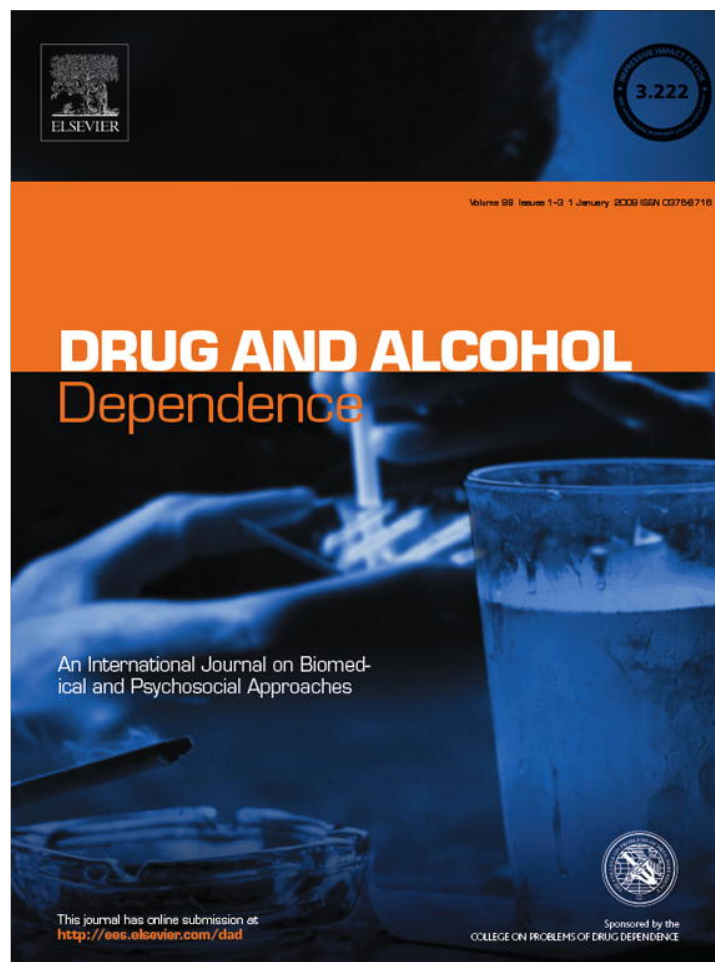


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Association of psychiatric and substance use disorder comorbidity with cocaine dependence severity and treatment utilization in cocaine-dependent individuals

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Abstract

The relations among psychiatric and substance dependence disorders and treatment utilization are of interest both for their clinical management and for health services. We examined these relations using six self-reported indices of cocaine dependence severity and three self-reported measures of treatment utilization and self-help group participation for cocaine dependence. The sample consisted of dyads: namely, a cocaine-dependent adult proband ($N=449$) and a cocaine-dependent sibling ($N=449$). Psychiatric and substance use disorders were assessed with the Semi-structured Assessment for Drug Dependence and Alcoholism. We controlled for the nesting within families of proband-sibling dyads and for demographic features using generalized estimating equation linear and logistic regression analyses. We found that psychiatric disorders were associated with an increased likelihood of cocaine dependence treatment or self-help group participation, but with only one of six indices of cocaine dependence severity. Bipolar disorder and antisocial personality disorder were associated with greater past heavy cocaine use, and with utilizing self-help but not treatment. Major depressive disorder and posttraumatic stress disorder were associated with treatment utilization and overall services utilization, respectively. The presence of other substance use disorders (SUDs) was the strongest correlate of cocaine dependence severity. Results suggest that co-occurring substance dependence and psychiatric disorders warrant attention in cocaine dependence assessment, treatment, and self-help. Published by Elsevier Ireland Ltd.

Keywords: Cocaine; Dependence; Psychiatric; Comorbidity; Services utilization

1. Introduction

Cocaine use is widespread, affecting as many as one in six adults across a wide range of socioeconomic strata and ethnocultural groups in the United States (Shaffer and Eber, 2002) and internationally (http://www.who.int/substance_abuse/facts/cocaine/en/ accessed May 15, 2008). Cocaine dependence, while less prevalent, may affect as many

as 3% of the adult U.S. population (Shaffer and Eber, 2002) and is associated with substantial social, vocational, and medical impairment and healthcare and legal costs to the individual and society.

Cocaine use often is associated with psychiatric comorbidity, e.g., antisocial personality disorder (ASPD; 24%), major depressive disorder (MDD; 18%), posttraumatic stress disorder (PTSD; 12%) (Falck et al., 2004), and a three-fold risk of panic attacks (O'Brien et al., 2005). Studies have shown that almost half of patients in treatment for a cocaine use disorder may have comorbid ASPD (Carroll et al., 1997), one-third to one-half a history of PTSD (Back et al., 2000; Brady et al.,

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2004; Mills et al., 2005), and 20% an affective disorder (Carroll et al., 1997). ASPD (Arndt et al., 1994) and depression (Carroll et al., 1997; Ziedonis and Kosten, 1991) have been shown to be associated with poorer response to addiction or psychiatric treatment by cocaine-abusing or dependent adults. PTSD similarly has been shown to be associated with poorer response to addiction treatment by opiate dependent (Hien et al., 2000) and mixed substance use disorder (Ouimette et al., 2003) patients, including higher rates of cocaine use (Hien et al., 2000).

