to the deadline (Henningfield and Fant, 2016). Indeed, the alkaloids mitragynine and 7-hydroxymitragynine have been identified to interact with the opioid receptors although the interaction is not entirely elucidated with some researchers indicating a full agonist activity with lower potency than morphine and others suggesting a partial agonist activity with higher potency than morphine (Kruegel et al., 2016; Prozialeck et al., 2012). Receptor-binding studies identified both mitragynine and 7-hydroxymitragnine as partial agonists at the human μ-opioid receptor and a partial antagonist at human κ-opioid receptors with several other alkaloids present in Kratom only acting on μ-opioid receptors with lower potency (Kruegel et al., 2016). The oxidized alkaloid 7-hydroxymitragynine displays a stronger binding affinity towards the opioid receptors compared to the classical full opioid agonist morphine (Matsumoto et al., 2004). In addition, *in vitro*

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assays and animal studies indicate that mitragynine may also interact with several non-opioid receptors in the CNS including adrenergic and serotonergic receptors that may contribute to its antidepressant and mood-altering effects (Boyer et al., 2008).

1.1. Purpose of study

Irrespective of its pharmacology, little is known about the use pattern and potential health impact of Kratom preparations in the US. The research underlying this article was conducted to answer the following questions:

- Who is consuming Kratom and for what purpose?
- What perceived beneficial and detrimental effects are reported by Kratom users if dose and frequency of consumption are considered?
- Does Kratom present with an abuse potential and withdrawal symptoms?

2. Methods

2.1. Survey setting, approval, and data collection

An online anonymous cross-sectional survey was conducted in October 2016 of 10,000 current Kratom users. Qualtrics (Qualtrics, Provo, UT) was used to collect the data. The survey was made available as an announcement on the homepage of the American Kratom Association (http://www.americankratom.org/) and their various social media outlets (American Kratom Association Facebook page, website forums, and membership email distribution) with follow-up reminders in weekly intervals until 10,000 responses were reached. In addition, information about the survey was shared on various other websites frequented by Kratom users such as http://www.speciosa.org or http://www.drugs-forum.com. Participants were offered no incentive to complete the survey. The survey (supplementary material) was designed and classified based on common variables used by the CDC Behavioral Risk Factor Surveillance System (BRFSS) (Silva, 2014). The protocol was approved by the Institutional Review Board at the University of Florida (IRB #2016-01581). Participants had to acknowledge they were 18 years or older before starting the survey and that they participated of their own free will in the study. Collection of data started on October 2nd and concluded on October 26th 2016 once 10,000 responses were collected. Only completed responses (8049 or 80.5%) were included in the data analysis. Internet protocol addresses were not stored with the data but used to prevent multiple responses from the same device to ensure anonymity and prevent ballot stuffing. The recruitment method utilized for this study likely introduced selection bias because of the use of electronic distribution techniques that may skew towards a younger and economically fluent population that has access to such technology thus resulting in underrepresentation of other socio-demographic groups such as low income and those lacking online skills or accessibility to the internet (Brown et al., 2014).

2.1.1. Survey format

Demographic data (age, gender, marital status, ethnicity, location by ZIP code, employment status, insurance coverage, household income, and education), overall health status (weight, height, self-rated overall health, smoking status, alcohol and caffeine consumption, reasons for healthcare provider visit, self-rated pain level, and self-reported diagnosed health conditions), Kratom use experience (source of Kratom information, length of medical condition prior to Kratom use, reason(s) for Kratom use, treatment for substance use disorder, change in medical condition with use of Kratom, amount and frequency of Kratom use, Kratom preparation, beneficial effects with Kratom use, negative effects with Kratom use, Kratom withdrawal symptoms and severity, need for health care treatment because of Kratom use), opinion on Kratom legislation and regulation (disclosure of Kratom use with healthcare provider, effect of Kratom ban on user, regulation of Kratom product quality, access restriction to Kratom by state or federal government). The complete survey is attached as supplementary material.

2.2. Data analysis

The data were analyzed in Microsoft Excel 2013 (version 15.0, Microsoft, Seattle, WA) and GNU PSPP (http://www.gnu.org/software/pspp/, version 0.10.4-g50f7b7). The frequency of Kratom dosing was binned into seven equally spaced categories (Tables 3 and 4). Chi-square analysis was applied for level comparison among nominal and ordinal variables against expected values for goodness of fit (single variable Chi-square goodness of fit assuming equal counts for expected values). Binomial logistic regression was used to compare levels of variables against a reference level to obtain odds ratios and 95% confidence intervals. For each logistic regression, all pertinent independent variables were included in the same model comparing all levels against each other (no adjustment for specific comparisons among levels, post-survey power calculation resulted in at least 85% power and 93% confidence for all models).

