



Published in final edited form as:

*Drug Alcohol Depend.* 2008 July 1; 96(0): . doi:10.1016/j.drugalcdep.2008.02.008.

## DSM-IV criteria-based clinical subtypes of cannabis use disorders: Results from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC)☆

Carlos Blanco<sup>a,b,c</sup>, Elizabeth Ogburn<sup>a,b,c</sup>, José Pérez de los Cobos<sup>d</sup>, Juan Lujan<sup>a,b,c</sup>, Edward V. Nunes<sup>a,b,c</sup>, Bridget Grant<sup>e,\*</sup>, Shang-Min Liu<sup>a,b,c</sup>, and Deborah S. Hasin<sup>a,b,c</sup>

<sup>a</sup>New York State Psychiatric Institute, New York, NY 10032, United States

<sup>b</sup>Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032, United States

<sup>c</sup>Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY 10032, United States

<sup>d</sup>Addictive Behaviors Unit of Psychiatry Department, Hospital de la Santa Creu i Sant Pau, 08025 Barcelona, Spain

<sup>e</sup>Laboratory of Epidemiology and Biometry, Room 3077, Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, M.S. 9304, 5635 Fishers Lane, Bethesda, MD 20892-9304, United States

### Abstract

Prior research documented high homogeneity of alcohol use disorders (AUDs) as clinical entities. However, it is unknown whether this finding extends to other substance use disorders. We investigated this by examining the prevalence of all possible DSM-IV criteria-based clinical subtypes of current and lifetime cannabis use disorders in the general population. The number of possible (i.e., theoretical) clinical subtypes of cannabis abuse and dependence based on different combinations of the DSM-IV criteria was calculated using the combinatorial function. This number was compared with the subtypes actually observed in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a large U.S. national sample ( $N=43,093$ ). Clinical and demographic correlates of the subtypes were examined with  $\chi^2$  tests whose target population was the United States civilian non-institutionalized population. All DSM-IV cannabis abuse and dependence criteria were assessed with the Alcohol Use Disorder and Associated Disabilities Interview Schedule—DSM-IV Version (AUDADIS-IV). Of all possible cannabis dependence subtypes, 29 (69%) were observed in the 12-month timeframe, and 41 (98%) in the lifetime timeframe. The corresponding numbers of subtypes for cannabis abuse were 12 (75%), current and 15 (100%), lifetime. These findings suggest that, in contrast to alcohol disorders, cannabis use disorders were highly heterogeneous. Future research should investigate whether there are

☆The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or the U.S. government.

© 2008 Published by Elsevier Ireland Ltd.

\*Corresponding author. Tel.: +1 301 443 7370; fax: +1 301 443 1400. bgrant@willco.niaaa.nih.gov (B. Grant)..

### Conflict of interest

None.

*Contributors:* All authors participated in writing and reviewing drafts of this manuscript and interpretation of the data. Drs. Blanco and de los Cobos wrote the initial draft; Ms. Ogburn and Drs. Hasin, Nunes, de los Cobos, Lujan and Blanco conducted the analyses and literature reviews. Dr. Grant collected the data. All authors contributed to and approved the final manuscript for submission.

differences in the course and treatment response of these clinical subtypes of cannabis use disorders, and the heterogeneity of other substance use disorders.

## Keywords

Cannabis use disorder; Subtypes; Epidemiological survey; DSM-IV criteria

---

## 1. Introduction

Cannabis is by far the most commonly abused drug in the U.S. (Compton et al., 2004) with an estimated current prevalence of 1.13% (or 2.3 million Americans) for abuse and 0.32% (corresponding to 670,000 Americans) for dependence. Despite the high prevalence and associated impairment of cannabis use disorders (Hall and Solowij, 1998; Bovasso, 2001; Pope et al., 2001; Taylor et al., 2002), little is known about their clinical features. An important aspect not examined to date is the heterogeneity within cannabis abuse and dependence as clinical entities.

The examination of the heterogeneity of clinical entities has traditionally focused on the use of latent variable techniques, such as latent class analysis, factor analysis, and item response theory. Three previous factor analyses have suggested that cannabis use disorders are highly homogeneous in their latent structure, and can be parsimoniously described by two factors: one resembling cannabis abuse, and the other resembling cannabis dependence (Blanco et al., 2007; Swift et al., 2001; Teesson et al., 2002), closely paralleling the categories proposed in DSM-IV (American Psychiatric Association, 1994). A recent study suggested that cannabis use disorders could be described by one factor, suggesting an even higher degree of homogeneity than previously hypothesized (Agrawal and Lynskey, 2007).

A major advantage of latent variable techniques is their ability to uncover previously undetected associations among variables, which can then guide further epidemiological and biological research. Their applicability in clinical settings is more limited. Clinicians must decide on a treatment plan after asking patients directly about the disorder criteria. They are not equipped to apply latent variable techniques in their clinical practices. An alternative, complementary approach to examine the heterogeneity of cannabis use disorders is the identification of clinical subtypes based on DSM-IV criteria. This approach has the appeal of relying on the official diagnostic nomenclature, while also following the procedures generally used to assess patients in clinical practice.

DSM-IV requires that three of the six criteria be met for a diagnosis of cannabis dependence, and that one of the four criteria be met for a diagnosis of cannabis abuse (American Psychiatric Association, 1994). Therefore, a wide variety of symptom combinations could qualify for the diagnoses of substance abuse or dependence, but the actual heterogeneity that exists in cannabis use disorders is unknown. One way to investigate the heterogeneity of cannabis abuse and dependence is to determine the number of possible combinations of criteria (i.e. theoretical subtypes) for each of these disorders, examine the number of subtypes that are actually observed in the general population, and determine the relative prevalence of each subtype. The results of such work would reveal how many subtypes actually occur, and what the most common subtypes are. If a few subtypes account for a high percentage of individuals with cannabis use disorders, this would reduce concerns about the heterogeneity of the diagnostic categories. A large number of observed subtypes would suggest the need to provide information about the subtypes present in any clinical or neurobiological study, since subtype composition of the samples may help to explain the differences in results across studies.

