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Rashad Mohammed Alsanosy
1) Substance Abuse Research Centre, Jazan University, 11420, Jazan, Saudi Arabia
2) College of Medicine, Jazan University, 11420, Jazan, Saudi Arabia

Corresponding Author:
Rashad Mohammed Alsanosy
1) Substance Abuse Research Centre, Jazan University, 11420, Jazan, Saudi Arabia
2) College of Medicine, Jazan University, 11420, Jazan, Saudi Arabia

Individual and integrated effects of potential determinants of chronic use, withdrawal symptoms and reward of *Catha edulis* (Khat) amongst regular users

Rashad Mohammed Alsanosy

Abstract
The current study was designed to investigate the demography, pattern of use, individual and integrated determinants of chronic use, withdrawal symptoms and reward of Khat amongst regular users in Saudi Arabia. This community-based and cross-sectional study was performed in 2016. Data were collected from 514 regular users with structured and self-administered questionnaire. Descriptive analysis, Chi-squared test of association, factor analysis and logistic regression were performed using SPSS software. Variables included in the logistic regression model were marital status, residence, age of starting Khat chewing, chewing experience (Years), time of chewing session and post-session action of Khat (time in hours). Principal components analysis (PCA) with orthogonal transformation was used to check possibly correlated variables. Majority of the respondents are married, possess pre-university education, are employed, less than 42 years old and live in urban areas. The average of age of starting Khat chewing is 18.57±3.09 years old. The average of Khat chewing experience is 15±9.48 years and about 40% are using it on daily basis. Post-session effect of Khat was observed to last for 2.17±1.5 hours. Sense of vigor and alertness and sexual performance improvement were felt by 97.5% and 64.4%, respectively. 434(84.4%) of the sample rewarded euphoria and relaxation and a sense of complacency upon use of Khat. PCA revealed the extraction of four factors which explained 69.14% of the total variance expected in the questions regarding rewarding. It is observed that 69.3%, 47.7%, 42.4%, 46.7% and 30.7%, experienced hostility towards others, insomnia, violence towards others, anorexia and weight loss, respectively. Factor analysis showed the extraction of four factors which explained 69.99% of the total variance expected in the questions regarding withdrawal symptoms of Khat cessation. Modeling of chronic use revealed a significant dependence on age of starting Khat chewing and chewing experience (years). This study gave new ideas regarding Khat withdrawal symptoms and reward in Saudi Arabia. It provides a significant task in depicting information to shape coherent awareness for preventive and clinical interventions.

Keywords: Khat; withdrawal symptoms; reward; Saudi Arabia

Introduction
Khat (*Catha edulis* Forsk. *Celastraceae*) is an undeciduous tree growing wildly or/and cultivated commercially in East Africa and the Arabian Peninsula [18]. The use or abuse of addictive substances, like Khat is a major socio-medical issue that threatens the community peace worldwide [9]. This phenomenon becomes a tradition to region of the Middle East, African Horn nations and some parts of central Asia [24]. The Khat phenylalkylamines comprise cathinone, cathineand norephedrine. These compounds are structurally related to amphetamine and noradrenaline [15]. Khat chewing has been proven to be efficient procedure of extracting cathinone and cathine [4].
Laboratory based research have been broadly used to investigate the addictive behavior and potential toxicological features due to effect of Khat, however research on Khat potential dependence, behavioral and cognitive effects in human subjects is not that extensive. Several of the available studies have been done only in the context of observational and single-case studies. Literature shows that there a lot of experimental work has been done in stimulating the addictive behavior and toxicity in animals in response to Khat constituents. In turn, all these studies have met at a substantial midway point of that developmental toxicities of Khat's addictive constituents are dose-related. However, despite the literature on Khat is fairly extensive, and so many researchers have documented the potential adverse impacts of

addictive constituents of Khat on mental and psychiatric health, very rare population based studies exist to substantiate those statements in the Kingdom of Saudi Arabia [3, 12, 14, 18, 23, 26].

With exception to the limited research used animal models, to date most of the studies done on use, rewarding and withdrawal effects of Khat in Saudi Arabia are also rare. This situation enhances an immediate research effort to cover this substantial scale gap in knowledge as regards the patterns of Khat use and its potential rewarding effects and withdrawal symptoms among chronic Khat abusers.

Methods

Study design and sampling

This study used a community-based and cross-sectional design. The duration of the study was from January 2016 to December 2016. Participants (15 years and above) who used Khat frequently in the past 12 month were included in the study. Male participants were only included in the study. Questionnaire was managed by medically-educated personnel to guarantee the best level of data integrity and participant's confidence.