3. Results

3.1. Demographics

The survey was completed by 8049 participants (completion rate: 80.5%) and only completed responses were included in the data analysis. A majority of respondents were male (56.91%), between the ages of 31–50 years (55.09%), married or partnered (54.25%), white non-Hispanics (89.39%), employed for wages (56.83%), with private insurance through their employer or self-insurance (61.31%), an annual household income of $35,000 or higher (63.24%), and had at least some college education (82.32%) (Table 1). Each variable indicated a significant difference among the levels as evaluated by chi-square statistics.

3.2. Reasons for Kratom use

Among those respondents who currently use Kratom, a majority have used it for more than 1 year but less than 5 years (56.59%) and a substantial percent (40.05%) discussed the use of Kratom with their healthcare provider (physician, nurse, or pharmacist). The primary source of initial Kratom information was through internet searches (45.8%) or recommendation by friends (27.4%) (Table 1). Kratom was most commonly consumed in powdered form with a beverage followed by taken in pill form or consumed in pure powder form (Table 2).

Self-reported necessity for treatment for a medical/physical or mental health issue related to Kratom use (“Have you ever needed medical or mental health care treatment because of your Kratom use?”) was low (51/7893 or 0.65%).

Kratom use related to an illicit drug dependency, i.e. relieving the withdrawal symptoms of current or prior use of an opioid or another illicit drug, was more likely in participants between the ages of 21–30 years (OR: 1.89, CI: 1.02–3.51), those with self-insurance (OR: 1.57, CI: 1.18–2.10), Medicaid (OR: 2.11, CI: 1.49–3.00), Medicare (OR: 2.41, CI: 1.53–3.79), or no insurance (OR: 1.97, CI: 1.51–2.59), while females (OR: 0.63, CI: 0.51–0.78), married participants (OR: 0.69, CI: 0.54–0.87), and retired (OR: 0.26, CI: 0.07–0.93) and unable to work (OR: 0.29, CI: 0.16–0.51) were significantly less likely to use Kratom for this purpose (Table 3). Participants who consumed Kratom for a prescription drug dependency, i.e. an initially legally prescribed opioid or other medication that led to a dependency to the medication with resulting misuse and associated withdrawal and overdose symptoms, were more likely to be ages 21 years and older (ORs: 2.32–3.6), being partnered (but not married) (OR: 1.37, CI: 1.12–1.68), having Medicare

Table 1
Kratom user demographics. Chi-square test for goodness of fit assuming equal distribution among expected values for each group was used to compare groups with $p < 0.05$ as significance level.

