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Concurrent Use of Khat and Tobacco is Associated with Verbal Learning and Delayed Recall Deficits

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Abstract

Aims—The present study assessed whether cigarette smokers who are also regular khat users would demonstrate greater impairments in verbal learning and recall compared to both non-smokers who are khat users and control subjects.

Design—An independent measures, between-subjects design with two co-variables.

Setting—An outpatient, university research center in Taiz, Yemen.

Participants—Subjects were 175 Yemeni college students (90 men, 85 women) ranging in age from 18 to 38. Seventy-Five subjects were self-reported chronic cigarette smokers and khat users, 48 non-smoking subjects were self-reported to be chronic khat users and 52 non-smoking subjects reported no current use or history of khat use.

Measurements—Verbal learning and verbal memory recall was assessed by subject performance on the Arabic version of Rey Auditory Verbal Learning Test (RAVLT).

Findings—There were statistically significant differences ($p < 0.05$) observed in RAVLT acquisition learning Trials 2–5 and on delayed recall measures between concurrent khat and cigarette users compared to both the khat only group and the control group of nonusers of khat and cigarettes. On each of these trials, concurrent users recalled fewer words, demonstrating a slowed rate of verbal learning. This same pattern of performance was also seen on delayed recall measures. Khat use alone did not affect immediate or delayed recall of previously learned words.

Conclusions—Khat users who smoke cigarettes have lower rate of verbal learning and delayed recall of previously learned verbal material than Khat users who do not smoke cigarettes. This may be due to pre-existing differences between these groups of subjects.

Keywords

khat; cathinone; smoking; verbal learning; delayed recall

INTRODUCTION

The stimulant leaf khat comes from a tree that grows in countries bordering the Red Sea, along the east coast of Africa and in west Asia [1,2]. Khat is commonly used in East Africa and the Arabian Peninsula [3,4], as well as by immigrants from these regions who reside in Western countries, primarily Great Britain and the United States [5,6]. Khat is chewed by users for its euphoric effects and as a recreational drug, and chewing khat has an important

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role in both traditional and religious ceremonies [4,7]. Khat use is highly prevalent in many countries in Africa and Asia, with 75% of men using khat in some countries [9], and worldwide approximately 6 million individual portions of khat are consumed daily [10]. Recent reports indicate that 80–90% of East African males use khat daily and 10–60% of East African females use khat daily [6,11,12].

The psychostimulant component of khat is cathinone, which is released within 15–45 min during chewing [8]. Khat ingestion produces several central nervous system effects, including increased motor stimulation, euphoria, and a sense of excitement and energy [10,13,14]. It also results in decreased appetite and increased blood pressure and heart rate. These effects indicate that khat acts through similar central mechanisms as other known stimulants such as amphetamines; both cathinone and amphetamine increase the activity of dopaminergic and noradrenergic transmission [15–17]. While the nature of khat dependence remains under active debate, there is accumulating evidence indicating the existence of a withdrawal syndrome and a low level of tolerance. Withdrawal symptoms usually include inertia, nightmares, trembling, depression, sedation and hypotension [1].

Use of excessive amounts of khat has been found to significantly increase the risk for psychosis or psychotic-like episodes similar to those observed in amphetamine users [6,12,18], including paranoid delusions and significant mania. Depression, dysphoria, and negative affect may also be related to long-term use of khat and seems to be particularly evident during cessation [19, 20, 21].

There are observations that suggest cognitive effects of chronic and acute khat use. Although khat has a stimulating effect that reportedly enhances attention and performance during the first few hours of use, it may also increase the risk for road accidents and vehicular fatalities. This may be due to increased anxiety and tension that usually appears after several hours of use and also due to distracted users drinking water, smoking, or preparing and cleaning the khat leaves while driving [22,23]. Presumably, impairments such as this would affect a variety of tasks that require vigilance, divided attention, visual scanning, and motor coordination.

To date there have been a paucity of well-controlled laboratory studies investigating the effect of khat use on neurobehavioral functioning, despite the need for such studies. Colazato, et al [24] have recently reported that khat users in their small sample demonstrate impaired inhibitory control compared to non-users. In a subsequent study, this same research group [25] reported that a small sample of 20 regular khat users demonstrated impairments in cognitive flexibility and monitoring of information in working memory compared to 20 non-users. Our own group has noted working memory deficits in long term khat users in a preliminary study [26]. The current study in Yemen is the first large scale laboratory investigation to examine the effect of chronic khat use on verbal learning.

