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The contribution of cannabis use to psychotic symptoms among methamphetamine treatment entrants

NDARC Technical Report No. 294

THE CONTIBUTION OF CANNABIS USE TO PSYCHOTIC SYMPTOMS AMONG METHAMPHETAMINE TREATMENT ENTRANTS

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Technical Report Number 294

ISBN: 978-0-7334-2652-0

TABLE OF CONTENTS

List of Tables

List of figures

ACKNOWLEDGMENTS

This research was funded by the Australian Government Department of Health and Ageing. Data was collected as part of the Methamphetamine Treatment Evaluation Study (MATES) which was funded by both the Australian Government Department of Health and Ageing and the National Health and Medical Research Council (NHMRC).

EXECUTIVE SUMMARY

Background and aims

Methamphetamine users are at a high risk of psychosis due to the drug's psychosis-inducing action and the higher prevalence of chronic psychotic illnesses among this group compared with the general population. High levels of cannabis use among methamphetamine users may also contribute to their risk of experiencing psychotic symptoms: there is growing evidence that cannabis may increase the risk of psychotic symptoms, particularly among people who are vulnerable to psychosis.

The current study aimed to examine whether cannabis use was associated with a higher prevalence of clinically significant psychotic symptoms among methamphetamine treatment entrants. The study utilised baseline data from the Methamphetamine Treatment Evaluation Study (MATES) to determine whether symptoms of psychosis in the month prior to treatment entry were related to the frequency of cannabis use or the severity of cannabis dependence during this time. Further analyses were undertaken to determine whether any relationship between cannabis use and psychotic symptoms could be better accounted for by concurrent methamphetamine or other drug use, demographic factors or comorbid psychiatric conditions. Based on previous evidence, it was expected that:

1. cannabis use would be associated with a small to moderate dose-response increase in psychotic symptoms among methamphetamine treatment entrants;
2. the relationship between cannabis use and psychosis would be more pronounced among people with a history of a chronic psychotic disorder (i.e. Schizophrenia, Schizoaffective Disorder, or Bipolar Affective Disorder);
3. the relationship between cannabis use and psychosis would be attenuated by controlling for other drug use, demographics and comorbid psychiatric disorders.

Methods

This study utilised baseline data collected as part of the Methamphetamine Treatment Evaluation Study (MATES), a large-scale ongoing longitudinal study of treatment outcomes for methamphetamine dependence. Participants in the study were individuals entering drug treatment (residential rehabilitation, detoxification or counselling) with methamphetamine as a primary or secondary drug of concern. Participants were interviewed soon after treatment entry regarding their cannabis use and psychotic symptoms in the month prior to treatment. Cannabis measures included number of days used cannabis in the past month (frequency), and Severity of Dependence Scale score in the past month (dependence). Psychotic symptoms were measured using the Brief Psychiatric Rating Scale (BPRS) subscales of suspiciousness, unusual thoughts, and hallucinations applied to the past month. BPRS subscale scores range from one to seven, with a score of four or more indicating a symptom is clinically significant. In addition, information was collected about methamphetamine use, previous diagnoses with a chronic psychotic disorder and a range of demographic, drug use and additional mental health variables. Major Depression, Social Phobia and Panic Disorder in the past year were measured using the Composite International Diagnostic Interview (CIDI). Chronic psychosis was defined as having being told by a doctor the participant may have Schizophrenia, Schizoaffective Disorder or Bipolar Affective Disorder.

The prevalence of psychotic symptoms was examined for the total sample and the sample stratified by having been diagnosed with a chronic psychotic disorder. Spearman correlations were carried out to examine univariate relationships between cannabis use (frequency and dependence) and the severity of psychotic symptoms (suspiciousness, unusual thoughts, and hallucinations) and to identify potential confounders. Confounders were defined as variables significantly related to both cannabis use and psychotic symptoms ($p<0.05$). Logistic regression analyses were carried out to examine the association between past month cannabis use and clinically significant past month psychotic symptoms. Both unadjusted and adjusted odds ratios were estimated with analyses controlling for previous psychotic diagnosis and potential confounders. Analyses of the sample were stratified by whether participants had a diagnosis with a chronic psychotic disorder to examine whether the relationship between cannabis use and psychotic symptoms varied between methamphetamine users with and without a history of a chronic psychotic illness.

Results

Participants were typically male (75%), 31 years old (mean), and unemployed (80%). Nearly all were dependent on methamphetamine (97%), and they had used the drug on a median of 16 days in the month prior to treatment (range 0–28). Nearly all (98%) reported lifetime cannabis use, and they had used cannabis on a median of 14 days in the past month. Twenty-one per cent of participants had a history of a chronic psychotic disorder (i.e. they reported having previously been told by a doctor they had Schizophrenia, Schizoaffective Disorder or Bipolar Affective Disorder).

Fifty-two per cent of participants reported a clinically significant psychotic symptom in the month before treatment, with suspiciousness being more common than unusual thought content or hallucinations (38%, 26% and 31% respectively). When the sample was restricted to participants previously diagnosed with a chronic psychotic disorder (n=84), prevalence of reporting a clinically significant psychotic symptom in the past month increased (71%) with hallucinations most common, followed by suspiciousness, and unusual thoughts (53%, 48% and 37% respectively). Among those participants without a history of a chronic psychotic disorder (n=316) the prevalence of reporting a clinically significant psychotic symptom in the past month was slightly smaller, with suspiciousness the most commonly reported symptom, followed by hallucinations and unusual thoughts (35%, 24% and 22% respectively).

In univariate analyses cannabis use (days used and dependence) was associated with more severe suspiciousness (r_s=0.138, $p<0.01$; r_s=0.157, $p<0.01$) and unusual thoughts (r_s=0.137, $p<0.01$; r_s=0.164, $p<0.01$), but not hallucinations (r_s=0.013, $p>0.05$; r_s=0.024, $p>0.05$). In logistic regression analyses, the unadjusted odds ratios for cannabis use (days used and dependence) as a predictor of clinically significant suspiciousness and unusual thoughts indicated small positive relationships (days of use OR=1.3 to 2.0; dependence OR=1.7 to 2.7). The relationship between cannabis use and suspiciousness was attenuated and no longer significant after controlling for potential confounders, including pre-existing psychotic disorders, methamphetamine use, age of first use, and past year anxiety disorders (OR=1.2 to 1.5, $p>0.05$). The relationship between cannabis use and unusual thoughts was similarly

attenuated after controlling for potential confounders, with only moderate cannabis use associated with increased risk of unusual thoughts (OR=2.5, $p<0.05$). When the sample was restricted to participants with a history of a chronic psychotic disorder, the odds ratios (both unadjusted and adjusted) between cannabis use and suspiciousness were slightly smaller than for the total sample (psychotic disorder OR=0.9 to 1.6; adjusted OR=0.6 to 1.0), while the odds ratios for cannabis use as a predictor of unusual thoughts was similar to those in the total sample (psychotic disorder OR=1.0 to 2.5; adjusted OR=1.0 to 2.9). None of the relationships between cannabis use and psychotic symptoms were statistically significant when the sample was restricted to participants with a history of a chronic psychotic disorder. Among those participants without a history of a chronic psychotic disorder, the odds ratios between cannabis use and suspiciousness were a similar size to the total sample (OR=1.4 to 1.9; adjusted OR=1.3 to 1.6), as were the odds ratios between cannabis use and unusual thoughts (OR=1.6 to 2.5; adjusted OR=1.5 to 2.4). The current study found no evidence of a relationship between cannabis use and hallucinations.

Discussion

The current study found that the relationship between cannabis use and psychotic symptoms among methamphetamine treatment entrants is small and largely accounted for by other factors, including worse methamphetamine use and increased likelihood of pre-existing psychotic disorders and anxiety disorders. The risk of experiencing psychosis associated with cannabis use was similar, or possibly less, with regards to suspiciousness among methamphetamine users with a history of a chronic psychotic disorder. Future studies examining the relationship between cannabis use and psychosis among methamphetamine users need to adjust for methamphetamine use, pre-existing psychotic disorders, and anxiety disorders. The current study indicates that advising methamphetamine treatment entrants to reduce cannabis use will have a small impact, at most, on their psychotic symptoms.