In addition to frequently being comorbid with substance use disorders (SUDs), psychiatric disorders may be associated with an increased severity of these disorders (Cacciola et al., 2001; Compton et al., 2005b; Kidorf et al., 2004; Mills et al., 2007; Skinstad and Swain, 2001; Watkins et al., 2004). Further, substance dependence disorders may be associated with increased severity of anxiety disorders such as agoraphobia and PTSD (Grant et al., 2006), major depressive disorder (MDD; Kandel et al., 2001; Kessler et al., 1994, 2005; Regier et al., 1990), bipolar disorder (Cassidy et al., 2001; Kessler et al., 1994; Regier et al., 1990), and Cluster B personality disorders, especially antisocial personality disorder (ASPD; Kandel et al., 2001).

However, the relationship between psychiatric and SUD comorbidity and illness severity and impairment is not necessarily consistent across domains of illness severity and impairment and may be the result of multiple concurrent psychiatric disorders rather than a single comorbid psychiatric disorder. For example, Mills et al. (2007) reported that opiate dependent treatment recipients with PTSD (compared to those who did not meet criteria for PTSD) were less likely to be employed, more impaired physically and psychosocially, and more likely to have a history of overdose or suicidality; but they also reported using heroin less frequently in the past month, reduced heroin use as successfully, and did not report higher levels of other drug use. Participants with PTSD in the Mills et al. (2007) study also were 1.6–2.5 times more likely than those without PTSD to meet criteria for major depression, ASPD, and borderline personality disorder as well as PTSD. Another study of opiate dependent treatment recipients found that PTSD was associated with a longer history of drug use and more severe psychiatric symptoms than patients not diagnosed with PTSD, but comparable reductions in heroin, cocaine, and alcohol use and better treatment attendance and retention (Trafton et al., 2006).

Given the serious morbidity and costs of cocaine dependence, this study was designed to examine the relationship to severity of cocaine dependence of both specific comorbid psychiatric disorders and the added burden that may occur when multiple comorbid psychiatric disorders are present. Although the study's focus was on psychiatric comorbidity and cocaine dependence, the presence of other substance dependence diagnoses also was assessed. Symptom severity and psychosocial impairment tend to be heightened with polysubstance dependence, as well as the risk of exposure to traumatic stressors, PTSD, and other psychiatric morbidity (Salgado et al., 2007). Therefore, it is important to distinguish between the effects of psychiatric versus SUD comorbidity when examining potential correlates of cocaine dependence severity.

The rationale for focusing on the *severity* of cocaine dependence is that there is a nascent research literature showing potential relationships between psychiatric or SUD comorbidity and SUD severity. MDD was associated with risky behavior and cocaine use in a community study (Wild et al., 2005). In a clinical sample, bipolar disorder co-occurred commonly with substance use disorder, with an increased likelihood of mixed and rapid cycling mania, a chronic clinical course, medical disorders including liver disease, and both suicide attempts and completed suicides (Krishnan, 2005). PTSD has been associated with suicide attempts; co-occurring mood, anxiety, and personality disorder; overall psychiatric morbidity; family and social problems; marital violence; self-reported employment problems; and the number of episodes of substance abuse treatment—in both treatment samples (Back et al., 2000; Tarrier and Sommerfield, 2003; Wasserman et al., 1997) and non-treatment samples (Parrott et al., 2003; Thevos et al., 1993). ASPD also has been shown to be related to the severity of alcohol, psychiatric, and legal problems and risky sexual behavior among cocaine-abusing research treatment recipients (Ladd and Petry, 2003) and of SUD symptoms in community samples (Goldstein et al., 2007).

However, no study has examined the relationship of psychiatric and SUD comorbidity specifically with cocaine dependence severity, nor across a range of psychiatric disorders and a range of indices of impairment. Studies show evidence of more social, vocational, and legal problems when psychiatric disorders co-occur with cocaine dependence than with alcohol dependence (Brady et al., 2004; Thevos et al., 1993), suggesting that psychiatric morbidity may be particularly related to exacerbated symptom severity or impairment in cocaine dependence. In the present study, cocaine dependency severity was operationalized by specific indices that are consistent with the *DSM-IV* (American Psychiatric Association, 1994) criteria for substance dependence and psychometric measures of dependence severity (Miele et al., 2000), i.e., the number of withdrawal symptoms and of other dependence symptoms (Sofuoglu et al., 2003). In addition, other measures were used to characterize the increasingly heavy and dangerous use over a long time period that occurs when dependence is severe (i.e., number of days during the period of heaviest cocaine use ever; age of first heavy use of cocaine; history of overdoses). A criterion feature of substance abuse, adverse legal consequences (i.e., arrest related to cocaine use), was included because of the severe impact of involvement in the criminal justice system.

A second objective of the present study was to examine the association of psychiatric and SUD comorbidity with the utilization of treatment and self-help for cocaine dependence. The severity of cocaine dependence (Kampman et al., 2004) and mental distress (Dennis et al., 2005) has been associated with SUD treatment outcomes. However, the role of psychiatric comorbidity in the *utilization* of SUD treatment services has not been well studied (Chassler et al., 2006; Grella et al., 2003; Hansen et al., 2004; Van Ness et al., 2004). Cocaine or alcohol dependence severity at entry to SUD treatment has been shown to be associated with less treatment use in the next 6 months (Carpenter et al., 2002), but the only study examining psychiatric

comorbidity found that PTSD was associated with *more* treatment use and retention (Trafton et al., 2006). The present study was designed to extend those findings by being the first, to our knowledge, to test the relationship between a range of psychiatric comorbidities and SUD treatment utilization.