Ethical consideration

This study was approved by the Institutional Review Board of Jazan University, Saudi Arabia. Informed written consent from the next of kin, caretakers, or guardians on behalf of the minors (15-18 years old) enrolled in this study was obtained. Some of the participants did not complete the written consent form, and those who gave verbal informed consent to willingly and voluntary participate in the study were included. During the conduction of the study, participants were informed that all the gathered data would be reserved confidentially, contribution was totally voluntary, and they had the right to leave the research at any occasion. Participants and students, upon agreement, were asked to tick on a box in the first page of the questionnaire indicating their willingness to take part in this study. This also helped to safely document the verbal consent. Data of the study was anonymously kept to protect participant privacy and confidentiality. Exclusion criteria included individuals who were very ill and unable to complete the study questionnaire, were younger than 15 years of age, refused to give informed consent, and were eligible participants who participated in the pre-testing and test-retest of the questionnaire.

Measures

Items for reward and withdrawal symptoms were built based on the relevant previous studies [2, 5, 30]. Questions for reward (fever, numbness, dizziness, hallucinations and fantasies, euphoria and relaxation and a sense of complacency, sense of vigor and alertness and improve sexual performance), and withdrawal effects (inability to work, pain in muscles and bones, weight loss, anxiety and restlessness, tiredness, insomnia, hostility towards others, violence towards others, anorexia and spasm and twitching of the limbs and hands) is written in English, and forward and backward translated by two independent bilingual translators who speak Arabic and English. Backward translation was performed to ensure that the original meaning of the questions was maintained even if the questions underwent several repetitions of the translation process. The study variables also included socio-demographic characteristics of the sample. Additional important variables included information on the history of the use of Khat. A pilot study was conducted on 30 respondents to pre-test the first draft of the questionnaire. Questionnaire was modified based on the recommendations of the pre-test results, and the data of the pilot study were not included in the last analysis.

Data analysis

Collected data were statistically analyzed using SPSS-23 (IBM Inc., USA). Data were described statistically using means, frequency, percentages were appropriate. Factor analysis using principal components analysis (PCA) was utilized to investigate the covariance and various parameters. Variables included in the logistic regression model were marital status, residence, age of starting Khat chewing, chewing experience (years), time of chewing session, frequency of use and post-session action of Khat (time in hours). All model fitting parameters were accordingly reported. A probability of $P<0.05$ was considered statistically significant.

Results

The response rate was 100% (n=514). Majority of the respondents are married, possess pre-university education, employed, less than 42 and live in urban areas (Table 1). Statistics of pattern of Khat chewing are demonstrated in Table 2. The average of age of starting Khat chewing is 18.57±3.09 years. As this study was the first of its kind to explore the reward and withdrawal consequences of Khat use, only experienced chewers were included. Whereby, the average of these chewers experience is 15±9.48 years and about 40% are using it on daily basis. Khat session extends in average of 6.4 hrs. Post-session effect of Khat was observed to last for 2.17±1.5 hours.

The results of the univariate and multivariate logistic regression analysis for potential individual and integrated factors possibly affecting Khat daily usage are shown in Table 3. A univariate analysis was performed to understand the individual relationship between daily usage and each independent variable followed by multivariate logistic regression analysis. Changes in odd ratio are demonstrated in Table 3. Modeling of Khat daily usage suggested that the most significant ($P<0.05$) independent predictors are age of starting Khat chewing and chewing experience (years). Additional variables were insignificant in the multivariate logistic regression.

Table 4 shows distribution and factor analysis using PCA for questions related to rewarding effects of Khat. Sense of vigor and alertness and sexual performance improvement were felt by 97.5% and 64.4%, respectively. 434(84.4%) of the sample rewarded euphoria and relaxation and a sense of complacency upon use of Khat. While fever, numbness, dizziness, were only experienced by 15.4%, 11.9% and 7%, respectively, of the respondents. Factor analysis revealed the extraction of four factors which explained 69.14% of the total variance expected in the questions regarding rewarding. As expected euphorbia, sense of vigor and alertness were extracted in the same factor as shown in Table 4. Differences between daily users and non-dailly users in these rewarding effects were analyzed using Chi-square test. Surprisingly, all effects showed significant differences ($P<0.05$) except for fever, numbness and sexual improvement.

Descriptive statistics and exploratory factor analysis for withdrawal effects of Khat cessation are depicted in Table 5. It is observed that 69.3%, 47.7%, 42.4%, 46.7% and 30.7%, experienced hostility towards others, insomnia, violence

towards others, anorexia and weight loss, respectively. Factor analysis showed the extraction of four factors which explained 69.99% of the total variance expected in the questions regarding withdrawal symptoms of Khat cessation. Differences between daily users and non-dailly users in these withdrawal symptoms were analyzed using Chi-square test. Differences were observed only on questions related to inability to work, pain in muscles and bones, weight loss and anorexia.

