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Heterogeneity of Stimulant Dependence: A National Drug Abuse Treatment Clinical Trials Network Study

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We investigated the presence of DSM-IV subtyping for dependence on cocaine and amphetamines (with versus without physical dependence) among outpatient stimulant users enrolled in a multisite study of the Clinical Trials Network (CTN). Three mutually exclusive groups were identified: primary cocaine users (n = 287), primary amphetamine users (n = 99), and dual users (cocaine and amphetamines; n = 29). Distinct subtypes were examined with latent class and logistic regression procedures. Cocaine users were distinct from amphetamine users in age and race/ethnicity. There were four distinct classes of primary cocaine users: non-dependence (15%), compulsive use (14%), tolerance and compulsive use (15%), and physiological dependence (tolerance, withdrawal, and compulsive use; 56%). Three distinct classes of primary amphetamine users were identified: non-dependence (11%), intermediate physiological dependence (31%), and physiological dependence (58%). Regardless of stimulants used, most female users were in the most severe or the physiological dependence group. These results lend support for subtyping dependence in the emerging DSM-V. (Am J Addict 2009;18:206–218)

INTRODUCTION

In the United States, the Diagnostic and Statistical Manual of Mental Disorders—IV (DSM-IV)—Text Revision provides the official classification of mental and substance use disorders widely employed in clinical, research, educational, and statistical settings.[1] DSM-IV's categorical approach to classification of disorders has noteworthy advantages because it facilitates research, improves communications among clinicians and researchers, and serves as a necessary tool for collecting and communicating public health statistics.[1] The categorical classification, however, also constitutes a primary limitation because it works best when all members of a given diagnosis are homogeneous and when there are clear boundaries between distinct diagnoses.[1]

DSM-IV acknowledges this limitation and further suggests the presence of heterogeneity among individuals who share a diagnosis. DSM-IV subtypes substance users who meet criteria for Dependence into those with versus without a physiological component using the presence of either tolerance or withdrawal as a specifier.[1] The *physiological dependence (PD)* subtype is generally considered to be at a higher risk for immediate medical problems and an indicator of substance use severity relative to the other criteria.[1] The *non-physiological dependence (NPD)* subtype is characterized exclusively by a pattern of compulsive use.

This subtyping for Dependence is applied to all drugs. To date, only a few studies have examined directly the presence of subtypes of PD vs. NPD for stimulant users. Schuckit and colleagues[2] analyzed the data collected from a six-center collaborative study on the genetics of alcoholism. They found that users of cocaine or amphetamines who reported a lifetime history of withdrawal from their stimulant use had more stimulant use-related problems and symptoms compared with those without the history. Disney and colleagues[3] examined subtypes of DSM-IV Cocaine Dependence among opioid-dependent patients. The investigators found that patients who reported cocaine withdrawal with or without tolerence had a higher prevalence of lifetime psychiatric disorders and a more severe pattern of substance use than did patients without symptoms of cocaine withdrawal. The studies tend to favor the value of withdrawal in determining PD on stimulants as well as the importance of designating a physiological component because they concur with DSM-IV in showing that withdrawal

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serves a unique indicator of a severe pattern of substance use.[2,3] In contrast, the importance of tolerance alone in determining PD on stimulants is not clearly supported.[2,3]

The findings of previous studies also are limited in some ways. Schuckit et al. (1999) examined stimulant dependence symptoms as defined in DSM-III-R that occurred *sporadically* over the course of participants' lives. Because lifetime diagnoses are not specifically defined in DSM-IV,[1] it is unclear whether and to what extent results from lifetime symptoms apply to a current (past year) DSM-IV Drug Dependence that requires the occurrence of at least three criteria within a continuous 12-month period.[1] In addition, there are presently no known studies of subtypes of Amphetamine Dependence using DSM-IV criteria of current Dependence. Further, stimulant users in the prior studies were categorized into subgroups based primarily on presence or absence of symptoms of withdrawal or tolerance[2,3] a simple grouping method that does not use full information from all possible response patterns of all dependence criteria.

Previous studies have also not addressed the similarities and differences in dependence profiles between cocaine users and amphetamine users. DSM-IV reports that cocaine and amphetamines have a similar course of dependence because both are potent central nervous system stimulants with similar psychoactive and sympathomimetic effects.[1] However, cocaine differs from amphetamines in the molecular mechanisms by which the drugs interact with dopamine transporters[4] and in their duration of effects and pattern of use.[5,6] It is thus possible that their dependence profiles may differ. Cocaine has a short duration of action due to its short half-life of about 30–50 minutes, and cocaine users are likely to report binge patterns of use.[1,6] In contrast, both amphetamines and methamphetamine (7−31 hours and 4−5 hours, respectively) have much longer half-lives than cocaine.[5] Methamphetamine users typically use it fewer times per day compared with cocaine use.[1,6] These differences result in methamphetamine being present in the brain longer, as well as higher concentrations of dopamine in the synapse that can be toxic to human brains.[4]

At present, unobserved heterogeneity among stimulant users has not been empirically determined using latent class analysis (LCA).[7] LCA is developed specifically for identifying "unobserved" or "latent" heterogeneous classes or subgroups of individuals within a diverse sample of study participants.[7,8] In LCA, observed variables are imperfect indicators of an underlying latent variable with a finite number of mutually exclusive classes. It is particularly suitable when patterns of co-occurrence among dichotomous diagnostic symptoms are analyzed, and the choice of making an arbitrary decision on the cutpoint for diagnostic categories is avoided because diagnostic classification is provided directly by the model.[8] LCA helps elucidate appropriate symptom clusters by classifying drug users with diverse substance use characeristics into a few discrete homogeneous subgroups according to their distinct symptom endorsement profiles. The value of LCA in identifying empirically supported subtypes of psychiatric diagnoses and their latent structures have been demonstrated in a variety of disorders, such as Attention Deficit Hyperactivity Disorder,[9] Eating Disorder,[10] Post Traumatic Stress Disorder,[11] and Alcohol Dependence.[12]

