Dose-Related Psychotic Symptoms in Chronic Methamphetamine Users

Evidence From a Prospective Longitudinal Study

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Context: Methamphetamine is associated with psychotic phenomena, but it is not clear to what extent this relationship is due to premorbid psychosis among people who use the drug.

Objective: To determine the change in the probability of psychotic symptoms occurring during periods of methamphetamine use.

Design: Longitudinal prospective cohort study. A fixed-effects analysis of longitudinal panel data, consisting of 4 noncontiguous 1-month observation periods, was used to examine the relationship between changes in methamphetamine use and the risk of experiencing psychotic symptoms within individuals over time.

Setting: Sydney and Brisbane, Australia.

Participants: A total of 278 participants 16 years of age or older who met *DSM-IV* criteria for methamphetamine dependence on entry to the study but who did not meet *DSM-IV* criteria for lifetime schizophrenia or mania.

Main Outcome Measures: Clinically significant psychotic symptoms in the past month, defined as a score of 4 or more on any of the Brief Psychiatric Rating Scale items of suspiciousness, hallucinations, or unusual thought content. The number of days of methamphetamine use in the past month was assessed using the Opiate Treatment Index.

Results: There was a 5-fold increase in the likelihood of psychotic symptoms during periods of methamphetamine use relative to periods of no use (odds ratio [OR], 5.3 [95% CI, 3.4-8.3]; $P<.001$), this increase being strongly dose-dependent (1-15 days of methamphetamine use vs abstinence in the past month: OR, 4.0 [95% CI, 2.5-6.5]; ≥16 days of methamphetamine use vs abstinence in the past month: OR, 11.2 [95% CI, 5.9-21.1]). Frequent cannabis and/or alcohol use (≥16 days of use in the past month) further increased the odds of psychotic symptoms (cannabis: OR, 2.0 [95% CI, 1.1-3.5]; alcohol: OR, 2.1 [95% CI, 1.1-4.2]).

Conclusions: There was a large dose-dependent increase in the occurrence of psychotic symptoms during periods of methamphetamine use among users of the drug.

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METHAMPHETAMINE IS used by an estimated 14 to 53 million people worldwide.[1] A major public health consequence of the drug's use is a transient psychotic reaction. This state is very similar to acute paranoid schizophrenia, which is characterized by persecutory delusions and hallucinations.[2,3] Other psychotic symptoms, such as bizarre behavior and thought disorder, have been documented but are less consistently observed.[2-4] Symptoms typically last hours to days and recede once the drug has been eliminated from the body.[5] In keeping with the psychotomimetic properties of methamphetamine, the prevalence of psychotic symptoms is high among people who use the drug,[5-10] particularly dependent users,[8] and, in turn, is higher than in other groups of interest (eg, the general population and users of other drugs).[6,8-10]

Despite the well-established association between methamphetamine use and psychotic phenomena, evidence of a causal linkage from epidemiological studies is lacking. This is because existing evidence is derived entirely from case reports[2-4] and cross-sectional studies.[5-10] In these types of studies, it is difficult to confirm that psychotic symptoms were not premorbid to methamphetamine use. This is not a trivial consideration because drug use is concentrated among segments of the population that have a high risk for psychosis, namely young

men[11,12] and individuals with comorbid risk factors for psychosis (eg, a history of mental disorders and adverse life events[13-16]). Given that surprisingly high rates of psychotic phenomena have been reported even in general population samples (eg, Kendler et al[17] found that 28% of the US general population endorsed 1 or more psychotic symptoms on a psychosis screening instrument, and, using a similar approach, Scott et al[18] found that 11% of Australians endorsed at least 1 psychotic symptom), it is important to understand to what extent psychotic symptoms among methamphetamine users are attributable to the drug compared with other risk factors for experiencing psychosis that occur in this population.

