Chulalongkorn Medical Journal

Volume 63
Issue 3 *July 2019*

Article 7

7-1-2019

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Chula Med J Vol. 63 No. 3 July - September 2019; 179 - 185 DOI : 10.14456/clmj.1476.8

Original article

Characteristics and physical outcomes of kratom users at a substance abuse treatment center

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Background: Despite many disadvantages such as physical and mental disorders, family disruption, crime, etc., substance use disorder is continuously reported worldwide. Twenty - nine million people were reported to suffer from substance abuse. In addition, the survey found that only 1/6 of substance abusers throughout the world were able to access medical services. Kratom (*Mitragyna speciosa Korth*) has been used not only as medicine, but also as psychedelic drug for a long time.
Objective: To study behavioral and physical consequences of kratom use.
Methods: One hundred and six kratom users were recruited into this study at the Princess Mother National Institute on Drug Abuse Treatment (PMNIDAT). Collected data included 1) general information, 2) kratom use profile, 3) side effects from using kratom, 4) Naranjo's algorithm, and 5) Semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA) Section H. Statistics used to analyze these data were percentage, mean, standard deviation, independent *t*-test, Chi-square test, and Pearson's correlation.
Results: Kratom use was classified as either boiling (55.6%) or chewing (41.7%). A number of kratom users often took other substances. Although the boiling-pattern group took more other drugs, the chewing-pattern group significantly had more headaches, arthritis, nausea, or constipation when compared to the other.
Conclusion: Kratom substance users frequently use other substances. There are multiple adverse effects from both patterns of kratom use.

Keywords: Kratom, behavior, physical outcome.

According to the report from the United Nations Office on Drugs and Crime (UNODC) in 2016, 247 million people all over the world aged 15 - 64 years were illicit substance users. Twenty-nine million people had problems from substance abuse. In addition, the survey found that only 1/6 of substance users throughout the world were able to access medical services. Resulting from a drug suppression policy during 2013 - 2015 in Thailand, the numbers of arrested cases were 263,326, 209,430 and 149,805, respectively. The most arrested cases were kratom users. Moreover, arrested cases from kratom use had been rising between 2003 - 2010. In the past, kratom was chewed to increase work performance when exposed to sunlight. Kratom was also used as snacks, sacred offerings, or a free drink as tea. [1, 2] Some adolescents boil kratom with water, cola, cough-suppressing syrup, and other substances; this mixture is known as 4 X 100. Thais used kratom as a traditional medicine for a long time, and called it "Prasa-kratom".[3] Prasa-kratom's poison was weakened to be used for alleviating numerous conditions such as dysentery, diarrhea, abdominal pain, flatulence, muscle pain, insomnia, and sensitivity to sunlight. [4 - 6]

Kratom *(Mitragyna speciosa Korth)* stimulates the central nervous system (CNS) via more than 25 kinds of alkaloid; the most common alkaloid is mitragynine. [1, 8] Kratom can be used to suppress pain in the CNS due to mitragynine action on opioid receptors in the brain and reduce depressive symptoms by stimulating serotonin production.[3] Kratom can reduce smooth muscle movement in the gut by

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Received: June 14, 2018
Revised: August 21, 2018
Accepted: December 12, 2018

7-hydroxymitragynine's effect to inhibit contraction of the bowel, hence reducing diarrhea. [1, 3] One study found that kratom extract was able to reduce alcohol withdrawal seizures in mice that were induced to ethanol addiction.[9] According to the study of symptoms from kratom use, taking more than 20 leafs (mitragynine = 17 mg) resulted in severe symptoms of asthma, cold, shaking, and muscle twitching.[10] Mental symptoms were visual and/or auditory hallucination. [11] As for kratom withdrawal symptoms, the substance users might have muscle pain, insomnia, irritability, sleepiness, sluggishness, decreased appetite, shivering/twitching, lacrimation, diarrhea, abdominal pain, nausea, vomiting, and fever. Some had psychiatric symptoms such as depression, anxiety, paranoia, auditory hallucination, and illusion. [10 - 11]

At present, many researchers are interested in kratom and have studied the medical benefits of kratom, for example Japanese scientists have registered a patent for the use of kratom. Notwithstanding common kratom use in Thailand, there are few studies of kratom use and its adverse consequences. Therefore, it is important to study this issue in the Thai context in order to provide valid and reliable data for making appropriate public-health policies.

