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SUBJECTIVE EFFECTS TO MARIJUANA ASSOCIATED WITH MARIJUANA USE IN COMMUNITY AND CLINICAL SUBJECTS

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Abstract

Introduction—Marijuana is the most commonly used illicit drug among adolescents. Marijuana use induces both psychological and physiological responses, which can be interpreted by an individual in a variety of ways (i.e. subjective effects). We have examined subjective effects in adolescent, young adult community, and clinical populations to determine how patterns of use may be predicted by an individual's subjective experi bences with the drug.

Method—Participants were community and clinical sample subjects drawn from the Colorado Center of Antisocial Drug Dependence (CADD) and a sample of adjudicated youth from the Denver metropolitan area (aged 11–30). They were evaluated with the Composite International Diagnostic Interview - Substance Abuse Module (CIDI-SAM) and the Lyons battery for subjective effects. Scales for subjective effects were created using Mokken scale analysis. Multivariate linear and logistic regression was used to examine associations between the subjective scales and marijuana outcomes.

Results—Mokken scaling revealed two subjective effects scales, positive and negative. Both scales were significantly positively associated with marijuana abuse or dependence in both the community and clinical sample and regular use in the community sample. The negative scale was negatively associated with past six-month use in the community sample ($p<0.05$) and clinical sample, after controlling for age and gender effects.

Conclusions—These findings suggest that diverse subjective experiences with marijuana can be ordered hierarchically and that the resulting short scales can be used in either clinical or community settings. Further, they suggest that the potential for marijuana use problems is related to the type of subjective experience from marijuana exposure.

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Keywords

cannabis; subjective effects; etiology; youth; mokken scaling

1. Introduction

Among illicit drugs, marijuana is the most commonly used, with approximately half of all adolescents experimenting with the drug at least once during their lifetime (Perkonigg et al., 2008; von Sydow et al., 2002; Fergusson and Boden, 2008). As with many drugs of abuse, physiological and psychological responses vary between individuals and can be a function of the level of prior exposure. Though the etiological factors involved in regular use, abuse, and subsequent dependence are complex and multifaceted, subjective experiences following marijuana exposure have been useful in identifying those at risk (Grant et al., 2005; Fergusson et al., 2003). Moreover, as prevention efforts target initial use and treatment paradigms emphasize mitigating withdrawal experiences, examining subjective experiences may aid the refinement of these programs.

Interest in the subjective experiences with marijuana use grew from the belief in the 1950s that use involved the process of learning to identify and enjoy the effects (Green et al., 2003; Becker, 1953). Salient features of self-reported experiences often include relaxation, enhanced cognition and perception, improved mood, paranoia, depression and anxiety, and hallucinations. Heightened sexual pleasure and appetite, feelings of guilt, and talkativeness have also been endorsed. Generally, across both laboratory and questionnaire-based studies, it has been observed that these and other subjective experiences group into two broad categories of positive (e.g. euphoric, relaxed, less inhibited) and negative (e.g. depressed, sad, angry, ill) experiences (Green et al., 2003; Rossi et al., 1978; Block et al., 1998), despite seemingly opposite types of experiences being reported together (Grant et al., 2005; Davidson and Schenk, 1994; Wachtel et al., 2002).

Research examining subjective experiences using questionnaires has sought to elucidate the relationship between the experience of a drug and subsequent patterns of use. Results regarding positive experiences have been consistent across studies showing positive associations with measured phenotypes; findings with the negative subjective effects have been ambiguous though. For example, Davidson and Schenk (1994) reported correlations between a positive experience factor and latency to second use and level of lifetime use with no correlations observed with a negative factor and these outcomes. Similarly, Fergusson et al. (2003) reported a strong relationship between positive experiences with marijuana use prior to age 16 and dependence during young adulthood, but found no associations with negative experiences. Lyons et al. (1997) found that negative subjective experiences may be protective against length of regular use while Grant et al. (2005) found that both positive and negative experiences have been associated with marijuana abuse and dependence in an adult sample. Most recently, in a sample of adolescents, Scherrer et al., (2009) found that high responders (i.e. endorsed both positive and negative subjective effects), positive and mixed/relaxed responder classes were all significantly more likely than the low responders (i.e. very low endorsement for most subjective effects) to be heavier cannabis users with high responders having significantly larger odds of DSM-IV cannabis abuse and dependence.