The application of so-called fixed-effects analysis to longitudinal data sets can overcome confounding by premorbid factors. This type of analysis examines the likelihood of an event (eg, psychotic symptoms) during periods when an individual is exposed to a risk factor (eg, methamphetamine use) relative to when they are not exposed to that risk factor. Examining changes within individuals over time eliminates confounding by preexisting individual characteristics and other "time-invariant" factors (eg, heritable traits, personality, age, sex, and prior adverse life events). Factors that vary over time (eg, changes in other drug use that co-occur with psychotic symptoms) need to be adjusted for, as in any conventional regression analysis. Fixed-effects analysis is commonly applied within the economics literature, and to a lesser extent within public health research, to strengthen the argument for causal attribution.[19,20]

The aim of the present study was to better understand the causal contribution of methamphetamine use to psychotic symptoms by applying fixed-effects analysis to longitudinal panel data from a prospective cohort of methamphetamine users.[21] The relationship between methamphetamine use and psychotic symptoms was assessed over 4 discrete noncontiguous 1-month periods, while adjusting for concurrent changes in other drug use.

METHOD

PARTICIPANTS AND PROCEDURE

A total of 278 participants met *DSM-IV* criteria for methamphetamine dependence on entry to the study, and none met *DSM-IV* criteria for lifetime schizophrenia or mania. *DSM-IV* diagnoses were assessed using the Composite International Diagnostic Interview.[22] Participants were selected from a larger study, the Methamphetamine Treatment Evaluation Study (MATES) cohort, which is detailed elsewhere.[21] In brief, the MATES cohort included 400 people entering community-based drug treatment services in Sydney and Brisbane, Australia, for methamphetamine use, and 101 methamphetamine users from Sydney who were not in treatment (ie, recruited through needle and syringe programs and outreach services) but who screened positive for dependence on methamphetamine. Other inclusion criteria for MATES were being at least 16 years old, a comprehension of English, being willing to participate in follow-up interviews, and not having been in methamphetamine treatment, other inpatient drug treatment, or in prison, in the month prior to entering the study. These latter exclusion criteria were necessary in MATES to obtain a naturalistic baseline measure of drug use.

From the MATES cohort, 17 participants were excluded because they did not meet *DSM-IV* criteria for methamphetamine dependence on recruitment. A further 59 participants were excluded because they met *DSM-IV* criteria for either lifetime schizophrenia or a lifetime manic episode, and 138 participants were excluded because this diagnostic information was not available (ie, these participants did not partake in the follow-up interviews when diagnoses were made). A further 9 participants were excluded because they had not used methamphetamine during any of the 1-month periods analyzed in the present study.

A structured interview schedule was administered at baseline and at each follow-up (3 months, 1 year, and 3 years after the baseline interview). Recruitment of the cohort took place in 2006 and 2007, and follow-up interviews spanned the period from 2006 to 2010. Interviews were conducted face to face or by phone. All participants provided informed consent, were volunteers, and were reimbursed for their time and travel expenses (up to A$40 per interview). All of the participants in the present study were reinterviewed at 3 and 12 months after entry into the cohort, and 83% (230 of 278) of participants were interviewed at 3 years. The present study used data on drug use, psychotic symptoms, and health and social functioning in the past month at each of these 4 time points, totaling 1064 months of data for all of the participants combined.

MEASURES

Psychotic Symptoms

Psychotic symptoms were defined as a score of 4 or greater on any of the Brief Psychiatric Rating Scale items of suspiciousness, unusual thought content, or hallucinations, in the past month. Brief Psychiatric Rating Scale scores of 4 or greater indicate clinically significant or pathological symptom intensity.[23] This procedure has been used previously to measure the prevalence of psychotic phenomena among methamphetamine users.[8] Ratings were made by trained interviewers (honors level psychology graduates or an equivalent), and weekly meetings were held to review Brief Psychiatric Rating Scale ratings in order to maintain interrater agreement and avoid rater drift.[24] A selection of interviews (n=42) were audiotaped and rated by a second interviewer for interrater reliability. Interrater agreement for the definition of psychotic symptoms used in our study was 93%, yielding a κ of 0.86.