1. INTRODUCTION

1.1 Methamphetamine use and psychotic symptoms

Methamphetamine users are at high risk for experiencing psychosis. This risk results from a number of factors, including higher rates of psychotic illness among users of methamphetamine, the impact of methamphetamine use on pre-existing psychotic illness, and the psychosis-inducing action of the drug. A recent Australian study found that 13% of methamphetamine users screened positive for psychosis in the past year, and 23% reported experiencing clinically significant suspiciousness, unusual thought content or hallucinations during this period. The prevalence of psychotic symptoms among methamphetamine users was estimated to be 11 times higher than that seen among the Australian general population (McKetin et al., 2006).

The potential for methamphetamine to induce a transient psychotic state is well established (Connell, 1958). This effect has been observed in both clinical and experimental human studies (Bell, 1965; Davis and Schlemmer, 1980; Bell, 1973; Jonsson and Sjostrom, 1970) as well as animal research (Robinson and Becker, 1986; Ellison and Eison, 1983). Psychotic symptoms are temporally associated with methamphetamine use and typically last only a few hours (Curran et al., 2004), with more severe cases usually abating within a week of ceasing methamphetamine use (Chen et al., 2003). Methamphetamine-induced psychosis has a clinical presentation similar to paranoid schizophrenia, and is characterised by persecutory delusions, and auditory and/or visual hallucinations (Moorefield et al., 2004; Sato et al., 1992; Yui et al., 2000).

As well as inducing a transient psychotic state, in a minority of cases methamphetamine use is associated with longer lasting symptoms which recur in the absence of further methamphetamine use (Chen et al., 2003; Sato et al., 1992; Moorefield et al., 2004; Yui et al., 2000). In such cases symptoms last for months after ceasing use of the drug, with some examples of symptoms lasting years. Whether such symptoms represent a distinct clinical entity or schizophrenia is the subject of ongoing debate (Chen et al., 2003; Chen et al., 2005; Harris and Batki, 2000; Kokkinidis and Anisman, 1981). A number of studies have compared methamphetamine-induced psychosis with schizophrenia, with some concluding that methamphetamine psychosis is distinguishable by the absence of thought disorder, less

prominent negative symptoms and more prominent visual hallucinations (Yui et al., 2000), and others concluding that the two conditions are indistinguishable, with methamphetamine psychosis resembling the paranoid subtype of schizophrenia (Connell, 1958).

While the prevalence of psychosis is high among methamphetamine users, not all users of the drug experience psychotic symptoms. Currently identified risk factors for experiencing methamphetamine-induced psychosis are heavier use and/or dependence on the drug, and a predisposition or proneness to experiencing psychosis. While a single dose of methamphetamine is enough to bring on a transient psychotic episode in some instances (Curran et al., 2004; Murray, 1998), heavy use of methamphetamine and dependence on the drug is associated with increased likelihood of experiencing psychosis following methamphetamine use (McKetin et al., 2006; Farrell et al., 2002; Hall et al., 1996; Chen et al., 2003). There is also some indication that high-dose binge use of methamphetamine, typical of abuse, often precedes the onset of psychotic symptoms (Segal and Kuczenski, 1997). In addition to patterns of methamphetamine use, there is some evidence that a pre-existing proneness to psychosis increases the risk of experiencing psychotic symptoms following methamphetamine use (Chen et al., 2003; Chen et al., 2005). Chen and colleagues (Chen et al., 2003) found that psychotic methamphetamine users had more significant pre-morbid schizoid and schizotypal personality traits than non-psychotic methamphetamine users, and that these traits were positively related to how long psychosis persisted. A related study by the same authors found that psychotic methamphetamine users had greater familial loading for psychotic disorders (OR=5.4) compared with methamphetamine users who never became psychotic, and the greater this loading the longer psychosis lasted (Chen et al., 2005).

Methamphetamine use is also known to exacerbate psychotic symptoms among people suffering from schizophrenia and other psychotic illnesses (Harris and Batki, 2000; Yui et al., 2000). Curran (2004) reviewed studies which examined differences in psychotic response to stimulants in control subjects, individuals with schizophrenia in remission, and individuals with schizophrenia with pre-existing acute psychotic symptoms. There was a temporary increase in positive psychotic symptoms in over half of those with schizophrenia with acute symptoms, over a quarter of those with schizophrenia in remission, and 10% of control subjects. This is of particular clinical relevance given that methamphetamine users are more likely to suffer from schizophrenia and other psychotic disorders than the general population

(Degenhardt and Hall, 2001; Andrews et al., 2001a; Regeir et al., 1990; Anthony and Helzer, 1991).

1.2 Cannabis use and psychotic symptoms

The issue of whether cannabis use is associated with psychosis has received a great deal of research attention. Experimental and clinical research has indicated that cannabis can induce a transient psychotic state, increasing psychotic symptoms in healthy controls as well as precipitating and exacerbating relapse and/or increase in psychotic symptoms in individuals with a pre-existing psychotic illness (Green et al., 2003; Gupta et al., 1996; Darold, 1978; Hides et al., 2006). There is also a growing body of clinical and epidemiological data documenting the association between cannabis use and later psychosis or schizophrenia, in the absence of intoxication (Fergusson et al., 2005; Arseneault et al., 2004; Smit et al., 2004). While the causal nature of this association has not been confirmed, it suggests cannabis use could play a role in developing or triggering vulnerability to psychosis (Hall and Degenhardt, 1999).

Cannabis intoxication and psychosis

A number of studies have looked at current cannabis use and temporally-related transient psychotic symptoms. Experimental studies provide evidence that cannabis use increases psychotic symptoms in individuals with a pre-existing psychotic illness as well as healthy controls (D'Souza et al., 2005; D'Souza et al., 2004). D'Souza's (2005) study of the effects of delta-9-tetrahydrocannabinol (the principal active ingredient of cannabis) on psychosis and cognition among schizophrenic patients found modest, brief, transient exacerbation of core psychotic symptoms in schizophrenic patients, despite the fact they were clinically stable on therapeutic doses of antipsychotics. This is consistent with clinical and observational studies which have demonstrated an increased relapse rate in schizophrenic patients who use large amounts of cannabis (Linszen et al., 1998; Linszen et al., 1994).

The association between recent cannabis use and increased psychotic symptoms has also been found in non-clinical samples (D'Souza et al., 2004; Skosnik et al., 2001; Verdoux et al., 2002; Verdoux et al., 2003). For example, Verdoux (2003) examined the association between cannabis use, psychosis proneness and psychotic experiences in daily life among university students. Participants were classified as either low, medium or high on psychosis proneness

and then asked to complete ambulatory self-assessment of cannabis use and psychotic experiences at approximately three-hourly intervals over a week. Psychotic experiences were measured using four questions which asked participants to rate the perceived hostility of their situation, as well as any strange impressions, unusual perceptions or thought influence they experienced since the previous measurement occasion. Results indicated both cannabis use and vulnerability to psychosis were independently associated with transient psychotic symptoms and there was an interaction between these factors. There was a trend towards participants with high psychosis proneness being more likely to experience unusual perceptions and thought influence in periods of cannabis use; however, this effect was not observed among those low on psychosis proneness. Subjects low on psychosis proneness were significantly less likely to report perceived hostility (i.e. more likely to find people and the atmosphere friendly) in periods of cannabis use compared with periods not marked by cannabis use. This effect was not observed among participants high on psychosis proneness. A related study by the same authors found that among female university students frequency of cannabis use in the past month was independently associated with the intensity of both positive and negative psychotic experiences (Verdoux et al., 2002). This association was specific to cannabis and psychosis and was not seen for alcohol and psychosis, or cannabis and depression. The authors controlled for alcohol use and measured other drug use, but were unable to control for other drug use due to the very small frequency of use of other substances. A similar study with a non-clinical sample found consistent results; however, the association was limited to positive symptoms (Skosnik et al., 2001).