Methods

This is a retrospective analytic study. Target populations were kratom users who sought medical treatment at the Princess Mother National Institute on Drug Abuse Treatment (PMNIDAT) institute on drug abuse. Inclusion criteria were aged 18 years or over and previous use of kratom. A total of 106 cases were recruited by purposive sampling.

Sample size

$$n = \frac{(z_{\frac{\alpha}{2}} + z_{\beta})^2 \times (p_1(1-p_1) + p_2(1-p_2))}{(p_1 - p_2)^2}$$

$$n = \frac{(1.96+0.84)^2 \times (0.80(1-0.80)+0.60(1-0.60))}{(0.80-0.60)^2} = 78.4$$

In order to prevent errors from incomplete data, sample size was calculated to compensate 20 %.

$$\text{Thus} \quad n = \frac{100 \times 78.4}{80} = 98$$

Research Instruments

Demographic information contained check lists including gender, age, marital status, education, occupation, income, and health problems. Check lists of kratom use profile included information about how to use the kratom and kratom use with other drugs. A questionnaire for adverse effects included a set of question about physical and mental side effects during kratom use and after taking kratom within 1 month. The Naranjo's algorithm: a questionnaire designed by Naranjo CA, *et al*. for determining the likelihood of whether an adverse drug reaction (ADR) is actually due to the drug rather than the result of other factors. Naranjo's algorithm has an Intraclass Correlation Coefficient (ICC) = 0.92 [12], sensitivity = 75.5, and specificity = 67.2 [13] The semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA) Section H in Thai language contained an inquiry about substance abuse, method and substance use behavior. This questionnaire was first developed by Kalayasiri R, *et al*. The questionnaire has a test–retest reliability = 0.80 [14] and inter-rater reliability = 0.97. [15]

This study has been approved by the research ethics committee IRB No. 174/60 of the Faculty of Medicine, Chulalongkorn University and Approved Research Ethics 60033 Accreditation No. 041/2560 IRB No. 041/2560 from PMNIDAT institute on drug abuse.

Statistical analysis

Statistics used to analyze these data were percentage, mean, standard deviation (SD), independent *t* - test, chi-square test, and Pearson's correlation.

Results

One hundred and six participants consisted of males (76.4%) and females (23.6%) with a mean age of 32.6 years old (the minimum age was 18 years and the maximum age was 60 years) were recruited. Most of them were single (49.1%), self-employed or housemaker/free (54.8%), had sufficient income (62.3%), and no underlying diseases (76.4%). Kratom use was classified as boiled (55.6%), chewed (42.5%), or capsule (0.9%) (Table 1).

Table 1. The percentage, mean, and standard deviation of the sample and the personal factors of the subjects.

Variable	Subjects (n = 106)	
	Number	Percentage
Gender		
Male	81	76.4
Female	25	23.6
Mean age (years)	Mean ± SD = 32.6 ± 10.64, Min = 18.0,	
Max = 60.0, Median = 31.0		
Status		
Single	52	49.1
Spouse	39	36.8
Widow	5	4.7
Divorce/separation	10	9.4
Level of education		
Uneducated	7	6.6
primary school	27	25.5
Lower secondary school	45	42.5
High school	14	13.2
Diploma	5	4.7
Bachelor	8	7.5
Occupational classification		
Self employed	29	27.4
Housemaker/free	29	27.4
Merchant	19	17.9
Farmer	12	11.3
Company employee	12	11.3
Others	5	4.7
Family net income(baht)	Mean ± SD = 23,955.67 ± 56,012 Min = 0.0,	
Max = 500,000, Median = 14,750, Mode = 15,000		
Sufficient income		
Insufficient	40	37.7
Sufficient	66	62.3
Underlying disease		
No	81	76.4
Yes	25	23.6
Familial substance use		
Yes	68	64.2
No	38	35.8
Main form of kratom use		
Boiling (4 × 100)	60	56.6
Chewing	45	42.5
Capsule	1	0.9

The mean ages of kratom use were 26 and 20 years old in the chewing and boiling groups respectively; the age difference was statistically significant ($P < 0.001$) (Table 2).