	Frequency	Percent	Chi-square (significance)
Age			
18–20 years	212	2.63	$\chi^2_{df=6} = 5663$ ($p < 0.0001$)
21–30 years	2038	25.32	
31–40 years	2788	34.64	
41–50 years	1646	20.45	
51–60 years	966	12	
61 years and older	391	4.86	
Do not wish to answer	8	0.1	
Gender			
Female	3468	43.09	$\chi^2_{df=1} = 154$ ($p < 0.0001$)
Male	4581	56.91	
Marital status			
Single/never married	2612	32.45	$\chi^2_{df=4} = 5329$ ($p < 0.0001$)
Married	3639	45.21	
Partnered	728	9.04	
Divorced	964	11.98	
Widowed	106	1.32	
Ethnicity			
Black or African-American	61	0.76	$\chi^2_{df=6} = 37104$ ($p < 0.0001$)
Asian	95	1.18	
Hispanic or Latino/a	275	3.42	
White (Non-Hispanic)	7195	89.39	
American Indian or Alaska Native	97	1.21	
Other	164	2.04	
Do not wish to answer	162	2.01	
Employment status			
Employed for wages	4574	56.83	$\chi^2_{df=8} = 18148$ ($p < 0.0001$)
Self employed	1210	15.03	
Out of work for 1 year or more	124	1.54	
Out of work for less than 1 year	107	1.33	
Homemaker	498	6.19	
Student	455	5.65	
Retired	288	3.58	
Unable to work	683	8.49	
Do not wish to answer	110	1.37	
Insurance coverage			
Private insurance through employer	3808	47.31	$\chi^2_{df=6} = 7710$ ($p < 0.0001$)
Private insurance through self-insurance	1127	14	
Medicaid	650	8.08	
Medicare or Medicare & supplement	620	7.7	
No insurance	1134	14.09	
Other	404	5.02	
Do not wish to answer	306	3.8	
Education			
Did not complete High school	112	1.39	$\chi^2_{df=5} = 7373$ ($p < 0.0001$)
High School graduate or equivalent	1269	15.77	
Some college (e.g. AA, AS, or no degree)	3785	47.02	
Bachelor's degree (e.g. BA, BS, AB)	2013	25.01	
Advanced degree (e.g. MBA, MS, PhD, JD, MD)	828	10.29	
Do not wish to answer	42	0.52	
Household income			
less than $20,000	944	11.73	$\chi^2_{df=6} = 2029$ ($p < 0.0001$)
$20,000-$24,999	681	8.46	
$25,000-$34,999	897	11.14	
$35,000-$49,999	1248	15.51	
$50,000-$74,999	1534	19.06	
$75,000 or more	2308	28.67	
Do not wish to answer	437	5.43	
Time since first consumption of Kratom			
Less than 6 months	1167	14.79	$\chi^2_{df=4} = 1072$ ($p < 0.0001$)
6 months – 1 year	1491	18.89	
1–2 years	2211	28.01	
2–5 years	2256	28.58	
more than 5 years	768	9.73	
Negative effects if Kratom was not consumed within certain time period			
Yes, if not taking it for more than 12 h	240	14.53	$\chi^2_{df=3} = 953$ ($p < 0.0001$)
Yes, if not taking it for more than 24 h	304	18.4	
Yes, if not taking it for more than 48 h	159	9.62	
No	949	57.45	
Severity of negative effects if Kratom was not consumed			
1 (very severe)	67	9.53	$\chi^2_{df=4} = 410$ ($p < 0.0001$)
2	284	40.4	
3	254	36.13	
4	81	11.52	
5 (not severe at all)	17	2.42	
Medical or mental health care treatment needed because of Kratom consumption			
Yes, for mental health issues related to Kratom	21	0.27	$\chi^2_{df=2} = 15482$ ($p < 0.0001$)
Yes, for medical/physical health issues related to Kratom	30	0.38	
No	7842	99.35	
Kratom recommendation source			
Family member	707	8.96	$\chi^2_{df=5} = 6537$ ($p < 0.0001$)
Friend	2163	27.4	
Health care provider (physician, nurse, pharmacist)	266	3.37	
Internet search	3615	45.8	
Social media	652	8.26	
Other	490	6.21	
Kratom use discussion with healthcare provider (physician, nurse, pharmacist)			
Yes	3161	40.05	$\chi^2_{df=2} = 3743$ ($p < 0.0001$)
No	4537	57.48	
Do not wish to answer	195	2.47	

Table 2
Percent of self-reported Kratom preparations in response to the question "How do you usually use Kratom?", N = 8069.

	How do you usually use Kratom?
Store-bought liquid Kratom (shot)	0.52%
Powdered Kratom consumed with food	2.19%
Other	3.07%
Self-prepared Kratom tea	13%
Powdered Kratom (pure or in pill form)	32.64%
Powdered Kratom consumed with beverage	48.59%

(OR: 1.69, CI: 1.31–0.218), Medicaid (OR: 1.6, CI: 1.27–2.00), or no insurance (OR: 1.64, CI: 1.37–1.95), and earning between $35,000 to $49,999 (OR: 1.38, CI: 1.11–1.73) (Table 3) whereas being self-employed (OR: 0.77, CI: 0.65–0.92), a student (OR: 0.72, 0.53–0.99), or having a Bachelor's (OR: 0.46, CI: 0.30–0.72) or advanced degree (OR: 0.41, CI: 0.25–0.66) was associated with a significantly lower odds

Table 3
Reason for Kratom use. Odds ratios (OR), 95% Confidence Intervals (CI), and number of respondents (N) for each level grouped by age, gender, marital status, race, employment, insurance, education, and income. Binomial logistic regression was used. Values in italics indicate significant differences ($p < 0.05$) to reference group.