Two studies used this methodology with data from the National Longitudinal Alcohol Epidemiological Study (NLAES) to examine the homogeneity of alcohol use disorders (AUDs). The first study used DSM-III-R criteria for alcohol dependence, finding only 41% (189/466) of the theoretically possible subtypes (combinations of symptoms) in the general population (Grant et al., 1992). The second study used DSM-IV criteria and examined both alcohol abuse and dependence (Grant, 2000). This study found 11 (48%) of the theoretical subtypes of alcohol abuse and 53 (54%) of the theoretical subtypes of dependence in the general population. However, while this amount of heterogeneity might seem daunting in terms of understanding etiology and developing improved treatments, the number of *common* subtypes was actually much lower: 90% of respondents classified with abuse could be represented by three subtypes of abuse and 70% of respondents with dependence could be characterized by six subtypes of dependence, indicating relative homogeneity of both diagnostic categories (Grant, 2000).

No information of this type is available for substances other than alcohol. The goal of this study was therefore to examine clinical subtypes for DSM-IV cannabis abuse and dependence by analyzing data from a large national epidemiological study and obtaining nationally representative estimates of the relative frequency of each subtype among individuals with cannabis use disorders. Following the methodology developed by Grant for AUDs (Grant et al., 1992; Grant, 2000), we compared the number of theoretically possible subtypes of cannabis abuse or dependence with the empirical combinations observed, and identified the most commonly observed subtypes. We further examined the number of subtypes across important socio-demographic subgroups of the population, and the percent of observed subtypes that contained each diagnostic criterion. Given the results for AUDs (Grant, 2000), we anticipated that a relatively small number of subtypes of marijuana abuse and dependence would account for the majority of individuals with cannabis use disorders.

## 2. Methods

### 2.1. Sample

Subjects were participants in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a nationally representative face-to-face survey of 43,093 respondents aged 18 years and older conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 2001–2002. The target population of the NESARC was the civilian non-institutionalized population residing in the United States and District of Columbia, including Alaska and Hawaii. African-Americans and Hispanics were oversampled, as were young adults. The NESARC also included a group quarters sampling frame. Details of the sampling frame are provided elsewhere (Grant et al., 2003a,b, 2004a,b). The overall survey response rate was 81%. The NESARC sample was weighted to adjust for probabilities of selection of a housing unit or equivalent, household-and person-level nonresponse, the selection of one person per household and oversampling. Once weighted, the data were adjusted to represent the United States population on a variety of socio-demographic variables including region, age, sex, race and ethnicity based on the 2000 Decennial Census. For this analysis, we included all NESARC respondents who met the criteria for a DSM-IV cannabis use disorder, except Native Americans, a distinct group too small to analyze. Among these, 47.9% were male, 70.9% white, 11.1% African-American, 11.6% Hispanic, and 4.36% Asian. By age, 21.8% were 18–29; 30.9% were 30–44, 31.1%; were 45–64; 16.2% were 65 or older.

### 2.2. Measures

DSM-IV cannabis abuse and dependence were assessed with the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule—DSM-IV Version (AUDADIS-

IV) (Grant and Hasin, 2001), a fully structured diagnostic interview for non-clinician interviewers. The AUDADIS-IV includes an extensive list of symptom questions that operationalize each DSM-IV criteria for cannabis abuse and dependence separately. Each criterion for DSM-IV cannabis abuse was rated independently of whether or not dependence was present, allowing identification of cannabis-dependent individuals with and without abuse, and avoiding the biases that can be introduced when abuse is used as a screen for dependence (Hasin and Grant, 2004; Hasin et al., 2005). The high reliability and validity of the AUDADIS cannabis dependence diagnosis ( $\kappa = 0.70\text{--}0.94$ ) has been demonstrated in numerous clinical and general population studies in the U.S. and abroad (Grant, 1995; Chatterji et al., 1997; Cottler et al., 1997; Hasin et al., 1997; Ustun et al., 1997; Canino et al., 1999). The reliability of DSM-IV cannabis abuse is also adequate ( $\kappa = 0.65\text{--}0.86$ ) when diagnosed non-hierarchically (independently of cannabis dependence) (Chatterji et al., 1997; Vrasti et al., 1998; Canino et al., 1999), as done here. Clinical reappraisal studies showed good concordance between DSM-IV AUDADIS diagnoses of cannabis use disorders and those of psychiatrists (Canino et al., 1999; Cottler et al., 1997). In this study, we addressed both current (last 12 months), and lifetime cannabis abuse and dependence.

Following DSM-IV, cannabis dependence was defined in our main analyses as meeting at least three of the following six criteria at any time in the same 12-month period: (1) development of tolerance; (2) using cannabis in larger amounts or over a longer period than intended; (3) inability to cut down or reduce cannabis use; (4) spending large amounts of time to obtain, use, or recover from the effects of cannabis; (5) giving up important social, occupational, or recreational activities in favor of using cannabis; (6) continued use of cannabis despite its adverse consequences.