The boiling group significantly had much heavy use per day than the chewing group ($P = 0.012$). Boiling use significantly brought about more problems or opposition from family members, peers, monks, or coworkers than chewing users ($P = 0.001$). The chewing group (55.6%) used less other substances than boiling group (81.7%) (Table 3).

The most common neurological symptom was headache (30.5%) followed by staggering (21.0%) and blurred speech (15.2). Muscular system symptoms were muscle pain (39.0%), joint pain (22.9%), and arthritis (7.6%). Integumentary system symptoms

were dark skin or hyperpigmentation (41.9%), rigid skin (12.4%), and body rashes or skin inflammation (2.9%). Cardiac system symptoms were tachycardia (49.5%) and hypotension (4.8%). Digestive system symptoms were frequent urination (31.4%), constipation (24.8%), and nausea (14.3%). Respiratory system symptoms were xerostomia (49.5%), cough (21.0%), and frequent common cold (8.6%). Mental and psychiatric symptoms were insomnia (31.4%), appetite change (20.0%), and confusion (19.0%). Other symptoms were frequent urination (31.4%), weakness (22.9%), laziness (17.1%), and fatigue (16.2%).

The chewing group had significantly more headaches, arthritis, nausea, and constipation than the boiling group when compared to each other. (Table 4) Other side effects were not significantly different.

Not only were there no significant differences of mean scores of Naranjo's algorithm between the chewing group and boiling group, but also no association between adverse effects from using kratom in both groups.

Table 2. Personal factor profiles of kratom use in 105 participants by *t* - test.

Variables	Total (n = 105)	Chewing (n = 45)	Boiling (n = 60)	*t* -test	*P*- value
	Mean ± S.D.	Mean ± SD	Mean ± SD		
Age at beginning of kratom use (years)	23.19 ± 7.75, Min = 12.00, Max = 45.00, Median = 20.00	26.89 ± 8.31	20.42 ± 6.02	-4.425	< 0.001*
The duration of heavy kratom use in 1 month (days)	18.31 ± 11.90 , Min = 12.00, Max = 45.00, Median = 20.00	17.56 ± 11.80	18.89 ± 12.04	0.564	0.574
The duration of heavy kratom use (months)	9.54 ± 14.63, Min = 1.00, Max = 96.00, Median = 4.00	8.00 ± 10.78	10.70 ± 16.96	0.935	0.352
Onset of heavy kratom use	24.44 ± 8.15, Min = 13.00, Max = 52.00, Median = 22.00	28.58 ± 9.34	21.34 ± 5.39	-4.654	< 0.001*
Onset of first kratom dependence (years)	23.80 ± 8.49, Min = 13.00, Max = 48.00, Median = 23.00	26.58 ± 12.89	20.64 ± 7.42	0.625	0.534
Age of last kratom dependence (years)	28.17 ± 8.78 , Min = 18.00, Max = 49.00, Median = 25.00	32.17 ± 13.26	24.08 ± 8.03	0.518	0.606
Duration of kratom dependence (years)	1.46 ± 3.58, Min = 0.00, Max = 27, Median = 0.00	1.49 ± 24.50	1.43 ± 2.74	-0.078	0.938

Table 3. Personal factor profiles of kratom use in 105 participants by chi-square or Fisher's exact tests.