Although self-help support program participation has been associated with sustained recovery from SUDs (Staines et al., 2003), few robust predictors of the use of self-help programs have been identified in past studies with individuals with SUDs (Carpenter et al., 2002; Weiss et al., 2000). Studies of cocaine-dependent individuals have shown that the severity of substance dependence is associated with self-help program attendance (Carpenter et al., 2002; Weiss et al., 2000), and suggest that cocaine-dependent persons without a religious preference may be inclined to attend self-help programs (Weiss et al., 2000). These studies primarily involved treatment-seeking persons, and have not examined psychiatric diagnoses as a potential correlate of self-help program participation. Therefore, this study also serves as a first test of the relationship of psychiatric comorbidity to SUD self-help support program attendance.

The study's two hypotheses were that, among cocaine-dependent adults, after controlling for the effects of demographics and lifetime history of co-occurring substance dependence diagnoses, a history of one or more psychiatric disorders would be associated with: (1) greater cocaine dependence severity, and (2) a higher likelihood of utilization of cocaine-related treatment and participation in SUD self-help groups. To the extent that psychiatric morbidity is associated with increased cocaine dependence severity (Hypothesis 1), the findings of Carpenter et al. (2002) suggest that psychiatric comorbidity may be associated with *less* treatment use. However, Trafton et al.'s (2006) specific finding of increased SUD treatment use by patients with PTSD, along with the generally positive association between psychological distress and SUD self-help participation, support the hypothesis of a *positive* relationship between psychiatric comorbidity and SUD treatment or self-help utilization. The present study also extends the research literature on predictors of SUD treatment or self-help utilization by assessing utilization as a dichotomous variable, i.e., whether treatment or self-help were used at all, rather than the prior studies' focus on the amount of treatment or self-help utilization.

2. Method

2.1. Participants and recruitment

The sample was drawn from a cohort of pairs of adult siblings who were cocaine-dependent and recruited to participate in genetic linkage studies of cocaine (Gelernter et al., 2005) or opioid dependence (Gelernter et al., 2006). Probands and siblings were recruited at the University of Connecticut Health Center (Farmington, CT); Yale University School of Medicine (APT Foundation; New Haven, CT); Harvard Medical School (McLean Hospital; Belmont, MA); and the Medical University of South Carolina (Charleston, SC). Informed consent was obtained as approved by each institutional review board and subjects were paid for their participation. A certificate of confidentiality was obtained from the National Institute on Drug Abuse. For the present analysis, probands with cocaine dependence were selected if they had at least one sibling with cocaine dependence. Participants with a clinical diagnosis of schizophrenia or schizoaffective disorder were excluded (Gelernter et al., 2005, 2006). A total

Table 1

Demographics and lifetime prevalence of substance use and psychiatric disorders in a sample of cocaine-dependent probands and siblings

	Full sample	Probands	Siblings
Race/Ethnicity			
African–American	412(45.0)	206(45.9)	206(45.9)
Hispanic	117(13.0)	62(13.8)	55(12.2)
European–American	314(35.0)	156(34.7)	158(35.2)
Other	55(6.1)	25(5.6)	30(6.7)
Gender			
Male	451(50.2)	218(48.6)	233(51.9)
Female	447(49.8)	231(51.4)	216(48.1)
Marital status			
Married	134 (14.9)	61(13.6)	73(16.3)
Not married	764(85.1)	388(86.4)	376(83.7)
Employment status^a			
Employed	566(66.1)	298(66.2)	268(59.7)
Not employed	331(36.9)	150(33.8)	181(40.3)
Age	38.74(7.5)	38.62 (7.4)	38.86(7.5)
Years of education	11.39(2.10)	11.47(2.03)	11.31(2.17)
Lifetime diagnoses			
Alcohol dependence	446(49.7)	221(49.2)	225(50.2)
Opioid dependence ^a	406(45.3)	226(50.4)	180(40.1)
Cannabis dependence	268(30.1)	124(27.9)	144(32.3)
Sedative dependence	78(8.8)	38(8.6)	40(8.9)
Stimulant dependence	65(7.3)	31(7.0)	34(7.6)
MDD	123(14.4)	52(12.3)	71(16.4)
Bipolar disorder	47(5.4)	23(5.3)	24(5.5)
PTSD	107(12.4)	59(13.6)	48(11.2)
Agoraphobia/Panic	45(5.3)	22(5.1)	23(5.4)
ASPD	123(14.3)	60(13.9)	63(14.6)

Note: *N*(%) or *M*(*S.D.*) (for age, education) are presented. MDD, major depressive disorder; PTSD, posttraumatic stress disorder; ASPD, antisocial personality disorder.

^a Chi-square test for difference between proband and sibling sub-samples, $p < .05$.

of 449 proband/sibling pairs were identified. If probands had more than one cocaine-dependent full sibling, the sibling closest in age to the proband was selected for the analysis.

The demographic features of the proband and affected sibling samples are shown in Table 1. The average age of probands was 38.6 years (*S.D.* = 7.4) and 51% were women. The average age of siblings was 38.9 years (*S.D.* = 7.5), and 48% were women. The majority of subjects (~85%) were not married (i.e., divorced, separated, or widowed). The self-reported ethnic/racial distribution of the proband sample was 45.9% African–American (AA), 34.7% European–American (EA), 13.8% Hispanic, and 5.6% Native American, Pacific Islander or other minority groups. The sibling sample's self-reported ethnic/racial distribution was comparable but not identical to that of probands (Table 1). Most participants had either entered or attended but not completed high school, and most (63%) were unemployed, disabled, retired, or a student.

