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Association between Psychiatric Symptoms and Craving in Methamphetamine Users

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Abstract

This study examined the differences in psychiatric symptoms between adult methamphetamine users ($n = 46$) and control subjects ($n = 31$), the relationship between psychiatric symptoms and the intensity of methamphetamine craving, and whether psychiatric symptoms were correlated to methamphetamine drug-usage variables (ie, length of abstinence, frequency, duration, and lifetime grams). We found that depressive symptoms on the Center for Epidemiology Studies-Depression (CES-D) and many other psychiatric symptoms on the Symptom Checklist-90 (SCL-90) significantly correlated with craving methamphetamine on the visual analog scale (VAS) for craving.

Methamphetamine users had significantly more depressive symptoms (on CES-D) and psychotic symptoms (on SCL-90) compared to controls. There were no significant correlations between psychiatric symptoms and methamphetamine-usage variables. This study provides the first evidence to suggest that depressive symptoms (on CES-D) and psychiatric symptoms (on SCL-90) are strongly associated with the intensity of craving (on VAS) for the drug in methamphetamine users. However, the methamphetamine usage variables had no relationship with psychiatric symptoms. Therefore, methamphetamine users, regardless of their usage patterns, may benefit from treatment of their psychiatric symptoms in order to minimize craving and subsequent relapse to drug use.

INTRODUCTION

Methamphetamine is a powerful, widely abused, addictive stimulant that can be smoked, ingested, injected, or snorted. The user experiences high energy, a sense of well-being, and a pleasurable sensation of being high.¹ The negative effects are many and wide ranging, such as increased legal problems and violence,² medical problems such as cardiomyopathy,³ and increasingly risky sexual behavior⁴ that could lead to disease such as HIV infection. The psychiatric effects of methamphetamine use are problems such as psychosis,⁵ increased attempted suicide,² craving, and depression.^{6,7} Recent literature has shown that one of the risk factors for suicide attempts in methamphetamine users is symptoms of depression.⁷

Depression has been causally linked to craving of other drugs of abuse, but the relationship between depressive symptoms and craving has not been documented with methamphetamine. Although craving for methamphetamine has been shown to be a primary symptom motivating drug use and a significant predictor of future use,⁸ little is written on the association between

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craving for methamphetamine and psychiatric symptoms. In addition, the methamphetamine withdrawal period, also known as “the crash,” is often manifested by days of dysphoria,^{6,9} oversleeping, anxiety, and craving.⁶ However, the correlation between psychiatric symptoms not related to withdrawal and methamphetamine drug-usage variables (eg, length of abstinence) is poorly understood.

Therefore, the aims of this study are to evaluate

1. the relationship between psychiatric symptoms and intensity of craving in methamphetamine users;
2. whether there are differences in psychiatric symptoms between methamphetamine users and non-users; and
3. whether psychiatric symptoms are correlated to methamphetamine drug-usage variables.

METHODS

Subjects were recruited for a pilot study to evaluate methamphetamine users through local treatment facilities, using flyers or word-of-mouth. Subjects were compensated with nominal amount of cash for their participation. Inclusion criteria for all subjects included being ≥ 18 years old, able to provide informed consent, and demonstrating good health (as evidenced by physical examination, electrocardiogram, and screening blood work, including urine pregnancy test to rule out pregnancy). Methamphetamine user subjects had to have a history of current or past methamphetamine use or dependence, while control subjects were required to have no history of methamphetamine use and no illicit drug dependence. Exclusion criteria for all subjects included confounding neurological disorder; severe psychiatric illnesses (eg, schizophrenia, bipolar disorder, acute psychosis, or current severe major depressive disorder not related to drug withdrawals); significant chronic medical illness; and current or history of dependence on alcohol, opiates, inhalants, benzodiazepines, or barbiturates. Prior to the study, all subjects signed a written informed consent approved by our Institutional Review Board.

