The impact of amphetamine and cannabis use on the symptoms and clinical course of early psychosis

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Abstract

Amphetamines and cannabis are the most commonly used illicit substances in Australia and are associated with a range of severe mental health problems, including psychosis. While a number of studies have previously examined the symptom profiles of amphetamine users and cannabis users with psychosis, it remains unclear whether these patients experience differences in the severity and clinical course of their symptoms and behaviour compared to non-using patients with psychosis.

This thesis examined the demographics, psychiatric and family history, premorbid adjustment, clinical symptoms, and disturbed behaviours of 98 inpatients admitted to hospital with an early psychosis. The TimeLine Follow Back method was used to determine substance use in the 30 days prior to admission, allowing participants to be categorised according to the following drug classes: amphetamines, cannabis, amphetamines + cannabis, none. Participants were assessed at admission and then weekly until discharge (or for a maximum of eight weeks) with the Brief Psychiatric Rating Scale (positive symptoms, negative symptoms, mania symptoms, depression-anxiety symptoms) and the Disturbed Behaviour Rating Scale. Multi-level modelling (MLM) was used to determine statistically significant differences between each of the substance-using groups and their respective non-using groups on the severity of their symptoms and behaviour at admission and over the course of their hospitalisation. Importantly, MLM also allowed for these groups to be compared on the rate of symptom and behaviour

change during the first eight weeks of hospitalisation, providing evidence of any differences in clinical course.

The recent use of amphetamines was associated with: (1) less severe negative symptoms and more severe mania symptoms and disturbed behaviour at admission; (2) a faster rate of reduction in mania symptoms and disturbed behaviour during hospitalisation; and (3) less severe disturbed behaviour at week eight. The recent use of cannabis was associated with: (1) less severe negative symptoms and more severe symptoms of mania and disturbed behaviour at admission; (2) a faster reduction in positive symptoms, mania symptoms, and disturbed behaviour during hospitalisation; and (3) less severe positive symptoms, negative symptoms, and disturbed behaviour at week eight. The use of *both* amphetamines and cannabis in the 30 days prior to admission had no significant impact on the severity or clinical course of symptoms or behaviour compared to single drug use alone.

This thesis demonstrated that the recent use of amphetamines or cannabis in patients with early psychosis is associated with a significantly different presentation and abatement of some symptoms and behaviour compared to non-using patients with early psychosis. Symptoms of mania and disturbed behaviour most consistently differentiated substance users from non-users. The groups were largely comparable with respect to positive symptoms and no differences were found on symptoms of depression-anxiety. These findings highlight the importance of examining the substance use histories of patients presenting to hospital.

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Leanne Michele Geppert Date

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Chapter 1. An overview of the thesis

A significant increase in the use and abuse of amphetamines in the last decade has been paralleled by increased worldwide concern regarding these substances. Of particular concern is the impact of amphetamines on mental health, which includes, but is not restricted to, the development of psychotic symptoms. In some amphetamine users these sub-clinical symptoms develop into a diagnosable psychotic disorder that is not dissimilar to schizophrenia (Segal & Kuczenski, 1997a; Siomopoulos, 1976).

The 2004 National Drug Strategy Household Survey reported that 9.1% of those aged 14 years and over have used meth/amphetamines in their lifetime (Australian Institute of Health and Welfare, 2005a). This rate of use is second only to cannabis, which stands at 33.6% (Australian Institute of Health and Welfare, 2005a). As the prevalence of amphetamine use has grown, so too have the demands on health, emergency, and law enforcement services. More people are presenting to hospitals with problems associated with amphetamine use (Gray, Fatovich, McCoubrie, & Daly, 2007; Leamon, Canning, & Benjamin, 2000; Meredith, Jaffe, Ang-Lee, & Saxon, 2005; Stafford et al., 2006), and not uncommonly, ambulance and police services have been involved prior to their hospital presentation (Gray, Fatovich, McCoubrie, & Daly, 2007; Roche, 2006). Examples of presenting problems include self-harm and suicide attempts (Kratofil, Baberg, & Dimsdale, 1996), severe mental health problems such as hallucinations, delusions, paranoid thinking, depression, and anxiety (Degenhardt & Topp, 2003; Hall & Hando, 1994), and disturbed behaviours such as hostility and aggression (Zweben et al., 2004).

The literature provides clear evidence of an association between amphetamine use and the development of psychotic symptoms and disorders (Dawe & McKetin, 2004; McKetin, McLaren, Lubman, & Hides, 2006). The prevalence of psychosis in methamphetamine users is 11 times higher than that in the general population, with 13% having had a psychotic illness in the previous 12 months (McKetin, McLaren, Lubman, & Hides, 2006). The link between chronic, high-dose amphetamine use and psychotic illness has attracted particular attention given the severity of the illness and the potential for longer-term harm. Many early studies found amphetamine-induced psychosis to be indistinguishable from paranoid schizophrenia, with a preponderance of positive symptoms and little evidence of either negative symptoms or thought disorder (Bell, 1955; Connell, 1958; Sato, Numachi, & Hamamura, 1992). Both amphetamine-induced psychosis and schizophrenia have also been linked to excessive dopaminergic activity within the brain and both have demonstrated favourable responses to neuroleptics that act as dopaminergic antagonists (Angrist, Lee, & Gershon, 1974). The similarities between the two disorders were compelling enough for amphetamine-induced psychosis to be suggested as a model for schizophrenia (Akiyama, Hamamura, Ujike, Kanzaki, & Otsuki, 1991; Kokkinidis & Anisman, 1981).

Symptoms of mood (depression and mania), anxiety, and disturbed behaviour (violence, aggression, hostility) have received considerably less attention in the amphetamine and psychosis literature. While studies of amphetamine users have identified elevated levels of these clinical characteristics (e.g., Baker et al., 2004; Hall, Hando, Darke, & Ross, 1996; Hando, Topp, & Hall, 1997; Sommers & Baskin,

2006), the few studies that have examined these symptoms in users with psychosis have provided mixed findings, particularly with respect to depression and anxiety. Somewhat more compelling findings have been reported with respect to increased mania symptoms and disturbed behaviour in amphetamine-induced psychosis, however, the failure to include a comparison group of non-using psychosis patients is a common limitation.

Overall, the literature dealing with psychotic (and other) symptoms and amphetamine use is hampered by studies with small sample sizes. There are few studies that compare amphetamine users with psychosis and non-users with psychosis on the severity of their clinical symptoms and behaviour at admission to hospital. Even less common are studies that go on to compare substance users and non-users with psychosis on the clinical course of these symptoms and behaviours throughout hospitalisation.

A further gap in this area of research is the lack of consideration given to high levels of polydrug use within the Australian amphetamine-using population. An Australian study found 98.6% of 214 regular amphetamine users identified themselves as polydrug users, with tobacco (92.1%) and cannabis (72.4%) being the substances most commonly used (Baker et al., 2004). Cannabis use demands particular attention because it too has been suggested as a component factor in the development of psychotic symptoms and psychotic disorders (Arseneault et al., 2002; Caspari, 1999; Fergusson, Poulton, Smith, & Boden, 2006; Hides, Dawe, Kavanagh, & Young, 2006; van Os et al., 2002). While this thesis set out to focus on the impact of amphetamines on psychotic symptoms, the high rate of concomitant

cannabis use in the amphetamine-using population and evidence for its association with psychosis warranted consideration of the independent contribution of cannabis on psychotic symptoms.

The relationship between cannabis use, mood (depression and mania), anxiety, and disturbed behaviour was also examined. This component of the literature is mixed in its findings, particularly with respect to disturbed behaviour. It appears that the relationship between cannabis and these variables is influenced by a range of factors, including demographics, personality, environment, and other substance use (Degenhardt, Hall, & Lynskey, 2001a; 2001b; Hoaken & Stewart, 2003). Once these factors have been taken into consideration, there appears to be little evidence linking cannabis use with increased symptoms of depression, anxiety, or disturbed behaviour. However, a limited literature suggests that cannabis use is associated with increased symptoms of mania.

The current study also examined the synergistic effects of amphetamine and cannabis use on the severity and clinical course of symptoms and behaviour. This particular area of research remains unexplored, with no clear evidence indicating whether the use of both amphetamines and cannabis is necessarily linked to more severe symptoms or disturbed behaviour.

Thus, this thesis examined the impact of recent amphetamine and/or cannabis use on the clinical symptoms and behaviours of 98 psychotic inpatients at admission to hospital and then throughout the first eight weeks of their hospitalisation. All study participants were in the early stage of their psychotic illness. Using a sample in the early stage of their illness avoided the problems associated with extended

periods of institutionalization and long-term neuroleptic use, and the social and psychological consequences of living with a major mental illness.

In the first phase of analyses, participants were grouped (according to substance use in the 30 days prior to admission) and compared on a range of characteristics such as family history of psychosis, family environment, duration of untreated psychosis, and premorbid adjustment. The second phase of analyses consisted of multi-level modeling. Amphetamine users, cannabis users and amphetamine + cannabis users were compared to their respective non-using groups on the severity of their positive symptoms, negative symptoms, mania symptoms, depression-anxiety symptoms, and disturbed behaviour at admission. Next, the groups were compared on the rate of change (i.e., clinical course) in these symptoms/behaviours during the first eight weeks of their hospitalisation. Finally, the groups were compared on the severity of these symptoms/behaviours at week eight of hospitalisation.

The distinctive features of this study included: (1) a prospective design that was considerate of high concomitant cannabis use within the amphetamine-using population; (2) a moderate sized sample in which illness chronicity was controlled for; (3) an examination of both the independent and synergistic effects of recent amphetamine use and recent cannabis use; (4) a repeated-measures methodology that monitored changes in symptoms on a weekly basis for eight weeks, thereby providing a more continuous picture of change; (5) a statistical method of analysis (multi-level modelling) that was sensitive to hierarchical style data; and most importantly (6) the use of a non-substance-using control group of early psychosis

patients.

Chapter 2. Prevalence and effects of amphetamine and cannabis use

Prevalence and patterns of amphetamine use

There were an estimated 25 million people worldwide using amphetamines in 2005 (United Nations Office on Drugs and Crime, 2006). Within Australia, recent use (last 12 months) of meth/amphetamines fluctuated from 2.0% in 1993, to a peak of 3.7% in 1998, followed by a slight drop to 3.2% in 2004 (Australian Institute of Health and Welfare, 2005b). Lifetime prevalence of meth/amphetamine use is 9.1% for the Australian population, which is second only to cannabis (33.6%) (Australian Institute of Health and Welfare, 2005b).

According to the 2004 National Drug Strategy Household Survey (NDSHS), one in ten of the 532,100 recent meth/amphetamine users reported a minimum of once weekly use (Australian Institute of Health and Welfare, 2005a). Males and those within the 20-29 year old age group were the most likely to use meth/amphetamines, with an average initiation to use being 20.8 years. The majority of recent users preferred to use methamphetamine powder (74.3%), with crystal methamphetamine (38.6%) being the next most preferred form. There are over 100, 000 regular methamphetamine users in Australia and nearly 73, 000 of these people are dependent users (McKetin, McLaren, Kelly, Hall, & Hickman, 2005). Approximately three-quarters (75.6%) of amphetamine users inject (Lynch, Kemp, Krenske, Conroy, & Webster, 2003). Injecting has been associated with more severe consequences, particularly with respect to psychological problems (Hall, Hando, Darke, & Ross, 1996).

Amphetamines belong to the psychostimulant class of drugs, which includes

cocaine and ecstasy. The umbrella term 'amphetamines' is often used with reference to amphetamine sulphate and methamphetamine, given the difficulties experienced by substance users and researchers alike in accurately identifying the components of the amphetamine-type stimulant used. Wherever possible, the current study will report the particular type of amphetamine used (e.g., methamphetamine). The umbrella term 'amphetamines' will be used to denote both amphetamine sulphate and methamphetamine in those studies where discrimination between the two is not possible.

Amphetamine sulphate was the form of amphetamine most widely available in Australia in the 1980's (Chesher, 1993). Changes in legislation in the 1990's forced changes in the manufacture of amphetamines (Wardlaw, 1993), which resulted in methamphetamine becoming the most readily available form of amphetamine by 2001 (Topp et al., 2002). Methamphetamine is a chemical derivative of amphetamine sulphate, but has comparatively greater potential for central nervous system penetration and thus, it is a more potent form of the drug that produces similar effects to amphetamine but at lower doses (Dean, 2004). Due to the changes in availability of different amphetamine-type stimulants, in addition to varying potency and purity levels of the substance, it is likely that the impact of amphetamines on the individual and the community has increased over time. This underscores the importance of ongoing research with respect to the impact of amphetamines.

Polydrug use is extremely common within the amphetamine using population (Degenhardt, Coffey, Carlin, Moran, & Patton, 2007; Smit, Monshouwer, &

Verdurmen, 2002), with many primary amphetamine users reporting recent use (last six months) of at least three distinct drug classes (Darke & Hall, 1995). An Australian study of regular amphetamine users identified 98.6% of the sample as polydrug users, with tobacco, cannabis, and alcohol being most commonly preferred after amphetamines (Baker et al., 2004). The 2004 NDSHS found alcohol (87.2%), cannabis (67.6%), and ecstasy (49.4%) to be the concurrent drugs most commonly used by meth/amphetamine users (Australian Institute of Health and Welfare, 2005a). These findings highlight the extent of polydrug use and the difficulties clinicians and researchers face in determining the consequences specific to amphetamine use.

Effects of amphetamine use

Amphetamines act as powerful stimulants on the central nervous system, principally by releasing monoamines (dopamine, noradrenaline, and serotonin) (Dean, 2004; Snyder, 1996). Notably, excesses in these monoamines are also linked to serious mental health problems such as schizophrenia (Linszen, Dingemans, & Lenior, 1994; Snyder, 1996). More specifically, positive psychotic symptoms have demonstrated links with the dopaminergic system (Angrist, Peselow, Rubinstein, Corwin, & Rotrosen, 1982; Crow, 1980). Most of the changes to the brain following amphetamine use have been found to be reversible in animal studies, but are dependent upon abstinence from the drug (Melega et al., 1997; Rawson, Gonzales, & Brethen, 2002). The subjective effects of the drug are influenced by duration and pattern of use, dose, and route of administration (Nordahl, Salo, & Leamon, 2003).

Low dose amphetamine use is associated with a range of pleasant effects, which include an increased sense of energy, improved alertness and concentration, euphoria, intense emotions, enhanced self-esteem and libido, and a sense of general well-being (Nordahl, Salo, & Leamon, 2003; Tominaga, Garcia, Dzierba, & Wong, 2004).

Amphetamine use is also associated with a range of adverse effects. Acute intoxication leads to physical problems such as sweating, tremors, nausea, hot/cold flushes, chest and abdominal pain, high blood pressure, dizziness, increased heart rate and temperature, dilated pupils, cardiac arrhythmias, convulsions, haemorrhages, and renal problems (Degenhardt & Topp, 2003; Maxwell, 2005; Wickes, 1993). Longer-term use of amphetamines is associated with weight loss and malnutrition, seizures, stroke, impaired sexual functioning, chronic sleep problems, heart problems, and a reduction in lung functioning (Maxwell, 2005).

In addition to significant physical harms, there are considerable psychological consequences related to the use of amphetamines. In an Australian sample of crystal methamphetamine users, 91% reported one or more psychological symptoms directly related to their substance use (Degenhardt & Topp, 2003). Amphetamines can induce panic attacks, agitation, confusion, impaired cognitive and motor performance, compulsive behaviours, delusions, and aggressive behaviour (Australian Drug Foundation, 2002; Maxwell, 2005; Topp & Churchill, 2002). Up to three-quarters of regular amphetamine users report symptoms of anxiety, paranoia, and depression (Degenhardt & Topp, 2003; Hall & Hando, 1994; Kalechstein et al., 2000). Hallucinations and violence are also commonly experienced by at least 20%

of users (Degenhardt & Topp, 2003; Hall & Hando, 1994). Of particular concern is the link between amphetamine use and the development of a diagnosable psychotic illness (Dawe & McKetin, 2004). The relationship between amphetamine use and psychosis will be discussed in more detail in Chapter 3.

A recent study found that 26% of methamphetamine users identified psychological symptoms severe enough to warrant admission to a mental health facility (Zweben et al., 2004). The more severe mental health effects are typically associated with chronic, high-dose patterns of amphetamine use (Jenner & Mcketin, 2004; McKetin, Kelly, & McLaren, 2006; Meredith, Jaffe, Ang-Lee, & Saxon, 2005). Compared to non-users, amphetamine users have been found to be more likely to have intentional injuries, to be admitted to hospital more frequently, to have greater associated hospital costs, a longer length of hospital stay (Tominaga, Garcia, Dzierba, & Wong, 2004), and higher use of ambulance services (Richards et al., 1999).

Regular users of amphetamines develop a tolerance for the drug, which in turn, has been associated with escalating dose patterns and a transition to injecting (Darke, Cohen, Ross, Hando, & Hall, 1994; Hall & Hando, 1994). These factors can subsequently lead to the development of drug dependence. Crystalline methamphetamine, in particular, has demonstrated a significant risk for dependence (McKetin, Kelly, & McLaren, 2006). Once dependent, withdrawal symptoms are experienced by the majority upon cessation of amphetamine use (Srisurapanont, Jarusuraisin, & Kittirattanapaiboon, 2003). The withdrawal process varies in duration (from five days to three or more weeks) and severity depending on pattern

of use (Newton, Kalechstein, Duran, Vansluis, & Ling, 2004) and degree of dependence (McGregor et al., 2005). Common symptoms associated with cessation of amphetamine use are musculoskeletal pains, decreased energy, depressive symptoms, anxiety, severely disrupted sleep patterns, irritability, increased appetite, and agitation (Maxwell, 2005; McGregor et al., 2005; Newton, Kalechstein, Duran, Vansluis, & Ling, 2004).

The problems associated with amphetamine use have been considered to be more severe and greater in number than those of other psychostimulants such as ecstasy and cocaine (Williamson et al., 1997). For example, Rawson et al. (2000) found that methamphetamine users reported a greater number of psychiatric symptoms (e.g., hallucinations), more severe psychiatric symptoms, a higher prevalence of severe depression on entering treatment, and a more continuous pattern of substance use than cocaine users. The methamphetamine group also reported significantly more family problems, such as hostile interactions and difficulties maintaining communication. This emphasises the importance of examining amphetamines and other stimulants as independent substances, rather than as a collective stimulant group.

Prevalence and patterns of cannabis use

There is a high rate of cannabis use in the general population and in amphetamine using groups, highlighting the need to consider the contribution of cannabis in studies of amphetamine use. The 2004 NDSHS found that cannabis continued to be the most widely used illicit drug in Australia, with one third (33.6%) of the population reporting use in their lifetime and 11.3% reporting recent use

(previous 12 months) (Australian Institute of Health and Welfare, 2005a). Males (14.4%) were more likely than females (8.3%) to have used cannabis in the last 12 months, and they did so on a more frequent basis than females. Daily use was reported by 16.4% of recent cannabis users, with those in the 30 – 39 year age range most commonly reporting this pattern of use.

Polydrug use is also common amongst cannabis users. An Australian study found that cannabis abuse/dependence was associated with an 11-fold increased risk of reporting another type of substance abuse/dependence (Kavanagh et al., 2004). The 2004 NDSHS reported that 89.2% of recent cannabis users concurrently used other drugs (Australian Institute of Health and Welfare, 2005a). Of this group, 86.2% had used alcohol, 27.9% had used meth/amphetamines, and 24.2% had used ecstasy.

Effects of cannabis use

The effects of cannabis are dose dependent (Farrell, 1999), and are also influenced by factors associated with the individual user such as their health and weight, their concurrent use of other substances, and the extent of their previous substance use history (Australian Drug Foundation, 2005). The primary psychoactive component of cannabis is delta9-tetrahydrocannabinol, commonly known as THC (Ameri, 1999). THC rapidly passes from the lungs into the bloodstream and then the brain, where it connects to cannabinoid receptors. These receptors are involved with the dopaminergic system, and are commonly linked with pleasure, thought processes, movement, perception, and memory (Ameri, 1999; D'Souza et al., 2005).

Cannabis use is associated with a range of consequences that have short- and long-term effects on health and psychological well-being (Australian Drug Foundation, 2005; Hall, Solowij, & Lemon, 1994). Physically, cannabis intoxication increases appetite and heart rate, and leads to red eyes, dry mouth, and drowsiness. The psychological effects of cannabis include impaired concentration and short-term memory, a sense of calmness and relaxation, talkativeness, enhanced sensory perception, and disorientation to time and space. Some people also report hallucinations, paranoia, panic, fear, and depressed mood. Beyond the more immediate effects, cannabis use (particularly heavy, prolonged use) has been found to increase the risk of developing a psychotic illness such as schizophrenia (Andreasson, Allebeck, Engstrom, & Rydberg, 1987; Hall, 1998; Smit, Bolier, & Cuijpers, 2004; van Os et al., 2002). The relationship between cannabis, psychotic symptoms, and psychotic disorders will be examined in Chapter 4.

The risk of dependence is high for daily or regular users of cannabis, and those who report an early age of initiation to its use (Chen, O'Brien, & Anthony, 2005; Coffey, Carlin, Lynskey, Li, & Patton, 2003). Symptoms of withdrawal include aggressive behaviour, irritability, anxiety, tension, cravings, headaches, decreased appetite, disturbed sleep patterns, and to a lesser degree depressed mood, physical pains and discomfort, shakes, and perspiration (Astolfil, Leonard, & Morris, 1998; Budney, Novy, & Hughes, 1999; Vandrey, Budney, Kamon, & Stanger, 2005). These symptoms develop within 24 hours of ceasing cannabis use and can continue for several weeks. Four or more symptoms of withdrawal are typically experienced, and the majority of these symptoms are rated as moderately

severe (Budney, Novy, & Hughes, 1999).

Chapter 3. Amphetamines and psychosis

This chapter will focus on the link between amphetamines, sub-clinical symptoms of psychosis, and psychotic disorders. First, a review of the literature examining amphetamines and psychotic symptoms will be presented. This component of the research has centred around two main areas: experimental laboratory settings and community-based or treatment-seeking users reporting on their subjective experiences. Most laboratory studies were conducted more than two decades ago, but are valuable due to their use of healthy volunteers and detailed monitoring of changes induced by amphetamine administration. These studies generally focused on a range of self-reported psychological problems associated with use, including psychotic symptoms, mood, anxiety, and disturbed behaviour.

Second, a review of studies addressing amphetamine-induced psychosis and the clinical course of this disorder will be presented. Amphetamine-induced psychosis has been investigated in both longitudinal and cross-sectional studies. It is notable that while this component of the literature consists of many robust studies that have made considerable contributions to the area, nearly all of these studies failed to include a non-using group of psychosis patients within their sample, limiting our ability to determine true differences between amphetamine users with psychosis and non-users with psychosis.

Amphetamines and psychotic symptoms

The literature examining amphetamine use and the development of psychotic symptoms is compelling (e.g., McKetin, McLaren, Lubman, & Hides, 2006; Zweben et al., 2004). In studies of amphetamine users, paranoia/suspiciousness and

hallucinations have been the most common psychotic symptoms reported. From an Australian sample of methamphetamine users (*N* = 309), 23% reported clinically significant psychotic symptoms (suspiciousness, unusual thought content, and hallucinations) in the past year (McKetin, McLaren, Lubman, & Hides, 2006). A further 52% experienced these symptoms at a subclinical or 'mild' level. In another study, 64% of crystal methamphetamine users reported paranoia, with a substantial minority also reporting visual hallucinations (18%) and auditory hallucinations (13%) (Degenhardt & Topp, 2003). Hall et al. (1996) reported that 61% of regular amphetamine users experienced hallucinations and 59% experienced paranoia directly after using the substance. Even higher rates (81%) of psychotic symptoms (auditory and visual hallucinations, delusions of persecution and observation) were reported in a Japanese study of methamphetamine abusers (*N* = 116) (Matsumoto et al., 2002). As is common in Japanese studies of this population, polysubstance use was minimal, which may partially explain the notably higher rates of psychotic symptoms.