To examine the sensitivity of our assumptions to alternative conceptualizations, we conducted a series of supplementary analyses using different operationalizations of cannabis use disorders. Those comprised (1) analyses deleting criteria with the two lowest loadings on the abuse and dependence factors in our previous analyses (Blanco et al., 2007); (2) the inclusion of cannabis withdrawal as a symptom of cannabis dependence (Kouri et al., 1999; Budney et al., 2001; Smith, 2002); (3) analyses that considered cannabis use disorders as a unidimensional construct. For these analyses, we examined the subtypes that would arise if only 1 out of 11 criteria (to mimic the diagnostic threshold for abuse) or 3 out of 11 criteria (to mimic the threshold for dependence) were required.

### 2.3. Interviewers, training and field quality control

Approximately 1800 professional interviewers from the U.S. Bureau of the Census administered the AUDADIS-IV using laptop computer-assisted software with built-in skip logic and consistency checks. The interviewers had an average of 5 years experience on census and other health-related national surveys. All interviewers across the Census Bureau's 12 regional offices completed 10 days of standardized training through centralized training sessions directed by NIAAA and Census headquarters staff. For quality control, regional supervisors re-contacted a random 10% of all respondents and re-asked a subset of the interview questions to verify the accuracy of the interviewer's performance. This careful process showed that the interviewers performed at a high level, as indicated by the high reliability of the instrument (Grant et al., 2003a,b). In the very few cases when the accuracy of the interviews was uncertain, the interview data were discarded and the interview re-done by a supervising interviewer.

### 2.4. Data analysis

Consistent with the DSM-IV criteria for cannabis dependence, in our main analyses we did not include in our analysis the withdrawal symptom criterion, but included it in our

supplementary analyses. The total number of theoretical subtypes of cannabis dependence was determined by the combinatorial function, which calculates the number of possible ways of choosing  $r$  unordered items from a set of  $n$  items. The formula is  $n!/(n-r)!r!$ , where  $n = 6$  (i.e., the total number of diagnostic criteria) and  $r$  is between 3 and 6 (the number of criteria present for a positive diagnosis is three or above). For example, the number of potential subtypes for three out of six criteria may be calculated using the above mentioned formula, where  $n! = 6 \times 5 \times 4 \times 3 \times 2 \times 1$  and  $r! = 3 \times 2 \times 1$ . There are 15 possible subtypes for DSM-IV cannabis abuse and 42 for DSM-IV dependence.

In our main analyses, we examined current abuse and dependence independently and regardless of past status. In cases where criteria for both diagnoses were met, subjects were included only in the dependence category to avoid duplication. To capture additional empirical subtypes that might be present in the general population but not observed in cross-sectional assessment, we extended the approach by also examining lifetime diagnoses. For each number of criteria met, we report the number of theoretical subtypes and, for each timeframe separately, the number of subtypes that were actually observed in the sample. Because not all subtypes, even if present, have the same prevalence, we also report the percent of individuals by number of criteria met. Further, we used  $\chi^2$  tests of independence to compare the distribution of subtypes of each of these four diagnostic groups (current and lifetime abuse and dependence) by race, gender, age group, presence/absence of AUDs, presence/absence of other substance use disorders, and lifetime history of drug treatment. To increase the clarity and statistical power of these comparisons, for each diagnostic group we examined the three most common subtypes in each category separately, and collapsed all remaining subtypes into a residual category of "other subtypes". Analyses were conducted using SUDAAN, to account for the complex sampling design of the NESARC; results reported are based on the weighted analyses.

## 2.5. Supplementary analyses

In our supplementary analyses, we examined the proportion of theoretical subtypes observed in the NESARC sample following several alternative operationalizations of cannabis abuse and dependence. Inclusion of the withdrawal criterion raised the number of theoretical cannabis dependence subtypes to 99. Deletion of the two criteria (tolerance and spending large amounts of time to obtain, use, or recover from the effects of cannabis) with the lowest loadings on the dependence factor (Blanco et al., 2007) resulted in 16 theoretical subtypes. Deletion of the two criteria (social problems derived from substance use or legal problems due to the use of the substance) with the lowest loadings on the abuse factor generated three theoretical subtypes. When cannabis use disorders were considered a unidimensional category, there were 2047 theoretical subtypes if one criterion was set as the diagnostic threshold, and 1981 theoretical subtypes when three criteria were set as the diagnostic threshold.

## 3. Results

### 3.1. Demographic characteristics

Table 1 summarizes the demographic characteristics of individuals with current and lifetime cannabis abuse and dependence. The majority of individuals with any current cannabis use disorder were male, white and between the ages of 18 and 29. Most individuals meeting lifetime diagnostic criteria for abuse or dependence were also male and white. However, the highest prevalence of abuse was found in the 30–44 age group, rather than the younger group. Lifetime dependence had the highest prevalence in the 18–29 age group, closely followed by the 30–44 age group.



### 3.2. Current and lifetime dependence

Most subtypes including only three criteria were observed in both timeframes, and together accounted for half of the individuals with cannabis dependence (Table 2). However, the most prevalent single subtype was characterized by all six criteria for dependence. This subtype accounted for 10.5% of current and 18.7% of lifetime cases. Of the six theoretically possible subtypes with five criteria, five were observed for current diagnosis, and all six subtypes for lifetime diagnosis. The dependence subtype characterized by all criteria except giving up major activities in favor of cannabis use was the second most prevalent across all subtypes, accounting for 9.8% of current and 7.0% of cases lifetime, while the third most common subtype was characterized by all criteria except using cannabis in larger amounts or over a longer period than expected, accounting for 7.0% lifetime and 3.0% of current cases. Less than half of the subtypes with four criteria were observed for current diagnosis, but all were observed for lifetime diagnosis.