Detailed drug and psychiatric history was obtained on all subjects during face-to-face interviews by a trained research staff and verified by a physician (neurologist or psychiatrist). Drug use history included last use, quantity, frequency, and route of use for all illicit drugs. Because the drug patterns for subjects varied during different time periods in their lives, their history was detailed for each time period. The structured assessments included the Visual Analog Scale (VAS), which was used to assess current intensity of craving, and the Symptom Checklist-90 (SCL-90) and Center for Epidemiologic Study-Depression (CES-D) questionnaire to assess for psychiatric symptoms. Any subject who self-reported an unclear psychiatric diagnosis, was on psychotropic medications, scored greater than 15 on the CES-D, or had significant SCL-90 responses was interviewed by a board-certified neurologist or psychiatrist for an abbreviated psychiatric evaluation in order to clarify diagnosis and assess for stability. Urine toxicology tests (UTT) were performed using the Multi Drug Six-Panel Drug Test from Medimpex United (Bensalem, Pennsylvania, USA).

Data were analyzed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA). *p* values less than 0.05 were considered statistically significant. Trends are noted for $0.15 \geq p$ values ≥ 0.05 . The *t*-test and Fisher's exact test were used to compare demographic characteristics of methamphetamine users and non-methamphetamine users. Nonparametric analysis of variance was used to compare CES-D and SCL-90 scores between methamphetamine users and non-methamphetamine users. Spearman correlation was used to assess the relationships between craving, methamphetamine use, and psychiatric symptoms. The Simes procedure was used to adjust for multiple comparisons.¹⁰

RESULTS

Research Participants and Their Drug Usage

A total of 110 subjects were screened. Thirty-three subjects did not meet the study criteria and were not included in the analysis. Forty-six methamphetamine users (25 men and 21 women) and 31 healthy non-methamphetamine users (19 men, and 12 women) fulfilled study criteria and were included for analyses in this study (see Table 1). Forty-five out of 46 subjects reported that their drug of choice was methamphetamine. One of the recreational methamphetamine users reported that she had no drug of choice. Smoking the crystalline form of methamphetamine was the primary route of use in 96% (44/46) of our methamphetamine users. Only two methamphetamine users reported that they used primarily via the intravenous route. All methamphetamine subjects reported using methamphetamine for 2 months or more. The median duration of use was 102 months. Thirty-seven out of 46 (80%) were heavy methamphetamine users, defined as daily users. The median lifetime use was 861 grams, and the lowest reported lifetime use was 7.5 grams. Twenty-seven of 46 (59%) methamphetamine users reported that they were either in rehabilitation programs or abstinent from methamphetamine, and reportedly were abstinent for two weeks or more. The median length of abstinence was 17 days. Nineteen of 46 (41%) methamphetamine users reported they were current users of methamphetamine. Forty-five of 46 methamphetamine users had no other history of drug dependence (alcohol, opiates, inhalants, benzodiazepines, or barbiturates), but one methamphetamine-dependent subject had a remote history of cocaine dependence.

All except 4 of the 19 reported current methamphetamine users tested positive for methamphetamine/amphetamine on UTT, while 1 of the 27 reported abstinent methamphetamine users tested positive for the drug. Thus, a total of 16 out of 46 (35%) methamphetamine users had a positive methamphetamine/amphetamine on UTT. Four out of the 46 (9%) methamphetamine users had tested positive for tetrahydrocannabinol (THC) on UTT, with one being a combination of positive THC, benzodiazepine, opiates, and methamphetamine/amphetamine. Twenty-eight out of 46 (61%) methamphetamine users had a negative UTT. Of the 31 control subjects, four (13%) tested positive for THC, and one tested positive for benzodiazepine. Otherwise, all other control subjects were negative for other substances of abuse tested on UTT.

The subjects were between the ages of 18 and 51 years and were predominantly of mixed race and male. Education level was significantly higher for control subjects than the methamphetamine users ($p = 0.001$). The race distribution was slightly different between the two groups ($p = 0.07$), with a higher percentage of mixed race among methamphetamine users. Because the education level was significantly different and racial distribution showed a trend toward difference between the two groups, these variables were included as covariates in the comparison of CES-D and SCL-90 scores.

Craving Scale in Methamphetamine Users

Forty-five out of 46 methamphetamine users gave a self-report of their intensity of craving on the Visual Analog Scale (VAS). One methamphetamine user failed to complete the VAS form. The mean VAS score was 30.8 ± 30.8 on a scale of 0–100. Methamphetamine users who had more depression symptoms on the CES-D also had significantly higher intensity of craving on the VAS, with a Spearman correlation of 0.38 and $p = 0.01$ (see Figure 1). The association between CES-D and craving remained highly significant ($p = 0.005$) after controlling for length of abstinence, grams per lifetime use, duration, and frequency of use. Craving was also significantly correlated with most subscales on the SCL-90 (see Table 2). Nearly all of the correlations in Table 2 remained significant after correction for multiple comparisons.