A number of limitations exist in the study of subjective effects of marijuana. Although there is relative consistency regarding the relationship between positive subjective effects and marijuana use phenotypes, the relationship between negative subjective experiences and marijuana use phenotypes is unclear. Also, there has not been a study of self-reported

subjective effects to marijuana in a clinical population outside the laboratory. Lastly, the number of studies examining adolescents has been relatively small.

To address these limitations, we examined retrospectively reported subjective experiences with marijuana in a large community sample and a treatment-based clinical sample assessed using the Lyons battery (Lyons et al., 1997) and scaled using Mokken scale analysis (MSA). Our study was designed to examine (1) whether there are associations between subjective responses to marijuana use and patterns of use, abuse, dependence in an adolescent and young adult sample and (2) to determine whether Mokken scaling and potential associations are comparable for community and clinical subjects. The expectation was that there would be differential predictive power between positive and negative subjective effects with the negative subjective effects being protective against the studied phenotypes and that individuals in treatment would be more extreme in their responses with regards to subjective effects to marijuana.

2. Methods

2.1 Subjects

Our community-based sample was drawn from participants in the Colorado Center on Antisocial Drug Dependence (CADD), a large collaborative study that includes the Colorado Twin Registry (Rhea et al., 2006), the Colorado Adoption Project (Petrill et al., 2003), and the control sample of the Colorado Adolescent Substance Abuse Family Study (ASA; Stallings et al., 2003). Our clinical sample was drawn from adolescents in treatment for substance abuse (not exclusively marijuana) and delinquency, recruited as part of the ASA, and an additional 61 (12% of the clinical sample) adolescents who had been convicted and placed on probation (e.g. adjudicated) in the Denver metropolitan area (Hartman et al., 2008). The subjects in the present study were selected because they have used marijuana six or more times and had data available for the assessments described below.

2.2 Assessment

Patterns of marijuana use and abuse and dependence symptomatology were collected using the Composite International Diagnostic Interview- Substance Abuse Module (CIDI-SAM; Cottler et al., 1995). An additional set of supplemental questions for the CIDI-SAM was asked to evaluate age at first use and whether subjects progressed to regular use (i.e. use once/month for at least 6 months). Subjects who indicated that they had “used marijuana more than five times” in their lifetime were asked follow-up questions concerning abuse and dependence symptoms. Scoring algorithms based on whole life substance-related problems were used to derive the number of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for life-time abuse and dependence symptoms for marijuana.

Self-report subjective experiences were collected using a questionnaire developed by Lyons and colleagues (Lyons et al., 1997). This 23-item inventory assessed subjective responses for 10 classes of drugs, including marijuana. These questions included, “In the period shortly after you used marijuana, did it make you feel {subjective effect}?”, to which subjects answered yes or no. Responses were scored as 0/1, with 1 indicating they had such an experience. From this pool of items, Lyons et al. (1997) identified two primary factors for marijuana: a positive scale with an internal consistency, based on Kuder-Richardson formula 20, of 0.79 and a negative scale with an internal consistency of 0.63 (Lyons et al., 1997).

In the current study, a total of 1912 subjects were assessed using versions of the Lyons questionnaire, of which 1296 (68%) subjects were asked all 23 items. In response to interview length, a factor analysis was conducted on the Lyons questionnaire and 10 items with lower loadings were dropped. Thus, the remaining 32% of the study population were

given a shortened 13-item version (see Table 2). The 10 items dropped from the 23 item version were primarily negative or mixed items (i.e., *confused*, *anxious*, *jumpy*, *paranoid*, *depressed*, *laugh/cry*, *hear/see things not present*, *keyed-up*, *irritable*, and *confident*). A post-hoc comparison using Mokken scaling showed that clustering of items for the Mokken scales was similar for the full Lyons questionnaire and the shortened 13-item questionnaire. To maximize sample size, all analyses were conducted using the 13-item sub-set.