Predictor	N	Are you taking Kratom because of an illicit drug dependency (e.g. heroin, cocaine, amphetamine, marijuana)?		Are you taking Kratom because of a prescription medicine dependency (e.g. opioid pain killers)?		Are you taking Kratom because of a medical condition leading to acute or chronic pain?		Are you taking Kratom because of an emotional/mental condition (e.g. anxiety, depression, PTSD)?	
		Yes: 539, No: 6490		Yes: 1813, No: 5168		Yes: 4811, No: 2249		Yes: 4684, No: 2363	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age									
18–20 years (reference)	145								
21–30 years	1754	*1.89*	1.02–3.51	*2.46*	1.40–4.32	*1.96*	1.34–2.88	0.94	0.59–1.49
31–40 years	2502	1.7	0.9–3.20	*3.6*	2.04–6.36	*2.73*	1.84–4.03	0.7	0.44–1.11
41–50 years	1456	0.9	0.46–1.77	*3.14*	1.77–5.60	*5.06*	3.36–7.61	*0.5*	0.31–0.8
51–60 years	839	0.63	0.29–1.34	*2.58*	1.43–4.67	*4.65*	3.02–7.16	*0.36*	0.22–0.58
61 years and older	333	0.37	0.12–1.18	*2.32*	1.21–4.46	*7.07*	4.07–12.31	*0.23*	0.13–0.4
Gender									
Male (reference)	3982								
Female	3047	*0.63*	0.51–0.78	0.98	0.87–1.10	*1.6*	1.42–1.81	*1.3*	1.16–1.46
Marital status									
Single/Never married (reference)	2179								
Married	3293	*0.69*	0.54–0.87	1.14	0.98–1.33	*1.69*	1.47–1.95	*0.78*	0.68–0.9
Partnered	627	0.97	0.71–1.33	*1.37*	1.12–1.68	*1.38*	1.13–1.68	0.89	0.72–1.09
Divorced	844	0.79	0.56–1.13	1.1	0.90–1.35	*1.55*	1.25–1.91	0.92	0.75–1.11
Widowed	86	2.09	0.84–5.19	1.03	0.60–1.76	1.01	0.56–1.81	1.22	0.75–1.99
Race									
White (Non-Hispanic) (reference)	6433								
Black or African-American	49	1.11	0.38–3.24	0.91	0.46–1.80	1	0.53–1.88	0.91	0.49–1.69
Asian	80	1.6	0.80–3.20	*1.72*	1.06–2.78	0.86	0.54–1.37	1.26	0.75–2.12
Hispanic or Latino/a	245	0.58	0.33–1.01	1.23	0.92–1.64	0.81	0.61–1.07	*0.73*	0.55–0.96
American Indian or Alaska Native	82	1.67	0.81–3.45	1.02	0.62–1.68	*2.12*	1.14–3.94	0.73	0.46–1.16
Other	140	1.55	0.90–2.69	*1.68*	1.17–2.40	*1.77*	1.15–2.72	0.97	0.66–1.42
Employment									
Employed for wages (reference)	4190								
Self employed	1057	0.83	0.63–1.09	*0.77*	0.65–0.92	0.91	0.77–1.08	1.05	0.89–1.24
Out of work for 1 year or more	105	0.69	0.30–1.54	1.14	0.74–1.76	*1.91*	1.08–3.35	1.16	0.74–1.82
Out of work for less than 1 year	90	0.57	0.26–1.28	0.76	0.46–1.24	0.72	0.45–1.13	1.34	0.80–2.26
Homemaker	435	0.75	0.47–1.19	0.96	0.75–1.21	1.17	0.90–1.53	*1.34*	1.05–1.71
Student	331	0.88	0.59–1.31	*0.72*	0.53–0.99	0.88	0.68–1.14	*1.86*	1.34–2.59
Unable to work	579	*0.29*	0.16–0.51	0.87	0.68–1.10	*4.17*	2.83–6.14	0.84	0.66–1.06
Retired	242	*0.26*	0.07–0.93	0.8	0.54–1.18	1.07	0.69–1.66	0.88	0.63–1.23
Insurance									
Private insurance through employer (reference)	3526								
Private insurance through self-insurance	1003	*1.57*	1.18–2.10	1.14	0.95–1.37	0.94	0.79–1.11	1.09	0.92–1.29
Medicaid	586	*2.11*	1.49–3.00	*1.6*	1.27–2.00	1.25	0.98–1.59	*1.36*	1.08–1.73
Medicare or Medicare & supplement	543	*2.41*	1.53–3.79	*1.69*	1.31–2.18	1.31	0.96–1.79	*1.35*	1.05–1.74
No insurance	1011	*1.97*	1.51–2.59	*1.64*	1.37–1.95	0.99	0.83–1.18	*1.31*	1.10–1.57
Other	360	1.39	0.88–2.19	1.14	0.87–1.50	*1.43*	1.08–1.89	1.21	0.94–1.56
Education									
Did not complete High school (reference)	92								
High school graduate or equivalent	1083	1.06	0.51–2.21	0.76	0.49–1.19	1.1	0.66–1.86	0.64	0.38–1.07
Some college (e.g. AA, AS, or no degree)	3308	0.83	0.40–1.70	0.66	0.43–1.03	1.06	0.64–1.76	0.66	0.40–1.10
Bachelor's degree (e.g. BA, BS, BA)	1789	0.55	0.26–1.16	*0.46*	0.30–0.72	0.8	0.47–1.33	*0.59*	0.35–0.99
Advanced degree (e.g. MBA, MS, PhD, JD, MD)	757	0.55	0.24–1.22	*0.41*	0.25–0.66	0.74	0.44–1.24	0.6	0.35–1.01
Income									
less than $20,000 (reference)	835								
$20,000-$24,999	604	1.18	0.83–1.68	1	0.78–1.28	0.95	0.74–1.23	0.9	0.70–1.16
$25,000-$34,999	816	0.89	0.62–1.27	1.1	0.87–1.39	0.86	0.67–1.09	0.93	0.73–1.18