Laboratory studies have also provided evidence that repeated amphetamine administration can lead to the development of psychotic symptoms in healthy individuals without any prior history of psychosis (Angrist & Gershon, 1970; Bell, 1973; Ellison & Eison, 1983; Griffith, Cavanaugh, Held, & Oates, 1972; Janowsky & Risch, 1979; Krystal et al., 2005). The study by Griffith and colleagues (1970) was among the first to report the induction of psychotic symptoms in healthy volunteers with large doses of amphetamines. Psychotic symptoms were clearly evident within 120 hours of the first amphetamine dose, with two participants

showing symptoms of psychosis within the first 24 hours.

A recent study compared the effects of amphetamine and ketamine in a human psychopharmacological trial (Krystal et al., 2005). The substances were administered on four test days (each test day being separated by a minimum of three days) to 41 healthy individuals with no family history of mental illness. Psychotic symptoms were measured by the Positive and Negative Syndrome Scale (PANSS). Amphetamines produced positive symptoms (most significantly grandiosity, somatic concern, suspiciousness, and hallucinations) and psychomotor activation, all of which resolved spontaneously. There was a notable absence of perceptual changes, negative symptoms, or any cognitive impairment in those who were administered amphetamines.

Clinically significant psychotic symptoms can also emerge after only one dose of amphetamine (Chen et al., 2003; Connell, 1958; Dore & Sweeting, 2006; Gold & Bowers, 1978). An early study by Bell (1973) found that the administration of a single intravenous dose of methamphetamine resulted in the emergence of psychotic symptoms in 12 out of 16 patients with a history of amphetamine dependence. The majority of the group who experienced psychotic symptoms did so for up to two days, with one person continuing to experience sporadic psychotic symptoms for 26 days.

Stimulants have also been shown to worsen psychotic symptoms in those who already experience psychotic symptoms due to schizophrenia-type disorders. Curran et al. (2004) conducted a systematic review of 54 studies assessing stimulant use and psychosis. In the majority of these studies, a single dose of stimulant to a

person in the active phase of their psychotic disorder led to the worsening of their psychotic symptoms. An example more specific to amphetamines is a study involving 21 schizophrenia patients (Angrist, Rotrosen, & Gershon, 1980). Amphetamine administration was significantly associated with increased levels of general psychopathology, positive symptoms, and to a lesser degree, negative symptoms.

Overall, the literature consistently reports that amphetamines can induce or exacerbate symptoms of psychosis in healthy volunteers, regular amphetamine users, and clinical populations. The type and severity of symptom manifestation seems largely dependent on the development of substance dependence and patterns of use (including dose, frequency of use, and route of administration) (Batki & Harris, 2004; Ellison & Eison, 1983; Hall & Hando, 1994; McKetin, McLaren, Lubman, & Hides, 2006; Sato, Chen, Akiyama, & Otsuki, 1983).

Amphetamines and psychotic disorders

The chronic, high-dose use of amphetamines has also been found to precipitate the development of a diagnosable psychotic disorder (Chen et al., 2003; Dawe & McKetin, 2004; Ellison & Eison, 1983; Segal & Kuczenski, 1997a). Acute amphetamine-induced psychosis has been described as a "rapidly starting, noisy, violent and rapidly disappearing psychotic syndrome" (Jonsson & Sjostrom, 1970, p. 664). The symptoms of amphetamine-induced psychosis are often compared to those of paranoid schizophrenia (Bell, 1955; Connell, 1958; Siomopoulos, 1976), which include prominent positive symptoms such as persecutory and/or grandiose delusions and auditory hallucinations, with relatively intact cognitive functioning

and a normal range of affect (American Psychiatric Association, 2000). Based on these similarities, amphetamine-induced psychosis has been proposed as a model for schizophrenia (Ellison, 1994; Ellison & Eison, 1983; Kokkinidis & Anisman, 1981; Segal & Kuczenski, 1997a). There are, however, some phenomenological differences between schizophrenia and amphetamine–induced psychosis (Janowsky & Risch, 1979). While formal thought disorder and negative psychotic symptoms are common features of schizophrenia (Dore & Sweeting, 2006; Ellison & Eison, 1983; Kircher et al., 2001), there are relatively fewer reports of formal thought disorder (Chen et al., 2003; Sato, Chen, Akiyama, & Otsuki, 1983; Yui, Ikemoto, Ishiguro, & Goto, 2000) and negative psychotic symptoms (Tomiyama, 1990; Yeh, Lee, Sun, & Wan, 2001) in amphetamine-induced psychosis.

It is difficult to accurately determine the true rate of amphetamine-induced psychosis due to misdiagnosis, polydrug use, and inconsistencies between current mental illness classification systems and health monitoring programs (McIver et al., 2006). However, the recent increase in the use of amphetamines, particularly methamphetamine, appears to have resulted in an increase in both psychotic symptoms (Topp et al., 2002) and amphetamine-related psychoses (Roche, 2006; Srisurapanont et al., 2003). Of all Australian hospital patients discharged in 1999/2000 with a diagnosed substance-induced psychosis, 41% were due to amphetamines (Degenhardt, Roxburgh, & McKetin, 2007). These figures increased to 55% in 2003/2004, and amphetamine-induced psychosis now accounts for the largest proportion of all substance-induced psychosis diagnoses made at the time of discharge from hospital. Thus, amphetamines are associated with a greater number

of substance-induced psychoses than cannabis, even though cannabis is more widely used.

The proportion of amphetamine users who develop psychotic symptoms and disorders has been the focus of a number of recent Australian studies. In a study of 214 regular amphetamine users, 26.7% of those with a mental health problem had previously been diagnosed with a psychotic illness, and 71.4% of these people had received this diagnosis following regular use of amphetamines (Baker et al., 2004). Dyer and Cruickshank (2005) found that 14.4% of a methamphetamine inpatient treatment group (N = 202) had a documented history of psychotic disorder. These figures are notably higher than the prevalence of psychotic disorder in the general population, which is within the range of 4 – 7 per 1000 (Jablensky et al., 2000). More recently, the prevalence of psychosis in 309 methamphetamine users was found to be 11 times higher than that within the general population, with 13% identified by a psychosis screening instrument as having had a psychotic illness within the last year (McKetin, McLaren, Lubman, & Hides, 2006). Even after controlling for a history of psychotic disorder, nearly one-fifth of the sample had experienced a clinically significant psychotic symptom in the previous 12 months.

An interesting study by Wynn (2007) examined the occurrence of prior psychotic episodes in a sample of patients being treated for substance abuse (N = 24). The majority of participants abused benzodiazepines (66.7%), cannabis (62.5%), and amphetamines (58.3%). Twenty-two participants (91.7%) were diagnosed with a present or lifetime comorbid axis-1 disorder according to ICD-10 criteria. Psychotic (70.8%) and mood (66.7%) disorders were most prevalent. A key

finding of this study was that participants who identified amphetamines as their main substance of use were significantly more likely than those using other types of substances to have experienced a psychotic episode.

It is not clear why some amphetamine users go on to develop a psychotic illness while others do not. An underlying vulnerability to psychosis may differentiate between the two groups, particularly in cases of protracted amphetamine-induced psychoses. Methamphetamine users who had a life-time diagnosis of amphetamine-induced psychosis were found to have relatives with a significantly higher morbid risk for schizophrenia than families of methamphetamine users who had no history of amphetamine-induced psychosis (Chen et al., 2005). This familial risk was even higher amongst families of amphetamine users who had experienced a persistent (versus brief) amphetamine-induced psychosis. The same study found that people with a lifetime diagnosis of amphetamine-induced psychosis also had significantly more premorbid schizoid/schizotypal traits in childhood, in addition to higher rates of depressive, alcohol dependence, and antisocial personality disorders.

Amphetamines and the symptom profile of psychosis

Positive symptoms associated with amphetamine-induced psychosis usually consist of paranoid or persecutory themes (refer to Table 1 for a summary of studies assessing the nature of positive psychotic symptoms in amphetamine-induced psychosis patients). In all but one study shown (Srisurapanont et al., 2003), more than two-thirds reported auditory hallucinations and persecutory delusions, and more than 60% reported delusions of reference. Results for visual hallucinations were

more varied across the studies, with a range of 22.6% to 68.8%. However, in all cases, auditory hallucinations were more common than visual hallucinations. Reports by Bell (1973) and Ellison and Eison (1983) belong to a minority that have identified visual hallucinations as being more common than auditory hallucinations in this population.

Although less prominent, many studies also report negative psychotic symptoms to be a part of the symptom profile of amphetamine-induced psychosis. Negative symptoms include blunted affect, poverty of speech, diminished volition, psychomotor retardation, and emotional withdrawal. The measurement and reporting of negative psychotic symptoms varied immensely across the studies making comparison difficult in tabular form. For example, Chen et al. (2003) reported on specific negative psychotic symptoms such as flat affect and apathy, while Srisurapanont et al. (2003) reported on negative psychotic symptoms as a single category. The studies examining the symptom profile associated with amphetamine use and psychosis will now be discussed.

Table 1

Positive symptom profile of amphetamine-induced psychotic patients

Symptoms	Iwanami et al. (1994) % of N = 104	Harris & Batki (2000)[a] % of N = 19	Chen et al. (2003) % of N = 174	Srisurapanont et al. (2003) % of N = 168	Akiyama (2006) % of N = 32
Hallucinations					
Auditory	72.0	95.0	84.5	44.6	90.6
Visual	25.0	68.0	46.5	22.6	68.8
Delusions					
Persecutory	84.0	100.0	71.0	20.8	90.6
Of Reference	86.0	89.0	62.8	11.9	-
Grandiose	-	53.0	12.1	-	-
Bizarre	-	95.0	-	23.2	-

Note. [a] = Sample made up of 14 amphetamine-induced psychosis and 5 cocaine-induced psychosis patients.

Iwanami et al. (1994) reported on the clinical characteristics of Japanese inpatients (N = 104) diagnosed with amphetamine-induced psychosis according to DSM-III-R (American Psychiatric Association, 1987) criteria. Interviews were conducted within 72 hours of admission and continued throughout hospitalisation. Nearly half (47%) had also used other drugs, with alcohol and solvents being the most common. The symptom profile of most patients was likened to a paranoid psychotic state. Ideas of reference, delusions of persecution, and auditory hallucinations were most commonly identified. However, other hallucinations (including visual), disorientation, and depression were also found in at least 10% of patients. There was a marked absence of negative psychotic symptoms (social isolation, withdrawal, blunted or inappropriate affect, or poverty of speech) at presentation or anytime throughout hospitalisation. Although using a reliable diagnostic interview, Iwanami et al. (1994) failed to use a standardised measure of psychotic symptoms, relying instead on items listed in Connell's (1958) report on symptoms associated with amphetamine-induced psychosis. These were disorientation, ideas of reference, delusions of persecution, depression, and auditory, visual, and 'other hallucinations'. Thus, this study adds important descriptive information to the picture of amphetamine-induced psychosis, but limits comparison with other studies.

The cross-sectional study by Harris and Batki (2000) assessed 14 patients with amphetamine-induced psychosis and five patients with cocaine-induced psychosis that attended a psychiatric emergency centre. The Structured Clinical Interview for DSM-IV (SCID-IV) was used to diagnose psychotic and substance use

disorders. Each participant was interviewed once between one and 51 hours post-admission. Polydrug use was very high within the sample, with alcohol being the most prevalent substance used after stimulants. The PANSS identified a high level of positive symptoms (*M* = 30), paranoia (*M* = 12), thought disturbance (*M* = 16), depression (*M* = 12), activation[1] (*M* = 8), and general psychopathology (*M* = 46) compared to a sample of medicated schizophrenia patients (from a separate study). The mean scores for all these scales corresponded to a percentile rank between 70 (for the activation scale) and 95 (for the positive symptom scale) in schizophrenia patient norms. A quarter (26%) of participants also obtained substantial negative scale scores on the PANSS (*M* = 16). This mean score placed participants at the 17th percentile in relation to corresponding schizophrenia norms. Persecutory delusions (100%), auditory hallucinations (95%), bizarre delusions (95%), and delusions of reference (89%) were the most common symptoms. Other hallucinations were also experienced: visual (68%), olfactory (26%), tactile (26%), and gustatory (5.3%). Although the study had a small sample size consisting of patients with both amphetamine- and cocaine-induced psychosis, there was a clear resemblance in the findings of predominant positive psychotic symptoms and relatively few negative psychotic symptoms to other studies mentioned in the current discussion.

Batki and Harris (2004) used the same sample and PANSS scores to examine the relationships between the severity of psychotic symptoms and the levels of

[1] The activation subscale consisted of items often linked to mania: hostility, poor impulse control, excitement, uncooperativeness, poor rapport, and tension.

methamphetamine and amphetamine in blood and urine samples. Overall, there were no significant relationships identified between the levels of meth/amphetamine in blood or urine and negative psychotic symptoms. However, higher levels of meth/amphetamine in the urine and blood were associated with more severe positive psychotic symptoms, general psychopathology, and mania-type symptoms (as identified by the activation scale).

In another small study, the clinical symptoms of 32 female prisoners diagnosed with amphetamine-induced psychosis were assessed (Akiyama, 2006). Diagnoses were made by interview, although the use of standardised measures was not reported. Symptoms were assessed with the 24-item Brief Psychiatric Rating Scale (BPRS). Unfortunately, total and subscale BPRS scores were not reported. However, the researchers did state that patients exhibited negative symptoms that were comparable to those reported in the Mikami (2003) study (M = 1.4, SD = 2.3). The symptomatic profile was likened to that of schizophrenia, with a predominance of auditory hallucinations (90.6%), delusions of persecution (90.6%), thought broadcasting (75%), and visual hallucinations (68.8%). Depressive mood (90.6%) and suicidal ideation (68.8%) were also common.

A multi-site study (Australia, Japan, the Philippines, and Thailand) examined the psychotic symptoms of 168 amphetamine-induced psychotic inpatients (Srisurapanont et al., 2003). Diagnoses were made using the Mini-International Neuropsychiatric Interview-Plus and symptom severity was measured by the Manchester Scale. Persecutory delusions (77.4%), auditory hallucinations (72.6%), strange or unusual beliefs (58.3%), and thought reading (53.0%) were the most

prevalent lifetime psychotic symptoms. With respect to current psychotic symptoms, auditory hallucinations (44.6%), strange or unusual beliefs (23.2%), visual hallucinations (22.6%), and negative psychotic symptoms (21.4%) were the most prevalent. Delusions and hallucinations were rated as the most severe symptoms experienced in the week prior to assessment, while the negative symptoms of psychomotor retardation and poverty of speech were rated as the least severe. The rates of current positive psychotic symptoms in this sample were notably lower than those of other studies reviewed thus far. As noted by the researchers, this may be due to the exclusion of moderately and severely violent participants within the study sample. Further to this, the assessment of psychotic symptoms for some patients did not occur until the seventh day of admission, thus raising the possibility of symptom abatement prior to assessment.

Chen and colleagues (2003) examined methamphetamine users with (n = 174) and without (n = 261) a lifetime history of psychosis. Participants were drawn from a psychiatric hospital and detention centre. A diagnosis and symptom profile was obtained using the Diagnostic Interview for Genetic Studies (DIGS). The most common symptoms of those with amphetamine-induced psychosis included auditory hallucinations (84.5%), persecutory delusions (71.0%), delusions of reference (62.8%), visual hallucinations (46.5%), and delusions of mind reading (40.5%). Negative psychotic symptoms were also measured, with avolition/apathy (15.2%), flattened affect (17.6%), and inappropriate affect (11.6%) being identified, but at much lower rates than most positive symptoms.

Unfortunately, the majority of studies examining the symptomatic profile of

psychosis associated with amphetamine use do so without including a control group of psychotic patients who do not use amphetamines, thereby limiting our ability to make comparisons between the two groups. Two Japanese studies have attempted to address this issue. The first study (Tomiyama, 1990) compared 11 patients with amphetamine-induced psychosis to 11 patients with schizophrenia (matched for age and sex). The Scale for the Assessment of Positive Symptoms (SAPS) found no differences between the two groups regarding positive symptoms. However, the Scale for the Assessment of Negative Symptoms (SANS) identified significantly lower negative symptoms (affective flattening and alogia) in the methamphetamine group. While this study controlled for the effects of varying phase of psychotic illness within the sample by using only participants with a chronic illness, the findings are potentially limited with respect to their generalisability to patients in the early phase of their psychotic illness.

The second study (Mikami et al., 2003) assessed psychotic symptomatology as part of an investigation into the psychophysiological correlates of schizophrenia. Forty-eight patients with amphetamine-induced psychosis were compared to 30 patients with schizophrenia (age-matched). Diagnoses were made via the SCID-IV and psychotic symptoms were assessed using the BPRS. Participants diagnosed with amphetamine-induced psychosis obtained significantly lower scores on the positive symptom scale (M = 1.7, SD = 2.1 vs. M = 7.3, SD = 3.8), the negative symptom scale (M = 1.4, SD = 2.3 vs. M = 7.5, SD = 3.6), and the total BPRS scale (M = 10.5, SD = 5.0 vs. M = 31.2, SD = 17.0) compared to those with schizophrenia. It is likely, however, that these differences were at least partially due to the

amphetamine-induced psychosis group having had a significantly shorter duration of illness episode (time in years between the onset of illness and assessment point) (*M* = 6.0, *SD* = 5.3) than the schizophrenia group (*M* = 14.1, *SD* = 9.3). Also of note, are the relatively low BPRS scores obtained by participants of this study. This finding may have been influenced by the number of outpatients (*n* = 16) included in the study, who were most likely less ill than their inpatient counterparts (*n* = 32). Low BPRS scores may also be a reflection of the fact that both the using and non-using groups were maintained on a relatively high neuroleptic dose (amphetamine-induced psychosis group *M* = 1016, *SD* = 1353 and schizophrenia group *M* = 1363, *SD* = 899; chlorpromazine equivalents in mg). Further analyses were conducted with this sample by retrospectively categorising the amphetamine-induced psychosis group according to duration of psychotic symptoms (transient = < 10 days; prolonged = 10 – 31 days; or persistent = > one month). These results will be presented in the section of this chapter that is dedicated to the impact of amphetamines on the clinical course of psychosis.

Given the difficulties obtaining samples of study participants who use only one type of illicit substance, many studies of psychosis have categorised substance users (of any type) as one group and then compared these people with their non-using counterparts. While not specific to class of substance, these studies can still add to our understanding of differences in symptom profile between users and non-users with psychosis. Caton et al. (2005) compared patients with a primary psychotic illness (all of whom used substances) (*n* = 217) to patients diagnosed with substance-induced psychoses (*n* = 169). The most common substances used by those

in the primary psychosis group were cannabis (55.3%), daily or nearly daily alcohol use (23.0%), and cocaine (16.1%). The most common diagnoses in those with a substance-induced disorder were associated with cannabis (18.9%), alcohol (17.2%), and cocaine (15.4%). Notably, all participants were in the early phase of their psychotic illness (i.e., no hospitalisation outside the six-month period leading up to the current admission). Diagnoses were made using the Psychiatric Research Interview for Substance and Mental Disorders (PRISM). Psychiatric symptoms were measured by the PANSS. The substance-induced psychosis group obtained significantly lower scores on positive symptoms (M = 14.30, SD = 5.36 vs. M = 18.62, SD = 7.26), negative symptoms (M = 11.67, SD = 4.74 vs. M = 14.16, SD = 6.24), and general psychopathology (M = 28.44, SD = 6.86 vs. M = 33.29, SD = 10.46) than the primary psychosis group. The groups reported comparable rates of auditory hallucinations (primary psychosis = 68.7% and substance-induced psychosis = 69.8%). However, the substance-induced group were significantly more likely to experience visual hallucinations than the primary psychosis group (23.7% versus 14.7%).

Dixon et al. (1991) compared substance-abusing psychotic patients (n = 40) to non-using psychotic patients (n = 43) on a range of variables, including psychotic symptoms. The SCID was used to diagnose psychiatric and substance abuse/dependence disorders. The substance-abusing group most commonly used cannabis, alcohol, and cocaine, which is similar to the substance use patterns reported in the Caton et al. (2005) study. However, there are important contrasts between the findings of the Dixon et al. (1991) study and those of the Caton et al.

(2005) study. These differences may be partially attributable to all participants in the Caton et al. (2005) study having a history of substance use, despite not all meeting the criteria for a substance-induced psychosis. Dixon et al. (1991) found that substance-abusers and non-users did not differ on the Global Assessment Scale, the BPRS, or the SANS at admission (specific scores were not reported), indicating comparability across the two groups on general psychopathology, and positive and negative psychotic symptoms. A lack of significant difference in psychotic symptom profile was maintained even when the substance-abusers were re-grouped as either recent (DSM-III-R diagnosis of substance abuse/dependence in last six months) or past (substance users in remission) users, and again compared with non-users.

In their study of the relationship between substance abuse in psychosis and clinical presentation, Kovasznay et al. (1993) interviewed 250 patients with early psychosis. Participants were categorised as users (lifetime psychoactive substance abuse/dependence disorder) or non-users via the SCID. Cannabis was the most frequently used substance, followed by cocaine and stimulants. Users and non-users did not differ in the frequency of auditory or visual hallucinations, or delusions, and there was no difference found between the groups on the SAPS measure of positive symptoms. Interestingly, users obtained a significantly higher score on the depression-anxiety subscale of the BPRS, but their scores on the Hamilton Rating Scale for Depression were comparable to those of the non-users. This study also examined the influence of gender on outcome. Male users demonstrated significantly lower negative symptoms on the SANS and significantly higher total

BPRS scores when compared to non-users. This pattern was not found in females.

Rabinowitz et al. (1998) examined the impact of substance use (primarily alcohol, cannabis, stimulant, and cocaine use) on first-admission psychosis patients. Again based on SCID diagnoses, participants were categorised as those with no life-time substance abuse or dependence disorder (n = 289), those in full or partial remission of a substance use disorder at the time of hospitalisation (n = 185), and those with a moderate-severe current substance abuse or dependence disorder (n = 67). The SANS, SAPS, 18-item BPRS, and the Hamilton Depression Rating Scale were used to measure clinical symptoms. No significant differences were found between the using and non-using groups with respect to positive symptoms, negative symptoms, or depression symptoms.

Similar findings were obtained by Sevy et al. (2001), who also limited their sample to those in the early phase of their psychotic illness (i.e., first episode schizophrenia or schizoaffective disorder). Patients with a past or current history of substance misuse (n = 27) were compared to patients with no history of substance misuse (n = 91) on a range of variables, including baseline psychotic symptoms. Again, alcohol, cannabis, and cocaine were most commonly used by those in the substance-using group. As measured by the Schedule for Affective Disorders and Schizophrenia (including Psychosis and Disorganisation Items) (SADS), the SANS, and the Hamilton Depression Rating Scale, there were no statistical differences between the groups on positive, negative, or depressive symptom scores.