Lifetime cannabis use and later psychosis

Epidemiological research documents the observed association between lifetime cannabis use and later psychosis or schizophrenia. This association has been observed between any cannabis use, and heavier cannabis use, with many studies finding a dose response relationship, such that the risk of psychosis gets larger when more cannabis is used (Moore et al., 2007; Smit et al., 2004; Zammit et al., 2002). Some studies have also raised the possibility that exposure to cannabis at a critical time, specifically before the age of 15 (Arseneault et al., 2004; Stefanis et al., 2004), increases vulnerability to later psychosis, although this finding may reflect exposure to greater cumulative risk, rather than a sensitive period (Moore et al., 2007).

The association between cannabis use and later psychosis has been found in relation to a spectrum of outcomes, including self-reported psychotic symptoms through to schizophrenia (Smit et al., 2004). While the observed association is clear, whether or not it represents a causal relationship remains unclear. There is some speculation that the observed association is the result, or partially the result of, self-medication (Dornan et al., 2004). That is, people take cannabis to reduce some of the negative symptoms of schizophrenia or side effects of prescribed medications. The data in relation to this hypothesis is mixed, but longitudinal research has established that the effect is observed when cannabis use precedes psychotic symptoms (Fergusson et al., 2005; Zammit et al., 2002).

While longitudinal studies have provided fairly good data supporting an association between cannabis use and increased risk of later psychotic symptoms, they have been unable to completely address the possibility that the observed association is due to confounding factors or a third variable (i.e. a common vulnerability to both cannabis use and psychosis). Studies have controlled for a range of possible confounders, including use of other drugs, and have generally found that after adjusting for confounders the association between cannabis exposure and later psychosis is reduced but remains significant (Moore et al., 2007; Smit et al., 2004). The reduction in effect size after controlling for confounders has led some researchers to conclude that the observed association would disappear altogether if it was possible to control for all confounding factors (Weiser and Shlomo, 2005).

While uncertainty remains regarding whether the observed relationship is causal, it is hypothesised that cannabis use acts to increase vulnerability, particularly in already genetically vulnerable people but also in those without pre-existing vulnerability, lowering an individual's threshold for exhibiting psychotic symptoms. As with methamphetamine use, not everyone who uses cannabis will go on to develop psychosis or schizophrenia. The vast majority of people who use cannabis don't go on to develop psychosis; however, it is estimated that using cannabis roughly doubles an individual's chance of developing schizophrenia. It is not clear what additional risk factors make an individual more likely to develop psychosis following cannabis use, if indeed cannabis use is an etiological factor; however, it seems likely that vulnerability to psychosis is one factor (van Os et al., 2002; Caspi et al., 2005; Degenhardt et al., 2007; McGuire et al., 1995).

1.3 Methamphetamine and cannabis use and psychotic symptoms

No studies were found specifically examining the relationship between cannabis use and psychotic symptoms among methamphetamine users. A recent study looking at psychotic symptoms among methamphetamine users controlled for cannabis use but did not go beyond this in examining the relationship (McKetin et al., 2006). Similarly, epidemiological studies of the relationship between methamphetamine and psychosis have controlled for cannabis, and vice versa (Farrell et al., 2002; Hall and Degenhardt, 1999).

The high levels of cannabis use among methamphetamine users may contribute to the high prevalence of psychotic symptoms in this population. Drug treatment data indicates that a substantial proportion of clients entering treatment for methamphetamine report concurrent problems with cannabis (Australian Institute of Health and Welfare, 2007). The issue of whether cannabis use is associated with increased psychotic symptoms among methamphetamine treatment entrants is clinically relevant. Improved understanding of the role of cannabis will provide useful information - for example, whether to encourage clients to stop using cannabis as well as methamphetamine in order to alleviate psychotic symptoms.

1.4 The present study

The first aim of the present study was to examine whether cannabis use is associated with increased symptoms of psychosis and whether this relationship is dose-related. These relationships will be examined controlling for methamphetamine use, previous diagnosis of a psychotic illness (including Schizophrenia, Schizoaffective Disorder and Bipolar Affective Disorder) and other potential confounders. It was expected that cannabis use would be associated with a small to moderate dose-response increase in psychotic symptoms among methamphetamine treatment entrants, and this relationship would be attenuated after controlling for drug use, demographics and comorbid psychiatric disorders.

The second aim of the present study was to examine the relationship between cannabis use and psychotic symptoms separately for methamphetamine users with and without a history of a chronic psychotic illness. Previous research has indicated that cannabis use is associated with increased risk of relapse among individuals with a chronic psychotic illness, and it was expected that the relationship between cannabis use and psychotic symptoms would be

stronger among people with a history of a chronic psychotic disorder (including Schizophrenia, Schizoaffective Disorder, and Bipolar Affective Disorder).

In order to address these aims, data from the Methamphetamine Treatment Evaluation Study (MATES) - a large-scale longitudinal study of treatment outcomes for methamphetamine dependence - was utilised. Data from MATES was used to examine the relationship between cannabis use (both frequency and dependence) and psychotic symptoms (including suspiciousness, unusual thoughts and hallucinations) during the same period.

2. METHODS

2.1 Participants and procedure

This study utilised baseline data collected as part of the Methamphetamine Treatment Evaluation Study (MATES), a large-scale ongoing longitudinal study of treatment outcomes for methamphetamine dependence. Baseline data were collected between January 2006 and October 2007. Participants included individuals entering drug treatment centres with methamphetamine as a primary or secondary drug of concern. Drug treatment centres included in the recruitment pool were selected from those included in the Alcohol and Other Drug Treatment Services National Minimum Data Set (Australian Institute of Health and Welfare, 2006) within the greater Sydney metropolitan area, the Wollongong area and the greater Brisbane metropolitan area. The sample was recruited from a total of 27 treatment agencies. Index treatment modalities included detoxification facilities, drug-free residential rehabilitation agencies and drug counselling services. All individuals entering participating treatment centres were screened for eligibility for the study by treatment centre staff. Eligibility for inclusion in the study included: (i) no treatment for methamphetamine dependence in the preceding month, (ii) no imprisonment in the past month, (iii) no inpatient hospitalisation in the past month, (iv) aged 16 years or over, and (v) agree to give contact details for follow-up interviews. Eligibility criteria (i) to (iii) were included so that baseline data reflected a period of typical drug use, criterion (iv) as a requirement of ethics approval, and criterion (v) to enable participant follow-up.

The baseline sample included 400 individuals entering drug treatment with methamphetamine as a primary or secondary drug of concern. In addition to those who participated in the study at baseline, a further 116 individuals entering treatment for methamphetamine were screened but found to be ineligible; 65% as the result of drug treatment in the past month, 27% as the result of prison in the past month, and the remaining 8% for a variety of reasons including insufficient contact information and being under 16 years of age.

All participants completed informed consent and were reimbursed $30 per interview for time and travel expenses. Baseline data was collected via a face-to-face structured interview which took approximately one and a half to two hours to complete and was conducted as

soon as possible after treatment entry. The median number of days between entering treatment and being interviewed was four (range 0 to 29 days).

2.2 Measures

Demographics: demographics included current age, sex, employment status, country of birth, number of years of schooling completed, prison history, and net income in the past fortnight. Poverty was defined as an income below the Henderson poverty line (Melbourne Institute of Applied Economic and Social Research, 2007).

Psychotic symptoms: psychotic symptoms in the month prior to treatment entry were assessed using the Brief Psychiatric Rating Scale (BPRS) subscales of suspiciousness, unusual thought content and hallucinations (Ventura et al., 1993). These subscales assess the psychotic symptoms which characterise methamphetamine psychosis (Moorefield et al., 2004; Sato et al., 1992; Yui et al., 2000). The BPRS subscales assess symptom severity (ranging from one to seven) with a score of four or greater indicating symptoms of clinical significance (Ventura et al., 1993).

