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**Changes in the risk of psychotic symptoms during periods of methamphetamine use:
evidence from a prospective longitudinal study**

Running title: Methamphetamine use and psychosis

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Abstract

Context: Methamphetamine is associated with psychotic phenomena but it is not clear to what extent this relationship is due to pre-morbid 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 four non-contiguous one-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:** Participants (N = 278)

were aged 16 or over, met DSM-IV criteria for methamphetamine dependence on entry to the study, and 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. Number of days of methamphetamine use in the past month was

assessed using the Opiate Treatment Index. **Results:** There was a five-fold increase in the

likelihood of psychotic symptoms during periods of methamphetamine use relative to periods of no use (OR 5.3, 95% CI 3.4-8.3, $p < 0.001$), this being strongly dose-dependent (cf.

abstinence in the past month; 1-15 days of use OR 4.0, 95% CI 2.5-6.5; 16+ days of use 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.

Introduction

Methamphetamine is used by an estimated 14-53 million people world-wide [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, being 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 higher than in other groups of interest (e.g., general population, 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 [e.g., 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 males [11,12], and among individuals with comorbid risk factors for psychosis (e.g., history of mental disorders, adverse life events [13-16]). Given that surprisingly high rates of psychotic phenomena have been reported even in general population samples (e.g., Kendler *et al.* found that 28% of the US general population endorsed one or more psychotic symptoms on a psychosis screening instrument [17], and using a similar approach Scott *et al.* found 11% of Australians endorsed at least one psychotic symptom [18]), it is important to understand to what extent psychotic symptoms among methamphetamine users are

attributable to the drug compared to 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 (e.g., psychotic symptoms) during periods when an individual is exposed to a risk factor (e.g., methamphetamine use) relative to when they are not exposed to that risk factor. Examining changes within individuals over time eliminates confounding by pre-existing individual characteristics and other ‘time invariant’ factors (e.g., heritable traits, personality, age, gender, prior adverse life events). Factors that vary over time (e.g., 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 current study was to better understand the causal contribution of methamphetamine use to psychotic symptoms by applying a fixed effects analysis longitudinal panel data from a prospective cohort of methamphetamine users [21]. The relationship between methamphetamine use and psychotic symptoms was assessed over four discrete non-contiguous one-month periods, while adjusting for concurrent changes in other drug use.

Method

Participants and procedure

Participants (N = 278) all 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 (CIDI) [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 (i.e., 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, 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 were excluded because they met DSM-IV criteria for either lifetime schizophrenia or a lifetime manic episode, and 138 were excluded because this diagnostic information was not available (i.e., 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 one-month periods analysed in the current study.

A structured interview schedule was administered at baseline and each follow-up (3 months, 1 year and 3 years after the baseline interview). Recruitment of the cohort took place in 2006 and 2007, while 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 AUD40 per interview). All of the participants in the current study were re-interviewed at 3 months and 12

months after entry to the cohort, and 83% (n = 230) were interviewed at 3 years. The current study used data on drug use, psychotic symptoms and health and social functioning in the past month at each of these four time points, totaling 1,064 months of data for all of the participants combined.

Measures

Psychotic symptoms: Psychotic symptoms were defined as a score of four or greater on any of the Brief Psychiatric Rating Scale (BPRS) items of suspiciousness, unusual thought content or hallucinations, in the past month. BPRS scores of 4+ 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 (honours level psychology graduates or equivalent) and weekly meetings were held to review BPRS ratings in order to maintain inter-rater agreement and avoid rater drift [24]. A selection of interviews (n = 42) were audio-recorded and rated by a second interviewer for inter-rater reliability. Inter-rater agreement for the definition of psychotic symptoms used in this study was 93%, yielding a kappa of 0.86.

Methamphetamine use: Days of methamphetamine use in the past four weeks was measured using the Opiate Treatment Index [25]. Self-reported abstinence from methamphetamine use was confirmed in a sub-sample of the entire MATES cohort (n = 83) using hair toxicology, with false reporting of abstinence occurring in only 6% of cases (detailed elsewhere [21]). Main route of methamphetamine administration (oral, intranasal, smoked, intravenous) during the past four weeks was also recorded.

Polydrug use: Days of use in the past four 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 Short Form 12 respectively. Disability was defined as a score below 40 (> 1 Standard Deviation below the normative mean) [26]. Current employment status (unemployed, casual/part-time, full-time, student, 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 centre, boarding house/shelter or refuge, no fixed address or other) were assessed at each time point. 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 four discrete one-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 days of methamphetamine use in the past month, and other drug use measures (days of other drug use in the past month) were treated as covariates. All of the variables used in this analysis were time-varying (i.e., measured at each one-month period). Data were analyzed using Stata SE version 11.2 [29]. All tests were two-sided with significance set at $p < 0.05$.

Results

Characteristics of the sample

Participants had a mean age of 31.7 years (SD 8.1 years). The majority were male (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), 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 the study; they had used the drug for a mean of 13.1 years (SD 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% cf. 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 (i.e., delusions), and 51% involved hallucinations. Most of these symptoms were in the moderate rather than the severe range on the BPRS (i.e., 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 days of methamphetamine use and psychotic symptoms (Table 1). Psychotic symptoms were also predicted by other drug use (Table 1); however, the relationship between methamphetamine use and psychotic symptoms persisted after adjustment for the use of other drugs (model 1, Table 1). After adjusting for only those patterns of other drug use that showed evidence of an association with psychotic symptoms (i.e., 16+ days of alcohol and/or cannabis use in the past four weeks), methamphetamine use was associated with a five-fold increase in the odds of experiencing psychotic symptoms (OR 5.3, 95% CI 3.4-8.3, $p < 0.001$) and the dose-response effect remained (model 2, Table 1). This final model showed that frequent cannabis use and frequent alcohol use (i.e., 16+ days in the past four weeks) also increased the odds of experiencing psychotic symptoms.