Scheller-Gilkey et al. (2002) examined differences on clinical and cognitive function between schizophrenia patients with (n = 20) and without (n = 20) a history

of substance abuse. Participants were age-, sex-, and race-matched, and the SCID was used to confirm diagnoses of schizophrenia and substance abuse. Results from the Structured Clinical Interview for the Positive and Negative Syndrome Scale revealed no significant differences between users and non-users on positive symptoms (M = 19.10, SD = 4.46 versus M = 17.70, SD = 3.87 respectively) or negative symptoms (M = 21.60, SD = 6.41 versus M = 24.60, SD = 6.22 respectively).

Talamo et al. (2006) conducted a meta-analysis of the impact of substance use on positive and negative psychotic symptoms. Alcohol, cannabis, and cocaine were the most common substances represented within the eight studies of schizophrenia patients included in the meta-analysis. While total PANSS scores were not significantly different between those with a substance use disorder compared to those without, the substance-using group obtained significantly higher positive symptom scores and significantly lower negative symptoms scores.

In conclusion, there is overwhelming evidence that the symptom profile of amphetamine-induced psychosis primarily consists of positive psychotic symptoms (most predominantly, auditory hallucinations and persecutory delusions). Negative psychotic symptoms appear relatively less prominent, however, this type of symptom has not generally been given the same amount of consideration in its measurement or reporting. While there are numerous studies that describe the symptom profile of psychosis associated with amphetamine use, there is a marked absence of studies that specifically compare the type and severity of psychotic symptoms between amphetamine-using psychosis patients and non-using psychosis

patients. The two amphetamine-related studies that attempted to address this issue (Mikami et al., 2003; Tomiyama, 1990) found that amphetamine use was associated with fewer negative psychotic symptoms, and either similar or fewer levels of positive psychotic symptoms. However, it is difficult to draw strong conclusions from these studies due to limitations associated with sample size and issues related to participants' phase of illness. There are also several robust studies comparing non-using psychosis patients with substance-using psychosis patients (non-specific to class of substances used). Of the six studies discussed here, five found no significant differences between users and non-users in the severity of positive symptoms (Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Kovasznay et al., 1993; Rabinowitz et al., 1998; Scheller-Gilkey, Thomas, Woolwine, & Miller, 2002; Sevy et al., 2001). Four studies found no differences between the groups in the severity of negative symptoms (Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Rabinowitz et al., 1998; Scheller-Gilkey, Thomas, Woolwine, & Miller, 2002; Sevy et al., 2001). Despite such consistent findings in the literature addressing the general category of substance use, we remain uncertain about the independent impact of recent amphetamine use on the severity of psychotic symptoms. Further knowledge about the symptom profile of psychosis associated with amphetamine use and how it might differ from a psychosis with no associated substance use is important because it informs diagnostic and treatment practices, and provides indicators of prognosis. For example, the presence of a predominantly negative psychotic symptom profile is likely to be more responsive to an atypical antipsychotic medication regime (versus one involving conventional medications) (Lieberman et al., 2005; Peuskens, 2004).

Furthermore, a predominantly negative symptom profile has been associated with a poorer long-term prognosis (Lecrubier, Quintin, Bouhassira, Perrin, & Lancrenon, 2006; Murphy, Chung, Park, & McGorry, 2006; Nakaya & Ohmori, 2006), and in these circumstances, the patient would benefit from a range of additional psychosocial interventions being included in the treatment plan.

Amphetamines and the clinical course of psychosis

In the majority of cases, the psychotic symptoms that develop following the use of amphetamines are associated with a sudden onset and typically resolve within days of stopping substance use (Segal & Kuczenski, 1997b; 1999). However, there are a substantial minority of protracted cases that warrant the diagnosis of amphetamine-induced psychosis. Refer to Table 2 for a summary of time taken for psychotic symptom resolution in amphetamine-induced psychosis patients.

Table 2

Comparison between studies of time taken for symptom resolution in amphetamine-induced psychosis patients

Time Taken for Symptom Resolution[a]	Connell (1958) % of *N* = 30	Sato et al. (1982) % of *N* = 82	Tatetsu et al. (1956) % of *N* = 144	Konuma (1984) % of *N* = 192	Iwanami et al. (1994) % of *N* = 104
7 – 11 days	53	64	-	-	68
11 – 30 days	17	18	74	87	6
> 1 month	7	18	26	13	10
> 3 months	-	-	-	-	16
Undetermined	23	-	-	-	-

Note. [a] = For the purpose of comparison across studies in tabular form, the time periods for symptom resolution have been slightly changed for some studies and more specific details are provided in the text.

Sato and colleagues (1992) reviewed several studies (Connell, 1958; Konuma, 1984; Sato, Nakashima, & Otsuki, 1982; Tatetsu, Goto, & Fujiwara, 1956) on the clinical course of amphetamine-induced psychosis. Connell's early study (*N* = 30) found that 53% of patients took up to 10 days after drug discontinuation for their symptoms to resolve, 17% took between two and four weeks, and 7% took more than one month (Connell, 1958). In the study (*N* = 82) by Sato et al. (1982), 64% were free of psychotic symptoms by day 10. However, 18% took between 11 and 30 days, and a further 18% took more than one month to achieve symptom resolution. The majority of participants in the Tatetsu et al. (1956) (*N* = 144) and Konuma (1984) (*N* = 192) studies took between 11 and 30 days for symptom resolution. Overall, Sato et al. (1992) reported that more than three-quarters (82%) of amphetamine-induced psychosis patients obtained complete psychotic symptom resolution within one month following cessation of substance use. They suggested that the group of patients with protracted cases of psychosis (lasting well beyond the three to five days it takes for the body to excrete the substance) are evidence that methamphetamine abuse leads to longer-term brain dysfunction.

Iwanami et al. (1994) interviewed participants (*N* = 104) within 72 hours of admission and conducted assessments until discharge. The frequency of assessment interviews was not reported. Half of the participants (52%) experienced psychotic symptoms that resolved within one week (transient) of ceasing methamphetamine use and commencing antipsychotic medication. A further 16% were free of psychotic symptoms between weeks one and two, and another six percent experienced a psychotic state lasting between two weeks and one month. Ten

percent experienced enduring psychotic symptoms that ranged from one to three months. The remaining 16% had psychotic symptoms that continued for more than three months (persistent). There were no differences between the transient and persistent groups on duration of methamphetamine abuse, polydrug use, age, sex, or clinical symptoms (disorientation, ideas of reference, delusions of persecution, auditory and visual hallucinations, and depression). However, those in the persistent symptom group were significantly more likely to experience olfactory, gustatory, and tactile hallucinations.

Chen and colleagues (2003) assessed methamphetamine users from a detention centre (n = 333) and a psychiatric centre (n = 102). In total, 174 participants obtained a lifetime diagnosis of amphetamine-induced psychosis. Of those participants drawn from the detention centre who had developed psychosis, 91.7% had experienced psychotic symptoms that abated within one week of ceasing use. Participants with psychosis that were drawn from the psychiatric centre had slightly more persistent psychotic symptoms, with 26.4% exhibiting psychotic symptoms for more than one month after cessation of drug use, and a further 12.7% exhibiting prolonged psychotic symptoms for more than six months. The authors did not refer to the specific types of psychotic symptoms.

In a six month follow-up of 17 male patients with amphetamine-induced psychosis, Yeh and colleagues (2001) assessed changes in positive and negative symptoms, and overall psychological functioning. The SADS was used to measure positive symptoms, the SANS was used to measure negative symptoms, and the Global Assessment of Functioning scale (GAF) was used to evaluate overall

psychological functioning. Negative psychotic symptoms were found to be negligible at admission and follow-up, and except for anhedonia/asociality (which was associated with a significant reduction in severity), no significant changes were found on this symptom dimension between admission and follow-up. Apart from delusions of reference, all baseline scores of positive symptoms (suspiciousness, auditory hallucinations, persecutory delusions, thought broadcasting, and voice comment) had significantly improved by follow-up. Overall functioning on the GAF also showed significant improvement from baseline (M = 36.5, SD = 7.0) to follow-up (M = 62.7, SD = 15.2). Nearly half (47%) of the sample had re-used methamphetamine between baseline and follow-up assessments, however, re-users were not significantly different to abstainers with respect to symptom changes between these two assessment points. The researchers suggested that this pattern of improvement in positive symptoms and overall functioning, in combination with low baseline and follow-up scores for negative symptoms, is clearly different to that of a primary psychosis such as schizophrenia. Unfortunately, this assumption was not empirically tested by including a control group of non-using patients with a primary psychosis.

A review of medical charts from a Japanese hospital identified a total of 216 admissions resulting from amphetamine-induced psychosis (Nakatani et al., 1989). Most patients (63.7%) were discharged within 60 days of admission. More than a quarter of the sample (28.4%) remained inpatients beyond 61 days, and 7.9% were patients for more than 101 days.

Akiyama (2006) assessed the clinical course of psychotic symptomatology in

32 women with amphetamine-induced psychosis using the BPRS. Patients were prescribed haloperidol or risperidone in accordance with usual treatment regimes. Interviews were conducted biweekly or bimonthly until discharge (up to 120 months). Based on correlations between the positive psychotic symptom scale and the depression-anxiety scale of the BPRS, patients were categorised into three groups: low, moderate, or high ratings on the combined dimension of positive psychotic symptoms subscale and depression-anxiety subscale. In the group of participants rating low on the combined dimension, it took at least 20 weeks for psychotic symptoms to reduce in severity (according to total BPRS scores). The group with moderate ratings on the combined dimension took approximately 40 weeks to experience a reduction in total BPRS scores, while the high rating group continued to experience significant psychotic symptoms at 100 weeks. This study draws attention to the potential interaction between positive psychotic symptoms and mood, and the impact that these variables might collectively have on the clinical course of psychotic symptoms. Of note, is the considerably longer period taken for these symptoms to abate compared to other studies mentioned in this discussion.

Given the varying rates of symptomatic recovery, some researchers have proposed the categorisation of amphetamine-induced psychosis as follows: (1) transient - rapid symptom abatement within 10 days of substance cessation; (2) prolonged - symptom abatement within one month of substance cessation; or (3) persistent - enduring symptoms beyond one month despite substance cessation. Ujike and Sato (2004) found that 41% of their amphetamine-induced psychosis sample fell into the persistent category.

In the study by Mikami (2003), amphetamine-induced psychosis patients were retrospectively categorised into transient (*n* = 16), prolonged (*n* = 14), and persistent (*n* = 18) groups. The persistent group was further divided into those who were 'lightly disturbed' (*n* = 11) and 'severely disturbed' (*n* = 7), based on scores of < 50 and $\underline{\geq}$ 50 (respectively) on the GAF scale. The transient (*M* = 8.9, *SD* = 4.2), prolonged (*M* = 11.1, *SD* = 4.5), persistent – lightly disturbed (*M* = 8.7, *SD* = 3.8), and persistent - severely disturbed (*M* = 16.0, *SD* = 6.2) groups all scored significantly lower on the total BPRS score than the schizophrenia group (*M* = 31.2, *SD* = 17.0). Similarly on the positive symptom scale score, the transient (*M* = 1.4, *SD* = 2.3), prolonged (*M* = 1.3, *SD* = 1.2), persistent – lightly disturbed (*M* = 1.5, *SD* = 1.1), and persistent – severely disturbed (*M* = 3.3, *SD* = 3.6) groups scored significantly lower than the schizophrenia group (*M* = 7.3, *SD* = 3.8). With respect to the negative symptom scale, the transient (*M* = 0.0), prolonged (*M* = 1.1, *SD* = 2.7), and persistent – lightly disturbed (*M* = 1.9, *SD* = 1.4) groups obtained significantly lower scores than the schizophrenia group (*M* = 7.5, *SD* = 3.6). However, the persistent - severely disturbed group (*M* = 4.3, *SD* = 2.6) was not significantly different to the schizophrenia group on negative symptoms. These results suggest more similarities exist between protracted (rather than transient) cases of amphetamine-induced psychosis and schizophrenia-type disorders. However, the schizophrenia group in this study was not defined according to chronicity of psychotic illness, and so it is possible that these results may simply reflect a commonality of persistent, chronic symptoms in both groups.

While theses studies consistently reported that many patients with

amphetamine-induced psychosis experienced a resolution of psychotic symptoms within two weeks of ceasing substance use, it is clear that not all patients experienced an illness that remitted once the substance was excreted from their body. Little is known about the factors leading to different illness course in amphetamine-induced psychosis. It has been suggested that substance-abstinent patients with persistent psychotic symptoms have a pre-existing vulnerability to psychotic illness. Alternatively, they may have been experiencing the prodromal phase of schizophrenia alongside substance use. This substance use, in turn, may have hastened the onset of the active phase of the illness (Dawe & McKetin, 2004). It is also probable that diagnostic inaccuracy occurred in many cases, and this issue will be discussed further in Chapter 6.

It is also not clear from the studies of clinical course in amphetamine-using psychosis patients whether their pattern of symptom resolution is significantly different to that of the non-using psychosis population. Many inferences have been made about how these groups compare, however, no studies have incorporated both groups in their studies of clinical course. The Mikami (2003) study did include schizophrenia patients in their sample, however, rather than prospectively monitoring symptom abatement across time, they retrospectively categorised participants (from the substance-using group only) according to rate of recovery.

Taking a more general perspective, there are a number of studies (Caton et al., 2006; Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Ries et al., 2000) that have compared symptom change or resolution in those with psychosis and concurrent substance use to those with a primary psychosis. Caton et al. (2006)

examined the predictors of psychosis remission at one year follow-up of emergency admissions for primary psychosis (*n* = 186) and substance-induced psychosis (*n* = 133). Significantly more patients from the substance-induced group (77%) had achieved remission one year post-baseline assessment compared to the primary psychosis group (50%). Despite different rates of remission, the factors found to predict remission were similar for both groups: lower PANSS scores at baseline, better premorbid adjustment, shorter duration of untreated psychosis, and better insight into illness.

As previously reported, Dixon et al. (1991) assessed 83 psychotic inpatients within five days after admission and five days before discharge. The mean length of hospital stay was 47.4 days (*SD* = 25.7) for the using group and 61.1 days (*SD* = 54.4) for the non-using group. Forty participants were diagnosed with substance disorders of dependence or abuse (primarily associated with cannabis, alcohol, and cocaine). Substance-using participants were not significantly different to non-substance-using participants on the GAF, BPRS, or SANS measures at admission. However, the substance-using group obtained significantly lower total scores on the BPRS and the SANS, and lower BPRS subscale scores for thought disorder, paranoia-suspiciousness, and anergia at discharge. The sample was then grouped according to recent substance use (substance dependence/abuse last six months), past substance use (in remission for substance dependence/abuse), and no substance use. There were no differences between groups at admission. At discharge, recent substance users had significantly lower total BPRS scores and thought disorder scores than the non-substance users. Both the recent and past substance users also

obtained significantly lower paranoia-suspiciousness scores than the non-substance users at discharge. Overall, these results indicate that substance-using psychosis patients initially present with essentially similar clinical profiles to those with a primary psychosis. However, the substance-using patients with psychosis went on to display a more benign clinical course, evidenced by significantly fewer positive and negative symptoms at the time of discharge.

Ries et al. (2000) assessed 608 inpatients within 48 hours of admission and again at discharge. The mean length of hospital stay for the total sample was 15.4 days (*SD* = 10.7). All participants presented with acute schizophrenia and were categorised into either a dual diagnosis group (those who met criteria for substance abuse/dependence and schizophrenia [*n* = 275]) or a primary psychosis group. No information was provided about the most common substances used by participants in the dual diagnosis group. It is notable that 70% of this sample had two or more lifetime psychiatric inpatient hospitalisations, raising the possibility that a number of participants were presenting with a chronic psychotic illness. The groups were not significantly different on the total score of the Psychiatric Assessment Form (PAF) or any of the subscales (hallucinations/delusions, depression, elevated mood, hostility) at admission. The dually diagnosed group did obtain significantly higher ratings of suicidality on the PAF scale at admission, however, this difference lost significance at discharge. While the dually diagnosed group were rated with significantly less severe hallucinations and delusions at discharge than the primary psychosis group, there were no other significant differences between the two.

Unfortunately, these last three studies did not analyse data according to specific classes of substances and they each incorporated only two assessment points.

In summary, most studies reported that at least half of those with amphetamine-induced psychosis experienced symptom resolution within 10 days of ceasing substance use. This pattern of symptom recovery is consistent with reports that amphetamines are typically excreted from the body within five days of last use. Of particular interest are the smaller, but still substantial, percentages (ranging from 13% to 39.1%) of patients that took more than one month for their psychotic symptoms to abate. To date, there are no studies that have prospectively monitored and compared symptomatic and behavioural change in amphetamine-using psychosis patients and non-using psychosis patients during their hospital admission using multiple assessment points. Several studies reviewed here have compared the broader category of patients with varying substance-induced psychoses to those with a primary psychosis and no associated substance use. Caton et al. (2006) reported that the using group were more likely to achieve symptom remission within one year. They found users experienced a faster remitting psychotic illness. The findings of Dixon et al. (1991) and Ries et al. (2000) were not wholly consistent with respect to comparisons at discharge, but overall, the substance-using groups experienced significantly less severe hallucinations, delusions, negative symptoms, and general psychopathology than the primary psychosis group at this assessment point, despite the groups presenting with essentially similar symptom profiles at admission. No differences were found between substance users and non-users on measures of depression, anxiety, activation, or hostility at discharge. Unfortunately,

it remains unclear how the groups of these two studies compared on their respective clinical courses between the assessment points of admission and discharge. Notably, neither study controlled for chronicity of illness in their respective samples.

Chapter 4. Cannabis and psychosis

In this chapter, the relationship between cannabis and the development of psychotic symptoms and a diagnosable psychotic disorder will be considered. The literature involving cannabis use and psychosis is somewhat different to that of the corresponding amphetamine literature. There have been a number of robust longitudinal studies that have looked at the association between cannabis use, psychotic symptomatology, and the later development of a psychotic disorder. In most cases, large population cohorts have formed the basis of these studies. There have also been a limited number of studies involving community-based cannabis users that have reported on the adverse effects of cannabis use. These studies can be broadly classified into those that examine cannabis-using psychotic patients and those that examine patients diagnosed with a cannabis-induced psychosis. Despite the literature being extensive, the causal relationship between cannabis and psychosis remains equivocal (Fergusson, Poulton, Smith, & Boden, 2006) and there are a number of contentious issues with respect to the role of cannabis in psychosis.

Cannabis and psychotic symptoms

There is reasonable evidence that cannabis use is linked to the development of psychotic symptoms (Arseneault et al., 2002; Drewe, Drewe, & Riecher-Rossler, 2004; Ferdinand, Sondeijker et al., 2005; Ferdinand, van der Ende et al., 2005; Fergusson, Horwood, & Ridder, 2005). These symptoms usually occur in response to intoxication, and are most commonly transient and mild in nature (Moore et al., 2007). Cannabis use can lead to auditory and visual hallucinations, delusions, and thought disorder in both healthy volunteers and schizophrenia patients, with the

schizophrenia group demonstrating a particular vulnerability (D'Souza, 2004; Drewe, Drewe, & Riecher-Rossler, 2004; Favrat et al., 2005; Hall, 1998; Rehman & Farooq, 2007).

In an early epidemiological study examining the risk of psychotic experiences associated with substance use, the Diagnostic Interview Schedule (DIS) was administered to 4,994 people from the general population (Tien & Anthony, 1990). Twelve DIS questions related to psychotic symptoms were used to obtain information about psychotic experiences. From the total sample, 11.7% reported at least one psychotic experience. Of those who reported daily cannabis use (n = 235), 21.7% reported at least one recent psychotic experience. Any use of cannabis was associated with a 30% increased risk of psychotic symptoms. After controlling for daily cocaine use and alcohol use disorders, daily use of cannabis doubled the risk of psychotic symptoms.

Evidence of the potential for cannabis to worsen psychotic symptoms in those with schizophrenia has been given by Degenhardt et al. (2007). They examined the use of cannabis by people with schizophrenia and related disorders (N = 101). Participants were assessed monthly across ten months, with a particular focus on psychotic symptoms as measured by the BPRS. Cannabis use significantly predicted an increase in psychotic symptoms in the following month. This association remained significant despite other factors (e.g., medication compliance and amphetamine use) being entered into analyses.

Cannabis use has also been linked to psychotic relapse. A recent example has been provided by Hides et al. (2006), who found that a higher frequency of

cannabis use predicted psychotic relapse in a sample of 84 participants with recent-onset psychosis. Cannabis use persisted as a strong predictor even after controlling for medication adherence, other substance use, and duration of untreated psychosis. Interestingly, a bidirectional relationship was established, with increased psychotic symptoms being identified as a significant predictor of relapse to cannabis use.

Several longitudinal studies have provided evidence of a link between cannabis use and the later development of psychotic symptoms. The use of cannabis at ages 15 and 18 was associated with a higher incidence of schizophrenia symptoms at the age of 26 according to DSM-IV (American Psychiatric Association, 1994) criteria (Arseneault et al., 2002). Analyses controlled for the effects of psychotic symptoms evident at age 11. Cannabis use at the age of 15 was a specific risk for the diagnosis of a schizophreniform disorder at 26 years, possibly due to a longer exposure period to cannabis. This study determined that the increased risk for symptoms of schizophrenia was specifically due to cannabis, rather than other drugs.

A sub-sample of participants (n = 1,053) from the Christchurch Health and Development Study (CHDS) was assessed for current psychotic symptomatology at ages 18 and 21 years using the Symptom Checklist 90 (SCL-90) (Fergusson, Horwood, & Swain-Campbell, 2003). Cannabis dependence at the ages of 17/18 years and 20/21 years was assessed using the Composite International Diagnostic Interview (CIDI). Dependence was significantly associated with increased rates of psychotic symptoms at ages 18 and 21 years, even after controlling for confounding factors such as pre-existing psychotic symptoms and problems with family functioning.

A further study of the CHDS cohort (*n* = 1,055) reported on an additional assessment point at 25 years, finding a dose-response relationship between cannabis use and rates of psychotic symptoms (Fergusson, Horwood, & Ridder, 2005). After controlling for possible confounds (including prior psychosis and cannabis use, concurrent and prior mental disorders, and family functioning), daily use of cannabis was associated with rates of psychotic symptoms that were 1.6 -1.8 times higher than those experienced by non-users of cannabis.

Two studies conducted by Ferdinand and colleagues (Ferdinand, Sondeijker et al., 2005; Ferdinand, van der Ende et al., 2005) with a Dutch cohort study (*N* = 1,580) found a significant bidirectional association between lifetime cannabis use and lifetime occurrence of psychotic symptoms using the CIDI. The first study found that cannabis use significantly predicted future psychotic symptoms in those that were free of psychotic symptoms prior to cannabis use (Ferdinand, Sondeijker et al., 2005). Furthermore, psychotic symptoms significantly predicted future cannabis use in those who had never used cannabis prior to the onset of psychotic symptoms.

In the second study, the parent version of the Child Behaviour Checklist was employed as an additional measure to obtain scores on general psychopathology for the age range of 4 – 16 years (Ferdinand, van der Ende et al., 2005). Syndrome scale scores were also obtained for the following emotional and behavioural problems: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behaviour, and aggressive behaviour. Participants were followed-up across a 14-year period. Independent of general psychopathology, cannabis use and psychotic symptoms remained significant

predictors of each other. The anxious/depressed syndrome scale was the only one that (independently of cannabis use) predicted psychotic symptoms. Delinquent behaviour was the only syndrome scale that (independently of psychotic symptoms) predicted cannabis use. Both studies (Ferdinand, Sondeijker et al., 2005; Ferdinand, van der Ende et al., 2005) lend support to the self-medication theory by finding psychotic symptoms to be predictive of cannabis use later in life.