Psychiatric and substance use disorders were evaluated using the Semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA; Pierucci-Lagha et al., 2005, 2007). The most common lifetime DSM-IV (APA, 1994) psychiatric and substance dependence disorders are shown in Table 1. Combined psychiatric comorbidity was defined as having two or more *psychiatric* diagnoses. The preponderance of participants with multiple psychiatric disorders had only two such disorders, and therefore additional categories reflecting more extensive psychiatric morbidity could not be analyzed. The proband and sibling sub-samples had a comparable distribution of psychiatric diagnoses: 10–15% had histories of each of MDD, ASPD, and PTSD, while 5% had a history of each of panic disorder and agoraphobia or panic disorder and bipolar disorder.

The proband and sibling sub-samples also had a comparable distribution of lifetime substance dependence disorders – except that more probands reporting opioid dependence histories – with approximately half reporting alcohol or opioid dependence, more than a quarter positive for cannabis dependence, and fewer than 10% positive for dependence on sedatives or stimulants other than cocaine. Cocaine use in the past year by self-report was variable: one third of the sample reported no use; 20% of the sample reported infrequent use, less than once every 2 weeks on average; 15% of the sample reported using on average approximately once weekly; and a third of the sample reported frequent use, between two times a week on average to several times a day. Thus, about two-thirds of the sample appeared to be in full or partial remission from cocaine dependence, and one-third may still have been cocaine-dependent.

2.2. Measures

Based on the limited prior research findings in this area, five psychiatric disorders were selected as potential influences on cocaine dependence severity: MDD, bipolar disorder, PTSD, panic/agoraphobia, and ASPD. Indices of cocaine dependence severity were selected to reflect the extent of recent and past cocaine use, chronicity of cocaine use (i.e., age of onset), the degree of physiological and psychological addiction (i.e., number of dependence and withdrawal symptoms), and potential for severe harm to the individual (i.e., overdose, arrests).

The SSADDA was administered in a computer-assisted format to obtain lifetime psychiatric diagnoses. The SSADDA has been shown to have good inter-rater reliability ($\kappa = 0.50$ – 0.60 , with the exception of bipolar disorder, $\kappa = 0.43$) and good-to-excellent retest reliability at an approximately 2-week interval ($\kappa = 0.50$ – 0.76 , with the exception of MDD, $\kappa = 0.49$) for the five index psychiatric diagnoses in this study. The SSADDA had excellent inter-rater reliability for cocaine and opioid dependence ($\kappa = 0.83$ and 0.91 , respectively) and fair-to-good inter-rater reliability for alcohol, cannabis, and stimulant dependence ($\kappa = 0.48$ – 0.66), as well as good-to-excellent retest reliability ($\kappa = 0.66$ – 0.94) for these diagnoses (Pierucci-Lagha et al., 2005, 2007). Although designed based on the specific diagnostic criteria of the American Psychiatric Association's (1994) DSM-IV for each psychiatric disorder, the validity of the SSADDA for psychiatric disorders and substance dependence disorders has not been established. In addition to using the five psychiatric diagnostic categories as variables, a separate variable was constructed based on the presence of more than one psychiatric disorder (i.e., multiple psychiatric comorbidity), in light of findings from Mills et al. (2007).

SSADDA scores used as dependent variables in study analyses included indices selected to represent: (a) severity of cocaine use, and (b) use of treatment or self-help resources for cocaine dependence. Continuous measures of cocaine use severity included: number of days during the period of heaviest cocaine use; age of first heavy use of cocaine; and number of lifetime (a) withdrawal symptoms, and (b) cocaine dependence symptoms excluding withdrawal. Withdrawal and dependence symptoms were separated based on prior evidence that cocaine withdrawal symptoms are associated with more severe dependence (Sofuoglu et al., 2003). Dichotomous measures included history of cocaine overdose or arrest related to cocaine use. Finally, dichotomous scores were used to assess the utilization of services or supports for cocaine dependence, including any receipt of cocaine dependence treatment and any attendance in cocaine dependence self-help support programs.

2.3. Statistical analyses

Descriptive analyses were conducted to characterize the sample demographically and clinically, and we report data on psychiatric disorders with $\geq 5\%$ prevalence in the sample (Table 1). Based on an examination of the distributions of the cocaine-related and psychosocial impairment variables, all variables were approximately normally distributed. The primary study analyses were generalized estimating equation (GEE) linear and logistic regression analyses conducted to test the effect of psychiatric and substance dependence diagnoses and combined psychiatric comorbidity on cocaine-related impairment and service utilization. GEE is widely used as a method of dealing with correlated data in fitting the generalized linear model (Liang and Zeger, 1986). We used GEE to fit the model to account for the potential dependence among individu-

als within the same nuclear family. Analyses were conducted on a multivariate basis adjusting for proband versus sibling status, for demographics (i.e., gender, age, race/ethnicity, marital status, education, employment), for a history of other substance dependence diagnoses and multiple other substance dependence diagnoses, and for a history of each psychiatric diagnosis or multiple psychiatric diagnoses.