2.3 Statistical Analyses

While our primary interest was to examine the usefulness of MSA for subjective effects, we also performed confirmatory factor analysis (CFA) to compare the dimensionality from this sample to that obtained by Lyons et al. (1997). Because the results from CFA correlated highly with results from MSA (0.99 for the positive scale and 0.98 for the negative scale), we report only MSA-based analyses. Mokken scaling starts with a matrix containing information on the strength of the bivariate relationships between the *J* items under study. In factor analysis, this is either a correlation or covariance matrix. Mokken scaling uses a matrix with *H*-coefficicents (van Abswoude et al., 2004). Furthermore, Mokken scaling provides a nonparametric, iterative scale-building technique that identifies the smallest set of internally consistent scales from a given item pool. This model assumes the presence of latent traits that can be measured by subject responses to a set of items (Luinge et al., 2006; Watson et al., 2008). Mokken scaling is probabilistic and hierarchical, meaning that the items can be ordered by a degree of "difficulty"; individuals who agree with a more difficult item will tend to agree with less difficult items (DeJong and Molenaar, 1987; Meijer and Sijtsma, 1990; Luinge et al., 2006; Watson et al., 2007; Wismeijer et al., 2008). The scales are formed by taking pairs of items with the highest correlation and including other items that fit into the scale until there is no further improvement (Webber and Huxley, 2007). Loevinger's H coefficients, which indicate the fit of an item to the scale, were computed for each item (H_i) within a scale and for the scale as a whole (H). H >/= 0.4 are considered strong scales (Watson et al., 2007). In MSA, an item(s) can remain "unscaled" because it could not be added to one of the alternative scales without weakening the scale's homogeneity.

An advantage of MSA is the ability for direct comparability of scaling results between groups, which was evaluated by comparison of items selected for each scale and inspection of the H coefficients for items across subsamples. Mokken scaling was performed separately for the community and clinical samples. Furthermore, separate scaling was done by age (<17 vs. >/=17) and gender to test for potential differences and to ensure that scaling on the entire sample would not be a confounder. Since no differences were seen between any of the sub-groups, scaling was performed using the entire sample. Independent-sample t-tests were performed to detect any differences in sample means as a function of age, gender and group status (i.e. community vs. clinical) for the consensus positive and negative response scales.

To determine the relationship between positive and negative subjective experiences and marijuana use phenotypes, we conducted linear and logistic regression analyses, with the marijuana phenotype as the dependent variable and the two MSA-derived subjective experience scales as independent variables. Past six-month use was examined in two ways. First we treated it as a continuous variable (range 0 to 180 days) and applied linear regression models to test the association with our two subjective experiences scales. Second, to understand the relationship between past six-month use and subjective experiences among those who had desisted from using marijuana altogether, we create a use/no use variable. Because we examined responses from subjects of different ages and genders, we conducted linear and logistic regression analyses controlling for their effects in the association between both subjective effects scales and our marijuana use phenotypes. In these models, MSA-derived scales were adjusted by age and sex, which were then added to the regression

models as covariates, as well as controlling for non-independence due to more than one subject per family (i.e. clustering on family in Stata). All analyses were conducted using the statistical software STATA (version 10.1).

3. Results

3.1 Demographics

In our community sample of 1438 subjects who were between the ages of 11 and 30 years old and had reported using marijuana five or more times, the mean age was 19.3 (± 3.1 years), 58% were male and 82% were Caucasian. The mean number of days reported using marijuana in the past six months was 31.4 (standard deviation, sd: 54.8 days), with 31% of subjects reporting no use in the last six months. Subjects reported initiating marijuana use between the ages of 5 and 26, with a mean age of 15.3 (sd: 2.0 years). As shown in Table 1, a total of 336 (23%) subjects met DSM-IV marijuana abuse criteria and 263 (18%) met DSM-IV criteria for dependence. In the clinical sample, there were 474 subjects comprised of 87% males and 55% Caucasian. The mean age of the clinical sample was 17.4 (± 3.4 years). The mean number of days reported using marijuana in the past six months was 83.7 (sd: 68.2 days). The mean age of initiation was 12.2 years (sd: 2.0 years), with a range of 5 to 19 years of age. The majority of this sample met DSM-IV criteria for either abuse (34%) or dependence (51%). A total of 71 subjects did not meet diagnosis for either abuse or dependence (Table 1).