Henquet and colleagues (2005) also found that cannabis use during adolescence and young adulthood significantly increased the risk for developing psychotic symptoms at a four-year follow-up. This risk was magnified if the individual demonstrated a predisposition to psychosis, as indicated by scores on the paranoid ideation and psychoticism subscales of the SCL-90-R. A particularly strong association was found between cannabis use and more severe psychotic symptoms. These findings were independent of confounding factors, which included baseline use of other substances such as alcohol. This study, and others (Fergusson, Horwood, & Swain-Campbell, 2003; van Os et al., 2002), have disputed the self-medication hypothesis by demonstrating that early symptoms of psychosis were not predictive of later cannabis use.

In sum, several cannabis studies have linked use to the development of subclinical psychotic symptoms during the intoxication stage of use. Furthermore, longitudinal studies have produced evidence suggesting that cannabis use also plays a role in the development of psychotic symptoms beyond the intoxication stage. These studies have used a variety of standardised outcome measures to examine large sample sizes. A further advantage is that they have controlled several of the

possible confounding factors (e.g., sex, age, education, psychotic symptoms prior to cannabis use, personality, IQ), thereby strengthening the value of their findings. However, there are a range of factors that continue to bring about uncertainty with respect to a causal link between cannabis and psychotic symptoms (Fergusson, Poulton, Smith, & Boden, 2006). First, the measurement of cannabis use and psychotic symptomatology requires a more systematic and targeted approach. Second, the impact of confounding factors (e.g., polysubstance use, family and peer relationships, criminality, mental health problems) requires ongoing consideration. Finally, bidirectional relationships between cannabis and psychotic symptoms cannot be ignored, requiring further examination.

Cannabis and psychotic disorders

The relationship between cannabis use and the development of a diagnosable psychotic disorder has also received considerable attention in the literature. Whilst there is converging evidence for the role of cannabis in psychosis (Fergusson, Poulton, Smith, & Boden, 2006), the nature of this relationship is yet to be clearly defined.

Several Australian studies have provided evidence of a link between cannabis use and an increased risk for psychosis. A national survey found that 1.2% of the population screened positively for psychosis on the Psychosis Screener (Degenhardt & Hall, 2001). Positive cases were significantly more likely than non-cases to report recent cannabis use (last 12 months). Positive cases were also more likely to identify as weekly cannabis users and to meet DSM-IV (American Psychiatric Association, 1994) criteria for cannabis abuse or dependence. Another study of patterns of co-

morbidity in the Australian general population found that cannabis dependence was associated with a higher risk for screening positively on a psychosis screening instrument (Degenhardt, Hall, & Lynskey, 2001a). This association remained significant after confounding factors such as other substance use, demographics, and neuroticism were controlled. Alcohol use was only significant at the univariate level. More specific data on the incidence of cannabis-induced psychosis has been provided by an Australian review of hospital discharges associated with a diagnosis of substance-induced psychosis (Degenhardt, Roxburgh, & McKetin, 2007). In total, 39% were primarily due to cannabis in 1999/2000. This number increased slightly in the year 2003/2004 to 45%.

A number of frequently cited longitudinal studies have attempted to address the question of causality in the cannabis and psychosis field. In a 15-year follow-up study, Andreasson and colleagues (1987) examined substance use and the psychiatric history of Swedish men (N = 45,570) conscripted during 1969/70, using self-report questionnaires and ICD-8 criteria. Higher levels of cannabis consumption at conscription were significantly associated with higher rates of schizophrenia at follow-up. Compared to non-cannabis users, cannabis users had a 2.4-fold increase in risk for the development of schizophrenia. It is notable that the majority of participants diagnosed with schizophrenia had not previously used cannabis, suggesting that cannabis only accounted for a small part in the development of schizophrenia.

In a small sub-sample of the same cohort also at a 15-year follow-up, those with schizophrenia who had used cannabis on more than 10 occasions at the time of

conscription (n = 8) were compared to those who developed schizophrenia but reported no cannabis use at conscription (n = 13) (Andreasson, Allebeck, & Rydberg, 1989). The temporal relationship between cannabis use and psychiatric disorder was examined, as well as the contribution of other drugs to the development of schizophrenia and the nature of onset and clinical course of schizophrenia. There was a 2.1 relative risk of schizophrenia for those who reported using cannabis at least once, and this risk increased to 4.1 for those who had used it more than 50 times. Cannabis abuse was not preceded by psychiatric disorder and there was no significant difference between the groups with respect to family history of schizophrenia. Compared to non-users, cannabis users were identified as having a more sudden onset of psychotic symptoms than non-users.

Zammit and colleagues (2002) extended findings with the original Swedish cohort of Andreasson et al. (1987) with a follow-up at 27 years. Cannabis use at conscription was significantly associated with the later diagnosis of schizophrenia (according to ICD-8 and -9 criteria). Support for a dose-response relationship was again found, with those who had used cannabis on more than 50 occasions demonstrating the greatest risk. Amphetamines and personality traits did not independently predict schizophrenia. A limitation of this study, and previous studies using this same cohort, is that cannabis use was only measured at conscription and ongoing use of cannabis throughout the course of the study was not monitored.

van Os et al. (2002) attempted to fill this gap in the research by assessing both substance use and psychosis at three time points across four years. They examined the links between cannabis and psychosis in users with (n = 59) and

without (n = 4,045) a psychotic illness (aged 18 – 64 years). Cannabis use at baseline increased the risk of later developing a psychotic illness. Of interest was that baseline cannabis use was more strongly related to measures of psychosis than cannabis use at times two and three. The use of other drugs (psychostimulants, cocaine, phencyclidine, and psychedelics) was not associated with psychosis once cannabis use was entered into analyses.

A high-quality systematic review conducted by Moore and colleagues (2007) has provided focus with respect to the cannabis and psychosis literature, and included many of the studies mentioned previously in this chapter. Their review of 35 studies examining the psychotic and affective mental health outcomes associated with cannabis use concluded that this substance increased the risk of psychotic symptoms and disorders. Analyses revealed that any cannabis use was associated with an increased risk of approximately 40%, while heavy and frequent use was associated with a 50 – 200% increased risk of psychotic symptoms and disorders. Importantly, this finding was independent of confounding factors (such as family relationships, mental health history, criminality, and sociodemographic characteristics) and the effects of intoxication.

However, not all studies have found cannabis use to be associated with an increased risk of developing psychosis. Phillips and colleagues (2002) did not find cannabis use or dependence to be associated with the development of a psychotic disorder across a 12-month follow-up period. This study involved 100 people who were identified as ‘very high-risk’ for the development of psychosis, based on either trait/state risk factors, sub-threshold psychotic symptoms, or time-limited frank

psychotic symptoms. Exclusion criteria consisted of a previous acute psychotic episode or prior use of neuroleptic medication. Thirty-five participants had used cannabis in the previous year and 18 met DSM-IV (American Psychiatric Association, 1994) criteria for cannabis dependence. At follow-up, 32% of the total sample had developed psychosis. Cannabis users and non-users were not significantly different in their rate of transition to psychosis (37% vs. 29% respectively). Likewise, cannabis dependent participants and non-dependent participants were not significantly different in their transition to psychosis (39% vs. 31% respectively). The impact of other substances could not be examined due to low levels of their use. Notably, there was also a low level of cannabis use in the sample and an absence of ongoing monitoring of cannabis use after baseline measures.

Similar results were found in a Chinese sample (N = 62) (Lam, Hung, & Chen, 2006). Sixty-two participants were identified as 'high-risk' for developing psychosis and were assessed monthly for six months. Less than a third (29%) made the transition to psychosis during this period, and the majority (88.9%) of these did so within the first three months of monitoring. A history of substance misuse was not associated with the development of a psychotic disorder. However, the results were not specific to cannabis use and the sample contained very few substance users (14%). Unfortunately, comparability between these last two studies and the previous longitudinal studies is limited given differences in samples (i.e., conscripted men versus normal populations versus patients at high risk for developing psychosis) and marked differences in time to follow-up.

Overall, there is consistent evidence that cannabis use is a risk factor for the development of a diagnosable psychotic disorder. Some argue that cannabis plays a causal role in the development of psychosis, primarily based on the findings of a dose-response relationship after confounding factors have been accounted for (Arseneault et al., 2002; Fergusson, Horwood, & Ridder, 2005; Fergusson, Horwood, & Swain-Campbell, 2003; van Os et al., 2002; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). This proposal is further strengthened by the following evidence: (1) cannabis use can lead to relapse in schizophrenia (Linszen, Dingemans, & Lenior, 1994; Negrete, Knapp, Douglas, & Smith, 1986); (2) it can impact negatively on brain function (Dean, Sundram, Bradbury, Scarr, & Copolov, 2001; Leroy et al., 2001); and (3) it has been suggested as a model of psychosis based on laboratory studies (D'Souza, Cho, Perry, & Krystal, 2004; Voruganti, Slomka, Zabel, Mattar, & Awad, 2001). The missing piece of the causality puzzle is the lack of evidence that the incidence of schizophrenia is increasing as rates of cannabis use increase (Degenhardt, Hall, & Lynskey, 2003b; Semple, McIntosh, & Lawrie, 2005). Furthermore, not all cannabis users (not even all heavy cannabis users) go on to develop schizophrenia-type illnesses, as would be expected in the case of a causal relationship. Another ongoing challenge is the contribution of confounding factors in the relationship, many of which have not been adequately controlled or examined. Current literature best labels cannabis use as a component cause in the development of schizophrenia, indicating that it is one of several factors that, in conjunction with each other, lead to a psychotic illness (Arseneault, Cannon, Witton, & Murray, 2004).

Cannabis and the symptom profile of psychosis

The impact of cannabis use on the symptom profile of psychosis has primarily been examined by comparing cannabis users to non-users in samples of psychotic patients. This avoids the problems associated with diagnostic accuracy and captures a larger sample of the substance-using community as compared to samples limited to those with a diagnosable cannabis-induced psychosis.

Rehman and Farooq (2007) compared schizophrenia patients with (n = 50) and without (n = 50) concurrent cannabis use. Cannabis users (any use in the previous 12 months) were identified via self-report. Overall, cannabis users experienced significantly more positive symptoms (M = 18.66, SD = 6.91 vs. M = 15.24, SD = 6.31) and paranoia (M = 10.32, SD = 4.31 vs. M = 7.24, SD = 3.85), and significantly fewer negative symptoms (M = 15.26, SD = 7.02 vs. M = 22.59, SD = 9.02) than non-users as measured by the PANSS. On individual items of the PANSS, the cannabis-using group scored significantly higher on a number of symptoms that are frequently associated with mania: excitement; grandiosity; hostility; poor impulse control; uncooperativeness; anger; and difficulty in delaying gratification. Non-users scored higher on items related to negative symptoms including withdrawal, lack of spontaneity, and motor retardation.

Bersani and colleagues (2002) assessed the impact of cannabis use on chronic schizophrenia (illness duration in years M = 10.31, SD = 7.44). Substance use was determined via structured interview. The SAPS, SANS, PANSS, and 18-item BPRS were used to measure symptomatology. Cannabis users with psychosis (n = 54) (cannabis abusers and occasional cannabis users combined) obtained significantly

lower scores on the total (*M* = 41.5, *SD* = 19.9 vs. *M* = 54.5, *SD* = 23.6) and subscale scores of the SANS compared to non-users with psychosis (*n* = 71). Users also obtained a significantly lower score on the PANSS negative symptom subscale than non-users (*M* = 20.1, *SD* = 7.7 vs. *M* = 22.9, *SD* = 8.3). There were no significant differences on the positive symptom subscale of the PANSS (users *M* = 21.8, *SD* = 6.8 vs. non-users *M* = 21.1, *SD* = 7.3) and the only significant difference on the SAPS consisted of the non-users obtaining significantly higher scores on the thought disorder subscale (*M* = 15.7, *SD* = 8.2 vs. *M* = 12.6, *SD* = 6.8). The groups were also not significantly different on any of the subscales of the BPRS (anergia, thought disturbance, activation, paranoid-belligerence, depression, or total score). A positive family history for psychosis was more likely in the cannabis group.

A study by Peralta and Cuesta (1992) of schizophrenia patients also found no significant difference in positive symptoms (as measured by the SAPS) between those with (*n* = 23) and without (*n* = 72) a history of cannabis abuse in the past year. The groups were also generally similar according to the SANS measure of negative symptoms, with the only significant difference being that non-abusers scored higher on the alogia (poverty of speech) subscale.

A small study conducted by Compton et al. (2004) examined the positive and negative psychotic symptoms of patients with (*n* = 8) and without (*n* = 10) comorbid cannabis dependence. PANSS results showed that there were no significant differences between the two groups with respect to the severity of positive symptoms or general psychopathology. However, those identified as cannabis dependent obtained significantly lower negative symptom scores. This study is particularly

relevant to the current study given its sample of first-episode psychosis patients, however, the small sample size reduces the strength of any conclusions drawn from analyses.

Using similar inclusion criteria in their meta-analysis of negative psychotic symptoms (i.e., co-occurring substance use disorders and schizophrenia), Potvin et al. (2006) found that a dual diagnosis was associated with significantly fewer negative psychotic symptoms. This finding was specifically relevant to cannabis. Of note, was the finding that no studies included in the meta-analysis found significant differences between substance-using psychosis patients and non-using psychosis patients regarding positive psychotic symptoms.

A number of studies have also examined symptom profiles by comparing patients diagnosed with a cannabis-induced psychosis to those with a primary psychotic disorder. A small cross-sectional study compared cannabis-induced psychosis (n = 26) and acute schizophrenia (n = 35) patients on demographic, premorbid, and clinical features (Nunez & Gurpegui, 2002). Patients were diagnosed according to DSM-III-R (American Psychiatric Association, 1987) criteria. Urine drug screens were conducted to rule out other substance use. Patients with cannabis-induced psychosis were assessed at least one week after ceasing cannabis use to reduce the confound of intoxication. Those with acute schizophrenia were significantly more likely to have a history of psychotic disorder in a first- or second-degree relative. According to psychopathological features measured by the Present State Examination (PSE), cannabis-induced psychosis patients were more likely to experience depressed mood, expansive mood and ideation, irritability,

derealisation and depersonalisation, visual hallucinations, and a disturbance in sensorium than the acute schizophrenia patients. The groups were comparable in their experience of delusions, other types of hallucinations, and thought disturbance.

Imade and Ebie (1991) retrospectively compared symptom patterns of cannabis-induced psychosis patients (n = 70) with mania patients (n = 39) and schizophrenia patients (n = 163) using medical chart notes. Original diagnoses were confirmed by a psychiatrist, although use of standardised measures of diagnosis and substance use were not mentioned. Patients were rated according to a list of 25 symptom categories. The most common symptoms identified for each of the groups were as follows: the cannabis-induced psychosis group - aggression (70%) and anxiety (64%); the mania group - mood symptoms (92%) and insomnia (72%); and the schizophrenia group - forms of thought disorder (75%) and content of thought (62%). The cannabis-induced psychosis group demonstrated significantly fewer symptoms of distractibility, and content and form of thought, but significantly more anxiety compared to both of the other groups. They also demonstrated significantly less auditory and visual hallucinations than the schizophrenia group and significantly fewer problems with insomnia and mood than the mania group. Despite some significant differences between the groups, the researchers reported no particular symptomatic profile that was representative of cannabis-induced psychosis.

While the findings are mixed, the bulk of evidence suggests that cannabis users with psychosis generally experience fewer negative psychotic symptoms than non-users with psychosis. However, it appears that cannabis use has little impact on positive psychotic symptoms, a finding that was especially clear in studies that

ensured all participants were in similar phases of their psychotic illness. For example, Bersani et al. (2002) examined chronic patients while Compton et al. (2004) studied early psychosis patients, and both found no significant differences between substance users with psychosis and non-users with psychosis on positive symptoms. In the studies that examined cannabis-induced psychosis versus primary psychosis, there were some differences in the type of symptom most commonly experienced by each group, but there was essentially no symptom profile that was specific to cannabis-induced psychosis. Further research in this area is clearly warranted. The current literature is disadvantaged by a lack of studies that adequately test the synergistic contribution of other psychoactive substances. Further, several of the studies are compromised by their retrospective methodologies in the collection of symptom and substance use data.

Cannabis and the clinical course of psychosis

There are a small number of studies that have attempted to elucidate the relationship between cannabis use and the clinical course of psychotic symptoms. In contrast to the amphetamine literature, the majority of these have included a control group of non-using psychosis patients in their samples. However, there are some gaps within this literature that deserve mention. First, few studies have systematically examined the time frames associated with the resolution of psychotic symptoms in cannabis-induced psychosis. Second, many of the studies have compared the using and non-using groups (cross-sectionally) at only two assessment points (typically at hospital admission and discharge). Additional intervening measurements would have provided a more comprehensive insight into the direction

and rate of changes in symptom severity across time. Finally, a number of the studies focussed on the long-term clinical course and conducted their follow-up assessment one or more years after the baseline assessment, thereby reducing the relevance of their findings to the current study, which will focus on the clinical course of symptoms and behaviour during hospitalisation. With these factors in mind, a review of the impact that cannabis use has on the clinical course of psychosis will now be presented.

Stirling and colleagues (2005) examined the clinical, behavioural, and cognitive factors of 112 first-episode psychosis patients (with and without prior cannabis use) at their index episode, and then again 10 – 12 years later. Cannabis use ('yes' or 'no') was established by self-report and confirmed with a co-habitee where possible. The SAPS and SANS were used to measure positive and negative psychotic symptoms, although no mean scores or standard deviations were provided. At the index episode, cannabis users demonstrated significantly more positive psychotic symptoms and fewer neurological soft signs. However, users and non-users were indistinguishable regarding negative psychotic symptoms and premorbid adjustment (as measured by the Premorbid Adjustment Scale). At follow-up, users and non-users were not significantly different on any factor and presented as broadly comparable symptomatically. The lack of information regarding the recency of cannabis use in this sample is a limitation.

Caspari (1999) assessed early psychosis patients with (n = 27) and without (n = 26) a current cannabis abuse disorder (according to ICD-9 criteria) 68.7 $\pm$ 28.3 months after their hospital admission. The GAF was used to measure overall

psychosocial functioning, and psychopathology was measured with the BPRS. There were no significant differences between the groups on GAF scores, however, cannabis-abusing patients had required significantly more re-hospitalisations. Psychopathology profiles were also largely indistinguishable, with the only significant differences being more thought disturbance and hostility in patients with a cannabis abuse disorder.

Another study of first-episode psychosis patients (N = 203) examined the correlates and clinical impact of substance use (predominantly cannabis) across four assessment points (baseline, and at one, two, and three years) (Addington & Addington, 2007). Those who had misused substances over the past year (based on The Case Manager Rating Scale for Substance Use Disorders) were not significantly different to non-users on positive or negative psychotic symptoms at baseline as measured by the PANSS. Interestingly, the users went on to obtain significantly higher positive symptom scores (but still no significant differences in negative symptom scores) than non-users at all subsequent assessment points.

A longitudinal study was conducted with inpatients experiencing any type of psychotic symptom who returned a positive urine drug screen for cannabis (n = 61) (Mathers & Ghodese, 1992). Patients with psychotic symptoms and a negative urine drug screen were controls (n = 43). Psychotic symptoms were noted as absent or present by psychiatrists using ICD-9 criteria. The PSE was used to assess changes in symptomatology at one week, one month, and six months. At one week, cannabis users demonstrated significantly more problems with changed perception, thought insertion, non-verbal auditory hallucinations, delusions of control, and grandiose

delusions compared to the controls. At one month, the only significant difference was that cannabis users experienced more problems with delayed sleep. Finally, there were no significant differences between the groups at the six month assessment point. It is of importance to further consider the process used by this study to differentiate between cannabis users and non-users. Unlike the bulk of other studies, Mathers and Ghodese differentiated the two groups based on urine drug screen results alone. Thus, a non-user was someone who returned a negative screen for cannabis. While cannabis can be detected in urine up to one month post cessation of use (Vandevenne, Vandenbussche, & Verstraete, 2000), it is now understood that positive urine drug screens depend on both frequency and recency of substance use (Green, Young, & Kavanagh, 2005). Taking this into consideration, it is therefore difficult to categorise someone as a non-user based on a negative drug screen alone.

An early study conducted by Rottanburg and colleagues (1982) compared psychotic patients with (n = 20) and without (n = 20) cannabis-positive urine drug screens at admission and again seven days later. Both groups had a median of one previous psychiatric admission. Those positive for cannabis use had significantly more symptoms of hypomania and agitation than the controls at admission, but lower scores for auditory hallucinations, affective flattening, incoherent speech, and hysteria on the PSE. Cannabis use was significantly associated with marked improvement of psychotic symptoms at the one-week follow-up assessment (i.e., significant difference on PSE score between first and second interview), while the controls showed no evidence of significant changes regarding psychotic symptoms. Specifically, PSE scores were significantly reduced on the syndromes of hypomania,

agitation, self-neglect, sexual and fantastic delusions, delusions of reference and persecution, grandiose and religious delusions, and irritability. Notable is that the reduction in psychotic symptoms for the cannabis-using group at follow-up was paralleled by negligible traces of cannabis in urine drug screens.

Another study that focussed on the hospitalisation period compared cannabis-induced psychosis patients (n = 20) to schizophrenia patients (n = 20) on a range of demographic and clinical variables (Basu, Malhotra, Bhagat, & Varma, 1999). The two groups were largely indistinguishable with respect to demographics, family history of psychosis, and premorbid personality. Some significant differences were noted between the groups based on intake details (e.g., fewer cannabis users experienced hallucinations, self-referential ideas, restricted affect, incongruent affect, and formal thought disorder). Chart entries indicated that the cannabis users recovered significantly more quickly than non-users, with 15 users (versus one non-user) having recovered within four weeks of admission. The researchers concluded that cannabis-induced psychosis was "one of an acute-onset, short-duration, transient psychosis with some features shared with schizophrenia" (Basu, Malhotra, Bhagat, & Varma, 1999, p. 73). Unfortunately, the definition of recovery was not defined in this study and no standardised rating scales were used to diagnose patients or measure symptom change. The study was also limited because of the small sample size, the retrospective nature of data collection via hospital chart notes, and because the groups were significantly different in the duration of their untreated psychosis.

It is possible that the more rapid resolution of symptoms in cannabis-using psychosis patients is somewhat influenced by the response of this group to

neuroleptics. Thacore and Shukla (1976) studied 25 cannabis-induced psychosis patients and 25 paranoid schizophrenia patients. The cannabis-induced psychosis group demonstrated more violence, and experienced more symptoms of panic, flight of ideas, and bizarre behaviour at baseline assessment compared to the paranoid schizophrenia group. However, those with cannabis-induced psychosis also responded more rapidly to neuroleptics and experienced a more complete resolution of psychotic symptoms.