Differences on CES-D and SCL-90 between Methamphetamine Users and Control Subjects

Of the 46 methamphetamine users, 45 completed the SCL-90 and 44 completed the CES-D questionnaire. The mean CES-D score was significantly higher in methamphetamine users (15.2 ± 10.6) than control subjects (10.7 ± 8.4), after co-varying for race (p value = 0.03; see Table 3). However, this difference in CES-D was not significant after correction for multiple comparisons.

Methamphetamine users, compared to control subjects, had significantly higher scores on the SCL-psychosis subscale after controlling for race ($p = 0.04$). However, this difference was not significant after correction for multiple comparisons.

Because education did not significantly affect the results when it was included as a covariate, it was removed from the model.

Relationship between Methamphetamine-Usage Variables and VAS, CES-D, and SCL-90

None of the methamphetamine-usage variables correlated significantly with intensity of craving or CES-D. A cumulative amount of methamphetamine used in one's lifetime did not significantly correlate with any of the subscales of SCL-90. However, the length of abstinence from methamphetamine use was correlated inversely with all of the subscales of SCL-90, but reached significance only with phobia ($r = -0.36$, $p = 0.02$; see Table 4). Duration of methamphetamine use correlated only with the subscale of anxiety ($r = 0.33$, $p = 0.03$). Finally, frequency of use correlated only with the subscales of obsessive-compulsiveness ($r = 0.40$, $p = 0.0066$) and anxiety ($r = 0.31$, $p = 0.0363$). However, none of these correlations were significant after correction for multiple comparisons.

DISCUSSION

This is the first study showing that many negative mood states are significantly correlated with higher intensity of craving for methamphetamine. Our analysis shows that methamphetamine users who had more symptoms of depression on CES-D had higher subjective intensity of craving on VAS, independent of methamphetamine usage variables (ie, length of abstinence, grams per lifetime use, duration, or frequency of use). In addition, more psychiatric symptoms on the SCL-90 subscales significantly correlated with higher intensity of craving for methamphetamine. These correlations between negative mood and craving could be interpreted in several ways. First, there is evidence that negative mood states are the root cause of craving. For example, a study demonstrated that induced depressed mood produced significant increases in craving for opiates.¹¹ Similarly, negative mood states were associated with higher cravings for cigarettes,¹² opiates^{11,13} alcohol,¹⁴ and cocaine.^{15,16} In addition, depression has also been shown to increase other cravings, such as sweets, in animal and human models of depression and craving.^{11,17} Negative mood states, in the context of repeated attempts at self-medication, may become conditioned stimuli capable of triggering craving. Cue-induced craving during functional neuroimaging has shown that drug-dependent subjects have a physiologic link between craving and general dysphoric states.¹⁸ In the opposite vein, craving could be the cause of the negative emotions if subjects feel badly when experiencing unwanted feelings of craving. However, causation cannot be determined from our current study design; only strong associations between depressive or psychiatric symptoms and craving are documented.

We also found that methamphetamine users had more depressive symptoms, as indicated on the CES-D, compared to controls. Although this finding was no longer significant after correction for multiple comparisons, this finding is consistent with those in prior studies that found that methamphetamine users suffer more depressive symptoms compared to non-users.

2,19 Thus, we interpret our data as a strong trend for more depressive symptoms among methamphetamine users compared to non-users, and that these symptoms are likely clinically significant. One possibility for the trend for higher depressive symptoms in our methamphetamine users may be related to their lower educational level compared to controls. Although we did not obtain further detailed socioeconomic data in these subjects, it is probable that because their educational level was lower, their yearly income was also lower. Living below poverty is associated with increased odds of depression, as shown in other studies.^{20, 21}

Our data also show that methamphetamine users, compared to controls, had significantly higher scores on measures for psychosis, but this finding was also no longer significant after correction for multiple comparisons. However, the finding of higher scores for psychosis is also similar to previous reports showing that methamphetamine users have significantly more psychosis symptoms compared to non-methamphetamine users.^{5,22} Thus, we again conclude that our methamphetamine users showed a strong trend for more psychosis symptoms than non-users and that these symptoms are likely clinically significant.