The predicted probability of psychotic symptoms (based on model 2) is shown in Figure 1. 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 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 1).

We also adjusted for concurrent changes in health and social functioning that co-occurred with psychotic symptoms (i.e., 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 (methamphetamine use cf. abstinence: 1–15

days OR 2.25, 95% CI 1.29–3.90, $p = 0.004$; 16 + days OR 3.90, 95% CI 1.80–8.45, $p < 0.001$).

[Table 1 and Figure 1 about here.](#)

Discussion

We found that the likelihood of experiencing psychotic symptoms was five 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 using heavily (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 indicates a need to increase awareness of the drug's potential impact 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 (e.g., dilated pupils, increased respiration, increased blood pressure), hyperactivity, alertness, energy, wakefulness and euphoria. Common signs of chronic use include anorexia, sleep disturbances and labile mood. Improved diagnostic guidelines would be helpful to distinguish between methamphetamine psychosis and schizophrenia, as 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]. While existing evidence is insufficient to make clinical recommendations,

drug treatment facilities that treat methamphetamine users none-the-less require skilled medical practitioners to prescribe anti-psychotic medication and/or sedation in the event of psychiatric emergencies. Not only are protocols needed for the emergency psychiatric management of patients presenting with methamphetamine psychosis, but 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 favour of behavioural therapies, such as contingency management and cognitive behavioural 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 an effective strategy to reduce both problematic methamphetamine use and its psychiatric sequelae.

In this 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. While 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 and colleagues [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 sub-threshold 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.

Limitations

While fixed effects models eliminate confounding by stable individual-level characteristics, such as gender and premorbid status, such models can still be confounded by time-varying factors (e.g., life stressors that may increase the risk of developing psychotic symptoms). The current 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 (e.g., unemployment, 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 (e.g., sleep deprivation [37, 38]) which contributed to the manifestation of psychotic symptoms.

Although the fixed effects analysis used in the current 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. While there is growing evidence of an association between cannabis use and psychotic symptoms [39], and chronic heavy alcohol consumption can also cause psychotic symptoms [38], within the constraints of the current 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 [e.g., 2-4], the experimental induction of psychotic symptoms [40], and the strong dose-response relationship between methamphetamine use and psychotic symptoms observed in the current study.

The outcomes from this 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 (who were primarily treatment seekers) compared to 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. While the current 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.

Conclusion

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 impact 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. While psychotic symptoms appeared to be largely circumscribed to periods of methamphetamine use, the long-term impact of methamphetamine use on a person's vulnerability to psychosis needs to be better understood.

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Figure 1. The predicted probability of psychotic symptoms by level of methamphetamine, alcohol and cannabis use.

Table 1. The relationship between drug use and psychotic symptoms

	Psychotic symptoms		Unadjusted effects	univariate	Model 1 ^a	Model 2 ^b		
	No (n = 791)	Yes (n = 273)	OR(95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Methamphetamine, No. months (%)								
No use (ref)	397 (50)	55 (20)						
1-15 days	303 (38)	126 (46)	4.8 (3.0-7.6)	< 0.001	4.2 (2.5-7.3)	< 0.001	4.0 (2.5-6.5)	< 0.001
16-28 days	91 (12)	92 (34)	15.8 (8.6-28.7)	< 0.001	12.0 (5.8-25.1)	< 0.001	11.2 (5.9-21.1)	< 0.001
Cannabis, No. months (%)								
No use (ref)	393 (50)	81 (30)						
1-15 days	201 (25)	67 (25)	2.4 (1.5-4.1)	0.001	1.1 (0.6-2.0)	0.88		
16-28 days	197 (25)	125 (46 ^c)	7.2 (4.1-12.6)	< 0.001	2.2 (1.1-4.3)	0.03	2.0 (1.1-3.5) ^d	0.02
Alcohol, No. months (%)								
No use (ref)	310 (39)	103 (38)						
1-15 days	365 (46)	114 (42)	1.6 (1.0-2.5)	0.07	0.9 (0.5-1.6)	0.73		
16-28 days	116 (15)	56 (21 ^c)	4.3 (2.2-8.5)	< 0.001	2.1 (0.9-4.8)	0.09	2.1 (1.1-4.2) ^d	0.03
Tobacco, No. months (%)	688 (87)	247 (90)	2.0 (0.8-5.0)	0.12	0.9 (0.3-2.6)	0.81		
Ecstasy, No. months (%)	86 (11)	58 (21)	2.8 (1.6-4.9)	< 0.001	1.1 (0.5-2.1)	0.90		
Hallucinogen, No. months (%)	24 (3)	13 (5)	1.3 (0.5-3.5)	0.59	0.3 (0.1-1.5)	0.15		
Cocaine, No. months (%)	90 (11)	62 (23)	3.4 (2.0-6.0)	< 0.001	0.1 (0.5-1.9)	0.87		
Heroin, No. months (%)	120 (15)	62 (23)	1.7 (1.0-3.0)	0.07	1.0 (0.5-1.9)	0.88		

^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 due to rounding error.

^d Relative to less than 16 days of use