A number of studies have associated cannabis use with unremitting symptoms of psychosis, and it is important to note that these studies have linked this type of clinical course with ongoing cannabis use throughout the assessment period. Negrete et al. (1986) found that cannabis users were more likely to have an unremitting type of psychotic illness. They examined the effects of cannabis use on symptoms of schizophrenia across a six month period. Based on information provided by hospital medical charts and urine drug screens, schizophrenia patients were categorised as follows: cannabis use within the past six months (active-users) (n = 25); previous cannabis use but not within the past six months (past-users) (n = 51); and no prior cannabis use (never-users) (n = 61). All delusional and hallucinatory symptoms were rated as absent, transient, or continuous based on medical chart entries for a six month study period. Continuous delusions and hallucinations were most commonly observed for the active-users group, and they made the most visits to hospital. Past-users most commonly experienced transient delusions. The groups were no different with respect to medication dosage prescribed during the study. Unfortunately, the lack of precision with respect to

measurement of psychotic symptoms limits the generalisability of this study.

In a study of recent onset psychosis patients (N = 119), assessments of psychotic symptoms and cannabis use were conducted at admission and at a four year follow-up (Grech, van Os, Jones, Lewis, & Murray, 2005). All participants had an onset of psychosis within the five years prior to their admission assessment. They were assessed using the PSE and the Operational Criteria Checklist for Psychotic Illness. Alcohol and illicit substance use were measured using a semi-structured interview targeting frequency of use, length of use, and age of initiation to use. The sample was divided into four groups according to cannabis use: cannabis use prior to both assessment points; cannabis use prior to admission but not follow-up; no cannabis use prior to admission but use at follow-up; and no history of cannabis use. The group who had used cannabis both prior to admission and at follow-up were significantly more likely to experience severe positive psychotic symptoms compared to the remaining three groups during the follow-up period (56.3% vs. 33.3%, 33.3%, and 23.0% respectively). They were also more likely to experience a continuous course of psychotic illness, with 62.5% of this group having unremitting psychotic symptoms (compared to 44.4%, 41.7%, and 32.8% respectively). The four groups were not significantly different with respect to the experience of negative symptoms during the follow-up period (60.0%, 44.4%, 54.5%, and 50.8% respectively).

In sum, the role of cannabis use in the clinical course of psychotic symptoms and behaviour has not yet been clearly defined. A small number of studies have examined the impact of cannabis use on the long-term clinical course of psychosis

(Caspari, 1999; Mathers & Ghodese, 1992; Stirling, Lewis, Hopkins, & White, 2005). While these studies reported some differences between users and non-users at the first assessment (e.g., Stirling, Lewis, Hopkins, & White, 2005 found significantly more positive psychotic symptoms in cannabis users), the groups were generally indistinguishable with respect to psychopathology at follow-up assessments, which were conducted one or more years post-admission. Several studies monitored the time it took for psychotic symptoms to resolve. Rottanburg et al. (1982), Basu et al. (1999), and Thacore and Shukla (1976) reported that cannabis use was associated with a more rapid resolution of psychotic symptoms, although there were also studies that provided findings to the contrary (Grech, van Os, Jones, Lewis, & Murray, 2005; Negrete, Knapp, Douglas, & Smith, 1986). Importantly, when cannabis use was associated with an unremitting clinical course, it was in the context of ongoing substance use throughout the assessment period. There are several factors hampering the literature surrounding the clinical course of psychosis in the context of cannabis use. First, the main focus has rested on positive and negative psychotic symptoms, with little attention having been given to changes in other associated symptoms such as mood symptoms or disturbed behaviour. Second, the comparison between groups has generally been based on data collected at a minimal number of time points, thereby failing to provide a continuous picture of change. Third, the synergistic impact of other commonly used substances (such as amphetamines) has not been adequately considered.

Chapter 5. The influence of amphetamines and cannabis on mood, anxiety, and behaviour

A review of the literature examining the impact of amphetamine use and cannabis use on mood, anxiety, and disturbed behaviour will be presented in this chapter. In consideration of mood, symptoms of both depression and mania will be examined. The review of disturbed behaviour will focus on the potential for amphetamines and cannabis to induce violent, hostile, and/or aggressive behaviour.

Amphetamines, mood, and anxiety

There is clear evidence linking the use of psychostimulants with mood changes and increased anxiety (Sommers, Baskin, & Baskin-Sommers, 2006; Zweben et al., 2004). These symptoms typically present as part of the substance withdrawal and intoxication phases (depression and anxiety respectively), but they may also be associated with a separate comorbid psychiatric disorder (Baker & Dawe, 2005; Dyer & Cruickshank, 2005; McGregor et al., 2005; Srisurapanont, Jarusuraisin, & Kittirattanapaiboon, 2003; Weiss, Griffin, & Mirin, 1989).

In a study of depressive symptoms in methamphetamine users (N = 182), 37.6% were rated with a moderate to severe depression on the Beck Depression Inventory (BDI) (Semple, Patterson, & Rant, 2005). The significant association between methamphetamine use and symptoms of depression was not mediated by perceived stigma, social problems, or other health problems. People who had used methamphetamine on more days in the last 30, and more frequently on days of use, exhibited more severe symptoms of depression.

In an Australian study (N = 214), 71% of the amphetamine-using sample

scored in the moderate or severe depression range on the BDI-II (Baker et al., 2004). A diagnosis of major depression had previously been given to 27.6% of the total sample, and 64.4% of these cases were diagnosed after regular amphetamine use. A Taiwanese study of 325 methamphetamine users (used >20 times in the past year) reported somewhat lower rates, with 6.2% of the sample meeting DSM-IV (American Psychiatric Association, 1994) criteria for a diagnosis of major depression (Lin et al., 2004).

Dyer and Cruickshank (2005) found that depression was the most common psychiatric problem for dependent methamphetamine users (N = 202). As measured by the BDI-II, 34.7% of participants experienced a clinical depression that was moderate in severity, and total scores were similar to those of clinically depressed outpatients. The influence of methamphetamine intoxication was tested by comparing those with a positive saliva test for the substance to those with a negative saliva test. Although not reaching significance, those with a positive saliva test obtained lower total scores on the BDI-II.

Levels of anxiety have also been found to be consistently elevated within the amphetamine-using population, particularly in female users of methamphetamine (Zweben et al., 2004). An Australian study found that more than half (63%) of their amphetamine-using sample experienced anxiety symptoms (Hando, Topp, & Hall, 1997). Similarly, in a study of 45 crystal methamphetamine users, 70% self-reported symptoms of anxiety (Degenhardt & Topp, 2003). Another study of regular amphetamine users (N = 301) found that 48% of the sample had experienced anxiety symptoms prior to ever using amphetamines, while 76% of the sample reported

anxiety symptoms after they began using amphetamines (Hall, Hando, Darke, & Ross, 1996). Nearly half (48%) of those who experienced anxiety directly after an episode of amphetamine use rated the severity of the anxiety symptoms as 'extremely high'. On average, anxiety symptoms lasted for 24 hours.

Contrasting results have been found in an Australian cohort study (Degenhardt, Coffey, Carlin, Moran, & Patton, 2007). Participants (N = 1,943) were interviewed up to eight times between the ages of 14 – 15 years and 24 – 25 years, with the aim of identifying predictors and consequences of amphetamine use. Participants were classified as amphetamine users on the basis of self-reported use in the previous six months. Symptoms of depression and anxiety were measured by the revised Clinical Interview Schedule and antisocial behaviour was measured by the Self-Report of Early Delinquency Scale. Symptoms of depression/anxiety experienced as an adolescent did not significantly predict adult amphetamine use. While there was an association between symptoms of depression/anxiety and amphetamine use (cross-sectional relationship at the age of 24), significance was lost at the multivariate level of analyses.

Remarkably less information is available about the rates of depression, and particularly anxiety, experienced by amphetamine-induced psychosis patients. In the study by Akiyama (2006) previously mentioned, depression was measured using the 24-item BPRS. Nearly all (29) of the 32 female amphetamine-induced psychosis patients were found to have depressed mood, and the symptoms of depression persisted for at least several months despite pharmacological interventions. Unfortunately, it was not determined whether these depressive states were the result

of a premorbid mood disorder, part of the withdrawal process, or part of a current comorbid illness. Further to this, the findings with respect to depressed mood may have been confounded by the sample consisting of incarcerated women.

In the study conducted by Harris and Batki (2000), stimulant-induced psychosis patients (N = 19) obtained a mean PANSS score of 12 for depression, which corresponded to the 80th percentile in schizophrenia patient sample norms for depression. Anxiety levels were not reported.

Iwanami et al. (1994) reported that 9.6% of their amphetamine-induced psychosis sample exhibited symptoms of clinical depression. These rates are equivalent to those of clinical depression within the general population (i.e., 10%) (Andrews, Poulton, & Skoog, 2005), and notably less than estimated rates within the longitudinal course of a schizophrenia illness (approximately 25%) (Siris, 1995).

Despite a relative lack of information regarding the rates of depression in amphetamine-induced psychosis patients, there is some evidence linking increased depression (Franco, Galanter, Castaneda, & Patterson, 1995; Nigam, Schottenfeld, & Kosten, 1992) and increased levels of anxiety with the more general presentation of psychotic illness and substance use (Hambrecht & Hafner, 2000; Huppert & Smith, 2005). A recent study used the Diagnostic Interview for Genetic Studies to assess lifetime history of psychotic disorders, substance use disorders, and anxiety disorders (Goodwin et al., 2003). The prevalence rate for anxiety symptoms and disorders in the sample of inpatient schizophrenia patients with a comorbid substance use disorder was 31.5%. This figure is clearly greater than the estimated one-year prevalence rates (10.6%) for anxiety disorders in the general population

(Somers, Goldner, & Waraich, 2006).

An Australian study of early psychosis patients (N = 84) found that amphetamine/ecstasy/cocaine users (self-reported use in the past three months) experienced significantly higher levels of anxiety and depression than their non-using counterparts (Preston et al., 2003). Users obtained a significantly higher depression/anxiety score on the BPRS than did non-users (M = 3.2, SD = 0.93 vs. M = 2.5, SD = 1.1 respectively). Users also obtained a significantly higher score on the BPRS hostility/suspicion subscale compared to non-users (M = 2.8, SD = 1.1 vs. M = 2.1, SD = 1.1 respectively).

Providing somewhat conflicting findings to the Preston et al. (2003) study, Baigent and colleagues (1995) examined the self-reports of 53 schizophrenia patients who used substances (primarily alcohol, cannabis, and amphetamines). The Brief Symptom Inventory and the Schizophrenia/Substance Abuse Interview were used to assess symptomatology and substance use. Interestingly, the majority (80%) of participants reported using substances for the main purpose of relieving dysphoria and anxiety, with amphetamines being identified as particularly helpful in improving subjective well-being.

Several studies already reviewed in Chapter 3 of this thesis have also found limited evidence of a significant relationship between substance use in psychotic patients and increased levels of depression and/or anxiety. Dixon et al. (1991) found similar rates of depression-anxiety in substance users and non-users on the BPRS, while Ries et al. (2000) and Sevy et al. (2001) examined depression only and again found no differences between the groups on the Psychiatric Assessment Form and

Hamilton Rating Scale for Depression (respectively). Dixon et al. (1991) and Ries et al. (2000) also found no differences between groups on depression/anxiety at follow-up assessment points. Scheller-Gilkey et al. (2002) found no differences between groups with respect to anxiety levels (measured by the Speilberger State Trait Inventory). However, substance users were found to have significantly higher levels of depression than non-users (M = 13.55, SD = 7.16 vs. M = 5.35, SD = 4.68 respectively) as measured by the Modified Hamilton Rating Scale for Depression. Interestingly, Kovasznay et al. (1993) found that substance users obtained significantly higher scores for depression-anxiety symptoms on the BPRS than non-users, but the two groups were similar in their scores on the Hamilton Rating Scale for Depression.

Mania symptoms are also frequently reported by amphetamine users. They are an acute, transient response to the use of amphetamines and are primarily associated with intoxication (Brown, Suppes, Adinoff, & Thomas, 2001; Clark et al., 2000; Meredith, Jaffe, Ang-Lee, & Saxon, 2005). These symptoms are believed to be a response to increased levels of dopamine (Snyder, 1973) and changes in the brain related to serotonin and norepinephrine levels (Groves & Rebec, 1976; Sloviter, Drust, & Connor, 1978). The association between mania symptoms and amphetamine use (particularly longer-term use) has led to the suggestion that this relationship may serve as a model for acute mania (Fibiger, 1991; Frey et al., 2006; Jacobs & Silverstone, 1986; Post, 1992; Silverstone, Pukhovsky, & Rotzinger, 1998). Common mania symptoms include increased alertness and self-confidence, enhanced mood, heightened activity levels, decreased need for sleep, racing

thoughts, distractibility, and restlessness (Asghar, Tanay, Baker, Greenshaw, & Silverstone, 2003; Silverstone, Pukhovsky, & Rotzinger, 1998).

In a study of 301 amphetamine users, 25% of the sample reported symptoms of mania prior to their first use of amphetamines, while 50% reported these symptoms following their first use of amphetamine (Hall, Hando, Darke, & Ross, 1996). Nearly half (48%) of those who experienced mania reported that their symptoms occurred directly after an episode of amphetamine use. The mania symptoms typically lasted one or two days.

Ten healthy volunteers were part of an impact study of amphetamines on mood and changes in the brain (Vollenweider, Maguire, Leenders, Mathys, & Angst, 1998). The Inventory of the Association for Methodology and Documentation in Psychiatry was used to obtain total syndrome scores for 'manic-depression' and 'schizophrenia', in addition to subscale scores for mania and other clinical variables. Amphetamine administration was associated with a significantly higher overall syndrome score for manic-depression compared to baseline scores, which was mostly represented by an increase in excessive elation, euphoria, accelerated thinking, and internal tension. Following amphetamine administration, participants scored highest on the mania subscale compared to all other subscales (apathy, somatic and retarded depression, paranoia, hypochondria, thought disorder, neurological deficits, hallucinatory-disintegration, and vegetative reactions).

A study by Silverstone et al. (1998) of 16 healthy volunteers also found that an acute dose of amphetamine can induce subclinical mania symptoms: light-headedness, racing thoughts, heightened energy, restlessness, and alertness.

With respect to studies involving amphetamine-induced psychosis patients, little consideration has been given to the symptoms of mania. However, Harris and Batki (2000) did find that amphetamine-induced psychosis patients obtained a score (M = 8) on the PANSS activation subscale that corresponded to the 70th percentile rank in schizophrenia patient norms. As previously noted, this subscale consists of symptoms commonly associated with mania.

However, there are inconsistencies within the field that raise uncertainty about the nature of the relationship between amphetamines and mania symptoms. Often, mania symptoms are short-term, and in the majority of cases do not develop into a diagnosable mood disorder. Some studies have shown that amphetamines actively reduce symptoms of mania (Brown & Mueller, 1979; Garvey, Hwang, Teubner-Rhodes, Zander, & Rhem, 1987; Max, Richards, & Hamdan-Allen, 1995), or at least bring about different physiological and metabolic changes that are not seen in mania (Asghar, Tanay, Baker, Greenshaw, & Silverstone, 2003). Notably, the mania symptoms associated with amphetamine use are not attenuated by lithium (Silverstone, Pukhovsky, & Rotzinger, 1998). These findings diminish the strength of the argument for amphetamines serving as a model for mania. The relationship between amphetamine use and symptoms of mania is important to further understand, primarily due to evidence that manic-like hyperactivity is associated with greater degrees of impairment to the brain (Frey et al., 2006) and because of the significant impact that symptoms of mania can have on an individual and their interaction with others.

Overall, amphetamine users have been found to experience elevated levels of

depression, mania, and anxiety when compared to the general population. With respect to amphetamine-induced psychosis, the consideration given to mood and anxiety symptoms has been limited, with most of these studies focussing on positive and negative psychotic symptoms within this population. There is some evidence that symptoms of mania, and to a lesser degree depression, are elevated in patients with amphetamine-induced psychosis, although no control groups have been incorporated in the studies to specifically test this. Unfortunately, no studies of anxiety symptoms in the amphetamine-induced psychosis population were identified. The bulk of literature examining the broader group of substance-using psychosis patients versus non-using psychosis patients suggests that symptoms of depression and anxiety are generally comparable across both groups, although there were some studies with contrasting results. Further research is clearly warranted, with a particular call for studies to measure differences in the symptoms of depression, mania, and anxiety between amphetamine-using patients with psychosis and their non-using counterparts.

Amphetamines and disturbed behaviour

Substance use has been associated with heightened levels of disturbed behaviour and violence, and other high-risk behaviours such as unsafe sexual practices, suicide, and criminal activity (Baskin-Sommers & Sommers, 2006; Verdoux et al., 2001; Verma, Subramaniam, Chong, & Kua, 2002). Violence and aggression (towards self and/or others) following the use of stimulants (particularly methamphetamines) has also been well documented, and many studies have identified significant levels of disturbed behaviour in intoxicated users (Asnis &

Smith, 1978; Baskin-Sommers & Sommers, 2006; Kratofil, Baberg, & Dimsdale, 1996; Krystal et al., 2005; Maxwell, 2005; Miles et al., 2003; Roche, 2006; Sommers & Baskin, 2006; Sommers, Baskin, & Baskin-Sommers, 2006; Tominaga, Garcia, Dzierba, & Wong, 2004). Acts of violence have been consistently reported by regular users of amphetamines (Degenhardt & Topp, 2003; Hall & Hando, 1994; Hall, Hando, Darke, & Ross, 1996; Hando, Topp, & Hall, 1997). However, the relationship between amphetamine use and disturbed behaviour is complex, and appears to be dependent on individual differences including personality, the environment, and substance dose (Hoaken & Stewart, 2003; Murray, 1998).

Sommers and Baskin (2006) examined violence in a sample of 205 methamphetamine users. Participants were interviewed at length about specific events and their context using a structured, open-ended technique. Violence consisted of "any form of deliberate physical harm inflicted on another individual" (Sommers & Baskin, 2006, p. 83). A quarter (27%) of participants reported an act of violence while intoxicated by methamphetamine. The majority (65.5%) of those reporting violence were male and half (51.4%) of the cases of violence involved domestic relationships. Predictors of violence were exposure to family of origin deviance (e.g., child abuse) and the subsequent consequences (e.g., arrest), a prior history of violence in the context of substance use, poor social functioning, initial age of methamphetamine use, and the expression of aggression during childhood.

An English study examined links between violent crime, aggression, and amphetamine use (N = 86) (Wright & Klee, 2001). Nearly half (47%) of the heavy amphetamine users had committed a violent crime, defined as the infliction of

physical harm to another. The most common circumstances identified as precipitants of violence were amphetamine intoxication (34%), provocation (26%), and the experience of paranoid delusions (17%). Approximately a quarter (24%) of participants believed that their amphetamine use and violent crime were directly linked, and they identified intoxication, withdrawal, polydrug use, and episodes of amphetamine-induced psychosis as the primary risk factors for their violence. Nearly two-thirds (62%) also reported ongoing problems with aggression that were associated with their amphetamine use. Aggression was defined as hostile or destructive behaviour that did not involve physical harm to another.

A dual diagnosis of substance use disorder and psychotic disorder has also been strongly associated with a greater risk for violence and aggression (Cuffel, Shumway, Chouljioa, & McDonald, 1994; Ries et al., 2000; Soyka, 2000). Scott and colleagues (1998) found in their study of patients with comorbid substance use and psychotic disorders (n = 27) and psychosis only patients (n = 65) that those with a dual diagnosis were significantly more likely to behave aggressively and with hostility (as measured by the Health of the Nation Outcome Scales), to have a history of criminal offences (self-reported), and to have a recent history of assault (self-reported).

A more recent study of psychotic patients (N = 168) found that those with a dual diagnosis were up to nine times more likely to demonstrate disturbed behaviour, but only after they made contact with a treatment service (Milton et al., 2001). Interestingly, psychotic symptoms were not a significant predictor of aggression in this sample.

In a review of first-episode psychosis patient characteristics, Malla and Payne (2005) reported that high rates (20 – 30%) of violence and/or verbal aggression were associated with first-episode psychosis, particularly prior to and at first presentation. They went on to identify substance misuse as one of the key factors associated with disturbed behaviour in this sample.

Community mental health patients (N = 233) diagnosed with comorbid substance abuse/dependence and a psychotic illness (schizophrenia, schizoaffective disorder, bipolar disorder, or delusional disorder) were compared on illness characteristics, including violence and self-harm (Miles et al., 2003). Violence and self-harm were measured by a purpose designed scale, although definitions were not provided. Nearly one-quarter (n = 55) of the sample were identified as primary stimulant users (including cocaine, amphetamines, khat, and ketamine). Those with a comorbid stimulant use disorder and psychotic illness were significantly more likely than those with comorbid disorders involving alcohol or cannabis to have a life-time history of violence. Notably, the various substance-using groups were indistinguishable with regard to other associated factors such as utilisation of treatment services and self-harm.

It is unclear whether there is a direct causal role in the relationship between amphetamine use and aggression (Black & Degenhardt, 2005). Goldstein (1985; 1989) proposed a three-factor model that identifies the psychoactive impact of the substance, the crime associated with funding substance use, and the lifestyle associated with dealing and trafficking drugs as the primary reasons behind violence. With respect to amphetamines, the psychoactive impact of use refers to the ‘toxic’

blend of common amphetamine-induced symptoms such as increased self-importance, heightened activity levels and energy, and paranoid thoughts as leading to a higher risk of violence during intoxication (Wright & Klee, 2001). Intoxicated users are typically more paranoid and hypersensitive to external threat, increasing their potential to react aggressively (Sommers & Baskin, 2006). Notably, paranoid delusions have been identified as one of the primary components of mental state that are associated with violence (Junginger, 1996; Nestor, Haycock, & Doiron, 1995), and this type of delusion is also strongly associated with amphetamine use. It has also been suggested that disturbed behaviour in amphetamine users may be associated with deficits in cognitive function (e.g., narrowed and distorted perceptual and interpretative abilities) and a reduced capacity for problem-solving (Sommers & Baskin, 2006). However, individual personality factors are likely to play at least an equally important role as pharmacological factors in the development of aggressive behaviour (Hoaken & Stewart, 2003).

The symptom profile of prominent positive psychotic symptoms and few negative psychotic symptoms has also been identified as a risk factor for increased violence. It is notable that this symptom profile is typical of amphetamine-induced psychosis. In a large study of schizophrenia patients (N = 1,410), positive psychotic symptoms (for example, persecutory ideation) increased the risk for minor (simple assault without injury or use of weapon) and serious (major assault with injury and/or involvement of lethal weapon) acts of violence (Swanson et al., 2006). In contrast, negative psychotic symptoms (for example, social withdrawal) reduced the risk of serious violence. The six-month prevalence of violence in the total sample

was 19.1%.

Foley et al. (2007) found similar results in a sample of first-episode psychosis patients (N = 157). In total, 29% of participants were violent when they first presented for treatment. Violence was measured by the Modified Overt Aggression Scale. There was no significant relationship identified between duration of untreated psychosis and violence. With respect to psychopathology, only positive psychotic symptoms (as measured by the PANSS) were significantly associated with violence.

In sum, amphetamine use has been shown to increase the risk for acts of violence and aggression. However, it is noted that other factors (e.g., early exposure to conflict/violence and psychotic symptoms) contribute to the strength of this relationship. It has also been reported that there is a higher incidence rate of aggression and violence in psychotic populations compared to those of other psychiatric illnesses (Foley et al., 2005; Pearson, Wilmot, & Padi, 1986; Tardiff, Marzuk, Leon, & Portera, 1997). In early psychosis patients, the reported incidence rates of violence and aggression have ranged from 29% to 75% (Foley et al., 2007; Steinert, Wiebe, & Gebhardt, 1999) depending on definitions used, and substance use has been identified as a significant predictor (Foley et al., 2005). What we are less clear about is how amphetamine users with psychosis directly compare to non-using psychosis patients with respect to the severity of their disturbed behaviour. There are no known prospective studies that have specifically compared inpatient amphetamine users with psychosis to non-users with psychosis on the severity of their disturbed behaviour. We are also unclear about how the disturbed behaviour of these groups changes across the course of hospitalisation. A better understanding of

this profile can be used to prescribe more effective treatment regimes (e.g., the use of behavioural programs and medications that assist in behavioural management) and to create a more responsive ward milieu. This information also clearly improves the clinician's ability to assess safety risks.