Numerous studies have shown long-term effects of methamphetamine use on a number of cognitive tasks [27–31] including specific impairments in working memory, attention, speed of information processing, and executive function [28,32–36]. Individuals with a history of methamphetamine use display working memory deficits in such tasks as the immediate recall component of the auditory verbal learning test [37] and the working memory components of the California computerized assessment package [38]. Fox, Jackson, and Sinha [39] have recently reported that cocaine dependent individuals demonstrated a significantly reduced verbal learning curve on trials 2–5 of the Rey Auditory Verbal Learning Test (RAVLT) compared to matched controls, despite no observed difference on the first free recall trial of the RAVLT. This was consistent with the earlier work of Mittenberg and Motta [40] and Hoffman et al. [41] showing impaired word recall and verbal

learning deficits in their samples of chronic psychostimulant users. More recently, Reske et al [42] have reported a similar pattern of verbal learning deficit on trials 2–5 of the California Verbal Learning Test (a list learning test similar to the RAVLT) in their sample of occasional, non-dependent prescription amphetamine users.

The purpose of the present study was to assess whether regular khat users would demonstrate similar impairments in verbal learning - compared to control subjects - as those impairments seen in samples of chronic and episodic amphetamine and psychostimulant users. A secondary goal was to investigate whether there is an additive psychostimulant effect if khat-using subjects are also concurrent cigarette smokers. A complex interaction between the presumed amphetamine-like effects of khat use and tobacco use is possible. Long-term smoking contributes to dysregulation of the neurobiological response and acutely nicotine affects stress response hormonal and physiological measures [56,57]. The extent to which concurrent use of khat and tobacco might interact in influencing cognitive or stress-related biobehavioral functions is not known. Although both amphetamine and nicotine are dopamine agonists, there are observed differences in their effects on behavioral measures. Amphetamine has been observed to improve performance on cognitive processes such as attention and psychomotor functioning, but appears to impair performance in other areas of cognitive functioning, such as those requiring visual scanning or the ability to filter out irrelevant information [58].

Our focus for addressing the effect of concurrent tobacco use was prompted by several studies reporting that chronic smokers demonstrated poorer performance than non-smokers on measures of auditory-verbal learning and/or memory [43–47]. More recently, Durazzo, Meyerhoff, and Nixon [48] have reported poorer performances by smokers compared to non-smokers on measures of verbal learning and verbal memory as measured by their performance on the California Verbal Learning Test.

METHODS

Participants

Subjects were 175 Yemeni college students (90 men, 85 women) ranging in age from 18 to 38. Seventy-Five subjects were self-reported chronic, regular khat users and daily tobacco smokers (50 men and 25 women), 48 subjects were self-reported to be chronic, regular khat users (15 men and 33 women) and 52 non-smoking subjects (25 men, 27 women) reported no current use or history of regular khat use (see Table 1). The average age of the chronic khat users who smoked was 25.2 years ($SD=5.3$), the average age of the non-smoking regular khat users was 23.1 years ($SD=4.4$), and the average age of the non-users was 22.4 years ($SD=3.7$). Subjects were recruited using flyers posted at Taiz University and the surrounding community. Interested participants were invited to an onsite screening by study staff to assess their eligibility. This screening included a brief interview regarding medical history and substance use including khat and tobacco. Participants were included if they were free from major medical or psychiatric diseases (e.g., stroke, hypertension, diabetes, major depression, anxiety disorder, substance use disorder) and were taking no medications. Participants signed a consent form approved by Taiz University' Research Ethical Committee and received a monetary incentive for their participation equivalent to \$8 USD for this testing session and for two subsequent physiological measurement sessions that were completed for a companion study that examined khat use and cardiovascular measures. Khat users had to have been chewing khat on a daily basis for at least two years. In addition to the khat use, those who reported tobacco use (an average of 10 or more cigarettes per day for at least two years) were classified as concurrent users. All participants were college students, and as such are relatively homogenous in terms of their educational level (12–16 years of education).

Procedures

Verbal learning and recall was assessed using the Arabic language version of the Lezak adaptation of the Rey Auditory-Verbal Learning Test [49,50]. The original Lezak word list was used. The Arabic version of the original RAVLT has been used locally in Yemen and all instructions were delivered in Arabic (the local language).