Methamphetamine Use

The number of days of methamphetamine use in the past 4 weeks was assessed using the Opiate Treatment Index.[25] Self-reported abstinence from methamphetamine use was confirmed in a subsample of the entire MATES cohort (n=83) using hair analysis, with false reporting of abstinence occurring in only 6% of cases (detailed elsewhere[21]). Information on the main route of methamphetamine administration (oral, intranasal, smoked, or intravenous) during the past 4 weeks was also recorded.

Polydrug Use

The number of days of use in the past 4 weeks was measured for other drugs, including cannabis, heroin, cocaine, ecstasy, hallucinogens, alcohol, and tobacco.

Health and Social Functioning

Disability from poor physical and mental health in the past month was measured using the Physical and Mental Component Scales of the 12-Item Short Form, respectively. Disability was defined as a score of less than 40 (>1 SD below the normative mean).[26] Current employment status (unemployed, casual/part-time employment, full-time employment, student, or home duties), income (net legitimate income in the past fortnight), and living arrangement (public housing, privately rented dwelling, privately owned dwelling, parent's home, drug treatment center, boarding house/shelter or refuge, no fixed address, or other) were assessed at each time point. An unstable accommodation was defined as living in a boarding house/shelter or refuge, no fixed address, or "other" (which included caravans, sheds, or temporary accommodation with friends).

DESIGN AND STATISTICAL ANALYSIS

A repeated-measures within-subject design was used to examine the relationship between methamphetamine use and psychotic symptoms over 4 discrete 1-month time points. A fixed-effects logistic regression model was used to determine within-subject variability in how psychotic symptoms changed over time with concurrent changes in methamphetamine use. The main outcome measure was psychotic symptoms in the past month, the main predictor variable was number of days of methamphetamine use in the past month, and other drug use measures (number of days of other drug use in the past month) were treated as covariates. All of the variables used in this analysis were time varying (ie, measured at each 1-month period). Data were analyzed using Stata Special Edition version 11.2.[27] All tests were 2-sided with significance set at $P < .05$.

RESULTS

CHARACTERISTICS OF THE SAMPLE

Participants had a mean (SD) age of 31.7 (8.1) years. The majority were male participants (72%), single (72%), and unemployed (78%). Most were Australian born (89%) and nominated English as their preferred language (96%). They had a median of 10 years of schooling (range, 6-12 years of schooling), 44% had completed a tertiary technical or trade qualification, and 6% had completed a university degree.

All participants met *DSM-IV* criteria for methamphetamine dependence in the year prior to entering our study; they had used the drug for a mean (SD) of 13.1 (7.9) years, and 83% had injected it. Methamphetamine use occurred during 58% of the observed months. During months of methamphetamine use, participants used the drug on a median of 8 days (range, 1-28 days), and injection was typically their main route of administration (79%, compared with 14% smoking and 6% snorting or swallowing). Other drug use consisted primarily of tobacco (89% of months; median of 28 days of use), cannabis (57% of months; median of 20 days use), and alcohol (62% of months; median of 6 days use), with other drug use being less common.

Psychotic symptoms were present for 25% of the observed months, while 60% of the sample reported psychotic symptoms during at least one of the observed months in the study period. Of those months when psychotic symptoms were present, 71% involved suspiciousness, 35% involved unusual thought content (ie, delusions), and 51% involved hallucinations. Most of these symptoms were in the moderate rather than the severe range on the Brief Psychiatric Rating Scale (ie, scores of 4-5).