Other psychopathology: history of a chronic psychotic disorder (Schizophrenia, Schizoaffective Disorder, or Bipolar Affective Disorder) was assessed by asking participants whether they had ever been told by a doctor that they may have Schizophrenia, Schizoaffective Disorder, or Bipolar Affective Disorder). History of a diagnosis with 'drug-induced psychosis' and Attention-Deficit/Hyperactivity Disorder (ADHD) were assessed by asking whether they had ever been told by a doctor that they had either of these conditions. The Composite International Diagnostic Interview (CIDI) was used to assess whether participants met criteria for past year Major Depression, Social Phobia and Panic Disorder (with or without Agoraphobia) according to the Diagnostic and Statistical Manual of Mental Disorders (4th Edition; DSM–IV) (American Psychiatric Association, 2000). Psychological distress in the past month was measured using the Kessler Psychological Distress Scale (K10). Higher scores on this scale reflect higher levels of psychological distress (Kessler et al., 2000).

Cannabis use: frequency of cannabis use and cannabis dependence in the past month were measured and examined as predictors of psychotic symptoms. Frequency of cannabis use

was measured by asking participants on how many days they used cannabis in the past month, while cannabis dependence in the past month was measured using the Severity of Dependence Scale (SDS), a five-item scale that yields scores ranging from 0 to 15 (Gossop et al., 1995). Lifetime use and frequency of cannabis use in the past year were also measured. Self-reported drug use has been shown to be accurate, particularly when confidentiality is assured (as it was in this study) (Babor et al., 1987; Hser et al., 1992; Hser et al., 1999).

Methamphetamine use: frequency of methamphetamine use in both the past year and past month were measured. Frequency of methamphetamine use in the past month was measured by asking participants on how many days they had used methamphetamine, and the number of methamphetamine use occasions per day was measured using the methamphetamine use section of the Opiate Treatment Index (OTI). Main route of methamphetamine administration in the past month was also measured. Methamphetamine dependence in the past month was measured using the SDS, while the CIDI was used to assess past year methamphetamine Abuse and Dependence according to DSM-IV criteria, as well as age of onset of Dependence. Additional measures of methamphetamine use included age at first use, lifetime history of methamphetamine injection, and age first injected methamphetamine.

Other drug use: past year use and frequency of past month use (days) of all other major drug classes was measured. Age of first intoxication, lifetime injecting history and age of first injection were also measured.

Treatment characteristics: information about current and previous drug and alcohol treatment, and lifetime and past month prescription of antidepressant and antipsychotic medication, was collected.

2.3 Statistical analyses

Descriptive analyses were carried out to assess the sample. Medians were reported for non-normal data.

Spearman correlations were used to examine univariate relationships between cannabis use measures in the month prior to treatment (days of use and SDS score) and scores on each of the BPRS subscales (suspiciousness, unusual thoughts, and hallucinations) during this time. Potential confounders were defined as those variables that had a significant Spearman correlation ($p<0.05$) with both the BPRS subscale score and the cannabis use measure. In identifying confounders, demographics, drug use and mental health variables were considered.

Logistic regression was used to examine the relationships between cannabis use measures and clinically significant suspiciousness, unusual thoughts, and hallucinations (BPRS score greater than or equal to four). As a first step, unadjusted odds ratios were estimated for the relationship between each cannabis use measure and clinically significant symptoms on each BPRS subscale. Subsequent logistic regression models were used to derive odds ratios adjusted for previous diagnosis with a chronic psychotic disorder (Schizophrenia, Schizoaffective Disorder, and Bipolar Affective Disorder) as well as potential confounders (see Appendix for a list of potential confounders included in each logistic regression). Non-normal data were either normalised using a log transformation or collapsed into categories. Analyses which included frequency of cannabis use categorised days used cannabis as 'no use' (0 days), 'some use' (1–19 days), and 'almost daily or more use' (20–28 days). Analyses which included cannabis dependence categorized SDS scores as 'no use', 'no/low dependence' (SDS score = 0–2), 'moderate dependence' (3–7), and 'severe dependence' (8–15). Age first used methamphetamine was categorized as '0–17 years', '18–24 years', and '25+ years' and frequency of past month methamphetamine use categorized as 'little use' (0–7 days), 'moderate use' (8–19 days) and 'heavy use' (20–28 days). OTI methamphetamine score was categorised into 'less than daily' use and 'daily or more', and age first intoxicated was categorised into 'less than 15 years' of age, and '15 years and over'.

3. RESULTS

3.1 Characteristics of the sample

3.1.1 Demographics

Participants had a mean age of 31 years (SD 7.7) and three-quarters were male. The majority of the sample was born in Australia and thirty-nine percent reported a prison history. They had completed a median of 10 years of secondary education (range 0–12) and the majority were unemployed. Consistent with this, over three-quarters of the sample had an income (past fortnight) below the Henderson poverty line (Table 1).

3.1.2 Mental health history

Twenty-one per cent of the sample had a history of a chronic psychotic disorder (i.e. Schizophrenia, Schizoaffective Disorder, or Bipolar Affective Disorder). Just over a third of participants (34%) reported having previously been diagnosed with drug-induced psychosis by a doctor. Eighteen per cent of the sample reported having been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) by a doctor.

3.1.3 Other psychopathology

Forty-eight percent of the sample met DSM-IV criteria for Major Depression (past year), 24% for Panic Disorder (past year), and 24% for Social Phobia (past year). High levels of general psychological distress were also evident among participants as indicated by scores on the K10 (median 32, range 10–50).

3.1.4 Treatment characteristics

According to treatment agency records, methamphetamine was the primary drug of concern for 79% of participants, and a secondary drug of concern for the remaining 21%. When recruited into the study, just over half of the sample was entering residential rehabilitation, 37% detoxification facilities, and 10% drug counselling services. For 31% of participants this was their first entry to drug and alcohol treatment, while the remaining 69% had started treatment before. Very few participants were enrolled in opioid maintenance therapy. Sixteen per cent of participants had filled a prescription for antidepressants in the previous month, and 64% had been prescribed antidepressants in their lifetime. Eleven per cent of

participants filled a prescription for antipsychotics in the previous month, and 29% had been prescribed antipsychotics in their lifetime.

Table 1: Characteristics of the sample

	Total sample (N=400)
Demographics	
Age (mean)	31
Sex (% male)	75
Born in Australia (%)	87
Prison history (%)	39
Years of schooling (median)	10
Employment (%)	
Unemployed	81
Full-time employment	9
Casual/part-time employment	6
Home duties	3
Studying	2
Income below Henderson poverty line (%)	79
Self-reported history of chronic psychotic disorder[a] (%)	21
Self-reported history of ADHD (%)	18
DSM–IV diagnosis in the past year (%)	
Major Depression	48
Social Phobia	24
Panic Disorder[b]	24
Treatment characteristics	
Primary drug of concern (% methamphetamine)	79
Type of treatment (%)	
Residential rehabilitation	53
Detoxification	37
Drug counselling	10
First drug treatment episode (%)	31
Currently enrolled in opioid maintenance therapy (%)	3

[a]Schizophrenia, Schizoaffective Disorder or Bipolar Affective Disorder
[b]With or without Agoraphobia

3.2 Drug use

3.2.1 Drug use history

Participants first became intoxicated at around 13 years of age (median), usually with alcohol, cannabis or a combination of both. This was typically followed by first use of methamphetamine (median 17 years), and first injection of methamphetamine (median 18 years). The majority of participants were injecting drug users, and many had used methamphetamine for a number of years (median 11 years, range <1 year to 34 years).

3.2.2 Methamphetamine use

Almost all participants met DSM-IV criteria for methamphetamine Abuse and Dependence in the past year (Table 1), with the average age of onset of Dependence 22 years (range 12–49). The median Severity of Dependence Scale score was well above the cut-off score of 4 for problematic use. All participants had used methamphetamine in the past year with most using it three or more days a week. In the past month participants used methamphetamine a median of 16 days, more than once a day (median OTI score 2, range 0–40).

3.2.3 Cannabis use

Almost all participants reported lifetime use of cannabis with the majority having used it in the past year (Table 2). The median Severity of Dependence Scale score for the sample was one, with participants using on a median of 14 days per month. When the sample was limited to those people who had used cannabis in the past month (n=309) the median Severity of Dependence Scale score increased to four (range 0–15) and the median number of days used in the past month increased to 26 (range 1–28). Close to half the sample used cannabis almost daily in the past year (Table 2), indicating that participants who used cannabis often did so regularly.