For both current and lifetime dependence, the diagnostic criteria met by the highest proportion of individuals were inability to cut down, use despite physical/psychological problems, and large amounts of time spent in substance-related activities (Table 3). The least prevalent was the reduction or cessation of important social, occupational or recreational activities due to substance use. However, while this criterion was met by 24.3% of individuals with a current diagnosis of cannabis dependence, it was met by over 50% of individuals when using a lifetime diagnosis. The prevalence of all other criteria remained very similar across timeframes.

### 3.3. Current and lifetime abuse

Cases in which all four abuse criteria were met were observed only for lifetime diagnosis (Table 4). Of the theoretical subtypes characterized by three criteria, 2 (50%) of 4 were observed for current diagnosis, whereas all 4 were observed for lifetime diagnosis. The most common subtypes were those defined by hazardous use only (accounting for 64% of all individuals both current and lifetime), hazardous use plus social problems (accounting for 12% current and 13% lifetime), and social problems only (12% current and 10% lifetime). All subtypes characterized by one or two criteria were observed for both current and lifetime diagnoses. In both time periods, the vast majority of individuals fell into subtypes characterized by only one criterion (Table 4). When examining the prevalence of individual criteria, rather than subtypes, the most prevalent criterion was hazardous use, followed by cannabis use despite interpersonal problems in both periods. The neglect of role criterion was met by 5.1% of individuals with a current diagnosis and by 15.9% of individuals with a lifetime diagnoses. The legal problems criterion was endorsed by less than 10% of individuals, regardless of timeframe (Table 5).

### 3.4. Distribution of abuse and dependence subtypes by age, gender, race/ethnicity and comorbid substance use disorders

Table 6 shows that for most demographic groups, the subtype of lifetime abuse characterized by hazardous use only was substantially more prevalent than the others. Women, individuals younger than 30, and those without a history of AUDs were more likely to have the subtype characterized by social problems only, while whites, blacks and those with a history of substance use disorders were more likely to have the subtype characterized by both hazardous use and social problems. Males, individuals under 30 and those with a lifetime history of another substance use disorder were at increased risk of having subtypes that were relatively infrequent (grouped under “other”), and this pattern was even more marked for individuals with a lifetime history of treatment for substance use disorders.

There were no differences in the distribution of observed subtypes of current dependence by any demographic characteristic (data not shown). Similarly, there were no differences in the distribution of subtypes by any demographic characteristic among individuals with lifetime or current dependence regardless of whether the three most common subtypes were considered separately and the rest grouped under “any other subtype”, or the 10 most common subtypes (accounting for 70% of the subjects in the sample) were considered separately and the rest collapsed into a residual “any other subtype” category (results available upon request from the first author).

### 3.5. Supplementary analyses

Results of the supplementary analyses were largely consistent with the main analyses in suggesting a high degree of homogeneity in cannabis abuse, but substantial heterogeneity in cannabis dependence. Inclusion of the withdrawal criterion resulted in 36 (36.4%) observed subtypes of the 99 theoretical subtypes among those with 12-month cannabis dependence and 79 (79.8%) among those with a lifetime diagnosis. Nine (56.3%) of the 16 theoretical subtypes of dependence were observed among those with a 12-month diagnosis and 16 (100%) among those with a lifetime diagnosis when the two criteria with lowest loadings were not included in the analyses. All three theoretical subtypes were observed for abuse using the 12-month and, by implication, lifetime timeframe. Consideration of cannabis use disorders as a unidimensional construct generated 174 (8.5%) observed subtypes among those with a 12-month diagnosis and 567 (27.7%) among those with a lifetime diagnosis when only one criterion was set as a diagnostic threshold, and 138 (7.0%) and 514 (26.0%) when three criteria were required.

## 4. Discussion

DSM-IV criteria were examined to identify theoretically possible subtypes of cannabis dependence based on various combinations of the criteria. Using a large, nationally representative sample of the general population, we found that cannabis dependence appears to be a disorder with a broad variety of subtypes, regardless of demographic characteristics and comorbidity with other substance use disorders. In contrast, cannabis abuse appears to be more homogenous overall, but its clinical manifestations tend to vary depending on the socio-demographic characteristics of subjects, and whether or not they suffer from comorbid disorders.

Consistent with previous results in alcohol abuse (Grant et al., 1992; Grant, 2000), and the findings of previous factor analyses of cannabis use disorders (Blanco et al., 2007; Swift et al., 2001; Teesson et al., 2002) we found a high degree of homogeneity in cannabis abuse: a single subtype (hazardous use) accounted for 63% of subtypes of current cases and for 52% of lifetime cases, and three subtypes accounted for over 80% of the cases. Also consistent with the results of previous research (Hasin and Paykin, 1999; Grant, 2000; Schuckit et al., 2005), we found that, with the exception of subjects with a lifetime history of drug use disorders or treatment, the most common subtype of abuse consisted of hazardous use of the substance regardless of demographic group, followed by social/interpersonal problems with or without hazardous use. However, the prevalence of subtypes differed significantly by clinical and socio-demographic characteristics, suggesting that these variables may influence the clinical presentation of cannabis abuse.

The heterogeneity in the clinical presentation of cannabis dependence, regardless of timeframe considered, differs from the high homogeneity found for alcohol dependence (Grant, 2000). Further, while factor analyses consistently identified cannabis dependence as a unidimensional construct (Swift et al., 2001; Teesson et al., 2002; Blanco et al., 2007), our results suggest that there is no “typical” presentation of cannabis dependence cases even

when different operationalizations of cannabis dependence are used. This has epidemiological, nosological and clinical implications.