In light of the lack of evidence for empirically defined subtypes of stimulant users and their relevance for the emerging DSM-V,[13] the present study uses LCA to investigate whether heterogeneous subtypes of Stimulant Dependence exist as suggested by DSM-IV and whether dependence subtypes apply equally to cocaine users and amphetamine users.[1] The data source for this evaluation is drawn from a multisite study of the National Drug Abuse Treatment Clinical Trials Network (CTN).[14] This multisite CTN study provides us with an excellent and unusual opportunity to examine and compare the heterogeneity of Stimulant Dependence in a large and geographically diverse sample of stimulant users recruited from eight major treatment programs across the United States, and to meaningfully extend this line of research by using LCA to elucidate the underlying latent constructs not considered in earlier studies.[2,3] Within this large, geographically diverse sample of stimulant users, we investigate the similarities and differences in latent structures of DSM-IV dependence criteria for cocaine and amphetamines. The following questions are addressed in this report: 1) Are there distinct homogenous classes of stimulant users distinguished by their symptoms of dependence, namely PD, NPD, and non-dependence (ND)?; 2) Are different classes of stimulant users associated with distinct demographic and substance use-related characteristics (ie, years of stimulant use, current Substance Dependence, HIV risk, involvement with the criminal justice system, and history of psychiatric treatment); 3) Is the PD class associated with a more severe pattern of substance use than the others?; and 4) Are the dependence profiles of cocaine users similar to the profiles of amphetamine users?

METHODS

Data Source

Statistical analyses were performed on data from the public use files of a multisite study of the CTN, which evaluated stimulant use outcomes of an abstinence-based contingency management intervention in addition to usual care.[14] Participants were recruited from eight community-based treatment programs. All programs provide psychosocial counseling without administering methadone or other opioid agonists. Six programs were located in eastern, southeastern, or southwestern urban settings in the United States; one was located in the suburban Southeast, and one in the rural Southwest.

Patients with indications of stimulant use (cocaine, methamphetamine, or amphetamines) during their initial evaluation for treatment were invited to participate in the study. Eligible participants included patients who**:** (1) reported stimulant use within two weeks of study entry, (2) submitted a stimulant-positive urine sample at treatment entry, or (3) used stimulants within two weeks of entering a controlled environment (a detoxification unit, hospital, or correctional

facility) and exited the controlled environment within two weeks of study entry.[14] Before randomization, participants completed the intake assessment (demographics, psychosocial problems, and drug use and diagnoses).

Study Variables

Our primary outcome variables were subtypes of dependence symptom profiles derived from LCA of the seven criteria of Cocaine Dependence and of Amphetamine Dependence, separately. Guided by prior research,[2,3,15–17] we determined whether LCA-defined dependence subtypes differed by demographic characteristics (eg, sex and race/ethnicity), years of stimulant use and current Substance Dependence (severity of substance use), and other substance use-related problems, including HIV risk/injection drug use, involvement with the criminal justice system, and history of psychiatric treatment (comorbid psychiatric problems).

Demographic variables examined in this study included age at interview, sex, race/ethnicity (white, African American, Hispanic, other), years of education completed, and current marital status.

Current (past year) DSM-IV Substance Use Disorders were assessed by the DSM-IV Checklist.[18,19] Participants were asked about past year use of five classes of substances: amphetamines/methamphetamine, cocaine, opioids, alcohol, and marijuana. If participants reported use of a substance in the past year, they were asked about all seven DSM-IV dependence criteria associated with that substance. Participants who met criteria for Dependence on a given substance were not asked the Abuse questions of that substance; participants who reported using that substance but did not meet criteria for Dependence were asked the Abuse questions. This decision was based on resource consideration and on the fact that a diagnosis of DSM-IV Dependence excludes a diagnosis of Abuse.[1]

The following seven DSM-IV *dependence* criteria were assessed by the DSM-IV Checklist: (1) tolerance; (2) withdrawal; (3) substance often taken in large amounts or for longer periods of time; (4) persistent desire or unsuccessful attempt to cut down or control use; (5) a great deal of time spent in activities necessary to get the substance; (6) important activities given up; and (7) continued substance use despite knowledge of having persistent or recurrent physical or psychological problems. The following four *abuse* criteria were assessed: (1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home; (2) recurrent substance use in situations in which it is physically hazardous; (3) recurrent substance-related legal problems; and (4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

Consistent with DSM-IV,[1] participants who reported three or more symptoms of dependence from cocaine use were classified as having Dependence. Participants who did not meet criteria for Dependence but reported one or more criterion of Abuse from cocaine use were classified as having Cocaine Abuse.[1] The same logic was applied to each of the other substances. The proportion of past-year amphetamine users who used an amphetamine other than methamphetamine cannot be determined from the data; however, more than 90% of amphetamine users in the United States use methamphetamine.[20]

Years of cocaine or amphetamine use were characterized as years of use in participants' lifetimes. *Other substance use-related variables* included HIV risk (HIV status and injection drug use), involvement with the criminal justice system (on parole or probation and legal referral for treatment), and history of addiction and psychiatric treatment. HIV status was assessed by participants' self-report; participants also were queried regarding whether they had ever been tested for HIV. Injection drug use was assessed by querying participants regarding the most recent route of any drug use. Participants' reports of current status of being on parole or probation and legal referral for substance abuse treatment were dichotomized.