3.2.4 Other drug use

Polydrug use among the sample was common, with participants using a median of seven drug classes in the past year (range 2–12), and five in the past month (range 1–10). Alcohol was the other drug most commonly used (Table 2), with 23% of participants using it almost daily or more in the past month.

Table 2: Drug use in the sample

	Total sample (N=400)
Drug use history	
Age first intoxicated (median)	13
Age first used methamphetamine (median)	17
Ever injected a drug (%)	83
Ever injected methamphetamine (%)	83
Duration of methamphetamine use career (median)	11
Cannabis use	
Ever used (%)	98
Frequency of use (% past year)	
No use	13
Less than weekly	18
Weekly	7
Twice weekly	7
3-4 days a week	9
5+ days a week	47
Days of use in past month (median)	14
Severity of Dependence Scale (median)	1
Methamphetamine use	
Frequency of use (% past year)	
Less than weekly	6
Weekly	6
Twice weekly	12
3-4 days a week	39
5+ days a week	38
Days of use in past month (median)	16
OTI methamphetamine score (median)	2.0
Severity of Dependence Scale (median)	9
DSM–IV diagnosis of Dependence in the past year (%)	97
DSM–IV diagnosis of Abuse in the past year (%)	99
Main route of administration in the past month (%)	
Injection	67
Smoking	19
Swallowing	8
Snorting	2
No use	5
Polydrug use	
Drug classes used in past year (median)	7
Used in past month (%)	
Alcohol	73
Heroin	19
Cocaine	23
Ecstasy	28
Hallucinogens	5

3.3 Psychosis

3.3.1 Prevalence of psychotic symptoms

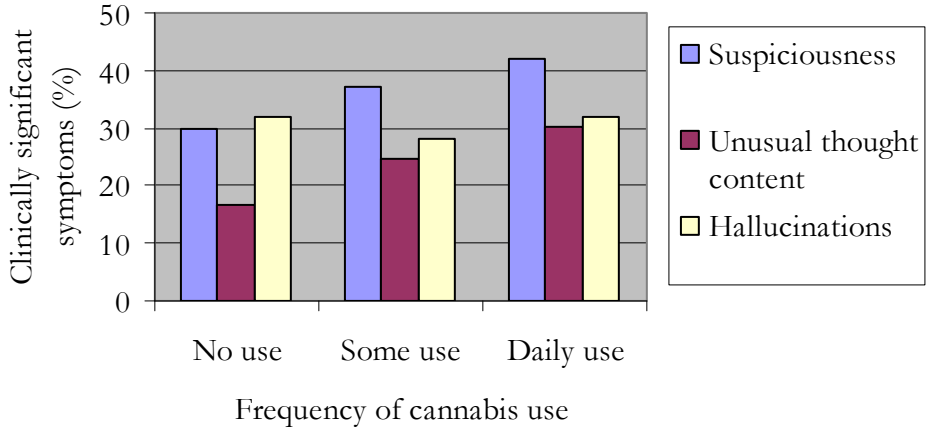
Just over half of participants experienced at least one clinically significant psychotic symptom in the past month. Suspiciousness was the most common symptom experienced at clinically significant levels in the past month, followed by hallucinations and unusual thought content (Table 3). The prevalence of clinically significant psychotic symptoms was slightly higher among participants with a history of a chronic psychotic disorder, with 71% of the sample experiencing at least one symptom in the past month. Among this group hallucinations were most common, followed by suspiciousness and unusual thought content. Almost half of the participants without a history of a chronic psychotic disorder reported clinically significant psychotic symptoms in the month before treatment (Table 3). Among this group suspiciousness was comparatively more common.

Table 3: Past month prevalence of clinically significant psychotic symptoms by previous diagnosis with a chronic psychotic disorder

	Prior diagnosis with a chronic psychotic disorder		
	No (n=316)	Yes (n=84)	Total (N=400)
Suspiciousness	35	48	38
Unusual thoughts	22	39	26
Hallucinations	24	55	31
Any symptom	47	71	52

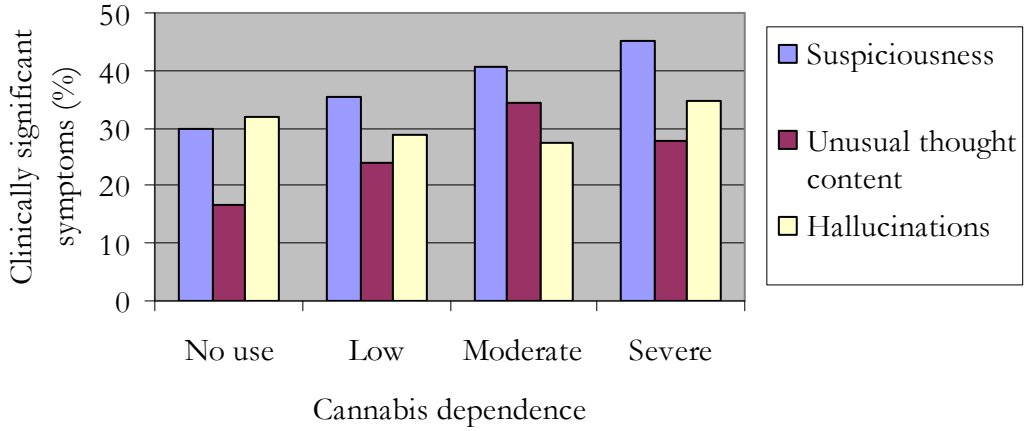
The prevalence of clinically significant suspiciousness in the past month increased as the frequency of cannabis use increased. Similarly, unusual thought content increased as frequency of cannabis use increased. The prevalence of clinically significant hallucinations changed little across different frequencies of cannabis use (Figure 1).

Figure 1: Past month prevalence of clinically significant psychotic symptoms by days used cannabis in the past month



The prevalence of clinically significant suspiciousness in the past month increased as cannabis dependence in the past month increased (Figure 2). The prevalence of clinically significant unusual thought content increased and then decreased slightly as cannabis dependence increased. The prevalence of hallucinations changed little as cannabis dependence increased (Figure 2).

Figure 2: Past month prevalence of clinically significant psychotic symptoms by cannabis dependence in the past month



3.3.2 Predictors of psychotic symptoms

Both frequency of cannabis use and cannabis dependence were related to suspiciousness and unusual thought content (Table 4). There was little relationship between cannabis use and hallucinations. Methamphetamine use (days used, dependence, and OTI score) was also significantly related to both suspiciousness and unusual thought content, but not hallucinations (Table 4). Younger age of first methamphetamine use was related to suspiciousness while younger age of first intoxication was related to unusual thought content. A number of mental health variables were also related to psychotic symptoms including history of a chronic psychotic disorder, Social Phobia (past year) and Panic Disorder (past year). There were no significant correlations between demographic characteristics and any psychotic symptoms (Table 4).

Confounders were defined as variables with a significant relationship to both a BPRS symptom (suspiciousness, unusual thought content, or hallucinations) (Table 4) and a measure of past month cannabis use (days used or dependence) (Table 5). Variables identified as potential confounders of the relationship between days used cannabis and suspiciousness included age first used methamphetamine, days used methamphetamine in the past month, OTI methamphetamine score, Panic Disorder (past year) and Social Phobia (past year). Potential confounders of the relationship between cannabis dependence and suspiciousness included age first used methamphetamine, history of a chronic psychotic disorder, Panic Disorder (past year), and Social Phobia (past year) (Table 5).

Potential confounders of the relationship between days used cannabis and unusual thought content included frequency of methamphetamine use, OTI methamphetamine score, age of first intoxication, Panic Disorder (past year) and Social Phobia (past year). Potential confounders of the relationship between cannabis dependence and unusual thought content included age of first intoxication, history of a chronic psychotic disorder, Panic Disorder (past year), and Social Phobia (past year) (Table 5).