#### 4.1. Epidemiological implications of the heterogeneity of cannabis dependence

Several findings indicated a high degree of heterogeneity of cannabis dependence. First, 97.6% of the theoretical subtypes were observed using the lifetime estimates, indicating the great diversity in which cannabis dependence can present. Second, the difference between the percentage of subtypes observed using the lifetime (97.6%) versus current (69.0%) timeframes shows that many individuals meet criteria for more than one subtype during their lifetime, indicating that there is also intra-individual heterogeneity in the presentation of the disorder. Third, our analysis could not identify any socio-demographic or clinical predictors of the diverse presentations of DSM-IV criteria-based subtypes, further stressing the heterogeneity of the individuals meeting criteria for any specific subtype.

The contrast between the heterogeneity described by the present analysis and the homogeneity of cannabis dependence found in factor analytic studies partially illustrates the complementary information provided by these two methods of examining cannabis dependence. There are two ways to reconcile these apparently divergent findings. One possibility, adhering to the traditional interpretation of a latent factor (Johnson and Wichern, 2001; Kline, 2004), is to postulate that cannabis dependence is an unobservable but truly *existing* entity, an abnormality that *causes* the phenomena described by the diagnostic criteria. This core abnormality, although the same across all cannabis-dependent individuals, would manifest itself by a specific combination of criteria depending on the particular characteristics of the person, thus yielding the different subtypes. This interpretation assumes that the effects of cannabis use are mediated by this core abnormality, common across all individuals with cannabis dependence. The nature of this latent variable, unknown at present, could be uncovered in the future.

Alternatively, the cannabis dependence factor can be simply interpreted as a statistically convenient way of expressing that all six cannabis dependence criteria (seven if the withdrawal criterion is included) are highly intercorrelated, but without assuming the existence of a unitary syndrome present in all cannabis-dependent individuals. This interpretation emphasizes that, in vulnerable subjects, cannabis use can directly and independently affect a variety of behaviors, although disruptions in those behaviors tend to co-occur. Future research should compare the heuristic value and empirical support for these competing conceptualizations of cannabis dependence. For example, if cannabis dependence is a true latent variable, brain-imaging techniques (given the appropriate resolution) should theoretically be able to locate a core abnormality in some region of the brain that would be present in all individuals with cannabis dependence. By contrast, if cannabis dependence only expresses high intercorrelation among the diagnostic criteria, brain-imaging techniques might be able to detect specific abnormalities corresponding to each criterion, but should not find a core abnormality across all cannabis-dependent individuals. Similarly if cannabis dependence is a true latent variable, genetic markers should be more strongly associated with the syndrome as a whole than with the individual criteria, while the opposite would be true if cannabis dependence is only a way of describing high criteria intercorrelation.

#### 4.2. Nosological implications of the heterogeneity of cannabis dependence

The results of our analyses can help improve our understanding of the dependence construct and may serve to inform DSM-V. An implicit assumption of DSM-IV is that the same dependence criteria are valid across substances, an assumption that has been recently challenged (Saunders et al., 2007). Our previous work (Blanco et al., 2007) supports a similar latent structure across substances of abuse. Our current findings, contrasting with the



homogeneity of presentation in alcohol dependence (Grant et al., 1992; Grant, 2000), suggest that the presentation of dependence syndromes varies by substance. A promising avenue for future research would be to examine which variables influence the differential expression of the latent construct of dependence across substances and individuals. Identification of those variables, currently subsumed in factor analyses in the indicators' error variance (and thus unanalyzed), would help to refine our understanding of dependence. Potential candidate variables may include issues related to social desirability (e.g., alcohol use may be socially more acceptable than cannabis use, leading to differential endorsing of specific criteria) or differences in some of the biological correlates of alcohol versus cannabis dependence. A challenge for future nosological efforts is the design of classification systems that allow for the flexible representation of common and unique aspects of dependence across different substances of abuse.

#### 4.3. Clinical implications of the heterogeneity of cannabis dependence

Our results also have diagnostic and treatment implications. Diagnostically, our results underscore the need for clinicians to recognize the diverse symptom presentations of cannabis dependence. The contrast between the mono-factorial structure of cannabis dependence and its heterogeneous clinical presentation suggests three potential approaches to treatment development. One option would be to devise specific treatment strategies for each subtype. The number of observed subtypes and their low prevalence make this approach impractical.

A second approach, consistent with the unidimensional structure of cannabis dependence and the classical interpretation of factor analysis (Kline, 2004), would be to target directly the postulated core abnormality common to all patients, i.e., adopt a uniform approach to treatment regardless of clinical presentation (i.e. subtype). Recent biological conceptualizations of substance dependence as disorders of motivation (Pérez de los Cobos et al., 1996; Kalivas and Volkow, 2005) or memory (Hyman, 2005) have contributed suggestions of what this core abnormality might be, but provide more limited guidance to orient current treatments.

Finally, a third approach would be exactly the opposite. Rather than targeting a hypothesized core abnormality, treatment strategies would target each symptom separately. This approach provides flexibility to adapt treatment to the patient's profile, and has met with moderate success in cognitive-behavioral treatments (Dennis et al., 2002, 2004).