(continued on next page)

Table 3 *(continued)*

Predictor	N	Are you taking Kratom because of an illicit drug dependency (e.g. heroin, cocaine, amphetamine, marijuana)?		Are you taking Kratom because of a prescription medicine dependency (e.g. opioid pain killers)?		Are you taking Kratom because of a medical condition leading to acute or chronic pain?		Are you taking Kratom because of an emotional/mental condition (e.g. anxiety, depression, PTSD)?	
		Yes: 539, No: 6490		Yes: 1813, No: 5168		Yes: 4811, No: 2249		Yes: 4684, No: 2363	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
$35,000-$49,999	1148	1.19	0.85–1.67	*1.38*	1.11–1.73	0.95	0.75–1.20	0.87	0.70–1.09
$50,000-$74,999	1436	0.8	0.55–1.15	1.2	0.95–1.50	0.92	0.73–1.17	0.82	0.66–1.03
$75,000 or more	2190	0.87	0.61–1.26	1.11	0.88–1.40	0.88	0.69–1.11	*0.74*	0.59–0.93

ratio to consume Kratom for a prescription drug dependency (Table 3).

Kratom was primarily used for a medical condition leading to or being associated with acute or chronic pain (68%) including acute or chronic pain as a medical condition itself. Participants were significantly more likely to consume Kratom for this purpose if 21 years or older (ORs: 1.96–7.07), female (OR: 1.6, CI: 1.42–1.81), married (OR: 1.69, CI: 1.47–1.95), partnered (OR: 1.38, CI: 1.13–1.68), or divorced (OR: 1.55, CI: 1.25–1.91), out of work for 1 year or more (OR: 1.91, CI: 1.08–3.35) or unable to work (OR: 4.17, CI: 2.83–6.14) (Table 3).

Kratom was also used by a substantial number of participants for an emotional or mental condition such as anxiety, depression, or PTSD (66.5% or 4684 respondents). Being female (OR: 1.3, CI: 1.16–1.46), a homemaker (OR: 1.34, CI: 1.05–1.71) or student (OR: 1.86, CI: 1.34–2.59), and on either Medicaid (OR: 1.36, CI: 1.08–1.73), Medicare (OR: 1.35, CI: 1.05–1.74), or having no insurance (OR: 1.31, CI: 1.10–1.57) was associated with a significantly higher odds ratio to use Kratom for this purpose whereas ages 41 or older, being married, having a Bachelor's degree, and earning $75,000 or more were indicative of a lower odds ratio (Table 3).

3.3. Self-reported beneficial effects of kratom use

The most self-reported beneficial effects of Kratom use were decreased pain (85.01%), increased energy (83.75%), and less depressive mood (80.00%) (Table 4). For increased energy, less depressive and anxious mood, elevated mood, and reducing or stopping the use of opioid pain relieving medications a dose-dependent effect was observed with lower amounts being linked to a lower odds ratio of experiencing the perceived beneficial effect. This was also reflected in the number of doses used per week although it was not significant for less anxious and elevated mood (Table 4). For reduction or discontinuation of opioid pain medication the threshold dose per Kratom use reported was 5 or more grams to be perceived as effective. No dose-dependent beneficial effect was observed for decreased pain, increased focus, or reduced PTSD symptoms.

3.4. Self-reported detrimental effects of Kratom use

Overall 20.93% (1652 out of 7893) of participants reported negative effects with the use of Kratom which were primarily gastrointestinal related including nausea and constipation. The most frequent self-reported negative effects from Kratom use were nausea (12.75%), constipation (9.17%), and dizziness or drowsiness (4.81%). Except for diarrhea, all negative effects appeared to be dose-dependent. For most negative effects, doses up to 5 g of Kratom presented with lower odds ratios than Kratom uses that consumed 8 g or more per dose (Table 5). Participants presented with lower odds ratios of developing nausea, constipation, or vomiting if they used 21 Kratom doses per week or less. Compared to higher doses and more frequent dosing per week, negative effects were less common as indicated by lower odds ratios with less frequent dosing and lower amounts consumed per dose (Table 5).

3.4.1. Reported potential Kratom withdrawal symptoms and toxicity

Self-reported withdrawal effects within 12–48 h related to discontinuation of Kratom use were reported by less than half (42.55%) of respondents who stated they experienced any negative effects with Kratom use (Table 1). The severity of the negative effects were rated as 2 (40.40%) or 3 (36.13%) on a 5-point Likert scale (from 1-very severe to 5-not severe at all).