Variables	Chewing (n = 45)		Boiling (n = 60)		χ^2	*P* - value
	Number	Percent	Number	Percent		
Duration (months)						
< 1 year/ > 1 year	7/38	15.6/84.4	9/51	15.0/85.0	0.006	0.938
Kratom was use at least once a week ≥ 1 month						
Yes/No	35/10	77.8/22.2	50/10	83.3/16.7	0.515	0.473
Heavy kratom use per day						
< 3 times a day/ >3 times a day and up	21/24	46.7/53.3	14/46	23.3/76.7	6.300	0.012*
Unable to focus on anything else						
Yes/No	5/40	11.1/88.9	15/45	25.0/75.0	0.073	0.084
Overdose						
Yes/No	9/36	20.0/80.0	10/50	16.7/83.3	0.661	0.799
Having problems because of using kratom						
Yes/No	23/22	51.1/48.9	49/11	81.7/18.3	11.140	0.001*
Being arrested by police because of using kratom						
Yes/No	2/43	4.4/95.6	4/56	6.7/93.3	0236	0.698

Table 3. (Con) Personal factor profiles of kratom use in 105 participants by Chi-square or Fisher's exact tests.

Variables	Chewing (n = 45)		Boiling (n = 60)		χ^2	*P* - value
	Number	Percent	Number	Percent		
At least 3 accidents in 12 months						
Yes/No	0/45	0/100	3/57	5.0/95.0	2.316	0.258
Drunkenness						
Yes/No	9/36	20.0/80.0	15/45	25.0/75.0	0.365	0.642
Being in a dangerous situation						
Yes/No	7/38	15.6/84.4	10/50	16.7/83.3	0.023	0.878
Abandon important intentions						
Yes/No	7/38	15.6/84.4	17/43	28.3/71.7	2.381	0.123
Emotional and mental symptoms						
1. Depression or anhedonia						
Yes/No	5/40	11.1/88.9	14/46	23.3/76.7	2.592	0.107
2. Feeling paranoid						
Yes/No	4/41	8.9/91.1	6/54	10.0/90.0	0.037	1.000
3. Poor concentration						
Yes/No	6/39	13.3/86.7	11/49	18.3/81.7	0.474	0.491
4. Hallucinations						
Yes/No	3/42	6.7/93.3	8/52	13.3/86.7	1.219	0.345
5. Fidget or squeamish leading to negligence work,						
Yes/No	4/41	8.9/91.1	8/52	13.3/86.7	0.502	0.479
Substance Abuse DSM-IV (at least 3 symptoms)						
Yes/No	23/22	51.1/48.9	34/26	56.7/43.3	0.320	0.572
No use of kratom for at least 3 months						
Yes/No	20/25	44.4/55.6	25/35	41.7/58.3	0.081	0.776
Other substances use						
No	20	44.4	11	18.3	19.75	0.001*
Cannabis	0	0.0	14	23.3		
Amphetamine	15	33.3	24	40.0		
Cannabis and Amphetamine	6	13.3	10	16.7		
Cannabis, Amphetamine and other	4	9	1	1.7		

Table 4. The relationship between side effects from kratom use and pattern of kratom use in 105 participants analyzed by Chi-square or Fisher's exact tests.

Variables	Chewing (n = 45)		Boiling (n = 60)		χ^2	*P* - value
	Number	Percent	Number	Percent		
Side effects						
Yes/No	44/1	97.8/2.2	58/2	96.7/3.3	0.114	1.000
Headache						
Yes/No	19/26	42.2/57.8	13/47	21.7/78.3	5.128	0.024*
Arthritis						
Yes/No	7/38	15.6/84.4	1/59	1.7/98.3	7.047	0.008*
Nausea						
Yes/No	10/35	22.2/77.8	5/55	8.3/91.7	4.051	0.044*
Constipation						
Yes/No	17/28	37.8/62.2	9/51	15.0/85.0	7.161	0.007*

Discussion

This study investigated the characteristics of kratom use and symptoms from using kratom. The majority of kratom users were in the boiling group (55.6%); the others were in the chewed group (41.75%). Kratom users usually took other drugs. When comparing between both groups, the chewing group (55.6%) significantly used fewer other substances than the boiling group (81.7%).