Histories of alcohol abuse treatment and of drug abuse treatment were defined as participants' self-report of having ever been treated for alcohol abuse or drug abuse, respectively. History of outpatient or inpatient mental health treatment was assessed by participants' self-report of treatment for psychological or emotional problems (not including treatment for substance abuse), as an outpatient, or in a hospital or inpatient setting, respectively. For each treatment, continuous variables (number of times treatment was received) were examined to determine its association with subtype of dependence profiles.

Study Sample

Analyses were performed on data from a total of 415 participants aged 18 years or older who were recruited from eight major community-based treatment programs associated with the CTN. All participants reported past year use of either cocaine or amphetamines from the DSM-IV Checklist. Findings from the original trial that report response to the treatment intervention are presented in detail elsewhere.[14]

This study was declared exempt from review by the Duke University Institutional Review Board because it used existing, de-identified, public use data files. The study from which the de-identified data files were derived[14] was conducted under institutional review board approval at the relevant institutions, and all participants provided written informed consent prior to study enrollment.

Data Analysis

We first examined the frequency of stimulant use and categorized stimulant users into users of cocaine, amphetamines, or both. We then compared demographics, stimulant use, DSM-IV Substance Dependence, and other substance use-related characteristics among the three groups. Next, we determined profiles of dependence symptoms by LCA using Latent Gold.[21] We applied LCA to the seven DSM-IV criteria for Dependence on cocaine and amphetamines, respectively, to empirically determine homogeneous subtypes of users.

We used the information from the bootstrap p-values and Bayesian Information Criterion (BIC) statistic to assess model fit.[21] In the case of sparse data, the bootstrap of likelihood ratio statistic is recommended for assessing model fit.[21] The BIC takes into account parsimony of the model, and a lower BIC indicates a better model. We also considered the information from average weight of evidence, classification error, and bivariate residuals. Average weight of evidence is similar to BIC and takes classification performance into account; a low classification error (close to 0) is preferred. In general, bivariate residuals larger than 3.84 identify correlations between associated variable pairs that are not adequately explained by the model at the 0.05 level.[21]

We then examined the relation of LCA-defined dependence subtypes with prevalence of DSM-IV Dependence and mean number of dependence criteria endorsed by sex and by race/ethnicity due to their previously reported associations with stimulant use.[16,22] Finally, we conducted multinomial logistic regression procedures to determine whether LCA-defined dependence subtypes differed in demographics, stimulant use, and other substance use-related characteristics.

RESULTS

Demographic and Substance Use Characteristics

Of all stimulant users, 69% (n = 287) used cocaine but did not use amphetamines in the past 12 months (primary cocaine users); 24% (n = 99) used amphetamines but did not use cocaine in the past 12 months (primary amphetamine users); and 7% (n = 29) reported using both drugs (dual stimulant users).

Demographics

Compared with primary cocaine users (Table 1), primary amphetamine users were younger (31 vs. 38 years) and more likely to be White (67% vs. 24%) or Hispanic (29% vs. 11%). There were no African Americans among primary amphetamine users. Dual stimulant users resembled primary amphetamine users in age and race/ethnicity: they were younger than primary cocaine users (29 vs. 38 years) and likely to be White (69%) or Hispanic (24%).

Stimulant Use and Current DSM-IV Dependence

Dual stimulant users had fewer years of cocaine use (4.7 vs. 9.7 years) and amphetamine use (3.5 vs. 8.6 years) than primary users of each. Dependence diagnoses are consistent with participants' classifications: ≥80% of participants met criteria for DSM-IV Dependence for the drug designated as primary, while 69% of dual users met criteria for Dependence on cocaine and amphetamines, respectively. Primary cocaine users had a higher prevalence of Dependence on alcohol (43% vs. 11%) and opioids (12% vs. 3%) than did primary amphetamine users. Dual stimulant users also reported a comparatively high prevalence of Dependence on alcohol (38%), opioids (14%), and marijuana (45%).

Other Substance Use-Related Problems

Primary amphetamine users were more likely than primary cocaine users to be on parole or probation (47% vs. 29%) and to receive legal referral for treatment (41% vs. 27%), but they did not differ in injection drug use. Dual stimulant users were more likely than primary cocaine users to report injection drug use (24% vs. 11%). Primary cocaine users were more likely than primary amphetamine users to report a positive HIV status (8% vs. 0%), have been tested for HIV (87% vs. 71%), and have a history of treatment for alcohol (34% vs. 13%) and drug (81% vs. 53%) abuse as well as mental health problems at outpatient (38% vs. 26%) and inpatient (32% vs. 15%) settings. Dual stimulant users also were more likely than primary amphetamine users to report a higher rate of alcohol abuse treatment (48% vs. 13%) and history of outpatient (48% vs. 26%) and inpatient (41% vs. 15%) mental health treatment. Dual stimulant users had a lower rate of drug abuse treatment than primary cocaine users (66% vs. 81%).

Prevalence of Symptoms of DSM-IV Stimulant Dependence

Figure 1 displays the distribution of each dependence symptom. In general, primary amphetamine users were more likely to endorse "withdrawal" than other groups, and less likely than primary cocaine users to endorse "continued use despite having problems." Dual stimulant users endorsed most symptoms with a lower prevalence than primary users of cocaine or amphetamines.

LCA of Dependence Criteria

Cocaine

LCA of primary cocaine users suggested a four-class model as the best fit. Both the four- and five-class models fitted the data. We chose the four-class model due to its lower values of BIC, average weight of evidence, and classification error (0.08) than the five-class model.