Cannabis, mood, and anxiety

Studies of cannabis use, depression, and anxiety are relatively sparse (particularly with respect to adult populations) and inconclusive. Some have found an association between cannabis use (predominantly heavy use) and increased symptoms of depression and/or anxiety (Brook, Brook, Zhang, Cohen, & Whiteman, 2002; Brook, Cohen, & Brook, 1998; Fergusson, Horwood, & Swain-Campbell, 2002; Newcomb, Vargas-Carmona, & Galaif, 1999). However, several studies have identified common factors (biological, personality, social, and environmental) to both increased cannabis use and symptoms of depression and anxiety that cloud the nature of the relationship and question causality (Degenhardt, Hall, & Lynskey, 2001a; 2001b). Furthermore, there are accounts of cannabis reducing both symptoms of depression (Gruber, Pope, & Brown, 1996) and anxiety (Dixon, Haas, Weiden, Sweeney, & Frances, 1991). A review of this literature will be presented here.

A recent prospective study by van Laar et al. (2007) assessed the links between cannabis use in adults and the risk for developing mood or anxiety disorders at a three year follow-up. Participants of this study had no lifetime history of a mood disorder (n = 3881) or anxiety disorder (n = 3854) at baseline, and were categorised as either cannabis users (previously used more than five times) or non-users. At

follow-up, 11.7% of users (versus 5.0% of non-users) were identified as ‘at risk’ for a mood disorder and 8.2% of users (versus 5.4% of non-users) were ‘at risk’ for an anxiety disorder. After controlling for confounders such as neuroticism and parental psychiatric history, cannabis use increased the risk for major depression by a factor of 1.6. Cannabis use was not significantly associated with the risk for anxiety disorders.

An epidemiological catchment area study conducted baseline and 14 – 16 year follow-up assessments of substance use and depression (N = 1,920) (Bovasso, 2001). The DIS was used to assess symptoms, based on DSM-III-R (American Psychiatric Association, 1987) criteria. Eighty-three of the total sample were diagnosed with cannabis abuse at baseline. Depressive symptoms were reported by 81.9% of those who abused cannabis, which was a significantly higher rate of depressive symptoms than those without a cannabis abuse disorder at baseline. Participants who were diagnosed with a cannabis abuse disorder and reported depressive symptoms were also more likely to experience symptoms of mania. At follow-up, those with a baseline diagnosis of cannabis abuse were four times more likely to have symptoms of depression, with this association remaining significant after adjusting for potential confounding factors (e.g., alcohol abuse, stressful life events). Depressive symptoms did not predict later cannabis abuse.

A study of 259 young people across six years assessed the links between cannabis use, depression, and anxiety (Patton et al., 2002). The Clinical Interview Schedule – Revised was used to assess depression and anxiety. Self-report provided an indication of substance use. Higher rates of cannabis use as an adolescent were

associated with an increased prevalence of depression and anxiety in young adulthood, with a particular vulnerability experienced by females. Females had a more than five-fold risk of developing depression or anxiety if they used cannabis daily as an adolescent. Notably, neither depression nor anxiety in adolescence predicted frequent cannabis use in adulthood, failing to support the self-medication theory.

A longitudinal cohort study conducted in New Zealand also found a link between cannabis use and depression in those aged between 14 and 21 years (N = 1,265) (Fergusson, Horwood, & Swain-Campbell, 2002). At least weekly use of cannabis significantly increased the risk of depression as measured by the Diagnostic Interview Schedule of Children (DIS –C), juvenile delinquency, and suicidal behaviours. The effect of cannabis on juvenile delinquency and suicidal behaviours was mediated by age, with 14 – 15 year olds being more affected than 20 – 21 year olds by regular cannabis use. However, the effect of regular cannabis use on depression remained consistent across all age ranges.

An American population study used diagnostic interviews to examine comorbidity in cannabis use disorders (N = 43,093) (Stinson, Ruan, Pickering, & Grant, 2006). It was determined that 29.9% and 24.1% of those with a recent cannabis use disorder (previous 12 months) were diagnosed with mood and anxiety disorders respectively. Rates were even higher in those with a lifetime cannabis use disorder, with 39.6% and 30.5% having mood and anxiety disorders (respectively).

Importantly, several studies have extended this area of research and found that the association between cannabis use and depression/anxiety is mediated by

other variables. An American population-based study found that cannabis use and dependence showed a somewhat elevated risk for a diagnosis of major depression (Chen, Wagner, & Anthony, 2002). However, it was emphasized by the researchers that the association was modest, and the effects of cannabis on depression were likely to have been mediated by unmeasured variables and the retrospective nature of the study.

Fergusson and Horwood (1997) examined the links between cannabis use by 15 and 16 year olds and their psychosocial adjustment between the ages of 16 and 18 years using the CIDI. Although increased cannabis use was significantly associated with major depressive and anxiety disorders, statistical significance was lost once other antecedent variables (e.g., family functioning, parent/peer relationships, and individual factors such as self-esteem) were included.

A representative Australian sample (N = 10,641) was used in two separate studies (Degenhardt, Hall, & Lynskey, 2001a; 2001b) to determine the impact of cannabis, alcohol, and tobacco use on a range of mental health problems. Both studies found that cannabis use had a strong univariate relationship with affective and anxiety disorders. However, no level of cannabis use (use, abuse, or dependence) was significantly associated with a DSM-IV diagnosis of affective or anxiety disorder once demographics, other substance use, and neuroticism were incorporated into analyses. The effect of cannabis use on mood and anxiety disorders was most significantly mediated by the inclusion of other substance use.

A longitudinal population study of cannabis use and mental health was conducted using self-reports of substance use and the DIS-C (McGee, Williams,

Poulton, & Moffitt, 2000). At 15 years of age, cannabis use was significantly higher in those with anxiety/depressive disorders, however, this association lost significance at the ages of 18 and 21 years. Cannabis use in adolescence did not significantly elevate the risk for developing anxiety or depressive disorders.

More recently, cannabis dependent participants (N = 119) were assessed using structured diagnostic interviews and the BDI-II to determine the self-medication hypothesis of depression (Arendt et al., 2007). In reference to periods of intoxication, a minority of participants rated the occurrence of their symptoms of depression (10.9%) and anxiety (10.9%) as 'often' or 'always'. Notably, the majority reported that cannabis use commonly produced a range of pleasurable effects such as relaxation (89.1%) and happiness (58%). Anecdotal reports (Gruber, Pope, & Brown, 1996) have supported these findings, with the presentation of cases that specifically associate cannabis use with the alleviation of depressive symptoms. Although it is noted that the dose of cannabis used in these cases was relatively low and not taken by the users to achieve euphoric effects. A more robust study by Dixon et al. (1991) of substance use in patients with schizophrenia found the effects of cannabis to be anxiolytic and activating.

A 10-month prospective study of cannabis use and depression was conducted with schizophrenia-type patients who had a recent history of cannabis use (Degenhardt et al., 2007). Participants were assessed monthly (across 10 months) using the BPRS and the Calgary Depression Scale for Schizophrenia (N = 101). Substance use was based on self-report, with cannabis use being represented as the number of days used in the last 28. Cannabis had been used in the past month by

69% at baseline and 43% at the 10-month follow-up. There was minimal use of amphetamines in the past month at either of these assessment points (11% and 3% respectively). Cannabis use did not significantly increase depression scores in the following month. Likewise, depression scores were not predictive of cannabis use in the following month.

Contrasting results were found in a study of early psychosis patients (N = 84) (Preston et al., 2003). Early psychosis was defined as first psychotic illness (or within 12 months of onset). The largest diagnostic proportion of participants (31%) consisted of those who met criteria for substance-induced psychosis. Cannabis users (n = 47) were found to have significantly higher levels of anxiety/depression than non-users (M = 2.93, SD = 1.1 vs. M = 2.30, SD = 1.0 respectively) on the BPRS.

The literature examining the relationship between cannabis use, depression, and anxiety has been recently reviewed by Moore et al. (2007). Their analyses revealed that these factors showed some evidence of association, however, the role of cannabis as a causal factor was not established. Findings of the studies reviewed were less than convincing given their lack of consideration for a range of important issues such as reverse causality, the effects of intoxication or withdrawal, and the contribution of confounding factors. In conclusion, Moore et al. (2007) identified the use of cannabis as a concern with respect to affective outcomes, but emphasised the lack of robust evidence surrounding this relationship.

Although notably less attended to in the research, mania and hypomania have also been associated with cannabis use. An early study considered this link in a sample of psychotic men with and without cannabis use (Rottanburg, Robins, Ben-

Arie, Teggin, & Elk, 1982). Cannabis use was confirmed with urine drug screens and symptoms were measured by the PSE. The groups were not significantly different in neuroleptic dose. Cannabis-using psychotic patients (n = 20) demonstrated significantly more symptoms of hypomania and agitation than non-using controls (n = 20).

Nunez and Gurpegui (2002) found that the mania-type symptoms of expansive mood and ideation were more common in those diagnosed with a cannabis-induced psychosis versus those with an acute schizophrenia according to DSM-III-R (American Psychiatric Association, 1987) criteria. Similarly, Johns (2001) and Carney et al. (1984) reported that heavy cannabis use can lead to a functional psychosis with distinct hypomanic features.

Further evidence for a link between cannabis and mania was provided by a study of bipolar affective disorder patients (N = 50) (Strakowski, DelBello, Fleck, & Arndt, 2000). The SCID was used to determine diagnoses of bipolar disorder and substance use disorders. The Young Mania Rating Scale and the Hamilton Depression Rating Scale assessed mania symptoms and depression symptoms (respectively). Cannabis use was positively associated with a longer duration of manic episodes that were more severe in nature, but interestingly, had no impact on the duration of depressive episodes.

Using a population sample (N = 4,815), Henquet et al. (2006) prospectively examined cannabis use and the expression of mania at three assessment points across three years using the CIDI. Cannabis use at baseline significantly increased the risk of manic symptoms at follow-up. A dose-response relationship was evident, with

increased cannabis exposure being associated with an increased risk for manic symptoms. Notably, cannabis use remained a significant predictor despite the subsequent inclusion of possible confounding factors (e.g., prior manic or depressive symptoms, other substance use, and importantly, incidence of psychotic symptoms). Cannabis use at follow-up was not associated with manic symptoms at follow-up, suggesting that the relationship is unlikely to be based on the acute effects of cannabis.

Cannabis use has also been reported to alleviate symptoms of mania (Grinspoon & Bakalar, 1998), however, it is noteworthy that these reports were anecdotal in nature and the dose of cannabis used was relatively low. A literature review of cannabis use and bipolar affective disorder by Ashton et al. (2005) concluded that the link between cannabis use and symptoms of mania and hypomania were dose-dependent, with small doses being unlikely to increase the risk of developing these symptoms. They proposed that the THC component of cannabis is linked to the development of both psychotic and mania-like symptoms in users.

Overall, there is some evidence that cannabis users (compared to non-users) experience increased levels of depression and anxiety. However, once confounding factors (e.g., other substance use, family factors, neuroticism) were controlled in analyses, little support was found for a significant relationship between cannabis use and more severe symptoms of depression or anxiety. The two studies that considered the impact of cannabis use on the symptoms of depression/anxiety in patients with psychosis obtained conflicting results. The most recent study reported no association between the use of cannabis in one month and increased symptoms of

depression in the following month (Degenhardt et al., 2007). The other reported that cannabis use was significantly associated with higher levels of depression/anxiety (Preston et al., 2003). Given the sum of these findings, it is unlikely that cannabis use plays a causal role in the development of these disorders. It is more probable that the impact of cannabis is only minor, and that a range of other risk factors (social, individual, family, environmental) are the common link between cannabis users and those who develop affective and anxiety disorders (Degenhardt, Hall, & Lynskey, 2003a; Moore et al., 2007). In contrast, there is converging evidence that cannabis use is associated with increased symptoms of mania. The significant relationship between cannabis use and mania symptoms persisted in one study despite the inclusion of several confounding factors (Henquet, Krabbendam, de Graaf, Have, & van Os, 2006). Of note, however, is the limited amount of research addressing this area. How the severity of mood or anxiety symptoms in cannabis users with psychosis directly compares to those with a primary psychosis requires further examination, particularly with respect to how these symptoms change across time within the two groups.

Cannabis and disturbed behaviour

Substance misuse, particularly polysubstance use, has been linked with violence, aggression, and hostility in both community and clinical samples (Soyka, 2000; Swartz et al., 1998). However, the bulk of evidence specifically concerning cannabis use and problem behaviour has not provided a robust link (Macleod et al., 2004). Cannabis use has not been found to significantly predict aggression in a student sample (Schaub, Boesch, & Stohler, 2006), or a clinical sample of patients

presenting to a psychiatric emergency service (Dhossche, 1999). Additionally, chronic cannabis users were not found to be significantly different to non-cannabis users on levels of aggression (Soueif, 1975).

Most of the research surrounding cannabis and aggression is related to the psychoactive component (THC) of cannabis (Hoaken & Stewart, 2003). Intoxication with low doses of cannabis has been associated with minimal levels of aggression, however, the significance of this relationship was lost once moderate or high doses were used (Myerscough & Taylor, 1986; Salzman, Van Der Kolk, & Shader, 1976; Taylor, 1976). Accordingly, animal studies have predominantly found that cannabis administration induces passive and subservient behaviours, and curbs attacking behaviour (Hoaken & Stewart, 2003; Miczek, 1978; Sieber, Frischknect, & Waser, 1980).

Macleod and colleagues (2004) conducted a review of longitudinal studies of cannabis use and reported that there was minimal evidence linking cannabis use to problem behaviours. They reported that due primarily to selection bias, minimal adjustment for confounding variables, and sample size, findings linking cannabis use to behavioural problems were to be cautiously accepted. However, there are a number of studies with conflicting findings that require consideration. A study of adult schizophrenia patients with (n = 50) and without (n = 50) cannabis use histories found that the former group exhibited more positive psychotic symptoms and increased levels of violent behaviour (Rehman & Farooq, 2007). They scored higher on a measure of paranoia and factors associated with violence (excitement, hostility, uncooperativeness, anger, poor impulse control, and a need for immediate

gratification). However, it is possible that the differences between these two groups may be at least partially the result of the substance-using group being significantly younger at onset of psychotic illness (thereby experiencing a longer illness course).

Studies of adolescents have more consistently linked cannabis use with disturbed behaviour. Rey and colleagues (2002) examined cannabis use among Australian adolescents (N = 1,261), finding that use was associated with more behavioural problems. Those who met DSM-IV (American Psychiatric Association, 1994) criteria for conduct disorder were more likely to be cannabis users. In a longitudinal study of adolescents/young adults (N = 1,265), cannabis use was associated with increased property/violent crime (Fergusson, Horwood, & Swain-Campbell, 2002). This association was strongest in the age group of 14/15 years. Regular and heavy cannabis use increased the risk. Monshouwer and colleagues (2006) reported clear links between recent cannabis use by adolescents (N = 5,551) and disturbed behaviours including delinquency and aggression. Again, the association was further strengthened by more regular cannabis use.

In reference to the studies that found a link between cannabis use and disturbed behaviour, it is noted that they are all potentially influenced by confounding variables that independently demonstrate a high risk for aggression, such as young age, polysubstance use, and psychotic symptoms (particularly positive symptoms) (Milton et al., 2001; Raja & Azzoni, 2005; Raja, Azzoni, & Lubich, 1997; Swanson et al., 2006). One example is provided by a study of male schizophrenia patients (N = 70) that found cannabis use alone did not predict violence (physical or verbal violence against self, others, or objects) (Koen et al.,

2004). However, a combination of alcohol abuse and cannabis use was significantly associated with violence. Of note, higher mean scores on the manic-excitement factor of the PANSS (consisting of poor impulse control, tension, hostility, uncooperativeness, and excitement) was also a significant predictor of violence. Caution must also be exercised when interpreting studies linking cannabis use with increased levels of disturbed behaviour given the potential bidirectional relationship between cannabis use and delinquency/aggression.

Mixed results in the literature may be partly due to the pattern of recent substance use and current phase of withdrawal the participants are in. Aggression has been found to occur more commonly during the early stages of withdrawal (Hoaken & Stewart, 2003). Chronic cannabis users with a current dependence disorder (n = 19) were compared with non-using controls (n = 20) on their aggressive responses to a computerised task (Kouri, Pope, & Lukas, 1999). All participants were required to abstain from using cannabis for 28 days, and their aggressive responding was measured five times across this period. The groups were not significantly different in their weekly alcohol consumption. The cannabis-using group displayed significantly higher levels of aggression during the first week of abstinence compared to controls and their own behaviour prior to abstinence. By day 28, the cannabis-using group returned to pre-withdrawal levels of aggressive responding. The link between cannabis use and aggression during the withdrawal stage may be explained by some of the common components of this stage: irritability, poor sleep, and agitation (Budney, Novy, & Hughes, 1999).

In conclusion, there is little evidence that unequivocally links cannabis use

with disturbed behaviour. Cannabis use has typically been associated with more passive and subservient behaviours, but under certain circumstances, has also been linked with an increase in irritability and aggression (Abel, 1977). However, stress, a prior history of violence or anti-social behaviour, withdrawing from chronic cannabis use, polydrug use, psychotic symptoms, and poor impulse control have also demonstrated the potential to increase disturbed behaviours, and often confound studies examining the impact of cannabis use on disturbed behaviour (Abel, 1977; Hoaken & Stewart, 2003; Swanson et al., 2006). Studies that have taken these confounding factors into consideration have generally not established a robust link between cannabis use and increased levels of disturbed behaviour.

Chapter 6. Contributing factors to symptom severity and clinical course

Additional factors relevant to the symptom profile and clinical course of psychotic illness will be examined in this chapter. First, the difficulties associated with accurate diagnoses of substance-induced psychosis will be considered. The significance and impact of premorbid adjustment, duration of untreated psychosis (DUP), and illness chronicity will also be presented. These areas have received considerable attention in studies of primary psychosis, and have been identified as significant predictors of symptom severity, longer response time to treatment, and poorer illness outcomes (Gunduz-Bruce et al., 2005; Rabinowitz, De Smedt, Harvey, & Davidson, 2002). However, notably less attention has been given to these factors specifically in relation to psychotic patients who use amphetamines and cannabis.

Diagnostic accuracy

Substance abuse in people with schizophrenia is associated with poor outcomes, more so than for those with either a psychotic or substance use disorder alone (Gregg, Barrowclough, & Haddock, 2007; Margolese, Malchy, Negrete, Tempier, & Gill, 2004). Despite the potential for such harm, substance use and related disorders are significantly under-detected (Kirchner, Owen, Nordquist, & Fischer, 1998; Ley, Jeffery, Ruiz, McLaren, & Gillespie, 2002) and/or commonly misdiagnosed in people with a psychotic illness (Caton et al., 2005; Ley, Jeffery, Ruiz, McLaren, & Gillespie, 2002; Schanzer, First, Dominguez, Hasin, & Caton, 2006). Emergency room clinicians have shown a failure to pursue substance use histories in 30% of cases presenting with psychosis (Gilfillan et al., 1998). This trend is also evident in mental health inpatient settings, with 54% of cases positively

identified for substance use by urinalysis not being assessed for substance use by the clinician (Ley, Jeffery, Ruiz, McLaren, & Gillespie, 2002). Clinicians' suspicions of which patients may have used substances based on observation and presenting problems have also been found lacking in accuracy (Claassen et al., 1997).

Accurate differential diagnosis between a primary psychotic disorder (that may or may not have associated substance use) and a substance-induced psychotic disorder primarily depends upon thorough historical accounts and targeted substance use assessments. Both of these are difficult to complete in the context of acute psychosis, particularly if the patient is presenting with their first psychotic episode and there is a lack of collateral data available. The DSM-IV-TR (American Psychiatric Association, 2000) primarily bases differential diagnoses on the temporal relationship between the substance use and onset of psychotic symptoms. A diagnosis of amphetamine-induced psychosis is associated with an intoxicated state, whereas onset of a primary psychotic disorder can precede substance use or occur during periods of abstinence (American Psychiatric Association, 2000). The course of symptoms is also significant. Persistent psychotic symptoms that continue for more than one month post-cessation of substance use are considered more likely to be associated with a primary psychotic disorder (American Psychiatric Association, 2000). However, in practise, these details are often difficult for the patient and the clinician to clearly determine during the first assessment (Rosenthal & Miner, 1997). The DSM-IV-TR (American Psychiatric Association, 2000) notes that distinguishing between the two disorders may be especially difficult at the outset. Polysubstance use complicates this situation further (Ananth et al., 1989). For these reasons,

diagnoses often change across the course of the patient care episode or at a later point when the patient is re-presenting with further psychotic episodes and the illness becomes more chronic in nature (Ananth et al., 1989; Jakobsen, Frederiksen, Parnas, & Werge, 2006; Kampman et al., 2004).

Caton and colleagues (2007) found that 25% of people initially diagnosed with a DSM-IV (American Psychiatric Association, 1994) substance-induced psychosis were later diagnosed with a primary psychosis at one year follow-up. All participants were in the early-phase of their psychotic illness at presentation to the psychiatric emergency centre. Specific to cannabis-induced psychosis, a Danish study identified that only 14.8% of those presenting for treatment of an index episode of cannabis-induced psychosis retained this diagnosis at three year follow-up (Arendt, Rosenberg, Foldager, Perto, & Munk-Jorgensen, 2005). The majority (44.5%) were diagnosed with a schizophrenia-spectrum disorder at follow-up, and the remaining 40.7% were diagnosed with a range of other disorders (including depression, anxiety, and personality disorders). Carlson et al. (2000) examined 53 patients with psychotic mania, which included patients with a substance-induced psychosis. It took six or more months to make an accurate diagnosis in some of these cases.

These studies emphasise the difficulties clinicians face in diagnosing early-phase psychosis in people using substances. It also raises uncertainty about whether researchers can reliably differentiate between substance-induced psychosis participants and primary psychosis participants (who use substances) in the context of a recent-onset psychotic illness. This may be particularly difficult in samples of

stimulant users (Shaner et al., 1998), given the many similarities between the two disorders with respect to symptom profile.

The potential long-term impact of misdiagnosis and/or under-detection of substance use in psychotic illness is significant. The original but inaccurate diagnosis may be maintained in later health service visits (Link, Struening, Neese-Todd, Asmussen, & Phelan, 2001), the patient may experience stigma associated with a primary psychotic illness (Mann & Himelein, 2004), the resulting treatment may involve unnecessary hospitalisation and/or medications (e.g., antipsychotics) (Carlson et al., 2003; Leucht, Pitschel-Walz, Abraham, & Kissling, 1999; Schnyder, Valach, & Heim, 1995; Schnyder, Valach, Mörgeli, & Heim, 1999), and substance use interventions and other relevant follow-up services may not be arranged (Kirchner, Owen, Nordquist, & Fischer, 1998; Rockett, Putnam, Jia, & Smith, 2003; Schanzer, First, Dominguez, Hasin, & Caton, 2006; Sorbara, Liraud, Assens, Abalan, & Verdoux, 2003).