Although we found trends for higher scores on depressive symptoms and psychosis symptoms in the methamphetamine users compared to controls, we did not observe a significant correlation between methamphetamine usage variables and depression, craving, or any other psychiatric symptoms after correction for multiple comparisons. These findings suggest that methamphetamine use alone, not pattern of use, is associated with a trend for having greater psychiatric symptoms when compared to non-users. However, a prior study found that methamphetamine users in behavioral treatment showed a progressive reduction in severity of depression over 16 weeks.²³ In contrast, many of our methamphetamine user subjects were not in treatment programs and were only evaluated once. Thus, it is difficult to speculate whether methamphetamine usage variables would have correlated with psychiatric symptoms or craving if our subjects were followed over time in treatment programs. Another potential explanation for the lack of correlation between the methamphetamine usage and their psychiatric symptoms may be that these individuals might have had greater depressive or psychiatric symptoms than non-users prior to their methamphetamine use.

Several limitations of this study warrant consideration. First, the sample sizes for the subject groups were relatively small, which limited our ability to further evaluate subgroup differences, such as comparing the active versus abstinent methamphetamine users. Such a comparison would have been more appropriate, as only methamphetamine users would have craving symptoms for the drug. Second, substance users can be poor historians, particularly when they are intoxicated, and hence their self-reported data may be less accurate. However, only about one-third of our methamphetamine users tested positive for methamphetamine on their UTT, and very few subjects appeared intoxicated or agitated during their evaluations. Also, our subjects appeared to have been truthful about their methamphetamine use, as evidenced by their matching UTT. Third, the variable phases of methamphetamine effects— either intoxicated, withdrawing, or recently abstinent—during the time of the subjects' visits could have influenced their responses and self ratings. Fourth, the average educational level of the methamphetamine-subjects was significantly lower than the non-methamphetamine users. Lower education and, hence, probable lower socioeconomic status may be related to greater depression²⁰; therefore, future research that assesses psychiatric symptoms should include socioeconomic data as covariates. Lastly, we only used a single-item scale to measure craving. It may be argued that single-item scales, like the VAS, are inadequate to capture the multifaceted and subjective nature of craving. Alternative approaches, such as the Cocaine Craving Questionnaire (CCQ),²⁴ may better capture the multidimensional nature of subjective craving. An adaptation of the CCQ to assess methamphetamine craving should be performed in future studies.

In summary, the present study provides first evidence to suggest that depressive symptoms (on CES-D) and many other psychiatric symptoms (on SCL-90) are highly correlated with intensity of craving for methamphetamine. Our results may provide support for the notion that negative mood states are fueling the subjective craving experience. Our findings also demonstrate that methamphetamine users are suffering from more depressive symptoms on CES-D and psychotic symptoms on SCL-90 compared to controls. Thus, in clinical practice, we propose that all methamphetamine users should be routinely assessed for craving, depression, and psychosis. Finally, we found that there were no significant correlations between psychiatric symptoms and methamphetamine-usage variables in methamphetamine users. Therefore, psychiatric symptoms, particularly depression and psychosis, may be important to alleviate in methamphetamine users regardless of their usage patterns. It is probable that treated depression in methamphetamine users may reduce suicide attempts or relieve craving itself, and thus may prevent relapse. However, the threshold for treatment of depression and psychosis for methamphetamine users remains unclear and should be a focus in future studies.

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FIGURE 1.
Correlation between CES-D scores and craving in methamphetamine subjects.

TABLE 1

Characteristics of methamphetamine and non-methamphetamine users

	Total (n = 77)	Methamphetamine users (n = 46)	Controls (n = 31)	P
Age				ns
Years	32.0 ± 8.3	32.9 ± 8.6	30.7 ± 7.7	
Range	18–51	18–51	20–50	
Sex				ns
Male (%)	44 (57)	25 (54)	19 (61)	
Female (%)	33 (43)	21 (46)	12 (39)	
Education (years)	12.84 ± 1.5	12.4 ± 1.3	13.5 ± 1.4	0.001
Race				0.07
Mixed (%)	30 (39)	22 (48)	8(26)	
Asians (%)	20 (26)	12 (26)	8 (26)	
White (%)	15 (19)	8 (17)	7 (23)	
Pacific Islander (%)	8 (10)	4 (9)	4 (13)	
Black (%)	4 (5)	0 (0)	4 (13)	
Lifetime use (grams)		861 (364, 3008)		
Length of abstinence (days)		17 (1,78)		
Duration of use (months)		102 (36, 168)		
Frequency of use (days per week)		7 (4, 7)		

Data are from 77 subjects (46 methamphetamine users and 31 control subjects) unless otherwise indicated. Data are presented as mean ± SD, frequency with range or percentage in parentheses. Drug use patterns are reported as median with 25th and 75th percentile in parentheses. Lifetime use of methamphetamine was calculated by using the amount used times frequency times duration of use, and summed for each period of use if there were more than one period of use.