Discussion

The current study was designed to explore the individual and integrated determinants of chronic use, rewarding and withdrawal effects of Khat among regular male chewers. The exclusion of female participants was anticipated, as Khat is not frequently used amongst women [20, 25] and the common unwillingness of Saudi women to contribute in studies of this kind [1]. This also could be explained by the need for homogenous sample for better generalization. Generally, it appears that Khat chewing is less attractive to women, although in Somali society, using of Khat has currently become more common among women of middle class and fairly educated [27]. People chew Khat frequently can experience constipation, related GIT disturbances, and anorexia. The socioeconomic effects of Khat abuse may be more important; with the likelihood that Khat chewing could turn into an obstacle to employment and decrease productivity. In KSA, where Khat is illegal, maintaining the chewing habit may force chewers into leading a hidden life, dealing with a criminal network [13, 29].

Khat leaves possess phytochemicals with psychostimulant properties, and have been consumed for centuries as leisure, spiritual and religious drug, mainly in some African and Arabian countries. With altering migration dynamics, epidemiological and clinical results may have altered [19, 22]. Experimental and clinical data substantiate its dependence potential as well as probable unwanted health effects associated to stimulant use; however, accessible survey studies do not concentrate on the prevalence of abuse or dependence [1]. Significantly higher Khat chewing prevalence and daily consumption were reported earlier to be associated with high level of education [11]. In our study, we found that more than 73.9% of the chewers are pre-university educates. Level of education may help policy makers and health educators to design appropriate Khat quitting campaign with acceptable rate of quitting success. The cost of Khat chewing in Saudi Arabia is high due to legal constrains and smuggling through Yemenis borders [28]. Therefore, 63% of the respondents were employers whom could afford to buy Khat at regular basis (Table 1).

Pattern of Khat chewing reported in this study was in line with previous studies [21]. Average age of starting Khat chewing was 18 years old. This is because of the easy accessibility of Khat to local adolescents. Post-session effect of Khat (time in hours) was observed to 2.17 hrs in this study. The amphetamine-like action of cathinone accounts for the increased nervous tension and irritability which follows the Khat session together with the peripheral catecholamine-releasing effects [10]. Modeling of Khat daily usage suggested that the most significant independent predictors are age of starting Khat chewing and chewing experience (years). Khat is used commonly in East Africa and the Arabian Peninsula, with reports indicating that 80–90% of East African males use Khat daily and 10–60% of East African females use Khat daily [31].

The current study is the first of its kind to report rewarding effects of Khat abuse using a systemic and reported survey. Sense of vigor and alertness and sexual performance improvement were felt by 97.5% and 64.4%, respectively. Given the CNS stimulant 'rewarding' actions of cathinone, if Khat leaves are continually used, drug dependence can develop [25]. This has been noticed in laboratory based studies, where both cocaine and cathinone showed similar results in the response rates of monkeys trained to press a lever for a drug reward. In these experiments, the more dependent the monkeys, the faster the response rate of lever pressing [32].

Inability to work, pain in muscles and bones, weight loss, anxiety and restlessness, tiredness, insomnia, hostility, violence, anorexia, spasm and twitching of the limbs and hands are the withdrawal symptoms used in our questionnaire to study the potential withdrawal symptoms associated with Khat cessation. It is observed that 69.3%, 47.7%, 46.7%, 42.4% and 30.7%, experienced hostility towards others, insomnia, anorexia, violence towards others and weight loss, respectively. Unceasing chewing of Khat may generate withdrawal symptoms but it is regularly mild and is characterized by only a mild depression [8]. There may be physical symptoms like slight trembling [31]. Some Physical symptoms of withdrawal such as those of morphine and alcohol do not occur in Khat users [16]. Pyrogenic and lethargic effects of Khat cessation were previously reported [2] as well as insomnia and Irritability [17].

Ethnopharmacological uses of Khat have been well documented in Somalia, Yemen and Ethiopia [6]. This enhances the chronic use of Khat and its social acceptability. The effects of chewing Khat are comparable to those of other amphetamines and alkaloids [7]. The current study is the first of its kind to explore reward and withdrawal effects of Khat among regular male chewers. Sense of vigor and alertness, sexual performance improvement, euphoria and relaxation and a sense of complacency upon use of Khat are the most rewarding effects of Khat use while hostility towards others, insomnia, violence towards others, anorexia and weight loss, are the most observed withdrawal symptoms. Further relevant clinical studies are required to substantiate the findings of this cross-sectional study.

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Table 1: Demographic characteristics of the study group.