In summary, the difficulties associated with differential diagnosis between substance-induced psychosis and primary psychotic disorders (with or without substance use) are substantial. Studies employing samples of early-phase psychosis patients need to be particularly cognisant of misdiagnosis and the potential this may have on findings. One solution to the problem of diagnostic uncertainty is to classify/categorise people with psychosis on the basis of self-reported recent substance use versus no substance use. This approach has been taken by several other recent studies in the field (e.g., Degenhardt et al., 2007; Preston et al., 2003; Rehman & Farooq, 2007).

Substance use, psychosis, and premorbid adjustment

An area that must be considered when comparing psychotic patients with and without substance use histories is premorbid adjustment. Surprisingly, given the poor outcome on many indices of functioning and illness factors associated with co-occurring substance use and psychosis, some early studies have found this group has better premorbid functioning compared to non-using psychosis patients (Arndt, Tyrrell, Flaum, & Andreasen, 1992; Breakey, Goodell, Lorenz, & McHugh, 1974; Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Ritzler, Strauss, Vanord, & Kokes, 1977). It has been suggested that substance-using psychotic patients with better premorbid functioning are more socially involved with others and, therefore, have greater access to substances. Alternatively, higher functioning individuals who are experiencing early psychotic symptoms might be more likely to seek out ways of managing these symptoms, with substance use being one option (Mueser et al., 1990).

An early study conducted by Breakey et al. (1974) assessed the premorbid adjustment of schizophrenia patients, using a modified version of the Phillip's Scale of Premorbid Adjustment. Substance users (n = 26) within the schizophrenia group were found to have significantly better premorbid adjustment than their non-using counterparts (n = 14). These results were supportive of those from an earlier study conducted by Bowers (1972).

Arndt and colleagues (1992) examined the premorbid adjustment of 131 patients with schizophrenia, and divided participants into groups of non-users and dependent users of alcohol, hallucinogens, cannabis, or stimulants. The primary

measure of premorbid adjustment was based on early measures by Phillips (1953) and Gittleman-Klein and Klein (1969). Overall, those who were both psychotic and substance dependent had significantly better premorbid adjustment than non-users on both the childhood and adulthood subscales. When substance users were classified into type of substance used, only alcohol, and to a lesser extent cannabis, showed an independent association with better premorbid adjustment. Notably, these particular substance-using groups contained the largest number of participants. They also contained fewer polysubstance users than either the stimulant or hallucinogen groups.

In a more recent study of inpatients diagnosed with a psychotic illness (N = 83), the Premorbid Adjustment Scale (PAS) was used to examine differences between those with a current or lifetime history of substance abuse/dependence and those without (Dixon, Haas, Weiden, Sweeney, & Frances, 1991). Diagnoses of psychosis and substance abuse/dependence disorders were made using the SCID. In contrast to results of the previous study, substance abusers and non-abusers were not significantly different on measures of premorbid adjustment during the childhood or adulthood age periods. However, better premorbid adjustment was demonstrated by the substance abusers regarding sexual adjustment in both early adolescence and late adolescence. Substance abusers exhibited worse premorbid adjustment in the area of scholastic adaptation in both the early and late adolescence periods.

There are also a number of studies where there have been no differences in premorbid adjustment between patients with comorbid substance abuse and psychosis and patients with psychosis alone. Sevy et al. (2001) compared substance

abusers and non-abusers from a sample of first-episode patients with schizophrenia and schizoaffective disorders (N = 118). The abusing and non-abusing groups were not significantly different on any of the PAS subscales of childhood (M = 0.97, SD = 0.78 vs. M = 1.24, SD = 0.87), early adolescence (M = 1.41, SD = 0.85 vs. M = 1.33, SD = 0.84), late adolescence (M = 1.66, SD = 1.10 vs. M = 1.58, SD = 1.06), or adulthood (M = 1.93, SD = 1.29 vs. M = 1.80, SD = 1.37) (respectively).

Similarly, Caton and colleagues (2005) examined differences in premorbid adjustment in those attending a psychiatric emergency department who were diagnosed with either a substance-induced psychosis (n = 169) or primary psychosis with concurrent substance use (n = 217). There were no differences between the substance-induced psychosis (M = 0.31, SD = 0.14) and primary psychosis (M = 0.32, SD = 0.14) groups based on total PAS scores. However, it is evident that the non-significant differences between groups in this study cannot be attributed to the presence or absence of substance use given that both groups contained substance users.

With specific reference to methamphetamines, Chen et al. (2003) examined the premorbid characteristics of users with (n = 174) and without psychosis (n = 261). Using the Premorbid Social Adjustment scale for the age periods of 5 – 11 years and 12 – 16 years, there were no significant differences between the groups.

Several references have also been made specifically concerning cannabis use and psychosis in this literature. In a study of cannabis use and neurocognition, the premorbid adjustment of psychosis patients was assessed using the PAS (Stirling, Lewis, Hopkins, & White, 2005). Cannabis users and non-users were not

significantly different on the four age bands of the PAS or the total score at admission. This finding was not supported in a review of the literature involving substance abuse in schizophrenia by Cantor-Graae et al. (2001), in which cannabis use was reported to be frequently associated with better premorbid adjustment. Caton et al. (2000) also reported that one of the differentiating factors between primary psychosis and substance-induced psychosis was that the latter was associated with better premorbid social adjustment, and that this was particularly relevant to cannabis use.

In summary, the bulk of recent studies have found no significant differences between substance-using psychotic patients and non-using psychotic patients on premorbid adjustment. However, given there is some evidence suggesting that these two groups can be differentiated based on premorbid adjustment, studies comparing psychotic patients with and without concurrent substance use should not ignore its potential contribution (Brunette, Mueser, Xie, & Drake, 1997). Further justification for consideration of this variable in the current study is given by findings that link poor premorbid functioning with more severe psychotic symptoms (positive and negative) in first episode psychosis (Addington, van Mastrigt, & Addington, 2003; Rabinowitz, De Smedt, Harvey, & Davidson, 2002).

Duration of untreated psychosis

Another area that has received considerable attention in studies of psychotic disorders is DUP. A study by McGlashan (1999) reviewed the length of DUP in several first-episode samples, finding that the mean was between one and two years. Evidence suggests that longer than average DUP periods are associated with more

severe psychotic symptoms (particularly positive symptoms) (Perkins, Gu, Boteva, & Lieberman, 2005), a poorer response to treatment (Gunduz-Bruce et al., 2005) and poorer illness outcomes (Drake, Haley, Akhtar, & Lewis, 2000; Loebel et al., 1992; Waddington et al., 1998). A study specific to first-episode psychosis patients (*N* = 92) also found that a longer DUP significantly predicted more severe positive symptoms (Wade et al., 2007). Shorter than average DUP in first-episode psychosis patients has been associated with better premorbid adjustment and less severe psychotic symptoms (positive and negative symptoms) (Larsen et al., 2001). Interestingly, a shorter DUP has also been associated with higher levels of substance use (Larsen et al., 2001) and more severe mania symptoms (Conus et al., 2006; Drake, Haley, Akhtar, & Lewis, 2000; Sipos, Harrison, Gunnell, Amin, & Singh, 2001). This particular link may be explained by the intensity of behaviours associated with both substance use and mania, and the problems they cause for others associated with the patient.

A person experiencing psychotic symptoms typically presents for treatment approximately one to two years post onset of those symptoms (Norman & Malla, 2001), however, people who use substances typically have even longer delays between their first psychotic symptom and first help-seeking contact (Cougnard et al., 2004; Green et al., 2004). DUP has been associated with poorer clinical outcomes in substance-induced psychosis (Caton et al., 2006), and needs to be considered as a possible confounding factor in any examination of psychotic symptoms and their clinical course.

Family environment

The family environments of patients with psychosis, most commonly those with a diagnosis of schizophrenia, have long been examined within the literature (Hooley, Woodberry, & Ferriter, 2005). Halford et al. (1991) studied the family environment of 57 first-admission psychosis patients. In this study, the Family Environment Scale (FES) (administered at admission) showed that higher levels of positive emotional expressiveness within the patients' families were significantly associated with less severe and fewer negative psychotic symptoms. Further links between family environment and psychosis have been established by Robert et al. (2004) in their study of 31 patients diagnosed with psychotic disorders or affective disorders. A diagnosis of psychosis was significantly associated with higher scores on the conflict subscale of the FES, while a diagnosis of affective disorder was linked with higher scores on the cohesion and expressiveness subscales. It was noted that patients with psychosis were significantly more likely to describe their families as controlling, than were those with affective disorders. With particular consideration of substance use, Caton et al. (2005) reported poorer family support in a substance-induced psychosis group compared to those in a primary psychotic-illness and co-occurring substance use group. However, it remains unclear whether psychosis patients with a substance use history are any different to non-using psychosis patients with respect to their family environment. Given the paucity of research on the differences between these two groups in family environment, and in consideration of previous findings that have shown family factors are predictive of psychotic symptom development (O'Brien et al., 2006) and illness outcome (Linszen

et al., 1997), it is imperative to consider the impact that family environment might have on psychotic symptoms and their clinical course.

Factors associated with chronicity of psychotic illness

Chronic psychotic disorders have been associated with a progressive decline in general functioning and worsening illness course in some patients (Peuskens, 2004; Seok Jeong et al., 2005). The patient's symptom profile is dependent upon the phase of illness they are in, with positive symptoms more prominent in the early phase (Edwards, McGorry, Waddell, & Harrigan, 1999; Kay, Fiszbein, Lindenmayer, & Opler, 1986). With progression of the disorder, these positive psychotic symptoms become less severe, while core negative symptoms remain relatively stable or become more prominent (Adams, Wilson, Gilbody, Bagnall, & Lewis, 2000; Mancevski et al., 2007; Murphy, Chung, Park, & McGorry, 2006; Sandyk, 1993). Thus, the symptom profile of patients with early psychosis is not the same as that of patients with a more long-standing illness (Drake et al., 2003). Long-term antipsychotic medication use exacerbates the problem of negative symptoms and is associated with side effects, social deficits, stigmatisation, cognitive deficits, and family and vocational problems (Adams, Wilson, Gilbody, Bagnall, & Lewis, 2000; Meltzoff & Blumenthal, 1966; Peuskens, 2004; Startup, 1998; Walton, 2000).

For these reasons, it is important to employ a sample incorporating patients in a similar phase of psychotic illness when comparing different groups on psychotic symptoms and clinical course. In order to control for the additional factors associated with a chronic psychotic illness, it is also important to limit participants to those in the early phase of their psychotic illness. Few studies presented in this

thesis considered the impact of illness chronicity and most used a mixed sample with respect to illness phase.

Chapter 7. The impact of amphetamines and cannabis on psychosis: A summary of the literature

Amphetamines and cannabis are the most commonly used illicit substances in Australia (Australian Institute of Health and Welfare, 2005a). Both substances are associated with a range of physical and psychological problems. Of considerable concern is the evidence linking amphetamine use and cannabis use with psychotic symptoms and diagnosable psychotic disorders (Ferdinand, Sondeijker et al., 2005; Iwanami et al., 1994; McKetin, McLaren, Lubman, & Hides, 2006; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). There is a vast literature that has examined the symptom profile and clinical course of psychosis associated with the use of amphetamines and cannabis, which has been reviewed in Chapters 3 and 4. The current study aims to extend existing literature by comparing psychotic inpatients who have recently used amphetamines and/or cannabis to psychotic inpatients who have not used substances on the severity and clinical course of a range of symptom dimensions (positive symptoms, negative symptoms, mania symptoms, depression-anxiety symptoms, and disturbed behaviour). A synopsis of the most crucial findings from the literature will now be presented, leading to the purpose and hypotheses of the current study.

The literature examining amphetamine use and psychosis is compelling, and has led to amphetamine-induced psychosis being proposed as one model of schizophrenia (Ellison & Eison, 1983; Kokkinidis & Anisman, 1981). Samples of healthy volunteers, community-based and treatment-seeking amphetamine users, and patients with psychotic disorders have been studied. A considerable collection of animal studies also complement this literature. Chronic, high-dose amphetamine use

has consistently been associated with the development of psychotic symptoms, and in some cases, amphetamine-induced psychosis. There is also evidence of psychotic symptoms emerging after only a single dose of amphetamine.

Several studies have examined the nature of psychotic symptoms in amphetamine-induced psychosis samples. Auditory hallucinations tend to be the most common type of hallucination experienced, with rates ranging from 44.6% up to 95% (Harris & Batki, 2000; Srisurapanont et al., 2003). Persecutory delusions are the most common type of delusion experienced, with rates ranging from 20.8% up to 100% (Harris & Batki, 2000; Srisurapanont et al., 2003). Negative symptoms have been found to occur at much lower rates, with some studies reporting no evidence of negative symptoms and others identifying them in up to 26% of patients (Harris & Batki, 2000; Iwanami et al., 1994).

While the literature provides evidence of prominent positive symptoms with comparatively few negative symptoms in psychosis associated with amphetamine use, there is a paucity of research that assesses how this symptom profile directly compares to non-users with psychosis. This limits our ability to clearly determine any differences between the groups with respect to symptom severity. The two studies (Mikami et al., 2003; Tomiyama, 1990) that have attempted to address this gap in the research have found that amphetamine-users have significantly lower negative symptom scores, and either similar or significantly lower positive symptom scores compared to non-users. However, the generalisability of these studies is limited by sample size, the use of chronic patients (Tomiyama, 1990), and by varying degrees of illness chronicity within the sample (Mikami et al., 2003). Fortunately, the literature comparing the broader category of ‘substance-abusers’

with psychosis to non-users with psychosis can be used to provide some guidance about the likely differences between users and non-users on clinical symptoms. Interestingly, many of these studies (e.g., Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Scheller-Gilkey, Thomas, Woolwine, & Miller, 2002; Sevy et al., 2001) found no differences between these two groups on the severity of their positive or negative symptoms at baseline assessment.

Next, the clinical course of symptoms experienced by amphetamine users with psychosis was reviewed. Slightly more than half experience symptoms that resolve within ten days of ceasing substance use (Connell, 1958; Iwanami et al., 1994; Sato, Nakashima, & Otsuki, 1982). This pattern of symptom 'recovery' in amphetamine users with psychosis is consistent with reports that amphetamines are typically excreted from the body within five days of ceasing use. However, there are at least six studies that report cases of protracted psychosis (ranging from 7% to 26.4% of sample participants) that take more than one month to resolve (Chen et al., 2003; Connell, 1958; Iwanami et al., 1994; Konuma, 1984; Sato, Nakashima, & Otsuki, 1982; Tatetsu, Goto, & Fujiwara, 1956). The reasons for varying lengths of symptom abatement are unclear. However, it has been proposed that prolonged cases of psychosis may be the result of a latent vulnerability to psychotic illness or the person may have already been experiencing a prodromal phase of psychotic illness that was hastened by substance use (Dawe & McKetin, 2004).

However, the differences in symptom course between psychotic patients with and without a recent history of amphetamine use remains unclear. To date, there appear to be no studies that have prospectively compared the rate of symptom resolution in an amphetamine-using group with psychosis to that of a non-using

control group with psychosis during the hospitalisation period. It is again necessary to refer to studies that have incorporated users of varying types of substances in their using group. There are two such studies relevant to this discussion (Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Ries et al., 2000). These studies have compared dual diagnosis patients to primary psychosis patients at hospital admission and again at discharge. Dixon et al. (1991) (N = 83) reported that dual diagnosis patients (primarily users of cannabis, alcohol, and cocaine) and non-using patients with a primary psychosis were not significantly different on severity of positive or negative symptoms, depression-anxiety symptoms, or activation. However, comparisons between the groups at discharge showed that while they were comparable on the severity of their activation and depression-anxiety symptoms, the substance-using group had significantly less severe positive and negative symptoms.

The more recent study by Ries et al. (2000) had a notably larger sample size (N = 608). They also found no differences between the dual diagnosis group and the non-using primary psychosis group at admission on total scores of the PAF and subscale scores for hallucinations/delusions, depression, elevated mood, and hostility. At discharge, the only significant difference between groups was less severe positive symptoms (hallucinations and delusions) in the substance-using group. Both of these studies (Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Ries et al., 2000) found that substance users and non-users were essentially indistinguishable with respect to symptom profile at admission, but that some significant differences were evident between the groups at discharge. Unfortunately, it remains unclear how the groups compared on their respective clinical courses between the assessment points at admission and discharge. Notably, the types of

symptoms that were significantly different were not consistent across the two studies and neither study examined specific classes of substance. Even more critical was that neither study controlled for chronicity of illness in their respective samples.

As reviewed in Chapter 5, amphetamine use has also been found to impact upon mood (depression and mania), anxiety, and disturbed behaviours (hostility, aggression, and violence). Moderately severe depression and mania symptoms are not uncommon experiences for meth/amphetamine users (34.7% and 50% respectively) (Dyer & Cruickshank, 2005; Hall, Hando, Darke, & Ross, 1996). Likewise, anxiety has been reported by more than 60% of amphetamine users (Degenhardt & Topp, 2003; Hando, Topp, & Hall, 1997) and disturbed behaviours have been found in up to 47% of amphetamine users (Wright & Klee, 2001). While amphetamine users with psychosis also appear to experience elevated rates of these symptoms (e.g., Akiyama, 2006; Harris & Batki, 2000; Miles et al., 2003), particularly mania and disturbed behaviour, there is little evidence that clarifies whether these symptoms are more or less severe than those experienced by non-using psychosis populations. Studies comparing the broader category of 'substance-using' psychosis patients to non-using psychosis patients have most commonly reported non-significant differences on measures of depression at baseline assessment (e.g., Kovasznay et al., 1993; Sevy et al., 2001). Those that have gone on to conduct follow-up assessments have also reported comparable depression-anxiety symptoms between the groups at this time point (e.g., Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Ries et al., 2000). It is of significance then that the current study will consider the impact of substance use on a range of symptom dimensions that includes depression, mania, anxiety, and disturbed behaviours, and

that the focus does not rest solely on positive and negative psychotic symptoms.

In any study of amphetamines and psychosis, both the independent and synergistic impact of cannabis must also be considered given its high rates of use in both the amphetamine-using and psychosis populations. The relationship between cannabis and psychosis is less clear than that between amphetamines and psychosis. While several robust longitudinal studies have linked cannabis use with the development of psychotic symptoms (Arseneault et al., 2002; Fergusson, Horwood, & Swain-Campbell, 2003) and increased risk for psychotic disorders (Andreasson, Allebeck, Engstrom, & Rydberg, 1987; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002), the nature of the relationship continues to be questioned. Uncertainty has been driven by poorly controlled confounding factors and evidence of a bidirectional relationship between cannabis use and psychosis (Fergusson, Poulton, Smith, & Boden, 2006). With these limitations in mind, there is evidence that suggests cannabis users with psychosis experience similar rates of positive psychotic symptoms to non-using psychotic patients, but comparatively fewer negative psychotic symptoms.

The role of cannabis use in the clinical course of psychotic symptoms and behaviour has also not been clearly defined. A small number of studies have examined the impact of cannabis use on the long-term clinical course of psychosis (Caspari, 1999; Mathers & Ghodese, 1992; Stirling, Lewis, Hopkins, & White, 2005). While these studies reported some differences between users and non-users at the first assessment (e.g., Stirling, Lewis, Hopkins, & White, 2005 found significantly more positive psychotic symptoms in cannabis users), the groups were indistinguishable with respect to psychopathology at follow-up assessments, which

were conducted one or more years post-admission. More relevant to the current study is research that has focussed on differences between cannabis users and non-users during the hospitalisation period. An early study by Rottanburg et al. (1982) found that psychotic patients who had used cannabis experienced significantly more symptoms of hypomania and agitation, and significantly less symptoms of affective flattening, incoherent speech, auditory hallucinations, and hysteria than non-users at admission. Importantly, the cannabis-using group exhibited marked symptomatic improvement on the PSE at a one week follow-up assessment on hypomania, agitation, self-neglect, irritability, and on a range of delusions. In contrast, non-users demonstrated negligible change, with the only significant reduction being associated with their score for 'worry'. In contrast, several studies (Grech, van Os, Jones, Lewis, & Murray, 2005; Negrete, Knapp, Douglas, & Smith, 1986) have specifically linked cannabis use with an unremitting course and more severe psychotic symptoms during hospitalisation, however, this type of clinical course has been linked to patients who continued to actively use cannabis throughout the assessment period.

Comparison across the few studies that have explored cannabis use and the clinical course of psychotic symptoms is made difficult with inconsistent methods of symptom and substance use assessment, and marked differences both in the number of assessment points and the intervals of time between assessment points. Further to this, comparability between the using and non-using groups in the majority of these studies is limited by the lack of control for illness chronicity. Another problem inherent to this area of research is that significant differences found between groups at discharge are often incorrectly considered to be evidence of significant differences in clinical course. It is important to consider that two groups might obtain markedly

different scores on a symptom measure at a particular time point, but the rate at which this symptom dimension reduced or increased in severity prior to this time might actually be similar between the two groups.

As with amphetamines, the impact of cannabis on the severity and clinical course of mood, anxiety, and disturbed behaviour will also be considered in this thesis. Again, the findings in the existing literature are mixed. Although cannabis use has been linked to increased symptoms of depression and anxiety (Patton et al., 2002; Stinson, Ruan, Pickering, & Grant, 2006), a number of robust studies have shown that this association loses significance when other factors (such as other substance use and demographics) are included in analyses (Degenhardt, Hall, & Lynskey, 2001a; 2001b). These findings are similar to those associated with cannabis use and disturbed behaviour. Cannabis use has rarely been linked with aggressive/hostile behaviours, and when there has been an association, it has been in the context of other substance use and a prior history of violence. Once these and other confounding factors have been taken into consideration, the significant association has been lost (Hoaken & Stewart, 2003; Macleod et al., 2004). Slightly clearer findings have been obtained in the few reports examining cannabis use and mania symptoms, with cannabis use being linked to increased levels of mania/hypomania in both clinical and normal populations, (Henquet, Krabbendam, de Graaf, Have, & van Os, 2006; Rottanburg, Robins, Ben-Arie, Teggin, & Elk, 1982). However, it has been noted that many of these results are based on high-dose use and further studies are warranted.

Finally, the literature review of the current study considered several additional factors (in Chapter 6) that have previously demonstrated a role with

respect to psychotic symptoms. Existing literature provides many examples of studies that have compared symptomatology between substance-induced psychosis patients and primary psychosis patients (with or without substance use histories). One of the primary risks inherent to the study of this sample type is that of misdiagnosis. Differential diagnosis between these groups depends on accurate historical accounts, targeted substance use assessments and most importantly, a clear understanding of the temporal relationship between any substance use and the onset of psychotic symptoms. These goals are particularly difficult to achieve if the study includes acutely unwell patients who are presenting with an early phase psychotic illness. A history of polysubstance use adds yet a further level of complexity to diagnosis (Ananth et al., 1989). Studies conducted by Caton et al. (2007) and Carlson et al. (2000) demonstrate the high rates of misdiagnosis within substance-induced psychosis patients. With these factors in mind, the current study will attempt to avoid the problem of diagnostic uncertainty (associated with the differential diagnosis between substance-induced psychosis and primary psychosis) by grouping patients with psychosis on the basis of self-reported recent substance use versus no recent substance use.