Each severity or treatment/self-help variable was treated as a dependent variable, and all demographic and diagnostic variables were entered simultaneously as independent variables in each multivariate GEE analysis. When the independent variable was dichotomous and the dependent variable was continuous, the raw mean and standard deviation (M[S.D.]) of the dependent variable are reported for the sub-group that was negative (labeled “No” in the Table column headers) for each independent variable (i.e., not African-American, unemployed, unmarried, not male; no history of the diagnosis) versus for the sub-group that was positive (labeled “Yes” in the Table column headers) for each independent variable (i.e., African-American, male; employed, married, past history of the diagnosis). When both the independent and dependent variables were dichotomous, the raw proportions of respondents endorsing the dependent variable were compared (and are shown in the two columns at the far right of the Table) for the sub-group that was negative (“No”) for each independent variable (i.e., not African-American, not male; unemployed, unmarried, no history of the diagnosis) versus for the sub-group that was positive for each independent variable (i.e., African-American, male; employed, married, past history of the diagnosis). When both the dependent and independent variables were continuous, the raw correlation between the variables is reported. All statistical tests are based upon adjusted regression coefficients, while the numbers in the Table columns labeled “No” and “Yes” show the raw (unadjusted) mean (S.D.) or proportion. Although multiple (10) regression tests were conducted, each with several dependent variables, the exploratory nature of the investigation and the conservative use of multivariate models led to our decision to report findings at the conventional $p < 0.05$ level rather than using a downward Bonferroni-like adjustment of the p level required for statistical significance.

3. Results

Results of the multivariate GEE analyses are reported in Table 2 for variables reflecting the severity of cocaine dependence, and Table 3 for treatment or self-help participation variables.

3.1. Severity of cocaine dependence

For the continuous variables reflecting severity of cocaine dependence, more days of cocaine use in the period of heaviest use was associated with older age; less education; being African-American; and a history of bipolar disorder, ASPD, and alcohol or opioid dependence (Table 2). Later age of first heavy cocaine use was associated with being older and unemployed, and with the absence of past opioid dependence. A greater number of lifetime cocaine dependence criteria (excluding withdrawal symptoms) was associated with a history of opioid, cannabis, alcohol, or sedative dependence. A greater number of lifetime cocaine withdrawal symptoms was associated with being female and with a history of cannabis, alcohol, or stimulant dependence.

Of the dichotomous variables reflecting cocaine dependence severity, past cocaine-related overdose was associated only with a history of opioid dependence. Past arrest for cocaine-related crimes was associated with male gender, a history of opioid dependence and the absence of a history of cannabis dependence.

Table 2

Multivariate demographic, psychiatric disorder, and substance dependence disorder correlates of cocaine dependence severity in a sample of cocaine-dependent probands and siblings

Independent variable	No ^a M(S.D.)	Yes ^a M(S.D.)	Chi-square	Pearson <i>r</i>
a. Continuous measures of cocaine dependence severity				
Days of cocaine use in heaviest month of use				
Age			5.48*	0.106
African–American	24.71(7.37)	26.00(6.28)	6.09*	
Education			6.60*	–0.108
ASPD	25.14(6.96)	25.76(6.81)	5.67*	
Bipolar disorder	25.19(6.97)	25.81(6.45)	4.93*	
Opioid dependence	24.57(7.21)	26.17(6.46)	14.88***	
Alcohol dependence	24.89(7.11)	25.70(6.70)	5.41*	
Age of first heavy cocaine use				
Age			112.76***	0.586
Employed	27.28(7.24)	28.51(7.70)	7.07**	
Opioid dependence	28.57(7.31)	27.45(7.82)	11.43***	
Number of lifetime cocaine dependence criteria excluding withdrawal				
Opioid dependence	5.05(1.10)	5.22(1.02)	3.86*	
Cannabis dependence	5.03(1.09)	5.34(0.97)	6.73**	
Alcohol dependence	4.90(1.16)	5.36(0.92)	27.43***	
Sedative dependence	5.09(1.08)	5.59(0.78)	4.91*	
Number of lifetime cocaine withdrawal criteria				
Gender (Male = Yes)	4.89(2.77)	4.47(2.71)	3.95*	
Cannabis dependence	4.45(2.75)	5.20(2.68)	4.16*	
Stimulant dependence	4.57(2.77)	6.06(2.01)	4.62*	
Alcohol dependence	4.24(2.71)	5.12(2.73)	15.53***	
	No ^a	Yes ^a	Chi-square	
b. Dichotomous measures of cocaine dependence severity				
Proportion ever had cocaine-related overdose				
Opioid dependence	0.094	0.229	7.33**	
Proportion ever arrested related to cocaine use				
Gender (Male = Yes)	0.430	0.570	14.72***	
Opioid dependence	0.462	0.544	6.97**	
Cannabis dependence	0.511	0.466	5.16*	

* $p < .05$, ** $p < .01$, *** $p < .001$.

^a Mean(standard deviation) of the continuous severity indices, or raw proportion of respondents answering positively for the dichotomous severity indices, where No = in the sub-group who were *not* African–American, employed, married, male, or did *not* have the index diagnosis; Yes = in the sub-group that *was* African–American, employed, married, male, or had the index diagnosis. Note: Results are adjusted for proband/sibling status. Bold numbers are the larger proportion for each comparison of “No” versus “Yes” sub-groups; ASPD = Antisocial Personality Disorder.

3.2. Utilization of treatment and self-help for cocaine dependence

Use of either treatment or self-help support programs for cocaine dependence was related to a history of MDD, PTSD, ASPD, bipolar disorder, and alcohol dependence (Table 3). Utilization of cocaine dependence treatment specifically was associated with a history of MDD and alcohol dependence. Self-help program attendance was associated with a history of ASPD, bipolar disorder, and alcohol or sedative dependence, as well as African–American ethnicity.