3.2 Mokken Scale Analysis

As shown in Table 2, Mokken scaling of the 13 subjective effects items revealed two scales using a total of 12 items. The items were comparable for the community and clinical subjects. Items in the positive scale were: relaxed, sociable, creative, euphoric, energetic, and increased sex drive. The items included in the negative scale were: lazy, drowsy, unable to concentrate, dizzy, out of control, and nauseous. The item assessing feelings of guilt did not fit into either scale. In the community sample, the average H-coefficient for the positive and negative effects scales was 0.40 and 0.49, respectively. The average H coefficients for the clinical population were 0.41 for the positive scale and 0.56 for the negative scale. Estimates of the Kuder-Richardson formula 20 (KR20), a measure of internal consistency similar to Cronbach's alpha, were 0.63 for the positive scale and 0.62 for the negative scale in the community subjects and 0.65 for both scales in the clinical subjects.

We examined whether the scaling of these 13 subjective effects items differs as a function of age (dichotomizing age by <17 and >/= 17) or gender in the community sample (the clinical sample is limited by size and gender skewness). Items scaled similarly in the subsamples as in the entire group. There were, however, observed mean differences in subjective responses, as a function of age and gender in both the community and clinical samples. In both groups, male subjects reported more positive responses than female subjects (community: $p<0.05$; clinical: $p<0.01$). In the community sample, older subjects had a significantly higher mean for the negative scale than younger subjects ($p<0.001$) and in the clinical sample the older subjects had a higher mean for the positive scale ($p<0.01$). Overall, subjects in the clinical sample reported significantly more positive effects ($p<0.001$) and fewer negative effects than those in the community sample ($p<0.01$).

3.3 Correlations

The positive and negative effects scales correlated modestly, 0.12 in the community subjects and 0.13 in the clinical subjects (data not shown). Not surprisingly, in both samples the Mokken derived scales and the CFA-derived factor were highly correlated (positive scale and positive factor: 0.99). The correlations were not perfect though, reflecting the absence of

feelings of guilt from the MSA negative scale (community: 0.97; clinical: 0.98). In the community and clinical subjects, there was a significant positive correlation between the positive scale and a diagnosis of dependence (0.32 and 0.22, respectively) and number of days used in the past six-months (0.28 and 0.12, respectively). The positive scale was significantly positively correlated with abuse (0.20) in the community subjects. The negative scale was positively correlated with a diagnosis of dependence in both groups (community: 0.25; clinical: 0.27) and with a diagnosis of abuse (0.12) in the community sample.

3.4 Regression analyses

Table 3 shows the results of the linear and logistic regression analyses. The positive scale was significantly associated with regular use in the community subjects (OR=1.52). In the community and clinical subjects there were significant associations between the positive effects scale and abuse (OR=1.32 and 1.27, respectively), dependence (OR=1.65 and 1.52, respectively) and past six month use (no use vs. any use) (OR=1.51 and 1.52, respectively). The negative effects scale was significantly associated with a diagnosis of abuse (OR=1.18) and past six month use (OR=0.89) in the community subjects and with dependence in both groups (community: OR=1.55; clinical: OR=1.61). When looking at past six month use as a continuous variable, the positive scale was significantly associated with past six-month use in both the community (β=0.27) and clinical (β=0.16) samples, whereas the negative scale was significantly negatively correlated with past six month use in the community sample (β= −0.07).

4. Discussion

Our goal was to determine, in both a community and a clinical population, whether subjective effects to marijuana associate with patterns of use and DSM-IV abuse or dependence status. Our results indicate that positive subjective experiences are associated with a higher degree of past six-month use and an increased risk for having a diagnosis of abuse or dependence in the both groups. Additionally, negative subjective experiences were also found to be positively associated with dependence in both group, abuse in the community subjects and negatively associated with past six month use in the community subjects.

We used Mokken scaling to examine thirteen items from the subjective effects scale developed by Lyons and colleagues (1997). Factor analysis constructs factors that are comprised of highly correlated items; Mokken scaling builds on this by systematically hierarchically ordering the items (DeJong and Molenaar, 1987). Mokken scaling yielded results that were consistent with previous studies utilizing the same or different questionnaires in adult or college-aged samples (Davidson and Schenk, 1994; Lyons et al., 1997; Green et al., 2003). Mokken scaling also tests for undimensionality of the scales and one can easily determine if there is sample independence (i.e. items scale the same across subgroups). While the Lyons questionnaire is intended to be multidimensional, the scales themselves, positive and negative, are unidimensional. The positive scale items of being relaxed, sociable, and creative had higher H-coefficients than increased energy or sex drive. The negative scale items of laziness, drowsiness and dizziness had higher H-coefficients than nausea or being out of control. This hierarchical ordering of experiences is reasonable, as early marijuana use is characterized by mild effects at low doses, with sedative effects being replaced by greater stimulation at higher doses with higher frequency of use. This interpretation is consistent with physiological data indicating marijuana causes CNS depression at low doses and stimulation at higher doses (Zuurman et al., 2008; Block et al., 1998).