As shown in Figure 2, the four classes differed in severity (an increase in endorsement probabilities from class to class) and PD components (tolerance and withdrawal). Class 1 *(ND: non-dependence)* identified 15% of primary cocaine users who reported minimal or no symptoms of cocaine dependence. Class 2 *(CU: compulsive use, 14%)* exhibited a high probability of endorsing symptoms of exclusively compulsive cocaine use (eg, being unable to cut down on cocaine use and giving up important activities for cocaine use). Class 3 *(TCU: tolerance-compulsive use, 15%)* was characterized by having a high probability of endorsing tolerance and being unable to cut down on cocaine use but a low probability of endorsing withdrawal. Class 4 *(PD: physiological dependence, 56%)* uniformly endorsed almost all seven criteria.

Amphetamines

Among primary amphetamine users, a three-class model (classification error = 0.08) was found to fit the data better than

TABLE 1. Sociodemographic and substance use-related characteristics (%) of non-methadone outpatient stimulant users by type of stimulants used

Characteristics	C: Cocaine only	A: Amphetamines only	C + A: Cocaine and amphetamines
Sample size, N	287	99	29
Age, mean (SE)	38.1 (0.47)	31.2 (0.81)*	29.2 (1.46)†
Years of education, mean (SE)	11.8 (0.12)	11.9 (0.17)	12.7 (0.37)†‡
Sex			
Male	41.5	50.5	44.8
Female	58.5	49.5	55.2
Race/ethnicity			
African American	59.2	0*	3.4†
White, non-Hispanic	24.0	66.7	69.0
Hispanic	10.8	29.3	24.1
Other	5.9	4.0	3.4
Marital status			
Married/co-habitating	23.3	26.3*	24.1
Married previously	38.0	24.2	20.7
Never married	38.7	49.5	55.2
Years of cocaine use, mean (SE)	9.7 (0.42)	. . . ..	4.7 (0.82)†
Years of amphetamine use, mean (SE)	. . . ..	8.6 (0.60)	3.5 (0.65)‡
DSM-IV Stimulant Use Disorders			
Cocaine Abuse	4.9	. . . ..	3.4
Cocaine Dependence	80.8	. . . ..	69.0
Amphetamine Abuse	. . . ..	7.1	3.4
Amphetamine Dependence	. . . ..	87.9	69.0‡
Other DSM-IV Substance Dependence			
Alcohol Dependence	42.5	11.1*	37.9‡
Marijuana Dependence	17.1	16.2	44.8†‡
Opioid Dependence	12.2	3.0*	13.8‡
On parole or probation	28.9	46.5*	20.7‡
Legal referral for treatment	27.2	41.4*	24.1
Injection drug use	11.1	16.2	24.1‡
HIV positive status	8.4	0	0
Ever been tested for HIV	86.8	70.7*	79.3
History of psychiatric treatment			
Alcohol abuse treatment	34.2	13.1*	48.3‡
Drug abuse treatment	81.2	52.5*	65.5†
Outpatient mental health treatment	38.1	26.3*	48.3‡
Inpatient mental health treatment	31.8	15.2*	41.4‡

HIV = human immunodeficiency virus; SE = standard error.
χ^2 test for categorical variables and t tests for continuous variables with a p-value < 0.05.
*C vs. A; †C vs. C + A; ‡A vs. C + A.

a four-class model. The three classes differed mainly on the severity dimension (Figure 3). Class 1 *(ND: non-dependence, 11%)* reported minimal or no symptoms of Amphetamine Dependence. Class 2 *(IPD: intermediate physiological dependence, 31%)* exhibited a moderate to high probability of endorsing six criteria. Class 3 *(PD: physiological dependence, 58%)* endorsed almost all seven criteria.

Dual Stimulant Users

The small sample size of dual stimulant users precluded us from conducting LCA. We explored whether including dual users in the group of primary users would influence the dependence profile. The dependence profile of all cocaine users was found to be similar to the profiles of primary cocaine users, and the dependence profile of all amphetamine users was similar to that of primary amphetamine users (data not shown).

LCA-Defined Dependence Subtypes by Sex and DSM-IV Dependence

We report in Table 2 LCA-defined dependence subtypes by sex and their relation with DSM-IV Dependence and mean

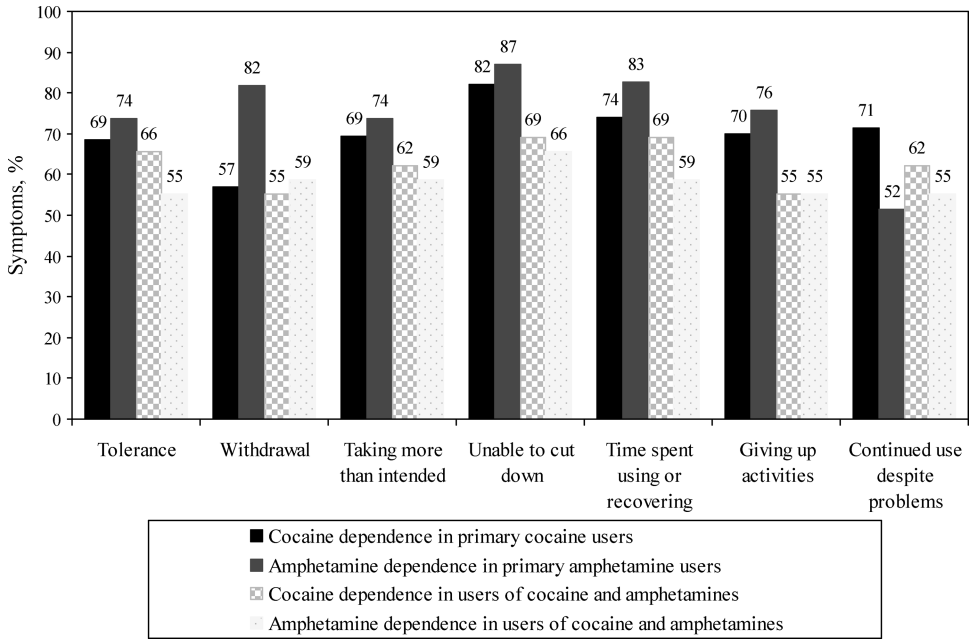

FIGURE 1. Prevalence of DSM-IV stimulant dependence symptoms by type of stimulants used (N = 415).

number of dependence criteria endorsed. LCA-defined dependence subtypes by race/ethnicity are not reported because they were not significantly associated with race/ethnicity. Due to the small sample size of dual stimulant users, this section focuses on primary users only.