The RAVLT is a very efficient neuropsychological instrument that is commonly used in clinical practice and research settings to assess episodic declarative memory. This test allows one to evaluate the components of acquisition and recall of information and also permits further investigation of separate memory processes [51]. The RAVLT assesses immediate verbal memory span, new learning and the rate of new learning, susceptibility to interference, and delayed recall of previously learned verbal material. The examiner reads aloud in Arabic a list (list A) of 15 nouns (with a one-second interval between each word) and the subject is asked to repeat back as many words as they can remember, in any order. The number of words recalled is recorded. Trial 1 therefore serves as an estimate of baseline list-learning ability for each treatment group in the present study. Following this first immediate free recall trial (trial 1), there are 4 subsequent free recall trials (trials 2–5). Each subsequent trial is administered in the same manner as trial 1 using the same 15 words presented in the same order and at the same rate. After each trial, the subject is asked to repeat as many words as they can remember, in any order, and the number of words recalled is recorded. Instructions are repeated before each trial to minimize forgetting. The maximum possible score on each trial is therefore 15 and the minimum possible score is zero.

Upon completion of trial 5, an interference list of 15 different words (list B) is presented using the same methodology of trials 1–5, followed by the free recall of as many words that the subject can recall from list B. Immediately following this immediate free recall trial, short-delayed recall memory of the first list is tested and each subject is required to again recall as many words as they can from list A, in any order (without further presentation of those words). After a 20 minute delay period, each subject is required to again recall from memory as many words as they can from list A, in any order to assess long-delay free recall. The number of words that were recalled in each RAVLT trial is recorded as the measure of recall.

Performance on Trial 1 and Trial B immediate recall measures relies heavily on auditory attention span. Acquisition memory Trials 2–5 more directly assess verbal learning rates. Short and long delay recall measures assess the subjects' ability to retrieve information from short-term memory storage after a time delay and exposure to the list B interference words.

To measure the ability to remember temporal order, an extra trial (Trial 8) was added to the standard administration following the methodology of Vakil and Blachstein [52]. In Trial 8, which followed the 20-minute recall trial, subjects were presented with the 15 first list words written in an order different from that in which the subjects had heard originally. Subjects were asked to rewrite the words in their original order. Difference scores were calculated between the correct serial order position and that position remembered by the subject and a derived sum of the standard deviations score (SOP) was calculated for further analysis.

In addition, a number of summary scores were also calculated using the methodology of Fox, et al. [39]. Total Learning (TL) was calculated by summing the number of correct words recalled across learning trials 1–5. Learning Rate (LR) was calculated by subtracting Trial 1 recall from Trial 5 recall. Proactive Interference (PI) was calculated by subtracting Trial 1 recall from Interference List B recall. Forgetting was assessed with 2 Long Term Retention (LTR) scores. LTR-1 was calculated by subtracting Trial 5 recall from Trial 7 (delayed recall). LTR-2 was calculated by subtracting Trial 6 recall from Trial 7 delayed

recall. Retroactive Interference (RI) was calculated by subtracting Trial 1 recall from the immediate recall trial (Trial 6) following the methodology of Rezvanfard, et al. [53]. Best Learning (BL) was defined as the Trial 5 score, consistent with the methodology of Vakil and Blachstein [52]. Finally, a method developed in MOANS (Mayo's Older Americans Normative Studies) was used to analyze learning, by standardizing the learning acquisition scores: the Learning Over Trials variable (LOT) was calculated by the total number of words recalled from all five trials minus five times the number of words recalled in Trial 1 [54].

Data reduction and analysis

Concurrent users were a bit older than nonusers (Main effect of group: $F(2,169)=4.43, p<.05$; follow-up tests: $p=.01$). Age was therefore used as a covariate in subsequent analyses. Each RAVLT variable was analyzed by a 3 group (concurrent users of khat and tobacco, khat-alone users, nonusers) $\times$ 2 gender (men, women) MANCOVA with age as a covariate, using Wilk's criterion to address two central hypotheses: (1) does khat use affect verbal learning and recall, tested via the comparison of the RAVLT performance of control subjects to khat users and (2) among khat users, does tobacco smoking affect verbal learning and recall tested via the comparison of the RAVLT performance of khat users to that of khat users who also are smokers. Bonferroni corrections were made for follow-up comparisons. Khat and smoking history variables were analyzed by one-way ANOVAs including gender as a between-factor as well as chi-square tests.