#### 4.4. Limitations and conclusion

Our study has the limitations common to most large epidemiological surveys. First, although the AUDADIS has high reliability and validity, diagnoses of substance use disorders rely on self-report, and are subjected to social desirability biases. Second, we examined cross-sectional data. Lifetime, but not 12-month, diagnoses or individual criteria endorsement may be subject to recall bias and to cognitive impairment associated with cannabis use (Pope et al., 2001). The cross-sectional nature of the data and the lack of treatment data in the NESARC also preclude us from testing the utility of the clinical subtypes identified in this manuscript. Studies with a longitudinal design or with treatment outcome data could be used to examine the clinical utility of these subtypes. Finally, the study is limited to adults. It is possible that different results would have been obtained in adolescents given their different patterns of self-report dependence criteria (Chen and Anthony, 2003). Our study also has some important strengths. It is based on the largest epidemiological study of cannabis use disorders in the U.S. population. Its rate of response was 81%, allowing for a high degree of generalizability of the results. It used an instrument, the AUDADIS, with extensive documentation of reliability and validity, and interviewers underwent extensive training and

careful supervision. The results were robust to different operationalizations of the abuse and dependence constructs.

In conclusion, our study is the first empirical investigation of the heterogeneity in cannabis use disorders using DSM-IV criteria. Our study found that while cannabis abuse is a relatively homogeneous entity, cannabis dependence is very heterogeneous in its clinical presentations. The contrast between this heterogeneity and the unidimensional latent structure of cannabis dependence described in factor analytic studies suggest competing conceptualizations of the cannabis dependence category. Future research should compare the explanatory power of both conceptualizations, with particular focus on their treatment implications.

## Acknowledgments

The National Epidemiologic Survey on Alcohol and Related Conditions was sponsored and conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), with supplemental support from the National Institute on Drug Abuse. Dr. Grant, co-author and corresponding author on this manuscript, participated along with her co-authors in design, interpretation of the data, reviews of draft versions of the manuscript and decision to submit the manuscript for publication. This research was also supported, in part, by the Intramural Program of NIAAA (Grant) and by grants K23 DA00482, R01 DA019606 and R01 DA020783 (Blanco) and K05 AA 014223 (Hasin) and the New York State Psychiatric Institute (Blanco, Hasin and Nunes).

## References

- Agrawal A, Lynskey MT. Does gender contribute to heterogeneity in criteria for cannabis abuse and dependence? Results from the national epidemiological survey on alcohol and related conditions. *Drug Alcohol Depen.* 2007; 88:300–307.
- American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. 4th ed. American Psychiatric Press; Washington, DC: 1994.
- Blanco C, Harford TC, Nunes E, Grant BF, Hasin DS. The latent structure of marijuana and cocaine use disorders: results from the National Longitudinal Alcohol Epidemiologic Survey (NLAES). *Drug Alcohol Depen.* 2007; 91:91–96.
- Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. *Am. J. Psychiatry.* 2001; 158:2033–2037. [PubMed: 11729021]
- Budney AJ, Hughes JR, Moore BA, Novy PL. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Arch. Gen. Psychiatry.* 2001; 58:917–924. [PubMed: 11576029]
- Canino G, Bravo M, Ramirez R, Febo VE, Rubio-Stipec M, Fernandez RL, Hasin D. The spanish alcohol use disorder and associated disabilities interview schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. *J. Stud. Alcohol.* 1999; 60:790–799. [PubMed: 10606491]
- Chatterji S, Saunders JB, Vraști R, Grant BF, Hasin D, Mager D. Reliability of the alcohol and drug modules of the alcohol use disorder and associated disabilities interview schedule-alcohol/drug-revised (AUDADIS-ADR): an international comparison. *Drug Alcohol Depen.* 1997; 47:171–185.
- Chen CY, Anthony JC. Possible age-associated bias in reporting of clinical features of drug dependence: epidemiological evidence on adolescent-onset marijuana use. *Addiction.* 2003; 98:71–82. [PubMed: 12492757]
- Compton WM, Grant BF, Colliver JD, Glantz MD, Stinson FS. Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. *JAMA.* 2004; 291:2114–2121. [PubMed: 15126440]
- Cottler LB, Grant BF, Blaine J, Mavreas V, Pull C, Hasin D, Compton WM, Rubio-Stipec M, Mager D. Concordance of DSM-IV alcohol and drug use disorder criteria and diagnoses as measured by AUDADIS-ADR, CIDI and SCAN. *Drug Alcohol Depen.* 1997; 47:195–205.
- Dennis M, Titus JC, Diamond G, Donaldson J, Godley SH, Tims FM, Webb C, Kammer Y, Babor T, Roebuck MC, Godley MD, Hamilton N, Liddle H, Scott CK, Committee CYTS. The cannabis