In order to understand whether self-reported subjective experiences were associated with more problematic patterns of use, we included in our analyses a number of clinically relevant phenotypes. Our finding that positive effects were associated with use and clinical diagnoses is consistent with previous studies in samples of young adults (Davidson and Schenk, 1994; Fergusson et al., 2003; Grant et al., 2005; Scherrer et al., 2009; LeStrat et al., 2009). Additionally, we replicated an observation by Grant et al. (2005) that negative subjective experiences were associated with dependence, although our point estimates are lower than what they observed. We observed a significant correlation between the positive and negative scale which was also seen by Davidson and Schenk (1994). LeStrat et al. (2009) found that increasing numbers of positive subjective effects was associated with increasing rates of cannabis dependence (OR ranged from 1.9 for one positive subjective effect to 28.7 for 5). Our data supports this finding, as we found an odds ratio range of 1.3 for one positive subjective effect and cannabis dependence to an OR of 14.9 for 5 or more positive subjective effects (data not shown).

As observed in our data, however, the relationship between negative experiences and outcomes is more heterogeneous than with positive effects. Although the varying associations observed between negative effects and marijuana outcomes may be due to sampling differences between the previous studies and the current one, item differences may be another reason. For example, the positive association reported by Grant et al. (2005) was based on a scale that excluded the items dizzy and nauseous due to low endorsement or poor discrimination. The study by Lyons et al. (1997), however, included these and other items in their negative experiences scale and reported a negative correlation with length of regular use and duration of regular use. Feeling dizzy, frightened, or passed out constructed the three-item negative effects scales tested in the study by Fergusson et al. (2003), which reported no relationship with dependence during young adulthood. Another explanation for the observed association with negative scale is that those who experience negative effects early do not progress past experimentation, signified by the lack of association with the negative scale the protective effect seen with this scale for past six month use, but those who are very sensitive to the effects of marijuana experience both strong positive and negative reactions and progress to more problematic use. These individuals would be comparable to the “high responders” seen by Scherrer et al. (2009), who had the highest rates of cannabis abuse and dependence. Although the prospect of identifying protective experiences is encouraging, conclusions about the impact or role of negative subjective effects should be considered preliminary and needing replication.

Out second aim was to determine whether there are differences in scaling and associations between community and clinical samples. Although the individual item mean scores are comparable, some of the associations between the scales and the marijuana phenotypes were not the same. For abuse and past six month use, the point estimates are similar in the clinical and community samples, but the results were not significant in the clinical sample due to the smaller sample size and larger confidence intervals. This suggests that clinically meaningful subjective experiences may be investigated using community-based samples.

Although a number of similarities between the community and clinical samples were identified, there were significant mean differences in total scale scores, with clinical subjects experiencing more positive and fewer negative effects than our community sample. These statistical differences may be due to several reasons. As suggested by Grant et al. (2005), recall biases due to experiences with previous drugs may subsequently influence retrospective ratings. In particular, multi-substance users may ignore or not remember their negative subjective experiences and instead endorse more positive experiences. Another potential reason may be that the clinical subjects are exposed to more pro-drug interactions or discussions with their peers, as well as siblings and parents, or that they are more prone to

enhance their social image resulting from marijuana (Prinstein et al., 2001; Bricker et al., 2006; Hampson et al., 2008; Yanovitzky, 2005). Finally, differences in the length of exposure to marijuana may be a factor that modifies ratings of subjective experiences.