RELATIONSHIP BETWEEN PSYCHOTIC SYMPTOMS AND METHAMPHETAMINE USE

Unadjusted analyses showed that psychotic symptoms were more common during periods of methamphetamine use and that there was a strong dose-response effect between number of days of methamphetamine use and psychotic symptoms (**Table**). Psychotic symptoms were also predicted by other drug use (Table); however, the relationship between methamphetamine use and psychotic symptoms persisted after adjustment for the use of other drugs (model 1 in our Table). After adjusting for only those patterns of other drug use that showed evidence of an association with psychotic symptoms (ie, ≥16 days of alcohol and/or cannabis use in the past 4 weeks), we found that methamphetamine use was associated with a 5-fold increase in the odds of experiencing psychotic symptoms (odds ratio [OR], 5.3 [95% CI, 3.4-8.3]; $P < .001$) and that the dose-response effect remained (model 2 in our Table). This final model showed that frequent cannabis use and frequent alcohol use (ie, ≥16 days in the past 4 weeks) also increased the odds of experiencing psychotic symptoms.

The predicted probability of psychotic symptoms (based on model 2) is shown in our **Figure**. In the absence of any methamphetamine use and low levels of cannabis and alcohol use (<16 days), the probability of psychotic symptoms was 7%, and this increased in a dose-response manner to 48% with 16 days or more of methamphetamine use. The addition of frequent cannabis and/or alcohol use (≥16 days) increased the probability of psychotic symptoms to between 61% and 69% (Figure).

We also adjusted for concurrent changes in health and social functioning that co-occurred with psychotic symptoms (ie, unemployment, unstable accommodation, low income, higher levels of psychological distress, and disability from both poor physical health and poor mental health) and found that these factors could not account for the relationship between methamphetamine use and psychotic symptoms: 1-15 days of methamphetamine use vs abstinence resulted in an OR of 2.25 (95% CI, 1.29-3.90) ($P = .004$); 16 days or more of methamphetamine use vs abstinence resulted in an OR of 3.90 (95% CI, 1.80-8.45) ($P < .001$).

COMMENT

We found that the likelihood of experiencing psychotic symptoms was 5 times higher during periods of methamphetamine use than during periods of no use, with evidence of a strong dose-response effect. The risk of experiencing psychotic symptoms increased from a low baseline level during months of methamphetamine abstinence (7%) to 48% when participants were heavily using

Table. Relationship Between Drug Use and Psychotic Symptoms

Type of Drug Use	Psychotic Symptoms, No. (%) of months		Unadjusted Effects		Model 1[a]		Model 2[b]	
	No (n=791 mo)	Yes (n=273 mo)	OR (95% CI)	Univariate *P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Methamphetamine use								
No use (reference)	397 (50)	55 (20)						
1-15 d	303 (38)	126 (46)	4.8 (3.0-7.6)	<.001	4.2 (2.5-7.3)	<.001	4.0 (2.5-6.5)	<.001
16-28 d	91 (12)	92 (34)	15.8 (8.6-28.7)	<.001	12.0 (5.8-25.1)	<.001	11.2 (5.9-21.1)	<.001
Cannabis use								
No use (reference)	393 (50)	81 (30)						
1-15 d	201 (25)	67 (25)	2.4 (1.5-4.1)	.001	1.1 (0.6-2.0)	.88		
16-28 d	197 (25)	125 (46)[c]	7.2 (4.1-12.6)	<.001	2.2 (1.1-4.3)	.03	2.0 (1.1-3.5)[d]	.02
Alcohol use								
No use (reference)	310 (39)	103 (38)						
1-15 d	365 (46)	114 (42)	1.6 (1.0–2.5)	.07	0.9 (0.5-1.6)	.73		
16-28 d	116 (15)	56 (21)[c]	4.3 (2.2–8.5)	<.001	2.1 (0.9-4.8)	.09	2.1 (1.1-4.2)[d]	.03
Tobacco use	688 (87)	247 (90)	2.0 (0.8-5.0)	.12	0.9 (0.3-2.6)	.81		
Ecstasy use	86 (11)	58 (21)	2.8 (1.6-4.9)	<.001	1.1 (0.5-2.1)	.90		
Hallucinogen use	24 (3)	13 (5)	1.3 (0.5-3.5)	.59	0.3 (0.1-1.5)	.15		
Cocaine use	90 (11)	62 (23)	3.4 (2.0-6.0)	<.001	1.0 (0.5-1.9)	.87		
Heroin use	120 (15)	62 (23)	1.7 (1.0-3.0)	0.07	1.0 (0.5-1.9)	.88		

Abbreviation: OR, odds ratio.
[a] Simultaneous regression including all variables
[b] Simultaneous regression including only those factors that showed evidence of a relationship with psychotic symptoms. Variables with empty cells were not included in the model.
[c] Percentage does not total 100 owing to rounding error.
[d] Relative to less than 16 days of use.