4. Discussion

The increasing use of Kratom is primarily associated with self-reported treatment of acute and chronic pain and for mood conditions such as anxiety and depression. Based on the known opioid-like mechanism for the active constituents mitragynine and 7-hydroxymitragynine, the results of this survey further support the use of Kratom for alleviation of acute and chronic pain. Interestingly, almost the same number of respondents took the preparation for a mood disorder indicating a differentiated mechanism of action which may include additional constituents aside from mitragynine and 7-hydroxymitragynine. Although there are indications that opioid receptor modulation does affect mood and can alleviate depression (Lutz and Kieffer, 2013), the partial agonist and antagonist effects at μ-opioid and κ-opioid receptors may not be the only mechanisms by which Kratom extracts exert their action. The purpose of this survey was not intended to further elucidate the mechanism of action for Kratom preparations but findings support prior reports of its effects. The US Kratom user population is diverse but tends to be middle-aged, middle-class, primarily white non-Hispanics in this survey. One limitation of this survey is the online delivery which may skew towards a younger population sample and underestimate the use of the preparation by older participants.

Both self-reported perceived beneficial and negative effects were dose-dependent and associated with increased frequency of dosing indicating a dose-response effect in this study. In most cases, doses up to 5 g taken up to 3 times per day (21 doses per week) was sufficient for the beneficial effects of Kratom. Negative or adverse effects requiring outpatient treatment or hospitalization due to Kratom consumption were only reported by 51 users indicating a low incidence of 0.65%. The self-reported negative effects were similar to those commonly reported by opioid users, mainly nausea, constipation, and drowsiness or dizziness (Michna et al., 2014). The results also confirm prior reports by poison control centers of the most common adverse effects of Kratom consumption which included tachycardia, agitation or irritability, drowsiness, nausea, and hypertension (Anwar et al., 2016). Given the confirmed action of Kratom constituents on opioid receptors, these results strengthen the proposed mechanism for its analgesic effects. The occurrence of negative effects with discontinuation of Kratom use provides the potential for a withdrawal syndrome and therefore may indicate a physical dependence development at least with continued higher doses of Kratom use. While opioid-like effects appear to be associated with higher doses of Kratom, elevated mood and anxiolytic and antidepressant effects were reported at lower doses as well in this

Table 4
Self-reported perceived beneficial effects of Kratom use. Odds ratios (OR), 95% Confidence Intervals (CI), and number of respondents (N) for each level grouped by amount/dose and doses/week. Binomial logistic regression was used. Values in italics indicate significant differences ($p < 0.05$) to reference group.

Predictor	N	Increased energy		Decreased pain		Increased focus		Less depressive mood		Less anxious mood		Reduced or stopped the use of opioid painkillers		Reduced PTSD symptoms		Elevated mood		Other	
		Yes: 6394, No: 1241		Yes: 6466, No: 1139		Yes: 5299, No: 2306		Yes: 6084, No: 1521		Yes: 5978, No: 1627		Yes: 3715, No: 3890		Yes: 1300, No: 6305		Yes: 5790, No: 1815		Yes: 1227, No: 6378	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Amount of Kratom per dose																			
Less than 1 g	504	*0.58*	0.40–0.83	1.12	0.77–1.61	0.86	0.64–1.16	*0.48*	0.34–0.68	*0.67*	0.49–0.92	*0.63*	0.48–0.84	1.17	0.82–1.66	*0.53*	0.39–0.73	0.79	0.56–1.11
1–3 g	3094	0.84	0.61–1.14	1.15	0.86–1.55	1	0.79–1.28	*0.67*	0.50–0.91	0.94	0.72–1.23	*0.72*	0.57–0.91	0.97	0.72–1.29	*0.76*	0.59–0.99	*0.65*	0.49–0.85
3–5 g	2487	0.92	0.67–1.26	1.14	0.85–1.54	1.01	0.80–1.29	0.8	0.59–1.08	1.11	0.85–1.46	*0.75*	0.59–0.94	0.97	0.72–1.30	1.07	0.82–1.40	0.76	0.58–1.01
5–8 g	1160	0.97	0.69–1.37	1.25	0.90–1.74	1.07	0.83–1.39	1.05	0.76–1.46	1.11	0.82–1.48	0.88	0.69–1.12	1.01	0.74–1.38	1.25	0.93–1.68	0.8	0.59–1.07
more than 8 g (reference)	360																		
Doses of Kratom per week																			
1–7	2607	*0.51*	0.26–0.99	0.65	0.34–1.23	*0.55*	0.32–0.94	*0.4*	0.20–0.81	0.59	0.31–1.09	*0.33*	0.21–0.52	0.83	0.44–1.55	0.44	0.23–0.83	0.62	0.35–1.08
8–14	2162	0.83	0.42–1.63	1.1	0.58–2.12	0.73	0.43–1.25	0.53	0.26–1.08	0.63	0.34–1.18	0.71	0.45–1.14	1.1	0.59–2.05	*0.48*	0.25–0.91	0.73	0.41–1.28
15–21	1834	1.06	0.53–2.09	1.21	0.63–2.32	0.84	0.49–1.45	0.62	0.31–1.26	0.71	0.38–1.34	1.06	0.67–1.69	1.4	0.75–2.62	0.56	0.29–1.07	0.8	0.45–1.41
22–28	554	1.01	0.50–2.07	1.41	0.70–2.82	0.83	0.47–1.45	0.61	0.29–1.27	0.71	0.37–1.37	1.14	0.70–1.86	1.57	0.82–3.00	0.58	0.29–1.13	0.94	0.52–1.71
29–36	295	1.31	0.61–2.82	1.22	0.59–2.53	0.72	0.40–1.28	0.69	0.32–1.48	0.76	0.38–1.51	1.15	0.69–1.92	1.67	0.85–3.28	0.52	0.26–1.05	1.1	0.59–2.03
37–48	76	1.07	0.41–2.80	1.62	0.59–4.44	1.04	0.49–2.22	0.67	0.26–1.70	0.71	0.31–1.63	1.03	0.54–1.97	1.83	0.82–4.09	0.74	0.31–1.77	1.02	0.47–2.23
more than 48 (reference)	77																		