RESULTS

On average, khat-alone users and concurrent users started chewing when they were 16 years old and have chewed khat 5 times a week for 5 years and 6.5 years respectively. There were no within group gender differences in these variables ($p<.07$). There were also no significant within group gender differences in smoking duration ($p<.14$) or duration of tobacco use ($p<.23$).

There were no significant group differences due to either gender or age on any of the RAVLT trials. There were no statistically significant differences in baseline recall in Trial 1 of the RAVLT between the group of regular khat users who smoked (concurrent users), the group of non-smoking regular khat users, and the control group of nonusers of khat and cigarette use ($F(2,174) = .291, p=.88$). There were also no statistically significant differences in the List B interference trial between the concurrent users, the khat only group, and the control group ($F(2,174) = 1.35, p=.25$). These results are consistent with previously reported studies of amphetamine users [39,42] and chronic smokers [48]. The results of post-hoc tests for Trial 1 are presented in Table 2 (comparing controls versus khat users and comparing khat users and concurrent smokers).

There were significant differences observed in RAVLT acquisition learning Trials 2–5 between concurrent khat and cigarette users compared to both the khat only group and the control group of nonusers of khat and cigarettes. On each of these trials, concurrent users recalled fewer words than either khat users or controls, demonstrating a slowed rate of verbal learning. The results were as follows: Trial 2 ($F(2,174) = 3.886, p=.01$); Trial 3 ($F(2,174) = 3.176, p=.02$); Trial 4 ($F(2,174) = 2.752, p=.03$); Trial 5 or Best Learning - BL ($F(2,174) = 2.336, p=.05$). Of note are the significant post-hoc differences between khat users and concurrent users - accompanied by no statistically significant differences in performance between controls and khat users - on Trial 5 or BL (a measure of best acquisition learning) and most importantly Learning Rate (a measure of acquisition learning and recall that takes into account baseline differences from Trial 1 (see Table 2)).

Concurrent users also recalled fewer words following a 20 minute delay than subjects in the khat only group and the control group ($F[2,174] = 2.35, p=.05$). Post-hoc tests (see Table 2) again reveal statistically significant differences between concurrent users compared to non-smoking khat users. Khat use alone did not affect delayed recall of previously learned words.

The Retroactive Interference effect (RI) was more pronounced in the regular khat user and smoker group ($F[2,174] = 3.02, p=.05$) and total learning across all trials (LOT) was markedly lower in the regular khat user/concurrent smoker group ($F[2,174] = 4.78, p=.01$). Post-hoc t-tests are consistent with differences between concurrent khat and cigarette users compared to non-smoking khat users. Khat use alone did not affect RI or LOT (see Table 2).

There were no statistically significant differences in recall of the correct serial position (SOP) of the RAVLT between the group of regular khat and cigarette users, the non-smoking khat user group, and the control group ($F[2,174] = 1.57, p=.211$), nor were there statistically significant differences observed for PI ($F[2,174] = 1.88, p=.156$), LTR1 ($F[2,174] = .18, p=.83$), or LTR2 ($F[2,174] = .21, p=.81$).

DISCUSSION

Contrary to expectation, subjects in this study that were chronic khat users but non-smokers were virtually indistinguishable from normal control subjects across all RAVLT measures of verbal learning and memory recall. Although this is somewhat at variance with the published amphetamine and psychostimulant literature, it agrees with some recent results from chronic amphetamine users. Reske et al [42] observed that although episodic users of prescription amphetamines in their sample demonstrated poorer performance on the California Verbal Learning Test than controls, their sample of chronic amphetamine users did not. The absence of effect in the present study may simply be related to the potency of the psychoactive components of khat versus other amphetamines. Cathinone appears to be only half as potent as amphetamine and cathine is roughly 7–10 times less potent than amphetamine [55].