4. Discussion

In this sample of cocaine-dependent adults who were recruited as sibling pairs for a genetics study, contrary to Hypothesis 1, psychiatric comorbidity was associated increased severity of cocaine dependence on only one of six cocaine

dependence severity indices: “Days of Use in the Heaviest Period of Use.” However, consistent with Hypothesis 2, several psychiatric disorders were associated with an increased likelihood of participation in cocaine dependence treatment or self-help programs. These findings were obtained after controlling for any non-independence of data from the proband and sibling sub-samples, and for demographics and history of other substance dependence diagnoses. SUD comorbidity was the most consistent correlate of cocaine dependence severity, though the direction of the relationship varied depending on the specific SUD and index of cocaine dependence severity. African–American, male, less educated, unemployed, or unmarried participants tended to report higher degrees of cocaine dependence severity, but these demographic factors were unrelated to use of treatment or self-help programs for cocaine dependence, except that African–Americans were more likely than others to report having attended self-help programs.

Table 3
Multivariate demographic, psychiatric disorder, and substance dependence disorder correlates of utilization of cocaine dependence-related treatment or self-help services

Independent variable	No ^a	Yes ^a	Chi-square
Proportion of participants who were ever in cocaine dependence treatment or self-help			
MDD	0.623	0.650	9.28**
PTSD	0.620	0.674	7.74**
ASPD	0.611	0.712	15.10***
Bipolar disorder	0.624	0.643	7.62**
Alcohol dependence	0.587	0.670	9.23**
Proportion of participants who were ever in cocaine dependence treatment			
MDD	0.278	0.357	4.96*
Alcohol dependence	0.248	0.349	4.45*
Proportion of participants who were ever in cocaine dependence self-help			
African–American	0.548	0.658	4.72*
ASPD	0.587	0.659	5.88*
Bipolar disorder	0.592	0.681	5.26*
Alcohol dependence	0.567	0.632	7.70**
Sedative dependence	0.593	0.641	4.50*

* $p < .05$, ** $p < .01$, *** $p < .001$.

^a No = the raw proportion of respondents who were *not* African–American or did *not* have the index diagnosis and received treatment or self-help; Yes = the raw proportion of respondents who were *African–American* or *had the index diagnosis* and received treatment or self-help Note: Results are adjusted for proband/sibling status. Bold numbers are the larger proportion receiving cocaine dependence treatment or self-help for each comparison of the “Yes” versus “No” sub-groups. MDD = major depressive disorder; PTSD = posttraumatic stress disorder, ASPD = antisocial personality disorder.

4.1. Hypothesis 1: relationship of psychiatric comorbidity with cocaine dependence severity

Bipolar disorder and ASPD were the only psychiatric disorders associated with any index of cocaine dependence severity. The finding that both were associated with more days of cocaine use during the period of heaviest cocaine use suggests that severe Axis I or Axis II morbidity may exacerbate cocaine use during heavy periods of use by cocaine-dependent individuals. This finding is consistent with recommendations that ASPD (Compton et al., 2005a) and bipolar disorder (Weiss et al., 2007) be carefully assessed in cocaine-dependent persons. This has treatment implications, since patients with comorbid ASPD and cocaine dependence were more likely to be abstinent from cocaine immediately after treatment and at 6-month and 1-year follow-up if they received a contingency management intervention in combination with methadone maintenance than if they received methadone maintenance alone (Messina et al., 2003). The need for differential treatment based on ASPD comorbidity was suggested by findings that cognitive behavior therapy was not effective in cocaine-dependent patients with comorbid ASPD but was more effective than contingency management with non-ASPD cocaine-dependent patients (Messina et al., 2003).

The finding that bipolar disorder was associated with more days of use in the period of heaviest cocaine use also suggests that bipolar disorder should be carefully assessed with cocaine-dependent individuals. With comorbid cocaine dependence and bipolar disorder, targeted psychotherapy has been found to be effective (Weiss et al., 2007), and open-label lamotrigine has shown promising results (Brown et al., 2006). Thus, identifying cocaine-dependent persons bipolar disorder

comorbidity also may lead to enhanced treatment planning and outcomes.

There are several potential explanations for the lack of association of psychiatric disorders with most of the cocaine dependence severity indices examined here. First, the most obvious explanation is that there is no relationship – or at most a circumscribed relationship – between psychiatric disorders and the severity of cocaine dependence. Prior studies have shown a mixed pattern of results, often finding that psychiatric disorders are associated with severity of or impairment due to SUDs on some indices (e.g., employment problems, suicide risk) but not on others (e.g., response to treatment) (Ladd and Petry, 2003; Mills et al., 2007; Trafton et al., 2006; Wild et al., 2005). SUD severity in particular has been quite variably related to psychiatric comorbidity, and thus the present findings tend to support the view that psychiatric comorbidity should not be assumed to lead to more severe cocaine dependence.

However, the null finding may be an artifact of statistical collinearity. MDD, bipolar disorder (Skinstad and Swain, 2001), PTSD, panic/agoraphobia disorder, and ASPD (Markon and Krueger, 2005) frequently are comorbid with most of the substance dependence diagnoses assessed in this study. Thus, the strong relationship of those other substance dependence diagnoses with cocaine dependence may have obscured the relationship of ASPD or bipolar disorder with cocaine dependence severity. The finding in previous studies of a relationship between psychiatric morbidity (e.g., PTSD; Parrott et al., 2003) and increased substance dependence severity or impairment was evident in unadjusted bivariate analyses (results not reported here but available from the first author), in which each psychiatric disorder assessed in this study was significantly associated with at least one (and usually several) indices of cocaine

dependence severity. This suggests that research may be needed to determine where indirect relationships link psychiatric and substance dependence disorders with cocaine dependence severity (e.g., using structural equation modeling). For example, dependence on substances (e.g., alcohol, cannabis, opioids) that are often used to self-medicate PTSD-related anxiety (Tarrier and Sommerfield, 2003) could mediate a relationship between PTSD and cocaine dependence severity that was not detected in the present study's multivariate regression models.