Cocaine

Compared with male primary cocaine users, there was a higher proportion of female primary cocaine users in the PD class (67% vs. 41%) (χ^2 df = 3, p < 0.001). All users in the PD class met DSM-IV criteria for Cocaine Dependence, and they also reported a highest mean number of dependence symptoms (6.8) than the CU (3.9) and TCU (3.8) classes. The vast majority of users in the CU (88%) and TCU (86%) classes also met criteria for Cocaine Dependence.

Amphetamines

Female primary amphetamine users also were more likely than male primary amphetamine users to be in the PD class (71% of females vs. 44% of males), but they were less likely

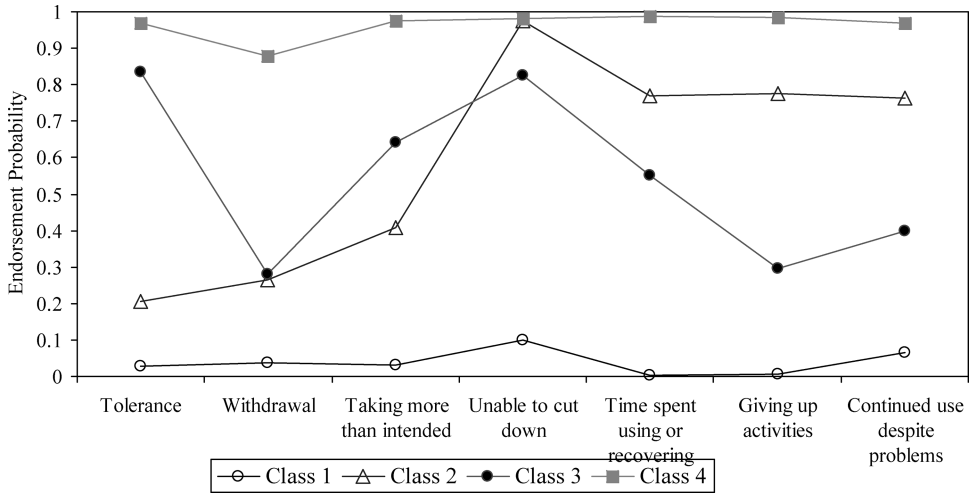

FIGURE 2. Latent class analysis of cocaine dependence symptoms among primary cocaine users (n = 287).

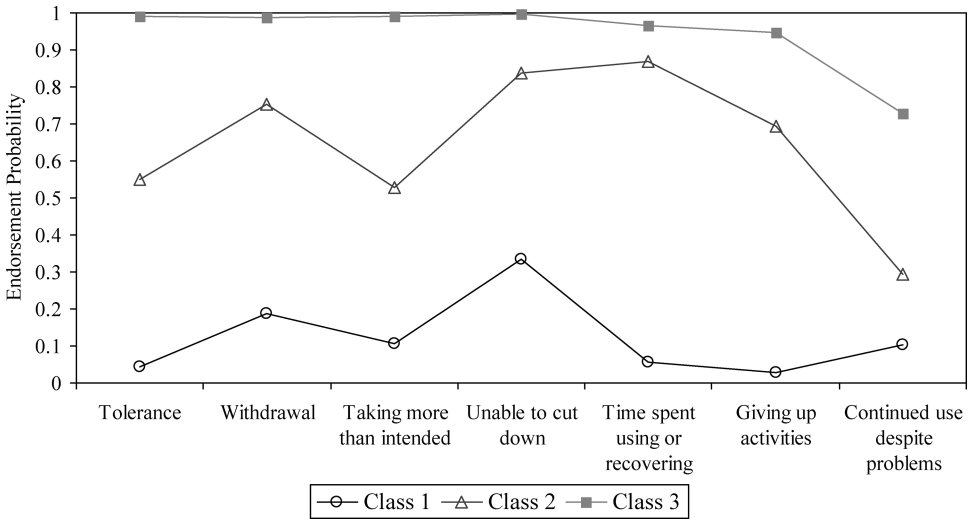

FIGURE 3. Latent class analysis of amphetamine dependence symptoms among primary amphetamine users (n = 99).

to be in the IPD class (20% vs. 42%) (χ^2 df = 2, p = 0.022). All amphetamine users in the PD class and 97% of users in the IPD class met DSM-IV criteria for Amphetamine Dependence, whereas none in the ND class did. The PD class had a higher mean number of amphetamine dependence symptoms (6.7) than the IPD (4.3) and the ND (0.6) classes.

Logistic Regression of LCA-Defined Dependence Subtypes

Cocaine

We conducted multinomial logistic regression analysis of LCA-defined cocaine dependence subtypes (class membership) among primary cocaine users (N = 287). We first examined bivariate association between dependence subtypes and each of the study covariates reported in Table 1. Given the sample size of primary cocaine users, we included only variables that were significant from bivariate analyses in the adjusted model (Table 3).