- youth treatment (CYT) experiment: rationale, study design and analysis plans. *Addiction*. 2002; 97(Suppl. 1):16–34. [PubMed: 12460126]
- Dennis M, Godley SH, Diamond G, Tims FM, Babor T, Donaldson J, Liddle H, Titus JC, Kaminer Y, Webb C, Hamilton N, Funk R. The cannabis youth treatment (CYT) study: main findings from two randomized trials. *J. Subst. Abuse Treat.* 2004; 27:197–213. [PubMed: 15501373]
- Grant BF. Comorbidity between DSM-IV drug use disorders and major depression: results of a national survey of adults. *J. Subst. Abuse.* 1995; 7:481–497. [PubMed: 8838629]
- Grant BF. Theoretical and observed subtypes of DSM-IV alcohol abuse and dependence in a general population sample. *Drug Alcohol Depen.* 2000; 60:287–293.
- Grant, BF.; Hasin, DS. The Alcohol use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version. National Institute on Alcohol Abuse and Alcoholism; Bethesda, MD: 2001. Available at [www.niaaa.nih.gov](http://www.niaaa.nih.gov) [accessed November 18, 2007]
- Grant BF, Chou SP, Pickering RP, Hasin DS. Empirical subtypes of DSM-III-R alcohol dependence: United States, 1988. *Drug Alcohol Depen.* 1992; 30:75–84.
- Grant, B.; Moore, TC.; Shepard, J.; Kaplan, K. Source and Accuracy Statement: Wave 1 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). National Institute on Alcohol Abuse and Alcoholism; Bethesda, MD: 2003. Available at [www.niaaa.nih.gov](http://www.niaaa.nih.gov) [accessed November 18, 2007]
- Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The alcohol use disorder and associated disabilities interview schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depen.* 2003b; 71:7–16.
- Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, Pickering RP, Kaplan K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch. Gen. Psychiatry.* 2004a; 61:807–816. [PubMed: 15289279]
- Grant BF, Stinson FS, Dawson DA, Chou SP, Ruan WJ, Pickering RP. Co-occurrence of 12-month alcohol and drug use disorders and personality disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch. Gen. Psychiatry.* 2004b; 61:361–368. [PubMed: 15066894]
- Hall W, Solowij N. Adverse effects of cannabis. *Lancet.* 1998; 352:1611–1616. [PubMed: 9843121]
- Hasin DS, Grant BF. The co-occurrence of DSM-IV alcohol abuse in DSM-IV alcohol dependence: results of the National Epidemiologic Survey on Alcohol and Related Conditions on heterogeneity that differ by population subgroup. *Arch. Gen. Psychiatry.* 2004; 61:891–896. [PubMed: 15351767]
- Hasin D, Paykin A. DSM-IV alcohol abuse: investigation in a sample of at-risk drinkers in the community. *J. Stud. Alcohol.* 1999; 60:181–187. [PubMed: 10091956]
- Hasin D, Carpenter KM, McCloud S, Smith M, Grant BF. The alcohol use disorder and associated disabilities interview schedule (AUDADIS): reliability of alcohol and drug modules in a clinical sample. *Drug Alcohol Depen.* 1997; 44:133–141.
- Hasin DS, Hatzenbueler M, Smith S, Grant BF. Co-occurring DSM-IV drug abuse in DSM-IV drug dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend.* 2005; 80:117–123. [PubMed: 16157234]
- Hyman SE. Addiction: a disease of learning and memory. *Am. J. Psychiatry.* 2005; 162:1414–1422. [PubMed: 16055762]
- Johnson, RA.; Wichern, DW. Applied Multivariate Statistical Analysis. Pearson Education; New York, NY: 2001.
- Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am. J. Psychiatry.* 2005; 162:1403–1413. [PubMed: 16055761]
- Kline, RB. Principles and Practice of Structural Equation Modeling. Guilford Press; New York: 2004.
- Kouri EM, Pope HG Jr, Lukas SE. Changes in aggressive behavior during withdrawal from long-term marijuana use. *Psychopharmacology (Berlin).* 1999; 143:302–308. [PubMed: 10353434]

- Pérez de los Cobos J, Batlle F, Casas M. Proposal for improving the integration of drug dependencies in psychiatric nosology. *Actas Luso. Esp. Neurol. Psiquiatr. Cienc. Afines.* 1996; 24:63–65. [PubMed: 8686562]
- Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. *Arch. Gen. Psychiatry.* 2001; 58:909–915. [PubMed: 11576028]
- Saunders, JB.; Schuckit, MA.; Sirovatka, PJ.; Regier, DA. *Diagnostic Issues in Substance Use Disorders: Refining the Research Agenda for DSM-V.* American Psychiatric Association; Arlington, VA: 2007.
- Schuckit MA, Smith TL, Danko GP, Kramer J, Godinez J, Bucholz KK, Nurnberger JI Jr, Hesselbrock V. Prospective evaluation of the four DSM-IV criteria for alcohol abuse in a large population. *Am. J. Psychiatry.* 2005; 162:350–360. [PubMed: 15677601]
- Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. *Addiction.* 2002; 97:621–632. [PubMed: 12084124]
- Swift W, Hall W, Teesson M. Characteristics of DSM-IV and ICD-10 cannabis dependence among Australian adults: results from the National Survey of Mental Health and Wellbeing. *Drug Alcohol Depen.* 2001; 63:147–153.
- Taylor DR, Fergusson DM, Milne BJ, Horwood LJ, Moffitt TE, Sears MR, Poulton R. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction.* 2002; 97:1055–1061. [PubMed: 12144608]
- Teesson M, Lynskey M, Manor B, Baillie A. The structure of cannabis dependence in the community. *Drug Alcohol Depen.* 2002; 68:255–262.
- Ustun B, Compton W, Mager D, Babor T, Baiyewu O, Chatterji S, Cottler L, Gogus A, Mavreas V, Peters L, Pull C, Saunders J, Smeets R, Stipek MR, Vrsti R, Hasin D, Room R, Van den Brink W, Regier D, Blaine J, Grant BF, Sartorius N. WHO study on the reliability and validity of the alcohol and drug use disorder instruments: overview of methods and results. *Drug Alcohol Depen.* 1997; 47:161–169.
- Vrsti R, Grant BF, Chatterji S, Ustun BT, Mager D, Olteanu I, Badoi M. Reliability of the Romanian version of the alcohol module of the WHO alcohol use disorder and associated disabilities: interview schedule—alcohol/drug-revised. *Eur. Addict Res.* 1998; 4:144–149. [PubMed: 9852366]

**Table 1**

Demographic characteristics of individuals with DSM-IV current and lifetime cannabis abuse and dependence in the NES ARC