Interestingly, chronic khat users in this sample that were also cigarette smokers demonstrated markedly poorer performances on several RAVLT measures of verbal learning and memory recall compared to either control subjects or chronic khat users. This could represent either a synergistic effect of khat use and cigarette smoking or this may possibly reflect the effect of smoking alone, consistent with the literature on the relationship of cigarette smoking and impaired performance on verbal learning and verbal recall measures [43–48]. In order to address the role that cigarette smoking alone plays in this observed effect, future studies of the effect of khat on verbal learning must include as an additional comparison group an age and education matched sample of cigarette smokers only. We were unable to recruit a sufficient sample of such subjects in the present study. We discovered that in this Yemeni college sample almost all tobacco smokers were also at the very least occasional khat users; informally, our research subjects indicated that this is typical of the general population in Yemen due to the widespread legal use of khat in that country [59]. Nevertheless, this limitation does not allow us to identify whether the observed effect seen in the concurrent user group was due to a combination of khat use and tobacco or to tobacco use alone. In addition, we cannot rule out the possibility that our concurrent user subjects had verbal learning deficits that preceded their use of khat and tobacco, although the essentially equivalent performance on RAVLT Trial 1 for all 3 groups suggests that this is less likely.

Although our subjects were excluded from further study if they admitted to the use of other co-morbid drugs or alcohol, we did not confirm this with urine drug screenings and this is a study limitation. Future research should incorporate biochemical and more structured methods to investigate drug use status and previous history of mood and psychiatric disorders. Further research is also needed to examine sleep patterns and possible sleep disorders in this population, which can be a confounding factor with subjects that are using psychostimulants.

One final limitation of the present study is our use of a single verbal learning test (RAVLT), albeit a very commonly used one. If suitable Arabic translations become available in the future, subsequent studies should investigate the performance of khat users on other verbal learning measures.

The use of khat and tobacco together is quite common in several countries and the observed poorer performance on RAVLT measures of verbal learning and recall in the present study is cause for concern. During khat chewing sessions, users consume large quantities of tobacco, and this may exacerbate the health burden associated with khat use [59]. We have previously observed that approximately 55% of all khat users are also regular smokers [55, 60], and this is supported by a study with medical students at Aden University showing that 42% of those khat chewers were heavy smokers; 9.3% of those subjects reported smoking only when they chewed khat [61]. Griffiths [62] reported that 60% of khat chewers studied also smoked cigarettes. More recently, Kassim, Islam, and Croucher [63] reported that 65% of their sample of U.K. resident Yemeni subjects were regular cigarette smokers and also that khat users employed tobacco smoking to enhance the impact of their khat chewing. In that study, increases in the level of severity of dependence on khat chewing were correlated positively with increases in the level of nicotine dependence. Given the deleterious effects of both tobacco and khat, this suggests a serious public health concern and the need for new models of intervention combining smoking cessation and substance abuse treatment.

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TABLE 1

Participant characteristics

	Control Subjects (n=52)		Khat Users (n=48)		Khat and Tobacco Users (n=75)	
	Men (n=25)	Women (n=27)	Men (n=15)	Women (n=33)	Men (n=50)	Women (n=25)
Age *	21.20 (2.8)	23.44 (4.1)	20.60 (2.5)	24.27 (4.6)	25.20 (5.5)	25.20 (5.0)
Duration of Khat use (yrs)			4.13 (4.2)	3.67 (3.7)	7.60 (4.6)	6.00 (4.3)
Duration of Smoking (yrs)					3.46 (4.4)	2.84 (3.8)

* F(2, 169)=4.43 (p<.05)

Table 2

Performance of khat users, khat and tobacco users, and non-users on the Rey Auditory Verbal Learning Test

Mean Number of RAVLT Words Recalled		Control (n=52)	Khat Users (n=48)	Concurrent Users (n=75)	F	p value
Trial 1	Mean	6.4	6.2	6.2	.291	.88
	S.D.	(2.9)	(2.3)	(1.9)		
Trial 5 (BL)	Mean	11.3	11.4*	10.4*	2.34	.05
	S.D.	(2.2)	(2.6)	(2.3)		
20' Delayed	Mean	10.9	11.0*	9.8*	2.35	.05
	S.D.	(2.8)	(2.4)	(2.6)		
Recall	Mean	5.0	5.2*	4.2*	2.58	.04
	S.D.	(2.8)	(2.5)	(2.6)		
Trial 1 (LR)	Mean	48.2	48.1*	44.0*	2.47	.05
	S.D.	(10.2)	(9.5)	(7.8)		
Retroactive	Mean	4.0	4.1*	3.0*	3.02-	.05
	S.D.	(3.1)	(2.4)	(2.4)		
Interference (RI)	Mean	16.4	17.4*	12.8*	4.78-	.01
	S.D.	(9.1)	(6.9)	(7.4)		

* significant post-hoc difference, $p < .05$