Compared with the ND class, young age, years of cocaine use, current Alcohol Dependence, and history of drug abuse treatment were associated with increased odds of being in the PD class. In addition, history of drug abuse treatment was associated with increased odds of being in the CU and TCU classes relative to the ND class.

Compared with the CU class, young age, female sex, Alcohol Dependence, and history of outpatient mental health treatment were associated with greater odds of being in the PD class. Compared with the TCU class, young age, years of cocaine use, Alcohol Dependence, and history of outpatient mental health treatment were associated with increased odds of being in the PD class. The CU class differed from the TCU class in years of cocaine use.

Amphetamines

As shown in Table 4, primary amphetamine users who were never married had increased odds of being in the IPD class (relative to the ND), and female primary amphetamine users were more likely than their male counterparts to be in the PD class (relative to the IPD).

DISCUSSION

Abuse of powerful stimulants like cocaine or amphetamines constitutes an important public health concern because of their risk for addiction, close link with HIV transmission, and other serious health consequences.[23,24] The present study contributes new and important information on heterogeneity of DSM-IV Dependence on cocaine and amphetamines in a large and geographically diverse sample of stimulant users recruited from eight major community-based treatment programs. The results from this study support the existence of different subtypes of stimulant users distinguished by their distinct symptom endorsement, and the PD subtype exhibits a more severe pattern of stimulant use than the others. Findings from this study also lend additional support for DSM-IV's subtyping for physiological versus non-physiological dependence, and indicate some differences in LCA-defined dependence profiles between cocaine users and amphetamine users.

Subtypes of Cocaine Users

DSM-IV specifies that drug-dependent users consist of PD (presence of either tolerance or withdrawal) and NPD (compulsive use without tolerance and withdrawal) subtypes and that the former is a severe indicator of drug use.[1] In line with this specification, we found four distinct classes of primary cocaine users distinguished by PD symptoms and severity of cocaine use (ie, total number of criteria endorsed). The LCA-defined PD class was characterized by exhibiting withdrawal and tolerance as well as compulsive use (ie, impaired control in use and cognition). This large group (56%) of primary cocaine users can be considered the most severe subtype because they uniformly endorsed

TABLE 2. Prevalence (%) of DSM-IV stimulant dependence by latent class membership among outpatient stimulant users

Primary cocaine users, n = 287	Class 1: ND Non-Dependence	Class 2: CU Compulsive use	Class 3: TCU Tolerance-compulsive use	Class 4: PD Physiological dependence	χ^2 or F test*
Prevalence of latent class, %					
Overall	15.3	13.9	14.6	56.1	
Male	21.8	19.3	17.6	41.2	19.2 (3)
Female	10.7	10.1	12.5	66.7	$p < 0.001$
Prevalence of DSM-IV Cocaine Dependence, %					
Overall	0	87.5	85.7	100	
Male	0	87.0	85.7	100	
Female	0	88.2	85.7	100	
Mean # of cocaine dependence symptoms (SE)					
Overall	0.2 (0.07)	3.9 (0.16)	3.8 (0.16)	6.8 (0.03)	$p < 0.001$
Male	0.3 (0.07)	3.9 (0.21)	3.7 (0.20)	6.7 (0.06)	$p < 0.001$
Female	0.2 (0.14)	3.9 (0.25)	4.0 (0.24)	6.8 (0.04)	$p < 0.001$
Primary amphetamine users, n = 99	Class 1: ND Non-Dependence	Class 2: IPD Intermediate physiological dependence	Class 3: PD Physiological dependence		χ^2 or F test*
Prevalence of latent class, %					
Overall	11.1	31.3	57.6		
Male	14.0	42.0	44.0		7.7 (2)
Female	8.2	20.4	71.4		$p = 0.022$
Prevalence of DSM-IV Amphetamine Dependence, %					
Overall	0	96.8	100		
Male	0	95.2	100		
Female	0	100	100		
Mean # of amphetamine dependence symptoms (SE)					
Overall	0.6 (0.20)	4.3 (0.18)	6.7 (0.06)		$p < 0.001$
Male	0.7 (0.29)	4.2 (0.21)	6.6 (0.10)		$p < 0.001$
Female	0.5 (0.29)	4.6 (0.31)	6.7 (0.08)		$p < 0.001$

SE = standard error.
*: χ^2 test for categorical variables and F test for continuous variables.

almost all seven dependence criteria. Their higher level of severity also is supported by results from the logistic regression analysis, which showed more years of cocaine use in the PD than the TCU class and a higher risk for having comorbid Alcohol Dependence and more prior episodes of mental health treatment than the TCU and CU classes.

The other less severe subtypes of primary cocaine users included the TCU (tolerance plus compulsive use, 15%), CU (exclusively compulsive use, 14%), and ND (non-dependence, 15%) classes. The TCU and CU classes clearly were more severe than the ND class in cocaine use in that they reported a significantly greater number of cocaine dependence symptoms and had greater odds of history of drug abuse treatment. The TCU class resembled the CU class in total number of dependence symptoms endorsed, but the CU class was slightly more likely than the TCU class to report more years of cocaine use. Together, these findings provide support for the existence of distinct subgroups of cocaine users.