A third possible explanation for the null relationship between psychiatric morbidity and cocaine dependence severity is that the relatively low self-reported levels of recent cocaine use by two-thirds of the sample suggest that this non-clinical sample is comprised primarily of individuals in recovery from cocaine dependence, with a sub-group still dependent. The finding that almost two-thirds have been in self-help support programs and one-third in treatment is consistent with this view, suggesting that a majority of study participants have been able to get help for their cocaine dependence. For the participants currently in remission, their self-reports of cocaine dependence severity are not only retrospective but may involve a gap of several years, and thus may be insensitive to potential exacerbating factors such as psychiatric disorders. The fact that psychiatric morbidity was assessed lifetime rather than currently raises the possibility that the psychiatric disorders also may have improved or been in remission. Thus, this sample may have under-represented the sub-group of actively cocaine-dependent persons with current psychiatric illnesses, and it is possible that these are the cocaine-dependent adults for whom psychiatric morbidity may have the greatest impact on cocaine dependence severity.

Finally, it is possible that respondents with psychiatric disorders received mental health treatment, which unfortunately was not assessed by the SSADDA. Mental health treatment could indirectly reduce the severity of cocaine dependence by enhancing the individual's functioning and emotional and behavioral regulation, as well as potentially leading to the identification of cocaine dependence and participation in substance dependence treatment or self-help. The finding that four of the five psychiatric disorders were associated with participation in either treatment or self-help supports the possibility that psychiatric disorders may lead to individuals receiving help for cocaine dependence and thus indirectly reduce cocaine dependence severity.

4.2. Hypothesis 2: relationship of psychiatric morbidity with treatment/self-help participation

Consistent with Hypothesis 2, psychiatric morbidity was positively related to treatment utilization (in the case of MDD). MDD, although unrelated to severity of cocaine dependence, was associated with the receipt of cocaine dependence treatment. The difference between this finding and those of Carpenter et al. (2002), who found that substance dependence severity at treatment entry was related to *less* treatment utilization, may be explained in several ways. First, psychiatric morbidity and cocaine dependence severity were not related in the present find-

ings. Second, participants were not treatment seeking. Third, the current study's findings are retrospective, in contrast to the prospective design in Carpenter et al. (2002).

Depression may either pre-exist and exacerbate cocaine dependence ("independent depression"), or be a sequela of cocaine-related psychobiological dysregulation ("substance induced depression") (Leventhal et al., 2006). Cocaine-dependent persons also may have trouble with emotion regulation soon after abstinence (Fox et al., 2007), and often are depressed when entering treatment (Carroll and Rounsaville, 2003). Thus, depression may lead cocaine-dependent individuals to seek or be referred for cocaine dependence treatment even though it does not necessarily increase the severity of the dependence *per se*. Correspondingly, pharmacotherapy for depression may reduce potential contributing factors to cocaine use (e.g., craving, euphoria), but it has not been shown to reduce cocaine use (Nunes et al., 1995; Schmitz et al., 2001; Ziedonis and Kosten, 1991). Whether depression increases the risk of cocaine dependence, as has been shown for alcohol dependence (Kuo et al., 2006), remains to be investigated.

Also consistent with Hypothesis 2, psychiatric morbidity was positively associated with the likelihood of self-help program participation. Specifically, ASPD and bipolar disorder, although unrelated to cocaine dependence treatment utilization, were positively related to self-help participation. The relationship of both bipolar disorder and ASPD with one index of cocaine dependence severity – the extent of use in the period of heaviest cocaine use – suggests that heavy cocaine use may be a link between these disorders and self-help participation. However, individuals with comorbid cocaine dependence and ASPD or bipolar disorder may not be identified (or self-identify) as being in need of cocaine dependence treatment. Thus, self-help may be a means to obtain support for sobriety in relation to cocaine use that may be more acceptable, or more often recommended or required, for cocaine-dependent individuals who also have ASPD or bipolar disorder. Given the initial evidence of efficacy of psychological treatments for comorbid cocaine dependence and bipolar disorder or ASPD, it may be important to encourage cocaine dependence self-help programs to provide educational information or materials about evidence-based treatment options for comorbid cocaine dependence and ASPD or bipolar disorder. However, caution is suggested in relation to pharmacotherapy of comorbid SUD and ASPD, based on the finding that antidepressant pharmacotherapy was beneficial only with cocaine-dependent adults who did *not* have comorbid ASPD diagnoses (Arndt et al., 1994).

PTSD, although also unrelated to cocaine dependence severity, was the only anxiety disorder that was associated with an increased likelihood of having received cocaine dependence treatment or participated in cocaine dependence self-help groups. Comorbid PTSD is associated with poorer treatment outcomes than cocaine dependence without PTSD across a variety of measures (Najavits et al., 2007). Pharmacotherapy has not been evaluated for comorbid cocaine dependence and PTSD, but several psychotherapy models have been developed and one – Seeking Safety (Najavits et al., 2006) – has shown evidence of

efficacy in several open and randomized clinical trials (Schafer and Najavits, 2007).