Table 4: Spearman correlations between cannabis use, other drug use, mental health, demographics and psychotic symptoms

	Psychotic symptoms in the past month		
	Suspiciousness	Unusual thoughts	Hallucinations
	r_s	r_s	r_s
Cannabis use			
Frequency (days)	0.138**	0.137**	0.013
SDS (score)	0.157**	0.164**	0.024
Methamphetamine use			
Frequency (days)	0.190**	0.185**	0.051
SDS (score)	0.115*	0.108*	0.079
OTI meth score	0.165**	0.132**	0.052
Duration of use (years)	0.018	-0.019	0.017
Age first used methamphetamine	-0.100*	-0.081	-0.028
Route of admin	-0.012	-0.003	0.075
Age first intoxication	-0.096	-0.101*	-0.082
Other drug use (days past month)			
Alcohol	0.028	-0.034	-0.081
Heroin	0.061	-0.003	0.104*
Cocaine	0.048	0.015	0.043
Ecstasy	-0.001	0.021	-0.069
Hallucinogen	-0.001	0.069	0.009
History of ADHD (%)	-0.046	-0.056	-0.013
History of a chronic psychotic disorder (%)	0.146**	0.234**	0.232**
Psychiatric diagnoses (% past year)			
Major Depression	0.094	0.071	0.019
Panic Disorder	0.140**	0.115*	0.161**
Social Phobia	0.147**	0.162**	0.180**
Demographics			
Age	-0.071	-0.079	0.012
Sex (0 female; 1 male)	0.044	0.088	-0.052
Unemployed (0 employed; 1 unemployed)	0.039	-0.042	0.038
Education (years)	-0.033	-0.045	-0.015
Prison history (0 no; 1 yes)	-0.007	0.035	-0.002
Below poverty line	0.018	0.020	0.030
Born in Australia (1 Australia; 2 other)	0.031	0.054	0.020

*p<0.05; **p<0.01

Table 5: Spearman correlations between cannabis use and variables related to psychotic symptoms

	Frequency of cannabis use (days) r_s	Cannabis dependence (SDS score) r_s
Methamphetamine use		
Frequency (days)	0.202**	0.019
SDS (score)	0.060	0.092
Age of first use	-0.180**	-0.123**
OTI Meth score	0.120*	0.038
Age first intoxication	-0.115*	-0.105*
Other drug use (days past month)		
Heroin	0.050	0.040
History of a chronic psychotic disorder (%)	0.082	0.146**
Psychiatric diagnoses (% past year)		
Major depression	0.070	0.093
Panic Disorder	0.131**	0.193**
Social Phobia	0.101*	0.146**

*p<0.05; **p<0.01

3.4 Cannabis use and suspiciousness

A small dose response relationship was observed between cannabis use (days used and dependence) and suspiciousness when confounding factors were not controlled for. This relationship was significant at the highest levels of frequency of use and dependence ('almost daily or more' use and severe dependence) (Table 6). Social Phobia (past year) was also significantly associated with increased likelihood of suspiciousness (Appendix, Table 8). The relationship between daily use of cannabis and suspiciousness was no longer significant after adjusting for confounding factors (history of a chronic psychotic disorder, frequency of methamphetamine use, OTI methamphetamine score, age first used methamphetamine, Panic Disorder, and Social Phobia) (Table 6). Similarly, the relationship between severe cannabis dependence and suspiciousness was no longer significant after adjusting for confounding factors (history of a chronic psychotic disorder, age first used methamphetamine, Panic Disorder, and Social Phobia); however, a small non-significant trend towards increased risk of suspiciousness associated with dependence remained (ORs ranged from 1.2–1.5)

The relationship between cannabis use and suspiciousness was slightly smaller for those participants previously diagnosed with a chronic psychotic disorder compared with the rest of the sample. However, none of the unadjusted or adjusted odds ratios reached significance when the sample was restricted to participants with a history of a chronic psychotic disorder.

3.5 Cannabis use and unusual thought content

Daily use of cannabis and moderate cannabis dependence both significantly increased the risk of experiencing clinically significant unusual thoughts when confounding factors were not controlled for (Table 7). History of a chronic psychotic disorder was also associated with increased likelihood of unusual thoughts (Appendix, Table 9). The relationship between daily cannabis use and unusual thoughts was no longer significant after adjusting for potential confounders (history of a chronic psychotic disorder, frequency of methamphetamine use, OTI methamphetamine score, age of first intoxication, Panic Disorder, and Social Phobia). However, the relationship between moderate cannabis dependence and clinically significant unusual thoughts remained significant (OR=2.5, $p<0.05$) after adjusting for potential

confounders (history of a chronic psychotic disorder, age of first intoxication, Panic Disorder, and Social Phobia).

The relationship between cannabis use and unusual thoughts was similar among participants with a pre-existing diagnosis of a psychotic disorder, with moderate cannabis dependence associated with increased risk of experiencing clinically significant unusual thoughts.

Table 6: Odds ratios and adjusted odds ratios for cannabis use (days used and dependence) as a predictor of clinically significant suspiciousness

	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Days used cannabis				
Total sample (N=400)		0.137		0.794
No use (reference)				
Some use	1.4 (0.8 – 2.5)	0.253	1.2 (0.7 – 2.2)[a]	0.512
Almost daily use +	1.7 (1.0 – 2.9)	0.047	1.2 (0.7 – 2.1)[a]	0.573
Chronic psychotic disorder (n=84)		0.525		0.776
No use (reference)				
Some use	0.9 (0.2 – 3.4)	0.862	0.6 (0.1 – 2.9)[b]	0.520
Almost daily use +	1.5 (0.5 – 5.1)	0.495	0.8 (0.2 – 3.8)[b]	0.552
No chronic psychotic disorder (n=316)		0.243		0.274
No use (reference)				
Some use	1.5 (0.8 – 2.9)	0.201	1.5 (0.7 – 2.9)[b]	0.274
Almost daily use +	1.7 (0.9 – 3.1)	0.097	1.3 (0.7 – 2.5)[b]	0.423
Cannabis dependence				
Total sample (n=400)		0.142		0.599
No use (reference)				
Not dependent	1.3 (0.7 – 2.3)	0.369	1.2 (0.6 – 2.1)[c]	0.603
Moderate	1.6 (0.9 – 3.0)	0.135	1.3 (0.7 – 2.6)[c]	0.377
Severe	2.0 (1.1 – 3.5)	0.027	1.5 (0.8 – 2.8)[c]	0.195
Chronic psychotic disorder (n=84)		0.794		0.806
No use (reference)				
Not dependent	1.0 (0.3 – 3.9)	1.000	0.6 (0.1 – 2.6)[d]	0.448
Moderate	1.1 (0.3 – 4.3)	0.901	0.8 (0.2 – 3.6)[d]	0.727
Severe	1.6 (0.5 – 5.9)	0.451	1.0 (0.2 – 4.2)[d]	0.961
No chronic psychotic disorder (n=316)		0.283		0.608
No use (reference)				
Not dependent	1.4 (0.7 – 2.6)	0.338	1.3 (0.7 – 2.6)[d]	0.420
Moderate	1.7 (0.8 – 3.5)	0.139	1.5 (0.7 – 3.1)[d]	0.282
Severe	1.9 (1.0 – 3.7)	0.069	1.6 (0.8 – 3.2)[d]	0.205

[a]Adjusted for history of a chronic psychotic disorder, frequency of methamphetamine use, age first used methamphetamine, OTI methamphetamine score, Panic Disorder, and Social Phobia.
[b]Adjusted for frequency of methamphetamine use, age first used methamphetamine, OTI methamphetamine score, Panic Disorder, and Social Phobia.
[c]Adjusted for history of a chronic psychotic disorder, age first used methamphetamine, Panic Disorder, and Social Phobia.
[d]Adjusted for age first used methamphetamine, Panic Disorder and Social Phobia.