TABLE 2

Correlation between VAS and psychiatric symptoms among methamphetamine users

	Spearman correlation	<i>p</i> value
CES-D	0.38	0.01 [*]
SCL-90 subscale		
Somatization (Som)	0.37	0.01 [*]
Obsessive compulsive (OC)	0.49	<0.001 [*]
Interpersonal sensitivity (IS)	0.37	0.01 [*]
Depression (Dep)	0.52	<0.001 [*]
Anxiety (Anx)	0.59	<0.001 [*]
Hostility (Hos)	0.18	0.25
Phobic anxiety (Pho)	0.52	<0.001 [*]
Paranoid ideation (Par)	0.30	0.05
Psychoticism (Psy)	0.41	0.005 [*]
Global severity index	0.46	0.002 [*]
Positive symptom distress index	0.36	0.02 [*]
Positive symptom total	0.47	0.001 [*]

* Significant *p* values after correction for multiple comparisons.

TABLE 3

Psychiatric symptoms in methamphetamine users and control subjects

	Methamphetamine user	Controls	<i>P</i> value [*]
CES-D	15.2 ± 10.6	10.7 ± 8.4	0.03
SCL-90 subscales			
Somatization	56.0 ± 12.1	52.5 ± 9.9	ns
Obsessive compulsive	61.6 ± 11.8	59.2 ± 11.6	ns
Interpersonal sensitivity	58.4 ± 11.9	55.7 ± 10.9	ns
Depression	61.4 ± 11.7	57.6 ± 11.5	ns
Anxiety	56.0 ± 14.3	54.6 ± 11.7	ns
Hostility	58.3 ± 11.5	53.1 ± 10.7	ns
Phobic anxiety	56.1 ± 12.2	51.0 ± 8.7	0.07
Paranoid ideation	58.0 ± 12.8	55.2 ± 10.6	ns
Psychotic symptoms	63.0 ± 12.9	57.3 ± 10.8	0.04
Global severity index	62.2 ± 11.4	57.3 ± 12.3	0.07
Positive symptom distress index	57.8 ± 10.3	53.8 ± 9.9	ns
Positive symptom total	60.5 ± 11.2	55.7 ± 10.7	ns

*
p values after controlling for race.

CES-D data are from 75 subjects (44 methamphetamine users and 31 controls).

SCL-90 data are from 76 subjects (45 methamphetamine users and 31 controls).

TABLE 4
Correlations between methamphetamine use history and VAS, CES-D, or SCL-90 subscales

	VAS	CES-D	SCL-Som	SCL-OC	SCL-IS	SCL-Dep	SCL-Anx	SCL-Hos	SCL-Pho	SCL-Par	SCL-Psy
Lifetime use (grams)											
R value	0.03	0.14	0.23	0.23	0.09	0.16	0.23	-0.10	0.13	0.02	0.01
p value	0.826	0.378	0.133	0.125	0.571	0.306	0.134	0.517	0.395	0.901	0.953
Log length of abstinence (days)											
R value	-0.26	-0.19	-0.26	-0.25	-0.22	-0.21	-0.28	-0.21	-0.36	-0.26	-0.17
p value	0.085	0.219	0.080	0.095	0.141	0.175	0.064	0.172	0.016	0.081	0.259
Duration of use (months)											
R value	0.08	0.23	0.29	0.23	0.04	0.16	0.33	-0.12	0.13	-0.03	0.18
p value	0.597	0.141	0.055	0.128	0.773	0.293	0.028	0.426	0.407	0.852	0.250
Frequency of use (number of days per week)											
R value	0.15	0.20	0.16	0.40	0.19	0.24	0.31	0.08	0.28	0.11	0.01
p value	0.319	0.188	0.282	0.007	0.216	0.113	0.036	0.584	0.058	0.473	0.965