These distinct patterns of LCA-defined dependence subtypes among primary cocaine users are consistent with previous findings suggesting that "dependence with withdrawal" constitutes a clinically important subgroup of dependence, with a severe pattern of drug use that will often require greater clinical attention.[2,3,25] The observed strong association between Alcohol Dependence and the PD class among primary cocaine users is also supported by other studies, which have shown that alcohol is frequently used by cocaine users to moderate the discomfort associated with discontinuing an episode of cocaine use and the transition from its desirable to less desirable effects as blood levels decline.[26] and that Cocaine Dependence is frequently comorbid with Alcohol Dependence.[27,28] Comorbid Cocaine and Alcohol

TABLE 3. Adjusted odds ratios and 95% confidence intervals from multinomial logistic regression analysis of cocaine dependence classes among outpatient cocaine users (n = 287)

LCA-defined cocaine dependence classes	Compulsive use vs. non-dependence CU vs. ND	Tolerance–compulsive use vs. non-dependence TCU vs. ND	Physiological dependence vs. non-dependence PD vs. ND	Physiological dependence vs. compulsive use PD vs. CU	Physiological dependence vs. tolerance-compulsive use PD vs. TCU	Compulsive use vs. tolerance-compulsive use CU vs. TCU
Age (continuous variable)	0.97 (0.91–1.03)	0.97 (0.92–1.03)	0.91 (0.86–0.96)*	0.94 (0.89–0.99)*	0.93 (0.88–0.98)*	0.99 (0.93–1.06)
Sex (vs. male) Female	0.56 (0.22–1.47)	0.85 (0.33–2.16)	1.52 (0.69–3.37)	2.71 (1.25–5.86)*	1.79 (0.82–3.90)	0.66 (0.26–1.70)
Years of cocaine use (continuous variable)	0.97 (0.90–1.04)	0.97 (0.90–1.04)	1.07 (1.01–1.14)*	1.01 (0.96–1.07)	1.11 (1.04–1.19)*	1.09 (1.02–1.18)*
DSM-IV Alcohol Dependence (vs. no)	1.53 (0.56–4.20)	1.22 (0.45–3.33)	3.48 (1.52–8.00)*	2.28 (1.04–4.98)*	2.85 (1.29–6.31)*	1.25 (0.47–3.36)
Number of prior drug abuse treatments (continuous variable)	1.96 (1.37–2.80)*	1.91 (1.33–2.73)*	1.95 (1.37–2.76)*	0.99 (0.89–1.11)	1.02 (0.90–1.16)	1.03 (0.88–1.20)
Number of prior outpatient mental health treatments (continuous variable)	1.06 (0.99–1.14)	0.72 (0.43–1.19)	1.12 (0.81–1.54)	1.57 (1.01–2.45)*	1.56 (1.01–2.42)*	0.99 (0.55–1.79)

LCA = latent class analysis.
The adjusted multinomial logistic regression model includes all variables listed in the first column.
*: p-value < 0.05.

TABLE 4. Adjusted odds ratios and 95% confidence intervals from multinomial logistic regression analysis of amphetamine dependence classes among outpatient amphetamine users (n = 99)

LCA-defined amphetamine dependence classes	Intermediate physiological dependence vs. non-dependence IPD vs. ND	Physiological dependence vs. non-dependence PD vs. ND	Physiological dependence vs. intermediate physiological dependence PD vs. IPD
Sex (vs. male)			
Female	0.47 (0.10–2.27)	1.96 (0.47–8.28)	4.18 (1.56–11.21)*
Marital status (vs. married/cohabitating)			
Separated, divorced, or widowed	4.05 (0.56–29.20)	2.72 (0.45–16.40)	0.40 (0.12–1.35)
Never married	7.76 (1.31–45.77)*	3.08 (0.61–15.59)	0.67 (0.17–2.22)

LCA = latent class analysis.
The adjusted multinomial logistic regression model includes all variables listed in the first column.
*: p-value < 0.05.

Dependences also reflect a robust indicator of a severe pattern of substance abuse,[27,28] a finding that is in line with this investigation.

Subtypes of Amphetamine Users

Similar to the results from primary cocaine users, we found a large severe group (58%) of the PD class among primary amphetamine users who endorsed almost all seven criteria of Amphetamine Dependence. This class also concurs with DSM-IV,[1] showing an association of withdrawal and tolerance with a large number of symptoms endorsed. However, differing from primary cocaine users, the LCA also identified an intermediate group of primary amphetamine users. This IPD group (31% of users) resembled the PD group in its symptom profile and prevalence of Amphetamine Dependence, but had a moderate probability of endorsing symptoms. Hence, these results do not find the presence of DSM-IV's NPD group—the compulsive use subtype—among primary amphetamine users.

We explored whether this difference in LCA-defined profiles is due in part to the difference between a four-class model of primary cocaine users versus a three-class model of primary amphetamine users. However, when the three-class model of primary cocaine users was examined in which the TCU and CU classes were combined into one class (data not shown), the combined TCU and CU classes formed a profile characterized by tolerance and compulsive cocaine use. Instead, the high rate of amphetamine withdrawal and its close association with a Dependence diagnosis as shown from LCA appeared, at least partly, to explain this discrepancy. We observed that there was a higher prevalence of amphetamine withdrawal (82% among primary amphetamine users) than cocaine withdrawal (57% among primary cocaine users), and that this high rating was consistent with the prevalence of Amphetamine Dependence (88%) noted in the sample. Thus, the high rate of amphetamine withdrawal precluded LCA to generate an additional NPD class (ie, compulsive use only) because withdrawal clustered with the other symptoms.

Infrequent Co-Use of Cocaine and Amphetamines

Another new and intriguing finding from this investigation concerns the very low rate of co-use of cocaine and amphetamines. Only 7% of all stimulant users recruited from eight major community-based outpatient programs across the United States reported use of both cocaine and amphetamines within a 12-month period. This small, but high-risk group of dual stimulant users deserves further investigation of their drug use patterns and treatment needs due to their young age, but many had already developed Dependence on both stimulants, as well as on alcohol and marijuana.