Table 7: Odds ratios and adjusted odds ratios for cannabis use (days used and dependence) as a predictor of clinically significant unusual thoughts

	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Days used cannabis				
Total sample (N=400)		0.048		0.340
No use (reference)				
Some use	1.7 (0.8 – 3.3)	0.145	1.5 (0.7 – 3.1)[e]	0.264
Almost daily use +	2.2 (1.2 – 4.2)	0.015	1.6 (0.8 – 3.2)[e]	0.144
Chronic psychotic disorder (n=84)		0.529		0.771
No use (reference)				
Some use	1.4 (0.3 – 5.8)	0.638	1.3 (0.3 – 5.9)[f]	0.721
Almost daily use +	2.0 (0.5 – 7.3)	0.296	1.7 (0.4 – 7.1)[f]	0.488
No chronic psychotic disorder (n=316)		0.146		0.398
No use (reference)				
Some use	1.7 (0.8 – 3.7)	0.204	1.6 (0.7 – 3.6)[f]	0.280
Almost daily use +	2.1 (1.0 – 4.4)	0.050	1.7 (0.8 – 3.7)[f]	0.181
Cannabis dependence				
Total sample (N=400)		0.052		0.115
No use (reference)				
Not dependent	1.6 (0.8 – 3.2)	0.186	1.5 (0.8 – 3.1)[g]	0.227
Moderate	2.7 (1.3 – 5.5)	0.007	2.5 (1.2 – 5.1)[g]	0.016
Severe	2.0 (1.0 – 3.9)	0.060	1.7 (0.8 – 3.4)[g]	0.160
Chronic psychotic disorder (n=84)		0.397		0.334
No use (reference)				
Not dependent	1.0 (0.2 – 4.5)	1.000	1.0 (0.2 – 4.6)[h]	0.993
Moderate	2.5 (0.6 – 10.7)	0.217	2.9 (0.7 – 13.3)[h]	0.161
Severe	2.0 (0.5 – 8.0)	0.311	2.0 (0.5 – 8.1)[h]	0.346
No chronic psychotic disorder (n=316)		0.184		0.261
No use (reference)				
Not dependent	1.8 (0.8 – 4.0)	0.148	1.7 (0.8 – 3.8)[h]	0.197
Moderate	2.5 (1.1 – 5.8)	0.029	2.4 (1.0 – 5.5)[h]	0.048
Severe	1.6 (0.7 – 3.8)	0.258	1.5 (0.6 – 3.6)[h]	0.339

[e]Adjusted for history of a chronic psychotic disorder, frequency of methamphetamine use, OTI Methamphetamine score, age first intoxication, Panic Disorder, and Social Phobia.
[f]Adjusted for frequency of methamphetamine use, OTI Methamphetamine, age first intoxication, Panic Disorder, and Social Phobia.
[g]Adjusted for history of a chronic psychotic disorder, age first intoxication, Panic Disorder, and Social Phobia.
[h]Adjusted for age first intoxication, Panic Disorder, and Social Phobia.

4. DISCUSSION

The current study found that cannabis use among dependent methamphetamine users entering treatment was associated with a small increase in the likelihood of experiencing clinically significant symptoms of suspiciousness and unusual thoughts. This association was attenuated after adjusting for confounders, including methamphetamine use and a prior diagnosis with a chronic psychotic disorder; however, a small non-significant positive relationship remained. The adjusted odds ratios for experiencing clinically significant suspiciousness ranged from 1.2 to 1.5, and for unusual thoughts they ranged from 1.5 to 2.5, with a dose-response relationship observed between some cannabis use variables and symptoms of psychosis, but not others. There was no evidence of a relationship between cannabis use and likelihood of experiencing hallucinations.

The factors that were found to modify the relationship between cannabis use and suspiciousness or unusual though content were: (i) methamphetamine use, (ii) age of first intoxication, (iii) lifetime diagnosis with a chronic psychotic disorder, and (iv) a past year diagnosis of an anxiety disorder. This suggests that the apparent relationship between cannabis use and psychotic symptoms among methamphetamine users is due in part to heavy cannabis users being more likely to have a history of a chronic psychotic disorder (i.e. Schizophrenia, Schizoaffective Disorder or Bipolar Affective Disorder), their using methamphetamine more often and substances at an earlier age, and their having a comorbid anxiety disorder.

The finding that methamphetamine use partly accounted for the higher levels of psychotic symptoms among heavier cannabis users makes sense because there is clear evidence that methamphetamine use increases the risk of psychosis (McKetin et al., 2006; Farrell et al., 2002). Similarly, being diagnosed with a psychotic illness would obviously increase the risk of psychotic symptoms among methamphetamine users (McKetin et al., 2006; Fergusson et al., 2005; Curran et al., 2004). It is less clear why meeting criteria for an anxiety disorder in the past year (Social Phobia or Panic Disorder) would be associated with higher levels of psychotic symptoms, however, this relationship has also been found in several earlier studies (Craig et al., 2002; Cosoff and Hafner, 1998; Penn et al., 1994; Goodwin et al., 2004; Gilbert et al., 2005; Freeman et al., 2008). This relationship could reflect the existence of a common

underlying determinant of psychosis, anxiety disorders and heavy drug use. Alternately, it could reflect measurement error as a result of overlap between some symptoms of anxiety and psychosis. Specifically, low-grade symptoms of suspiciousness on the BPRS include concerns about being watched or talked about by other people, which could be a manifestation of Social Phobia. Alternatively, persecutory ideation may lead to higher levels of Social Phobia because people feel that they are being watched or judged. The modifying effect of each of these variables was small and none individually explained the attenuation of the relationship between cannabis use and psychotic symptoms. This pattern is consistent with much previous epidemiological research examining the relationship between cannabis use and psychosis which has tended to find that the more confounders adjusted for the smaller the observed relationship (Smit et al., 2004).

The current study found evidence of a dose-response relationship between cannabis use and some psychotic symptoms, but not others. Evidence of a dose-response relationship has been observed in much of the epidemiological research, and has added support to the idea that there is a causal relationship between these factors. The Swedish cohort study found dose-dependent increased risk of schizophrenia associated with lifetime cannabis use (Zammit et al., 2002), and a number of recent reviews of research in the area have reached the same conclusion (Smit et al., 2004; Arseneault et al., 2004; Fergusson et al., 2005). A study of past year drug use and psychosis among prisoners found a positive association between cannabis dependence and psychosis, but only at the highest level of dependence (Farrell et al., 2002). It is unclear why the current study found a dose-response relationship between some variables and not others; however, one possible reason might be the fact that number of cannabis use occasions per day was not measured, limiting the sensitivity of the frequency of use measure. Another possible reason could be the inability to control for cumulative lifetime exposure to cannabis in the current study.

The size of the positive relationship between cannabis use and psychotic symptoms in the current study was slightly smaller that that found in much previous research. A recent review of longitudinal studies noted that the increased risk of psychosis or psychotic symptoms associated with cannabis use ranged from 1.77 to 10.9 with a median of approximately 2.3 (Fergusson et al., 2007), compared to 1.2 to 2.5 in the current study. It is unclear why the association observed in the current study was relatively small. One possibility is that this

reflects a real difference in the association between cannabis use and psychosis among dependent methamphetamine users compared to the general population. For example, the high levels of psychosis among methamphetamine users may have led to a ceiling effect for the impact of cannabis use on psychotic symptoms. Alternatively the small size of the association could result from the fact that analyses in the current study were able to control for a large number of confounders, some of which have not been adjusted for in previous research.

Research estimating the size of the association between cannabis use and psychosis has found that it is larger among 'vulnerable' people (those with a history of psychosis) (D'Souza et al., 2005; D'Souza et al., 2004; van Os et al., 2002). Findings from the current study were not consistent with this previous evidence, in that the relationship between cannabis use and suspiciousness was smaller among participants previously diagnosed with a chronic psychotic condition, with adjusted odds ratios ranging from 0.6 to 1.0. The relationship between cannabis use and unusual thoughts was similar among participants with and without a previous diagnosis of a chronic psychotic disorder. The adjusted odds ratios when the sample was restricted to participants with a chronic psychotic disorder ranged from 1.0 to 2.9 compared to 1.5 to 2.4 for the total sample. The small number of participants in these analyses, and the self-report nature of previously diagnosed chronic psychotic disorders, mean this finding must be interpreted with caution.