Table 5
Self-reported perceived negative effects of Kratom use. Odds ratios (OR), 95% Confidence Intervals (CI), and number of respondents (N) for each level grouped by amount/dose and doses/week. Binomial logistic regression was used. Values in italics indicate significant differences ($p < 0.05$) to reference group.

Predictor	N	Nausea		Vomiting		Diarrhea		Heart palpitations (rapid heartbeat, tachycardia)		Shortness of breath		Constipation	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
		Yes: 970, No: 6635		Yes: 309, No: 7296		Yes: 38, No: 7567		Yes: 54, No: 7551		Yes: 17, No: 7588		Yes: 697, No: 6908	
Amount of Kratom per dose													
Less than 1 g	504	*0.23*	0.15–0.35	*0.12*	0.06–0.26	0.18	0.02–1.66	*0.09*	0.03–0.34	*0*	0.00–0.08	*0.17*	0.10–0.30
1–3 g	3094	*0.35*	0.26–0.45	*0.18*	0.12–0.26	0.23	0.07–0.77	*0.14*	0.08–0.25	*0.03*	0.01–0.06	*0.4*	0.29 − 0.54
3–5 g	2487	*0.5*	0.38–0.65	*0.36*	0.25–0.52	0.57	0.19–1.74	*0.17*	0.10–0.31	*0.03*	0.01–0.06	*0.58*	0.43–0.78
5–8 g	1160	*0.58*	0.43–0.77	*0.53*	0.35–0.78	0.68	0.21–2.23	*0.15*	0.07–0.32	*0.03*	0.01–0.11	*0.59*	0.43–0.83
more than 8 g (reference)	360												
Doses of Kratom per week													
1–7	2607	0.59	0.34–1.05	*0.42*	0.19–0.96	0.2	0.02–1.70	6.43	0.25–164.34	1.15	0.25–5.31	*0.38*	0.20–0.70
8–14	2162	*0.46*	0.26–0.82	*0.36*	0.16–0.84	0.54	0.02–4.21	4.22	0.16–109.45	1.46	0.31–6.76	*0.44*	0.23–0.81
15–21	1834	*0.51*	0.29–0.91	*0.41*	0.18–0.94	0.41	0.05–3.31	3.72	0.14–97.51	1.46	0.31–6.83	0.59	0.31–1.10
22–28	554	0.64	0.35–1.18	0.59	0.25–1.41	0.12	0.01–2.00	6.41	0.24–173.91	1.52	0.30–7.67	0.58	0.30–1.13
29–36	295	0.77	0.41–1.46	0.39	0.14–1.04	0.23	0.01–3.79	10.26	0.38–279.22	0.25	0.04–1.45	0.66	0.33–1.32
37–48	76	0.62	0.27–1.46	0.54	0.15–1.95	0.93	0.06–15.37	33.53	1.22–921.44	1.15	0.09–14.29	0.71	0.29–1.74
more than 48 (reference)	77												