This infrequent co-use of cocaine and amphetamines among regular stimulant users may be related to their distinct demographic characteristics, as well as to their differences in pharmacological properties between the two stimulants. For example, similar to previous studies,[6,29] we found that cocaine users were older and primarily African American and that amphetamine users were younger and predominantly White. Sexton and colleagues[30] have suggested that differences between cocaine and amphetamines in their duration of effects, accessibility, and distribution networks may explain unique racial variations in the use of cocaine and amphetamines. Methamphetamine has been distributed predominately within White social networks, while cocaine was rooted in African American communities by the time that methamphetamine arrived on the scene.[30] Difficulty in accessing methamphetamine on a regular basis, established preference for cocaine, and dislike of methamphetamine's longer-lasting psychoactive and physiological effects might be related to the low rate of methamphetamine use among African Americans.[30]

Sex Differences in Physiological Dependence

Lastly, LCA helps elucidate clinically important findings that the majority of female primary cocaine users (67%) and female primary amphetamine users (71%) were in the most severe subtype characterized by tolerance and withdrawal plus compulsive use. Logistic regression analyses also supported the existence of female excess in the PD subtype. An *ex post facto* analysis was conducted to explore whether the observed sex differences in Stimulant Dependence might be influenced by a higher rate of mandated treatment for substance abuse problems (eg, legal referral for treatment and parole/probation) among women versus men. This speculation was not supported by the data. Instead, male primary cocaine users were found to have a higher rate of parole or probation than female users (42% vs. 20%, respectively; χ^2 test $p < 0.01$), and male primary amphetamine users reported a higher rate of legal referral for treatment than female users (54% vs. 29%, respectively; χ^2 test $p < 0.01$). One potentially useful direction of future research would be to determine if female stimulant users are more likely than their male counterparts to defer treatment until problems become severe. It is worth noting that previous studies also have reported a higher prevalence of Stimulant Dependence among female stimulant users compared with male stimulant users, and that sex-related biological and psychosocial differences might have accounted for reported differences.[2,31–34] By using LCA, we are not only able to test the existence of the PD subtype, but also to pinpoint the specific group that is affected heavily by their stimulant use. These findings may have implications for identifying stimulant users with more severe patterns of use that is useful for treatment planning. For example, they clearly show that sex-specific differences in response to treatment or interventions for Stimulant Dependence should be investigated in order to better help this severe group of female stimulant users.

Study Limitations and Strengths

These findings were based on treatment-seeking stimulant users who attended community treatment programs of the CTN. They may not be generalized to stimulant users who are not seeking treatment. Although the study sample is not representative of all treatment-seeking stimulant users, the recruitment of stimulant users from multiple geographically different regions across the nation increases the diversity of the sample, and it represents a major strength of this report. Before the establishment of the CTN, multisite studies of community-based drug abuse treatment were less common. In addition, these results are based on participants' self-reports, which may be influenced by reporting and memory errors. However, the use of self-reports is a common practice in this field. The fact that our findings replicate and extend findings of earlier studies provides some assurance of the validity of the data presented in this report.[35]

Further, the findings related to amphetamine users, as well as the lack of racial/ethnic differences in LCA-defined dependence profiles, require further investigation in larger samples. Last, due to resource constraints and the fact that a diagnosis of DSM-IV Dependence excludes a diagnosis of Abuse,[1] the category of Abuse was not assessed among participants who met criteria for Dependence on the substance in question. The Abuse diagnostic profiles thus were not examined.

This study also has some important strengths. It is the first known investigation using LCA to elucidate underlying latent structures of DSM-IV criteria for current Cocaine and Amphetamine Dependences. It helps test the existence of heterogeneity of Drug Dependence as specified by the DSM-IV[1] and pinpoints specific groups of users who are seriously affected by stimulant use and may warrant additional clinical monitoring or interventions. Another strength of the study that is important to evaluation of Drug Dependence in clinical settings is the geographically diverse nature of the sample recruited from eight community-based treatment programs across the nation and assessed using the same diagnostic tool. A third major strength is the fact that our comparisons of dependence profiles are based on two mutually exclusive groups of cocaine versus amphetamine users. Concern for misattribution of stimulant dependence symptoms is hence greatly mitigated.

Conclusions and Implications

These findings highlight the existence of clinically heterogeneous subtypes of dependence on cocaine and amphetamines distinguished by dependence criteria. They lend some support for the DSM-IV's subtyping for physiological vs. non-physiological dependence. However, DSM-IV employs a broad definition of the presence of either tolerance or withdrawal to define a physiological component.[1] Results from this investigation and others suggest that tolerance alone is not a good indicator for determining the importance of designating a physiologic component in DSM-IV.[2,3] For the emerging DSM-V, a more narrow definition requiring both tolerance and withdrawal should be considered and investigated further to validate its existence for different population subgroups of stimulant users.

These results also support the need to establish the clinical utility of subtyping dependence for treatment planning as implied by DSM-IV.[1] A few studies of cocaine-dependent patients have found that including the treatment of cocaine withdrawal symptoms appears to improve patients' retention and treatment response, and that cocaine-dependent patients respond differently to pharmacotherapy depending on their levels of cocaine withdrawal symptoms.[36–38] Given the presence of distinct dependence subtypes and associated severity, it is clinically important to test whether these subtypes are reliably associated with varying responses to one versus another type of treatment approach (eg, behavioral interventions, pharmacotherapy, or combined treatment) and whether the PD group requires more intensities of care than the non-PD groups. This issue has substantial heuristic and clinical utility and is clearly relevant to informing and guiding continuing efforts in the DSM to subtype Dependence syndromes. Finally, due to

distinct profiles in age and racial/ethnic background and little overlap in use, cocaine users and amphetamine users appear to represent two different groups of stimulant users.

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