The absence of a relationship between cannabis use and hallucinations in the current study was surprising. Research examining the relationship between cannabis use and specific psychotic symptoms has generally found evidence of a relationship. One reason why the current findings may differ from earlier research is that the current study examined the relationship between cannabis use and psychotic symptoms within the past month, whereas much of the earlier research has examined the impact of cannabis use on the later development of chronic psychotic disorders, such as Schizophrenia. Our findings suggest that cannabis use among methamphetamine users may be differentially associated with particular psychotic symptoms – specifically, cannabis use among methamphetamine users may be associated with higher levels of persecutory ideation rather than hallucinations. This finding is consistent with the results of one previous study which looked at particular psychotic symptoms among a community sample of adolescents and concluded that

hallucinations were less sensitive to the hypothesised sensitising effect of cannabis than paranoia (Stefanis et al., 2004).

4.2 Limitations

A number of limitations need to be kept in mind in considering these results. Perhaps most importantly, the current findings cannot be generalised to cannabis use among the general population. This is because methamphetamine treatment entrants are extremely vulnerable to psychosis when compared to the general population by virtue of methamphetamine-induced symptoms of psychosis and their elevated prevalence of chronic psychotic disorders. While the high levels of cannabis use and psychosis among methamphetamine users provide a valuable opportunity to look at proximal relationships between these phenomena, the relationship between cannabis use and psychosis in this population may be qualitatively different.

In the current study, having been diagnosed with a psychotic disorder was measured using self-report. The validity of such self-reported diagnoses in a drug-using population may be threatened by the potential to misdiagnose drug-induced psychotic symptoms as symptoms of a chronic psychotic disorder. However, this same threat may be equally present in diagnoses based on structured clinical interview or clinician judgment. Measurement of drug use and psychotic symptoms in the current study also relied on self-report; however, this was limited to the past month, a timeframe found to be reliable in previous studies (Darke et al., 1991a; Darke et al., 1991b; Ventura et al., 1993).

The cross-sectional design of the study prevented examination of the temporal relationship between cannabis use and psychosis. For this reason, no causal inference can be drawn between cannabis use and psychotic symptoms. While the high levels of cannabis use in the current sample allowed us to examine whether there was a dose-response relationship between cannabis use and psychosis, the almost ubiquitous lifetime use of cannabis meant that the impact of lifetime cannabis exposure on the likelihood of experiencing psychosis could not be examined. Interestingly, the almost universal lifetime cannabis use in the sample provided a crude, unintentional control such that the whole sample had been exposed to the same potential risk factor for vulnerability to psychosis.

4.3 Implications

The current findings suggest that cannabis use makes only a minor contribution to psychotic symptoms among methamphetamine treatment entrants, and that this contribution is similar, or possibly smaller, among people with a history of a chronic psychotic disorder (including Schizophrenia, Schizoaffective Disorder, and Bipolar Affective Disorder). Among methamphetamine treatment entrants without a history of a chronic psychotic disorder, much of the apparent relationship is related to concurrent heavy methamphetamine use and comorbid anxiety disorders. Therefore, it is important to assess and consider the impact of pre-existing chronic psychotic disorders, anxiety disorders and concurrent drug use, when examining whether or not cannabis use increases psychotic symptoms.

While the results of the current study do not provide a clear warning of the effects of cannabis use on psychotic symptoms, they indicate there may be some value in encouraging methamphetamine treatment entrants to cut down on cannabis as well as methamphetamine.

4.4 Conclusion

In conclusion, while cannabis use and psychotic symptoms were high among methamphetamine treatment entrants, little evidence was found for a relationship between these phenomena. There was some suggestion that the risk associated with cannabis use was similar among those with and without a history of a chronic psychotic disorder, but the use of self-report to measure pre-existing psychosis means this issue requires further investigation. The small positive relationship between cannabis use, suspiciousness and unusual thoughts was largely accounted for by higher methamphetamine use and increased prevalence of psychotic and anxiety disorders. If cannabis use plays a role in the high level of psychotic symptoms among methamphetamine users, it is very small; smaller than that found in previous research with general population samples. While there may be some benefit in advising clients to reduce cannabis use in order to reduce psychotic symptoms, this is likely to be small at most.

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6. APPENDIX

Table 8: Logistic regression model examining cannabis use (days used and dependence) as a predictor of clinically significant suspiciousness controlling for potential confounders

	Adjusted odds ratio (95% CI)	p-value
Days used cannabis		
No use (0)	-	0.794
Some use (1-19)	1.2 (0.7 – 2.2)	0.512
Almost daily use + (20-28)	1.2 (0.7 – 2.1)	0.573
Frequency of methamphetamine use		
Less than twice a week	-	0.208
Moderate use	1.4 (0.8 – 2.7)	0.260
Almost daily use	1.8 (0.9 – 3.6)	0.078
OTI meth score > 1 'daily or more use'	1.5 (0.8 – 2.6)	0.171
Age first used methamphetamine		
Less than 18 years	-	0.235
18-24 years	0.8 (0.5 - 1.3)	0.413
25 years or older	0.5 (0.2 - 1.2)	0.103
Panic Disorder	1.5 (0.9 – 2.5)	0.147
Social Phobia	1.8 (1.1 – 3.2)	0.024
History of a chronic psychotic disorder	1.4 (0.9 – 2.4)	0.179
Cannabis dependence		
No cannabis use	-	0.599
No/Low cannabis dependence	1.2 (0.6 – 2.1)	0.603
Moderate cannabis dependence	1.3 (0.7 – 2.6)	0.377
Severe cannabis dependence	1.5 (0.8 – 2.8)	0.195
Age first used methamphetamine		
Less than 18	-	0.126
18-24 years	0.8 (0.5 - 1.2)	0.307
25 years or older	0.4 (0.2 - 1.0)	0.053
Panic Disorder	1.4 (0.8 – 2.3)	0.215
Social Phobia	1.6 (1.0 – 2.7)	0.063
History of a chronic psychotic disorder	1.4 (0.9 – 2.4)	0.152

Table 9: Logistic regression model examining cannabis use (days used and dependence) as a predictor of clinically significant unusual thoughts controlling for potential confounders

	Adjusted odds ratio (95% CI)	p-value
Days used cannabis		
No use (0)	-	0.340
Some use (1-19)	1.5 (0.7 – 3.1)	0.264
Almost daily use + (20-28)	1.6 (0.8 – 3.2)	0.144
Frequency of methamphetamine use		
Less than twice a week	-	0.178
Moderate use	1.9 (0.9 – 4.1)	0.086
Almost daily use	2.0 (0.9 – 4.5)	0.078
OTI meth score > 1 'daily or more use'	1.5 (0.8 – 2.9)	0.172
First intoxicated 15 years or over	0.9 (0.5 – 1.6)	0.762
Panic Disorder	1.0 (0.6 – 1.8)	0.983
Social Phobia	1.6 (0.9 – 2.9)	0.091
History of a chronic psychotic disorder	2.1 (1.2 – 3.6)	0.007
Cannabis dependence		
No cannabis use	-	0.115
No/Low cannabis dependence	1.5 (0.8 – 3.1)	0.227
Moderate cannabis dependence	2.5 (1.2 – 5.1)	0.016
Severe cannabis dependence	1.7 (0.8 – 3.4)	0.160
First intoxicated 15 years or over	0.9 (0.5 – 1.5)	0.593
Panic Disorder	0.9 (0.5 – 1.7)	0.817
Social Phobia	1.5 (0.9 – 2.7)	0.133
History of a chronic psychotic disorder	2.2 (1.3 – 3.4)	0.004

Table 10: Logistic regression model examining cannabis use (days used and dependence) as a predictor of clinically significant hallucinations

	Odds ratio (95% CI)	p-value
Cannabis dependence		
No cannabis use	-	0.702
No/Low cannabis dependence	0.9 (0.5 – 1.6)	0.644
Moderate cannabis dependence	0.8 (0.4 – 1.5)	0.517
Severe cannabis dependence	1.1 (0.6 – 2.1)	0.685
Days used cannabis		
No use (0)	-	0.751
Some use (1-19)	0.8 (0.5 – 1.5)	0.552
Almost daily use + (20-28)	1.0 (0.6 – 1.7)	0.994