Characteristic	Abuse		Dependence	
	Current ( <i>n</i> = 427) % (S.E.)	Lifetime ( <i>n</i> = 2851) % (S.E.)	Current ( <i>n</i> = 133) % (S.E.)	Lifetime ( <i>n</i> = 530) % (S.E.)
Gender				
Male	72.5 (2.42)	66.3 (1.06)	72.0 (4.31)	64.6 (2.52)
Female	27.5 (2.42)	32.7 (1.06)	28.0 (4.31)	35.5 (2.52)
Race				
White	69.6 (2.88)	78.0 (1.21)	64.6 (4.80)	73.8 (2.12)
Black	12.0 (1.72)	9.1 (0.73)	14.3 (3.22)	9.7 (1.39)
Native American, Native Alaskan and Asian	3.8 (1.47)	2.4 (0.42)	3.4 (1.70)	2.9 (0.81)
Mixed race	4.7 (1.15)	43.4 (0.43)	8.3 (3.09)	4.8 (1.15)
Hispanic	10.0 (1.78)	7.2 (0.77)	9.4 (2.37)	8.8 (1.39)
Age (years)				
18–29	64.1 (3.10)	30.0 (1.13)	75.2 (4.46)	44.8 (2.69)
30–44	26.5 (2.65)	42.4 (1.20)	18.0 (4.28)	40.1 (2.78)
45–64	9.3 (1.99)	27.2 (1.07)	6.6 (2.60)	14.8 (1.99)
65+	0.1 (0.07)	0.4 (0.10)	0.3 (0.31)	0.3 (0.15)



**Table 2**

Theoretically possible and observed subtypes of DSM-IV cannabis dependence in the NESARC by number of criteria satisfied

Number of criteria satisfied	Number of theoretical (possible) subtypes	Number of observed subtypes	Percentages of theoretical subtypes observed	Percentages of all respondents with cannabis dependence
Current				
6	1	1	100.0	10.5
5	6	5	83.3	16.7
4	15	7	46.7	23.4
3	20	16	80.0	50.0
Total	42	29	69.1	100.0
Lifetime				
6	1	1	100.0	18.7
5	6	6	100.0	20.3
4	15	15	100.0	26.5
3	20	19	95.0	34.5
Total	42	41	97.6	100.0

**Table 3**

Empirical subtypes of DSM-IV current and lifetime cannabis dependence in the NESARC containing each diagnostic criterion

Number of criteria satisfied	Number of observed subtypes	Percentage of subtypes containing the criterion	Percentage of individuals fulfilling the criterion
<b>Current</b>			
Total	29	100.0	100.0
Tolerance	17	58.6	70.5
Larger amounts/longer period	17	58.6	59.3
Desire/attempts to stop or cut down	21	72.4	88.2
Time spent	19	65.5	70.1
Important activities given up	13	44.8	24.3
Using despite physical/psychological problem	20	69.0	65.8
<b>Lifetime</b>			
Total	41	100.0	100.0
Tolerance	25	61.0	70.9
Larger amounts/longer period	25	61.0	59.8
Desire/attempts to stop or cut down	26	63.4	86.7
Time spent	26	63.4	79.9
Important activities given up	25	61.0	52.0
Using despite physical/psychological problem	26	63.4	72.6

**Table 4**

Theoretically possible and observed subtypes of DSM-IV cannabis abuse in the NESARC by number of criteria satisfied

Number of criteria satisfied	Number of theoretical subtypes	Number of observed subtypes in the NESARC	Percentage of theoretical subtypes observed in the NESARC	Percentage of individuals by number of criteria satisfied
Current				
4	1	0	0.0	0.0
3	4	2	50.0	2.5
2	6	6	100.0	17.5
1	4	4	100.0	80.0
Total	15	12	75.0	100.0
Lifetime				
4	1	1	100.0	2.0
3	4	4	100.0	9.0
2	6	6	100.0	22.1
1	4	4	100.0	66.9
Total	15	15	100.0	100.0

**Table 5**

Empirical subtypes of DSM-IV current and lifetime cannabis abuse in the NESARC containing each diagnostic criterion

<b>Number of criteria satisfied</b>	<b>Number of observed subtypes</b>	<b>Percentage of subtypes containing the criterion</b>	<b>Percentage of individuals fulfilling the criterion</b>
Current			
Total	12	100.0	100.0
Hazardous use	6	50.0	81.9
Neglect of role	5	41.7	5.1
Using despite interpersonal problems	6	50.0	27.9
Legal problems	5	41.7	7.4
Lifetime			
Total	15	100.0	100.0
Hazardous use	8	53.3	82.1
Neglect of role	8	53.3	15.9
Using despite interpersonal problems	8	53.3	35.3
Legal problems	7	46.7	9.9

**Table 6**

Empirical subtypes of lifetime cannabis abuse in the NESARC by demographic and clinical characteristics

Characteristic	Hazardous use only	Social problems only	Hazardous use and social problems	Other	$\chi^2$	P-value
Race						
White	53.1	8.6	13.0	25.2		
Black	49.6	11.1	13.9	25.4	11.5	0.0935
Hispanic	42.8	15.9	8.7	32.5		
Sex						
Male	50.7	7.3	13.5	28.5	28.0	<0.0001
Female	52.7	13.4	13.8	20.1		
Age (years)						
18–29	39.4	13.1	15.4	32.1		
30–44	54.2	7.8	12.2	25.7	38.8	<0.0001
45+	59.9	7.5	13.7	18.9		
Lifetime alcohol use disorder						
Yes	54.3	7.1	13.7	24.9	30.1	<0.0001
No	39.0	18.6	13.3	29.2		
Lifetime drug use disorder						
Yes	42.5	8.0	16.7	32.8	48.7	<0.0001
No	56.7	10.1	11.7	21.5		
Lifetime drug treatment						
Yes	18.1	7.4	12.1	62.4	78.6	<0.0001
No	55.2	9.5	13.8	21.6		