Most kratom users had a family history of substance use (64.9%). The mean ages of onset of kratom use were also different i.e. the chewing group was 26 years, but the boiling group was 20 years. The boiling group significantly had much heavier use per day than the chewing group. Boiling use significantly brought about more problems or opposition from family members, peers, monks, or coworkers than chewing use. Common side effects from using kratom included tachycardia (49.5%) and dry mouth or throat (49.5%), dark skin (41.9%), muscle pain (39%), and headaches (30.5%). According to another study on the clinical symptoms of those using kratom without other substances [11], long-term effects were physical impairment due to working overload, scrawny, dry skin, black lips (due to melanocyte-stimulating substance), dry mouth, frequent urination, constipation, and psychiatric symptoms. Withdrawal symptoms were fatigue and pain.

Recent studies found that heavy consumption of kratom was associated with nausea, vomiting, fatigue, constipation, insomnia, dry mouth, frequent urination, and dark skin. [16]

Headaches and myalgia may be due to chronic μ-opioid stimulation. Mitragynine was found to modulate the μ-opioid receptor (μ-OR). [17] The μ-OR is coupled to a heterotrimeric G protein of the G_i/G_o family. Acutely, agonists bind the μ receptor, causing dissociation of the α and β-γ subunits. The β-γ subunit causes K^+ efflux, which reduces the membrane potential. The activated α subunit inhibits adenylyl cyclase (AC) to reduce the cAMP and PKA activity. The reduced conductance in nonspecific cation channels blocks further de-polarization. Opioid-receptor agonists act acutely to inhibit neuronal activity.

Chronic opioid-receptor stimulation causes up-regulation of the cAMP pathway in neurons of the locus coeruleus. Not only does a compensated CREB expression increase AC transcription, but also PKA accrues due to lessened degradation. Overall, the effect of chronic opioid stimulation is recovery of K^+ and cation channel function leading to normalized neuronal firing even in the presence of its agonists. This effect can explain why chronic heavy use of mitragynine can cause much pain and debilitating symptoms such as results in reduced gastric secretion, decreased appetite, less small-bowel movement, and constipation. [18 - 21]

The chewing group significantly had more headaches, arthritis, nausea, and constipation than the boiling group when compared to each other. The other side effects were not significantly different. That boiling use caused fewer adverse effects than chewing use which may be explained by 2 possible factors. First, the boiling group diluted kratom with water and other ingredients meaning they received a lower mitragynine concentration. Second, the boiling group used kratom less frequently than the chewing group hence they reduced mitragynine exposure and the chance of kratom tolerance. After evaluating the relationship of suspected side-effects from kratom use between the 2 groups by Naranjo's algorithm, there were no significant differences of mean scores and no association between total adverse effects and patterns of kratom use in both groups.

This study investigated the patients who used mitragynine with or without other narcotics including tobacco. There might recall biases due to asking for a history of kratom use in their lifetimes. The researcher tried to reduce this drawback by excluding the patients who were diagnosed with dementia or other memory impairments. In addition, the sample recruited were at PMNIDAT only and without any serious psychiatric symptoms. Therefore, the results are not generalizable for all kratom users.

It is recommended that future studies categorize the patients according to their severity of kratom use by a standard criteria such as DSM-5. The recruited sample should cover all types of patients so as to infer the results to general populations.

Conclusion

A number of kratom users often take other substances. There are various effects from both patterns of kratom use. The common side effects are dry mouth, tachycardia, dry throat, dark skin, muscle pain, and headaches. Although the boiling-pattern group took more other drugs, the chewing-pattern group significantly had more headaches, arthritis, nausea, or constipation when compared to each other.

Acknowledgements

I would like to offer my heartfelt thanks to all participants and staff members of PMNIDAT institute on drug abuse, officers from Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, and other persons for their suggestions and help.

Conflict of interest

None of the authors has any potential conflict of interest to disclose.

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