Multiple psychiatric comorbidity was not associated with cocaine dependence treatment or self-help participation, in contrast to prior findings (Bruce et al., 2005). This null finding may reflect a ceiling effect, such that the presence of even a single psychiatric disorder may be sufficient to account for increased utilization. Alternately, cocaine-dependent persons with multiple psychiatric disorders may preferentially seek mental health services.

4.3. *Co-occurring substance use disorders and cocaine dependence severity and services*

The multivariate findings consistently showed that a history of other substance dependence diagnoses was strongly related to the indices of cocaine dependence severity and both treatment and self-help participation. Consistent with prior studies' findings, opioid dependence was associated with past heavy cocaine use, lifetime dependence severity, past risky behaviors (i.e., overdose, arrests), and earlier age of onset of heavy cocaine use (Galea et al., 2006; Lynskey et al., 2004). Prior studies have also shown cocaine dependence to be associated with more severe opioid dependence (Bandettini Di Poggio et al., 2006), but this is the first to show that opioid dependence is associated with more severe cocaine dependence. The inverse relationship of opioid dependence suggests that heavy use of cocaine and opioids may not occur simultaneously, with each drug predominant at different times depending upon environmental conditions or the trajectory of the dependence syndrome and the role of self-medication.

Alcohol dependence also was associated with heavy past cocaine use and lifetime dependence severity, as well as lifetime withdrawal severity—consistent with prior findings of more severe medical (Salloum et al., 2004) and psychosocial problems (Flannery et al., 2004) among individuals with comorbid alcohol and cocaine dependence. Also, alcohol dependence was associated with the use of treatment or self-help for cocaine dependence. However, co-occurring alcohol and cocaine dependence may be less amenable to change through treatment or self-help programs than cocaine dependence alone (Schmitz et al., 2004) or alcohol dependence alone (Flannery et al., 2004). The increased cocaine dependence severity associated with co-occurring alcohol dependence may lead to treatment seeking and self-help participation, while also reducing cocaine-dependent persons' responsiveness to treatment or self-help services.

Sedative use disorders have been associated with increased cocaine dependence severity (Chutuape et al., 1997), consistent with the present study's finding, but not with other indices of cocaine dependence severity. Sedative dependence was prevalent among alcohol dependent persons (Schuckit et al., 2002); thus any possible relationship between sedative dependence and other indices of cocaine dependence severity may have been obscured by the collinear effect of alcohol dependence. Sedative use was unrelated to treatment utilization but was positively associated with cocaine dependence self-help participation. Co-occurring sedative and cocaine use has been associated with

poorer retention and drug use outcomes in patients in methadone maintenance (DeMaria et al., 2000). Thus, cocaine-dependent persons who also are dependent on sedatives may seek self-help as an alternative to formal treatment.

4.4. *Study strengths and limitations*

The study had several methodological strengths including the large, demographically diverse community sample of cocaine-dependent adults and closely age-matched siblings. Also, psychiatric and substance dependence disorders were diagnosed using a standardized structured interview (Pierucci-Lagha et al., 2005, 2007). Further, a range of indices of cocaine dependence severity was utilized rather than a single measure of symptom or impairment severity.

Study limitations include use of a convenience sample comprised of affected sibling pairs, which is not generalizable to all cocaine-dependent adults. The reliability of SSADDA psychiatric diagnoses is less than that for substance dependence diagnoses and the validity of these diagnoses has not been formally demonstrated. Because individuals with a clinical diagnosis of schizophrenia were excluded from participation, there are limitations to the applicability of these findings to a more severely mentally ill patient population. Several variables were used to represent cocaine dependence severity, which may have led to false positive findings, although the use of a conservative multivariate analysis strategy increases the likelihood that relationships between psychiatric comorbidity and cocaine dependence severity are meaningful. Study variables were self-report, which may not accurately describe dependence severity or treatment and self-help program use. Replication is needed with broader samples of cocaine users, confirmation of substance dependence (e.g., toxicology), and external measures of dependence severity (e.g., legal or work records) and service utilization (e.g., medical records).

4.5. *Conclusion*

After accounting for the effects of demographic factors and other substance dependence disorders, only bipolar disorder and ASPD were related to cocaine dependence severity. The presence of a co-occurring SUD consistently was associated with cocaine dependence severity, although some co-occurring SUDs were associated with increased cocaine dependence severity (e.g., opioids, alcohol) and others were associated with decreased cocaine dependence severity (e.g., marijuana). More specifically study findings suggest that severe psychiatric disorders such as bipolar disorder or ASPD may be associated with extended periods of heavy cocaine use. Therefore, interventions are needed to prevent extended heavy cocaine use when cocaine dependence co-occurs with serious mental illness or ASPD.

Moreover, in addition to bipolar disorder and ASPD, MDD and PTSD were associated with an increased likelihood of cocaine dependence treatment or self-help participation. While mood and anxiety disorders may not increase cocaine dependence severity, they may add psychosocial burden that could motivate cocaine-dependent adults to seek

treatment or self-help. This finding underscores the importance of targeted psychotherapy or pharmacotherapy for mood or anxiety disorders when they co-occur with cocaine dependence.

Author disclosures

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Author contributions

Gelernter, Kranzler, and Farrer designed the study and wrote the protocol. Gelernter, Kranzler, Weiss, and Brady oversaw recruitment and assessment of subjects. Farrer oversaw the development and maintenance of the database. Ford and DeVoe managed the literature searches and summaries of previous related work. Zhang, Ford, and Kranzler undertook the statistical analysis, and Ford wrote the first draft of the manuscript. All authors reviewed the manuscript for scientific content and approved the final manuscript.

Conflict of interest

None for any of the authors.

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