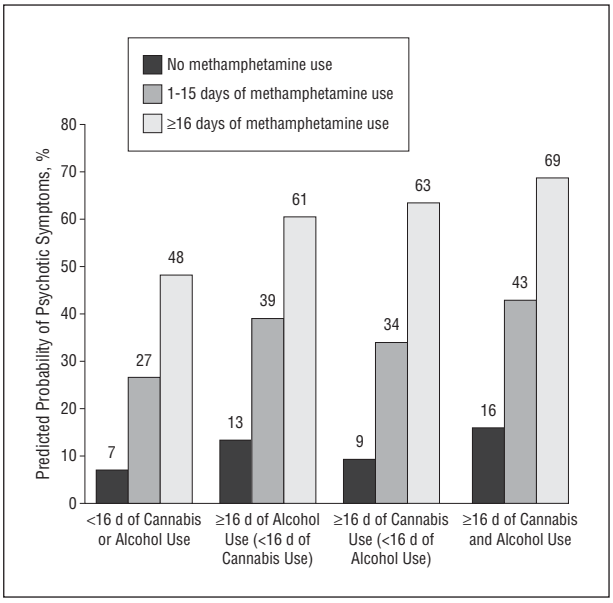

Figure. Predicted probability of psychotic symptoms by level of methamphetamine, alcohol, and cannabis use.

methamphetamine (≥16 days of use) and was further elevated with frequent cannabis and/or alcohol use (≥16 days) to between 61% and 69%.

The large increase in the risk of psychotic symptoms occurring during periods of methamphetamine use indicates a need to increase awareness of the drug's potential effect on mental health. Clinicians need to be vigilant for signs of methamphetamine use among patients who present with psychosis and to appreciate the role that methamphetamine plays in the generation of psychotic symptoms. Methamphetamine intoxication is marked by signs of sympathetic arousal (eg, dilated pupils, increased respiration, and increased blood pressure), hyperactivity, alertness, energy, wakefulness, and euphoria. Common signs of chronic use include anorexia, sleep disturbances, and a labile mood. Improved diagnostic guidelines would be helpful to distinguish between methamphetamine psychosis and schizophrenia because making this differentiation is fraught with difficulties, and current diagnostic criteria are poorly operationalized in diagnostic interview schedules.[28]

There is also a need for further investigation of potential treatments for methamphetamine psychosis.[29] Although existing evidence is insufficient to make clinical recommendations, drug treatment facilities that treat methamphetamine users nonetheless require skilled medical practitioners to prescribe antipsychotic medications and/or sedatives in the event of psychiatric emergencies. Protocols are needed for the emergency psychiatric management of patients presenting with methamphetamine psychosis; however, there is a broader need for the ongoing management of psychotic symptoms among methamphetamine users who seek help from drug treatment detoxification and rehabilitation services.[21]

Given that symptoms of psychosis show a strong temporal relationship with methamphetamine use and are most common during periods of heavy methamphetamine use, there is a good argument for providing methamphetamine treatment as a first-line intervention to reduce rates of psychosis among this population. The evidence base for treating methamphetamine dependence is limited,[30] with the current best evidence in favor of behavioral therapies, such as contingency management and cognitive behav-

ioral therapy.[31-34] Although these treatment options have been proven effective in clinical trials, they have not been widely implemented in practice. Implementing these treatments on a broader scale and/or developing other scalable effective treatment options would be effective strategies to reduce both problematic methamphetamine use and its psychiatric sequelae.