Findings from the current study should be interpreted with a number of limitations in mind. First, subjective responses were collected from subjects ranging between 12 and 30 years old. Though the scaling of subjective experience items was consistent across younger and older subjects, the older subjects could potentially have a much longer history of marijuana use. Equally, older subjects whose use ended years previously needed to recall experiences over a longer time period than young subjects, though the average number of years since first use was only 4.4 years. It could be, then, that younger subjects are reporting subjective effects from initial use while the older subjects are reporting subjective effects from current use or from their entire marijuana use history. Second, subjective experiences were only collected from those who reported using marijuana six or more times, and our data did not include reports from those who experimented only a few times. Those individuals who used fewer than 6 times may have had more negative experiences, which would impact the results regarding dependence and abuse. Third, because of the phrasing of the stem questions asked (*in the period shortly after you used marijuana, did it make you feel*), it is unclear whether subjects were reporting their initial experiences, experiences in the minutes or hours immediately following recent marijuana intake (at some undefined period) or the conglomeration of their marijuana experience, making causal inferences regarding the observed associations not possible. Fourth, between-subject differences related to dosage, quality of drug, depth of inhalation, and setting (Block et al., 1998; Heishman et al., 1989; Ilan et al., 2005) may be a relevant factor impacting their subjective experiences. It may be possible that subjective effects, or the recall of earlier subjective experiences, are modified by subsequent marijuana or other drug use behaviors; additionally, it is unknown whether concurrent drug use is impacting recall about subjective effects for marijuana.

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Table 1

Demographic information for community and clinical subjects

	Community (n=1438)		Clinical (n=474)	
	N	**%**	***N***	**%**
Male gender	834	58	413	87
White race	1,175	82	262	55
Diagnosis				
None	839	58.3	71	15.0
Abuse	336	23.4	163	34.4
Dependence	263	18.3	240	50.6
	Mean	*SD*	*Mean*	*SD*
Age at testing	19.3 years	3.07	17.4	3.4
Age initiation	15.2 years	2.03	12.2	2.04
Number times used in the past 6 months	31.8	54.8	83.7	68.2

Table 2

Lyons subjective effects items and Mokken scales in community and clinical subjects

	Community (n=1438)		Clinical (n=474)	
	Mean endorsement (standard deviation)	**Loevinger's H coefficient**	**Mean endorsement (standard deviation)**	**Loevinger's H coefficient**
Positive Scale				
Relaxed or Mellow	0.87 (0.34)	0.60	0.85 (0.36)	0.46
Sociable	0.54 (0.50)	0.38	0.67 (0.47)	0.43
Creative	0.51 (0.50)	0.42	0.50 (0.50)	0.43
Top of World	0.43 (0.50)	0.38	0.50 (0.50)	0.38
Energetic	0.23 (0.42)	0.39	0.32 (0.47)	0.43
Increased Sex Drive	0.16 (0.37)	0.34	0.24 (0.43)	0.32
Scale H		0.40		0.41
Negative Scale				
Lazy	0.70 (0.46)	0.55	0.72 (0.45)	0.65
Drowsy	0.57 (0.49)	0.49	0.52 (0.50)	0.60
Unable to Concentrate	0.47 (0.50)	0.48	0.35 (0.48)	0.56
Dizzy	0.18 (0.39)	0.55	0.15 (0.36)	0.49
Nauseous	0.07 (0.25)	0.45	0.05 (0.22)	0.58
Out of Control	0.06 (0.23)	0.38	0.09 (0.29)	0.45
Scale H		0.49		0.56
Unscaled Item				
Guilty	0.38 (0.49)	--	0.31 (0.46)	--

Table 3

Linear and logistic regression between marijuana Mokken scales and marijuana phenotypes*

	Community		Clinical	
	Positive Scale	**Negative Scale**	**Positive Scale**	**Negative Scale**
Linear Regression (β-coefficient and 95% CI)				
Number days used in the past six months	**0.27 (0.19–0.35)**	**−0.07 (−0.12- −0.02)**	**0.16 (0.08–0.23)**	−0.02 (−1.08–0.65)
Logistic Regression (OR and 95% CI)				
Regular use	**1.52 (1.39–1.65)**	1.05 (0.96–1.14)	***	***
Abuse	**1.32 (1.20–1.44)**	**1.18 (1.07–1.29)**	**1.27 (1.04–1.54)**	1.17 (0.93–1.48)
Dependence	**1.65 (1.49–1.84)**	**1.55 (1.34–1.68)**	**1.52 (1.25–1.87)**	**1.61 (1.28–2.04)**
Past 6 month use (none vs. any)	**1.51 (1.39–1.64)**	**0.89 (0.82–0.97)**	**1.52 (1.25–1.83)**	0.87 (0.72–1.05)

Bolded indicates a statistically significant estimate.

* adjusted for familial status

Note:

*** 99.5% of the clinical population uses regularly