	N	Percentage
Marital status		
Married	330	64.2
Single	171	33.3
Divorcee	13	2.5
Education level		
Pre-University Education	380	73.9
University	134	26.1
Occupation		
Unemployed	117	22.8
Employee	324	63.0
worker	18	3.5
teacher	55	10.7
Age (Years)		
Less than 26 yrs	143	27.8
26 to 35	148	28.8
36 to 42	153	29.8
>42	70	13.6
Residence		
Rural	110	21.4
Urban	404	78.6

Table 2: Pattern of Khat chewing

	Mean	SD	Minimum	Maximum
Age of starting Khat chewing	18.57	3.09	10	32
Chewing experience (years)	15.00	9.482	1	49
Session (Hours)	6.40	1.326	3	12
Post-session effect of Khat (time in hours)	2.17	1.5	1	15
Frequency of Khat chewing (N;%)				
More than once a day	14 (2.7%)			
Daily	200 (38.9%)			
More than once a week	179 (34.8%)			
Once a month	46 (8.9%)			
Irregularly	75 (14.6%)			

Table 3: Univariate and multivariate logistic regression analysis

Independent Varaibles	Regression Coefficient	P-value	Crude OR	Adjusted OR	95% C.I. for OR	
					Lower	Upper
Marital status (Reference groups: Divorced)		0.785				
Married	-0.181	0.785	0.723	.835	.228	3.060
Single	0.029	0.967	4.197	1.029	.261	4.063
Style of living (0: urban; 1: countryside)	-0.193	0.498	0.619	.824	.471	1.442
Age of starting Khat chewing	-0.119	0.002	0.919	.888	.823	.957
Chewing experience (years)	-0.180	0.000	0.827	.836	.804	.868
Post-session effect of Khat (time in hours)	0.124	0.173	1.340	1.132	.947	1.353
Session (Hours)	-0.074	0.449	0.985	.928	.766	1.125
Constant	5.726	0.000				

- Modeling of Khat daily usage was based on 0 for daily users and 1 for non-daily users
- Hosmer and Lemeshow goodness of fit test $\chi 2$= 17.226 P=0.028; -2 Log likelihood ratio = 461.74
- B: Regression coefficient; S.E: standard error of B

Table 4: Descriptive statistics and exploratory factor analysis using principal component analysis* for questions related to rewarding effects of Khat

Rewarding effects	Statistics (Yes)#	Component loading				Daily usage (χ^2 test)	
	Frequency (%)	1	2	3	4	χ^2	P-value
Fever	79 (15.4)	0.872				2.923	0.087
Numbness	61(11.9)	0.704				3.132	0.077
Dizziness	36(7)		0.729			6.043	0.014
Others (vomiting, increased appetite, bitter taste)	80(15.6)		0.721			4.603	0.032
Hallucinations and fantasies	83(16.1)		0.660			4.329	0.037
Euphoria and relaxation and a sense of complacency	434(84.4)			0.583		5.278	0.022
Sense of vigor and alertness	501(97.5)			0.882		0.055	0.84
Improve sexual performance	331(64.4)				0.900	5.925	0.00
Total variance explained	69.14						
Kaiser-Meyer-Olkin Measure of Sampling Adequacy	0.607						
Bartlett's Test of Sphericity	477.1 (P=0.000)						

*Extraction Method: Principal Component Analysis.
*Rotation Method: Varimax with Kaiser Normalization.
#Descriptive statistics are shown only for the 'Yes' answer

Table 5: Descriptive statistics and Exploratory factor analysis suing principal component analysis* for questions related to withdrawal effects of Khat cessation

Withdrawal effects	Statistics (Yes)#	Component				Daily usage ($\chi 2$ test)	
	Frequency (%)	1	2	3	4	χ^2	P-value
Inability to work	127 (24.7)	0.775				5.090	0.024
Pain in muscles and bones	166 (32.3)	0.754				16.322	0.000
Weight loss	245 (47.7)	0.705				21.69	0.000
Anxiety and restlessness	120 (23.3)		0.762			0.73	0.393
Tiredness	111 (21.6)		0.708			1.583	0.208
Insomnia	158 (30.7)		0.649			3.195	0.074
Other symptoms	140 (27.2)		0.637			5.541	0.019
Hostility towards others	356 (69.3)			0.845		0.389	0.533
Violence towards others	218 (42.4)			0.742		1.975	0.160
Anorexia	240(46.7)				0.805	7.886	0.005
Spasm and twitching of the limbs and hands	91(17.7)				0.617	3.617	0.057
Total variance explained	61.99						
Kaiser-Meyer-Olkin Measure of Sampling Adequacy	0.662						
Bartlett's Test of Sphericity	1033.01 (P=0.000)						
Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.							

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