In our study, we were able to demonstrate a clear dose-response increase in the occurrence of psychotic symptoms during periods of methamphetamine use. However, we were unable to determine the chronicity of psychotic symptoms or whether methamphetamine use increased longer-term vulnerability to psychosis. Although psychotic symptoms abated during periods of abstinence from methamphetamine use for the vast majority of participants, there remained a small minority of users who reported psychotic symptoms during periods of abstinence. These individuals may have been experiencing a more chronic form of methamphetamine psychosis, as characterized by previous research,[35] with symptoms persisting beyond drug use into periods of abstinence. These residual symptoms could also reflect a lasting vulnerability to psychosis with chronic methamphetamine use, as proposed by Sato,[36] leaving the individual prone to psychotic symptoms irrespective of their current drug use. Finally, the occurrence of psychotic symptoms in the absence of methamphetamine use may reflect a premorbid state, for example, participants who had subthreshold symptoms of a psychotic disorder, such as schizophrenia, which were not sufficient to meet *DSM-IV* diagnostic criteria and, therefore, did not result in their exclusion from the sample.

Although fixed-effects models eliminate potential confounding from stable individual-level characteristics, such as sex and premorbid status, such models can still be confounded by time-varying factors (eg, life stressors that may increase the risk of developing psychotic symptoms). The present study controlled for changes in polydrug use that occurred during the study period, and we were also able to show that crude changes in demographics and well-being (eg, unemployment and psychological distress) could not account for the relationship between methamphetamine use and psychotic symptoms. However, there may have been unmeasured factors that co-occurred with methamphetamine use (eg, sleep deprivation[37,38]) that contributed to the manifestation of psychotic symptoms.

Although the fixed-effects analysis used in the present study provides better evidence of a causal relationship between methamphetamine use and psychosis than that provided by previous cross-sectional studies, it does not indicate the direction of causality. Although there is growing evidence of an association between cannabis use and psychotic symptoms,[39] and there is evidence that chronic heavy alcohol consumption can also cause psychotic symptoms,[14] within the constraints of the present study, it cannot be determined whether psychotic symptoms led methamphetamine users to consume more cannabis and/or alcohol, or whether more frequent use of these drugs induced psychotic symptoms. In the case of methamphetamine use, the direction of cause and effect is supported by numerous historical case reports of methamphetamine psychosis,[2-4] the experimental induction of psychotic symptoms,[40] and the strong dose-response relationship between methamphetamine use and psychotic symptoms observed in the present study.

The outcomes from our study apply to dependent methamphetamine users and should not be generalized to samples of recreational stimulant users or to the general population. Dependent methamphetamine users, by virtue of many years of stimulant use and a range of common risk factors of drug dependence and psychotic disorders, are likely to be more prone to psychosis than the general population. Moreover, mental health disorders are particularly high among drug users who seek treatment,[41] elevating the likelihood of psychotic phenomena among this sample of participants (who were primarily treatment seekers) compared with drug users in the community. This is an important consideration with regard to the association between psychotic symptoms and frequent alcohol and/or cannabis use. Although the present study found evidence that frequent use of these drugs was associated with an increased risk of experiencing psychotic symptoms, this risk may not apply to less vulnerable populations.

There was a large dose-dependent increase in the risk of experiencing psychotic symptoms during periods of methamphetamine use, which was further elevated by concurrent heavy alcohol and cannabis use. Given the widespread use of methamphetamine globally, greater awareness is needed about the potential effect of this drug on mental health. The association between heavy alcohol and cannabis consumption is likely to have even more far-reaching public health implications, although this association needs to be confirmed in broader population samples. Better evidence is needed on how to manage symptoms of methamphetamine-induced psychosis, and evidence-based treatments for methamphetamine dependence need to be more broadly implemented to curb the high levels of use that induce psychotic symptoms. Although psychotic symptoms appeared to be largely circumscribed to periods of methamphetamine use, the long-term effect of methamphetamine use on a person's vulnerability to psychosis needs to be better understood.

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