Predictor	N	Stomach upset		Dizziness or drowsiness		Fainting		Irritability or agitation		High blood pressure (hypertension)		Other	
		Yes: 365, No: 7240		Yes: 366, No: 7239		Yes: 11, No: 7594		Yes: 190, No: 7415		Yes: 21, No: 7584		Yes: 356, No: 7249	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Amount of Kratom per dose													
Less than 1 g	504	*0.34*	0.18–0.63	*0.15*	0.08–0.30	*0.14*	0.02–0.90	*0.24*	0.10–0.58	*0.07*	0.01–0.40	0.72	0.40–1.28
1–3 g	3094	*0.4*	0.26–0.60	*0.22*	0.15–0.31	*0.03*	0.01–0.13	*0.37*	0.22–0.62	*0.08*	0.03–0.17	*0.6*	0.38–0.93
3–5 g	2487	*0.63*	0.42–0.95	*0.37*	0.26–0.52	*0.16*	0.06–0.44	*0.5*	0.30–0.84	*0.08*	0.04–0.20	0.74	0.47–1.15
5–8 g	1160	*0.63*	0.41–0.99	*0.51*	0.35–0.74	*0.14*	0.03–0.57	*0.49*	0.27–0.87	*0.18*	0.08–0.43	0.67	0.41–1.09
more than 8 g (reference)	360												
Doses of Kratom per week													
1–7	2607	*0.33*	0.16–0.66	*0.29*	0.14–0.59	7.69	0.02–3353.59	0.54	0.19–1.53	7.51	0.10–563.29	*0.4*	0.20–0.83
8–14	2162	*0.31*	0.15–0.62	*0.28*	0.14–0.58	3.01	0.01–1390.37	0.35	0.12–1.02	3.21	0.04–249.55	*0.27*	0.13–0.57
15–21	1834	*0.31*	0.15 − 0.63	*0.37*	0.18–0.75	3.32	0.01–1543.82	0.44	0.15–1.27	3.59	0.05–280.91	*0.39*	0.19–0.82
22–28	554	*0.32*	0.15–0.70	*0.49*	0.23–1.04	0.9	0.00–653.44	0.6	0.20–1.84	0.98	0.01–104.03	0.48	0.22–1.05
29–36	295	*0.39*	0.17–0.89	*0.38*	0.16–0.88	12.63	0.03–5938.29	0.76	0.24–2.45	5.09	0.06–461.13	0.44	0.18–1.03
37–48	76	0.65	0.23–1.82	0.78	0.28–2.12	0.89	0.00–11467.11	0.24	0.03–2.24	64.46	0.81–5116.00	0.42	0.12–1.44
more than 48 (reference)	77												

survey. Since mitragynine and 7-hydroxymitragynine act as partial agonists and antagonists at μ- and κ-opioid receptors, some of these psychoactive effects may be explained by this mechanism (Lutz and Kieffer, 2013). Furthermore, *in vitro* and *in vivo* models indicate that mitragynine and 7-hydroxymitragynine exert an antidepressant effect both through their action on opioid receptors as well as by acting on adrenergic and serotonergic receptors (Hazim et al., 2014; Idayu et al., 2011).

Further limitations of this survey are potential bias introduced through self-reporting and the online survey format. Although multiple responses through the same device were suppressed, a user may have submitted multiple responses using different devices. The sample population may not reflect the actual Kratom user population both in age and ethnicity distribution. Due to the cross-sectional nature and relative brief time period of data collection, the results offer but a snapshot of current Kratom consumption in the US within a rapidly changing legal environment causing both confusion and anxiety among users.

The American Kratom Association did not contribute financially to the design or conduct of the survey but a potential limitation is the availability of the survey through an organization that favors the use of and advocates for the continued legality of Kratom. This approach was chosen based on the broad outreach of the American Kratom Association specifically in the US (http://americankratom.org/about) and the specific targeting of current Kratom users in this study. The reach of the American Kratom Association is reflected by its website traffic with on average 2262 unique daily visitors and 9048 daily page views with a majority of the traffic (89.9%) originating from the United States (https://americankratom.org.cutestat.com/, Ash, 2017). The official Facebook page of the American Kratom Association (https://www.facebook.com/Americankratomassociation/) had 30,531 followers as of February 16, 2017 with 53% women and 46% men. The age distribution of website visitors was similar to that of survey participants with a majority of visitors being between 25 and 44 years old (Ash, 2017). This distinguishes the Kratom user population from other websites such as Erowid.org or Bluelight.org which are widely used forums for drug use discussions.

Because of the self-reported demographics of the survey the results should be interpreted with caution but provide initial insights into the current use pattern and health impact of Kratom in the US. The use of Kratom should be further investigated both for potential medicinal as well as recreational applications and how its use should be considered as per current and future regulations and legal implications.

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Conflict of interest

The author states no conflict of interest.

Contributors

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2017.03.007.

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