The next factor to be considered in Chapter 6 was that of premorbid adjustment. Premorbid adjustment has attracted considerable attention in the psychosis literature. Some early studies focussing on samples of psychotic patients with substance use histories have reported an association between substance use and better premorbid adjustment (e.g., Arndt et al., 1992; Bowers, 1972; Breakey et al., 1974). However, the bulk of studies in the area, which are also notably more recent in their publication (e.g., Caton et al., 2005; Chen et al., 2003; Sevy et al., 2001;

Stirling, Lewis, Hopkins, & White, 2005), found no differences between substance users with psychosis and non-users with psychosis on premorbid adjustment. Given the potential of premorbid functioning to differentiate between the two groups of psychotic patients, and in light of evidence that links poor premorbid adjustment to a greater severity in psychotic symptoms, it was considered important to examine this variable in the current study.

DUP has also been extensively examined in the psychosis literature. This factor has been associated with worse premorbid adjustment (Larsen et al., 2004), more severe psychotic symptoms (Perkins, Gu Boteva, & Lieberman, 2005) and overall poorer illness outcomes (Drake, Haley, Akhtar, & Lewis, 2000). Caton et al., (2006) reported a specific association between a longer DUP and worse clinical outcomes for patients with a substance-induced psychosis. Therefore, potential differences in DUP between the using and non-using groups of the current study were important to examine.

Like DUP, family factors have been exhaustively studied in samples of patients with psychosis. Studies of family environment have demonstrated links between the degree of control, conflict and emotional expressiveness within the family and a persons' psychotic illness and/or the severity of their symptoms (Halford et al., 1991; Robert et al., 2004). Family factors have also been linked to psychotic symptom development and clinical prognosis (O'Brien et al., 2006; Linszen et al., 1997). An obvious gap in the literature is the comparison of substance-using psychosis patients and non-using psychosis patients with respect to their family environment. Given that the current study intends to focus on the symptomatic and behavioural differences between psychosis patients with a recent

substance use history and non-using psychosis patients, it would seem valuable to consider the potential contribution of their family environment.

Finally, issues surrounding chronicity of illness were highlighted. Previous studies have demonstrated differences in symptomatology between patients experiencing an early phase psychosis and those experiencing a more chronic psychotic illness (e.g., Edwards, McGorry, Waddell, & Harrigan, 1999; Peuskens, 2004; Seok Jeong et al., 2005). With progression of a psychotic illness, many patients develop more prominent negative symptoms and less severe positive symptoms (Adams, Wilson, Gilbody, Bagnall, & Lewis, 2000; Mancevski et al., 2007). The negative impact of long-term antipsychotic use has also been highlighted in those with a chronic psychotic illness (Adams, Wilson, Gilbody, Bagnall, & Lewis, 2000; Walton, 2000). With these factors in mind, the current study ensured that all participants were in a similar phase of psychotic illness. Early phase psychosis was the focus of the study given the potential confounds that chronicity of illness presents.

In summary, the literature examining the symptoms and clinical course of psychosis associated with the use of amphetamines or cannabis has provided us with important information that has further developed our understanding about the experiences of this population and their needs with respect to prevention and treatment interventions. However, few of the existing studies have prospectively compared substance users to a non-using control group, thereby limiting our ability to truly define differences between the groups with respect to their symptom profile and clinical course of psychosis. Even fewer studies have controlled for the problems associated with illness chronicity, as outlined in Chapter 6. The literature

has also been hampered by problems associated with the accurate diagnosis of early psychotic disorders that occur alongside substance use. This study aims to address these issues and extend existing literature by: (1) comparing substance-using psychotic patients with non-using psychotic inpatients; (2) ensuring all participants are in the early phase of their psychotic illness, thereby avoiding the problems associated with chronic illness and also those that occur when samples consist of participants at varying stages of their psychotic illness; and (3) categorising the substance-use and non-substance-use groups based on whether amphetamines and/or cannabis have been used in the 30 days prior to hospital admission, rather than on diagnoses of substance-induced psychosis versus primary psychosis.

Purpose and hypotheses of the current study

The purpose of the current study is to compare the severity and clinical course of symptoms and disturbed behaviour between recent users of amphetamines and/or cannabis with early psychosis and their non-using counterparts during hospitalisation. Thus, the effects of having used amphetamines and the effects of having used cannabis in the 30 days prior to admission will be examined. Importantly, the synergistic impact of having used both amphetamines and cannabis in the 30 days prior to admission will also be considered. Differences in severity of symptoms and behaviour will be examined by assessing substance-using groups and their non-using counterparts at admission and again at week eight of hospitalisation. Differences in clinical course will be examined by repeated assessments of symptoms and behaviour at no greater than weekly intervals until week eight of admission. As suggested by Riecher-Rossler and Rossler (1998), this pattern of continuous assessment provides a more complete picture of change. In order to rule

out the potential confounds associated with premorbid functioning, DUP and family environment, the substance-using groups will be compared on these variables to the non-using group. Group differences would indicate the need for further analyses with regard to their contribution to symptom severity and clinical course.

The first major aim of this study is to examine the impact of recent amphetamine use on the four BPRS subscales of positive symptoms, negative symptoms, mania symptoms, and depression-anxiety symptoms, and on the total score of the Disturbed Behaviour Rating Scale (measure of disturbed behaviour). With respect to symptoms and behaviour at admission to hospital, it is hypothesised that in comparison to non-users, recent amphetamine users will experience: (1) significantly more severe mania symptoms; and (2) significantly more severe disturbed behaviour. No differences are expected between amphetamine users and non-users on the severity of their positive symptoms, negative symptoms, or depression-anxiety symptoms.

The bulk of relevant literature suggests that amphetamine users with psychosis experience a rapid resolution of symptoms. Thus, in the examination of the clinical course of symptoms and behaviour during the first eight weeks of hospitalisation, it is hypothesised that compared to non-users, amphetamine users will demonstrate: (1) a significantly faster reduction in positive symptoms; (2) a significantly faster reduction in negative symptoms; (3) a significantly faster reduction in mania symptoms; (4); a significantly faster reduction in depression-anxiety symptoms; and (5) a significantly faster reduction in disturbed behaviour.

The limited evidence focussing on differences between substance users and non-users at discharge from hospital reports fewer positive and negative symptoms

in the substance-using groups, but equal rates of depression/anxiety, activation, and hostility. With respect to differences in symptoms and behaviour eight weeks post-admission, it is hypothesised that compared to non-users, amphetamine users will experience: (1) significantly less severe positive symptoms; and (2) significantly less severe negative symptoms. No differences are expected between amphetamine users and non-users on the severity of mania symptoms, depression-anxiety symptoms, or disturbed behaviour.

The second major aim of this study is to examine the impact of recent cannabis use on the four BPRS subscales of positive symptoms, negative symptoms, mania symptoms, and depression-anxiety symptoms, and on the total score of the Disturbed Behaviour Rating Scale. While not as robust as the amphetamine literature, the cannabis literature does include evidence of a relationship between this substance and fewer negative symptoms. Furthermore, cannabis has been linked with increased levels of mania, but not depression or anxiety. It is therefore hypothesised that compared to non-users, recent cannabis users will experience: (1) significantly less severe negative symptoms; and (2) significantly more severe mania symptoms. No differences are expected between cannabis users and non-users on the severity of positive symptoms, depression-anxiety symptoms, or disturbed behaviour.

Next, an examination of the influence cannabis has on the clinical course of symptoms and behaviour across the first eight weeks of hospital admission will be conducted. The previous research addressing this area is limited, but generally suggests that cannabis users experience a more rapidly remitting psychotic illness. Therefore, it is reasonable to hypothesise that when compared to non-users,

cannabis-using psychotic patients will demonstrate: (1) a significantly faster reduction in positive symptoms; (2) a significantly faster reduction in negative symptoms; (3) a significantly faster reduction in mania symptoms; (4) a significantly faster reduction in depression-anxiety symptoms; and (5) a significantly faster reduction in disturbed behaviour.

With respect to differences in symptoms and behaviour at eight weeks post-admission, it is hypothesised that compared to non-users, cannabis-using psychotic patients will experience: (1) significantly less severe positive symptoms; (2) significantly less severe negative symptoms; (3) significantly less severe mania symptoms; and (4) and significantly less severe disturbed behaviour. No difference is expected between cannabis users and non-users on the severity of depression-anxiety symptoms.

The third major aim of this study is to consider the synergistic impact of having recently used both amphetamines and cannabis on the four BPRS subscales of positive symptoms, negative symptoms, mania symptoms, and depression-anxiety symptoms, and on the total score of the Disturbed Behaviour Rating Scale. This area of research has been largely overlooked with respect to the severity of symptoms and clinical course of psychosis, with no studies comparing this particular group of users to a group who had psychosis but had not recently used both substances. Given the lack of previous research examining the synergistic effects of amphetamines and cannabis, it is difficult to develop hypotheses with respect to all five dependent variables of the study. However, it is reasonable to make some hypotheses based on the areas of overlap between the amphetamine and cannabis literatures. For example, both amphetamines and cannabis have been found to be significantly

associated with an increased severity of mania symptoms. Thus, it is hypothesised that users of both amphetamines and cannabis will experience significantly more severe mania symptoms at admission than those who have not used both substances prior to admission.

Given the similarities in the literature between amphetamines and cannabis with respect to the clinical course of symptoms and behaviour, it is hypothesised that users of both substances will experience a significantly faster reduction on symptom severity for all four symptom variables and the disturbed behaviour variable in comparison to those who have not used both substances prior to admission.

Finally, it is hypothesised that users of both amphetamines and cannabis will experience significantly less severe positive and negative symptoms at Week 8 of admission when compared to those who had not used both substances prior to their current hospitalisation.

Chapter 8. The study: The impact of amphetamines and cannabis on the severity and clinical course of symptoms and behaviour during hospitalisation

Method

Participants

Participants were recruited across an 18 month period (October 2003 to March 2005) from the public adult mental health inpatient units of two suburban hospitals in Brisbane, Australia. Inpatients admitted for the treatment of an Axis I psychotic illness (schizophrenia, schizophreniform disorder, schizoaffective disorder, mood disorder with psychotic features, delusional disorder, brief psychotic disorder, or substance-induced disorder) as defined by DSM-IV-TR diagnostic criteria (APA, 2000) were approached for consent to participate in the study. Inpatients both with and without substance use histories were included in the study. In order to participate, inpatients were required to demonstrate and provide informed consent, to be between 18 and 65 years of age[2], to have experienced three or less psychotic episodes, and to be within three years of the initial diagnosis of a psychotic illness. Inpatients referred to the study who were diagnosed with an intellectual disability or who had a medical condition resulting in psychotic symptoms were excluded. Further details regarding the exclusion of patients will be provided in the 'Recruitment rate' section of this thesis.

[2] Negative symptoms are likely to increase in severity over the age of 65 (Gur, Petty, Turetsky, & Gur, 1996).

Measures

Demographics

Details on gender, age, marital status, living and employment circumstances, education level, and ethnicity were collected at admission using a purpose designed semi-structured interview and confirmed via hospital chart notes (refer to Appendix A).

Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses

The Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses (IRAOS) (Hafner, Riecher-Rossler, Hambrecht, Maurer, & et al., 1992) is a semi-structured interview that was used to retrospectively reconstruct the onset period and course of psychotic illness. The IRAOS has good interrater reliability (Kappa between 0.76 and 1.00), is compatible with DSM-III criteria, and demonstrates face validity, content validity with an expert panel, and convergent validity with case reports (Hafner, Riecher-Rossler, Hambrecht, Maurer, & et al., 1992). The IRAOS is based on three widely used measures: the Present State Examination (Wing, Cooper, & Sartorius, 1973), the Disability Assessment Schedule (WHO, 1988), and the Past History and Sociodemographic Description Schedule (Jablensky, Schwarz, & Tomov, 1980). All of these measures have shown acceptable construct validity (Luria & McHugh, 1974; Wing, Nixon, Mann, & Leff, 1977; Jung, Krumm, Biehl, Maurer & Bauer-Schubart, 1989), thereby supporting the validity of the IRAOS.

The current study employed components of Sections II (Sociodemographic and Historical Data) and III (Episodes and Intervening Intervals) of the IRAOS to

obtain information regarding the current psychotic episode, such as referral source and DUP (time from initial onset of psychotic symptoms to first treatment), in addition to details of previous episodes including psychiatric hospital admissions, outpatient care, and family psychiatric history. These details were collected at admission in conjunction with demographic details (refer to Appendix A).

Premorbid Adjustment Scale

The Premorbid Adjustment Scale (PAS) (Cannon-Spoor, Potkin, & Wyatt, 1982) is a semi-structured interview that was conducted at admission to assess premorbid functioning in the four major areas of socialisation, peer relationships, social-sexual relationships, and scholastic performance and adaptation (Mata et al., 2000) (refer to Appendix B for score sheet). Cannon-Spoor et al. (1982) reported good interrater reliability (intraclass correlation coefficient $\geq$ .74) and discriminant validity across a range of populations and in comparison to the widely used Phillips Prognostic Rating Scale (Phillips, 1953).

The PAS subscales employed for use in this study were early adolescence (12 – 15 years) (5 items), late adolescence (16 – 18 years) (5 items), adulthood (19 years and above) (5 items), and the general section (9 items). Each of the three aged-defined subscales measured sociability/withdrawal, peer relationships, scholastic performance and adaptation to school (where relevant), and socio-sexual relationships. The general section measured adjustment and functioning in broader terms via education, employment/schooling pre-hospitalisation, changes in employment/schooling, frequency of changes, social-personal adjustment, global assessment of functioning, interest in life, energy level, and independence.

This study followed standard scoring procedure for the PAS outlined by

Cannon-Spoor and colleagues, and thereby defined 'premorbid' as the six months prior to the first hospitalisation for psychosis or first florid psychotic symptom (Cannon-Spoor, Potkin, & Wyatt, 1982). Only those life periods that were able to be classified as 'premorbid' for each participant were rated. Furthermore, only those items in each subscale that were relevant to the individual were scored. Responses were scored on a 0 to 6 point scale. Subscale total scores were calculated by dividing the individuals' subscale score by their highest possible subscale score. An overall adjustment score was calculated by averaging the subscale total scores. Higher scores equate to higher levels of unhealthy adjustment, with scores $\geq$ .50 indicating poor adjustment. The minimum possible score is 0.0 and the maximum possible score is 1.0.

Family Environment Scale

The Family Environment Scale (FES) (Moos & Moos, 1994) is a 90-item self-report measure of the social and environmental characteristics of family life (refer to Appendix C). Four subscales of the FES were completed by participants at admission and were used to measure the environment of each participant's family of origin, for the purpose of comparing family environments between substance users and non-users. The FES has been widely used in family-related research concerning the course of psychotic illness (Phillips, West, Shen, & Zheng, 1998; Schnur & et al., 1986). Test-retest reliability results range from .68 to .86, proving to be reasonably stable. Internal consistency results are sound ($\geq$ .61) (Jacon & Tannenbaum, 1988; Moos, 1990; Moos and Moos, 1994). Face, content, and construct validity of the measure has been demonstrated by independent raters accurately categorising 67% of the statements into their respective subscale domains,

by favourable comparisons with other measures of family environment, and by the accuracy of the scale in distinguishing between different types of family environments (Bloom, 1985; Moos & Moos, 1994).

Four of the ten FES subscales were used in this study (cohesion, expressiveness, conflict, and control). The subscales of cohesion, expressiveness, and conflict are an index of the quality of family relationships, while the control subscale is a component of family system maintenance. Each subscale consisted of nine questions. Cohesion is a measure of the commitment and support provided by family members to each other (e.g., "family members really help and support one another"; "we put a lot of energy into what we do at home"). Expressiveness is a measure of the degree to which family members are encouraged to openly express their feelings (e.g., "family members often keep their feelings to themselves"; "it's hard to blow off steam at home without upsetting somebody"). Conflict is a measure of anger or conflict that is openly directed towards each other (e.g., "family members sometimes hit each other"; "we fight a lot in our family"). Control is a measure of how rule-bound the family is (e.g., "there are set ways of doing things in our family"; "family members are rarely ordered around"). The participant answered true or false to each statement and obtained four subscale scores (subscale score range 0 – 9).

The Structured Clinical Interview for DSM-IV Axis I

The Structured Clinical Interview for DSM-IV Axis I (Research Version; Patient Edition) (SCID-I/P) (First, Spitzer, Gibbon, & Williams, 1996) was conducted at admission to confirm the diagnosis of a psychotic disorder for each participant. This measure is widely used in the psychiatric population and

considered to be of diagnostic "gold standard" (Zimmerman and Mattia, 1999; Ventura, Liberman, Green, Shaner & Mintz, 1998). Modules B (Psychotic and Associated Symptoms) and C (Psychotic Disorders) were administered to participants by the interviewer, who has a Masters Degree in Clinical Psychology and eight years experience in community and tertiary mental health settings.

Checklist of Psychotic Symptoms

A checklist (first used by Chen et al., 2003 with methamphetamine psychosis patients) of positive psychotic symptoms, negative psychotic symptoms and associated behaviours was completed with each participant upon admission. This checklist is not a psychometric measure, but is useful in determining the nature of psychotic symptoms experienced within the sample (refer to Appendix D).

The Timeline Followback Method

The Timeline Followback (TLFB) method (Sobell & Sobell, 1992) collects retrospective data on daily substance use (refer to Appendix E). In the current study, this method was used in the first interview to collect information regarding amphetamine use, cannabis use, and other substance use (including alcohol, heroin, ecstasy, cocaine, and prescribed neuroleptic medications) in the 30 days prior to hospital admission. This technique uses a calendar recall process to obtain a detailed description of substance use. Guided by the interviewer, the participant marked significant events and other noteworthy occasions such as national holidays, birthdays, and pay days on a blank calendar and these reminder points were then used to prompt recall of substance use (type of substance, route of administration, frequency, and amount used) in the previous 30 days. This method has high test-retest reliability (co-efficients of $\geq$ .79), and convergent and discriminant validity

with other measures of drug use (Fals Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000).

Urine Drug Screening

As part of usual mental health unit admission procedures, all participants of the study were asked by hospital staff to voluntarily provide a urine sample for the purpose of an immunoassay analysis for substances of abuse. This analysis provided either an initial negative or positive result. If the analysis produced a positive result, the sample was further analysed using gas chromatography/mass spectrometry in order to accurately define the type of substance used. Both research sites adhered to the Australian/New Zealand Standard AS/NZS 4308:2001 "Procedures for the Collection, Detection, and Quantitation of Drugs of Abuse in Urine", which prescribes a national standard for the cut-off threshold for drugs of abuse detected. A positive result for amphetamines required a cut-off threshold of 300ng/ml or more, while cannabinoids required a cut-off threshold of 50ng/ml or more. Keeping in mind that a positive result depends on both frequency and recency of use (Green, Young, & Kavanagh, 2005), cannabis can be detected in the urine up to one month post cessation of use, while amphetamines can be detected in the urine up to five days post cessation (Vandevenne, Vandenbussche, & Verstraete, 2000).

Prescribed Medication

The type and dose of prescribed antipsychotic and benzodiazepine medications were recorded from hospital chart notes for each participant at admission.

Brief Psychiatric Rating Scale

Psychiatric symptoms were assessed at admission and at each interview

thereafter using the Brief Psychiatric Rating Scale (BPRS) - Expanded Version (4.0) (Ventura et al., 1993) (refer to Appendix F for score sheet). The BPRS has been widely used and evaluated over the past four decades, achieving excellence as a measure of psychiatric symptomatology, particularly with schizophrenia (Morlan & Tan, 1998; Panos, 2004; Velligan et al., 2005). The BPRS has strong validity as a measure of symptomatic change across time (Burlingame et al., 2006; Varner, Chen, Swann, & Moeller, 2000; Velligan et al., 2005), and the expanded version was intended for use as a repeated measure (Dingemans et al., 1995). The BPRS demonstrates good intra-rater and interrater reliability ($\geq$ .80) (Burlingame et al., 2006; Earnshaw, Rees, Dunn, Burlingame, & Chen, 2005). It also shows discriminant (Rhoades and Overall, 1988), construct (Ventura, 2000), and concurrent validity (Gur, Mozley, Resnick, & Levick, 1991; Ventura, Nuechterlein, Subotnik, Gutkind, & Gilbert, 2000), in addition to internal consistency (Dingemans, Linszen, Lenior, & Smeets, 1995).

The expanded version of the BPRS used in this study is a semi-structured interview of 24 items each scored on a 7-point continuum (1 = not present to 7 = extremely severe). Fourteen items (e.g., anxiety, suicidality, hostility, hallucinations, bizarre behaviour) are rated using the probe questions provided with the measure. The remaining ten items (e.g., blunted affect, tension, distractibility, and motor hyperactivity) are rated according to rater observations during the interview.

A recent factor analysis of the 24-item BPRS by Ventura and colleagues (2000) identified a four-factor solution in a sample consisting mainly of first episode psychotic patients. The factors consist of positive symptoms (bizarre behaviour, unusual thought content, disorientation, hallucinations, and suspiciousness), negative

symptoms (blunted affect, motor retardation, emotional withdrawal, and self-neglect), mania symptoms (motor hyperactivity, elevated mood, excitement, distractibility, hostility, and grandiosity), and depression-anxiety symptoms (depression, anxiety, suicidality, and guilt). The mania factor in this version of the BPRS provides a clear advantage over the 18-item BPRS and the PANSS, and was more clearly defined in the current solution than in the five-factor solutions previously reported by Burger et al. (1997) and Dingemans et al. (1995). The scoring range for each subscale is positive symptoms: 5 - 35, negative symptoms: 4 - 28, mania: 6 - 42, and depression-anxiety: 4 - 28. Higher scores equate to more severe symptoms.

The Disturbed Behaviour Rating Scale

The Disturbed Behaviour Rating Scale (DBR) was developed to assess the disturbed behaviour of psychotic inpatients in the early stage of their illness (Johnstone, Crow, Johnson, & MacMillan, 1986) (refer to Appendix G). This clinician-rated instrument was completed at admission and at each interview thereafter. The scale consists of five items: behaviour threatening to self, behaviour threatening to others, inappropriate or bizarre sexual behaviour, behaviour damaging to property, and other bizarre or inappropriate behaviour. Each identified behaviour type was rated on a 3-point scale according to frequency of occurrence in the previous two days (2 = repeatedly, 1 = once or twice, 0 = none at all). Ratings were made at the end of each interview based on self-report, interviewer observations, and hospital chart notes. Total scores were calculated for each participant with higher scores equating to more disturbed behaviour (range 0 – 10).

Procedure

The interviewer contacted senior clinical staff at each participating hospital site Monday through to Friday each week of the data collection period to determine the eligibility of new admissions and their perceived ability to provide informed consent. Inpatients meeting criteria were invited by their hospital case-worker to meet with the interviewer within 24 hours of their admission. Interested patients were provided with a consent and information form, in addition to verbal explanations that detailed the study and participant involvement (refer to Appendix H). When written and verbal consent was obtained by the interviewer (witnessed by the case-worker/primary nurse), the interviewer collected demographic information and administered the assessment battery across one or two initial interviews in the first 48-hours of admission to hospital. Follow-up interviews were then conducted to monitor changes in symptoms and behaviour during hospitalisation. The BPRS and the DBR were rated in each follow-up interview. Follow-up interviews occurred on day four or five of admission, day eight or nine, and then once weekly until the participant was discharged (or for a maximum of nine interviews[3]) (refer to Table 3). Each participant was re-familiarised with study aims and the premise of voluntary participation at follow-up interviews.

[3] Interview 9 was conducted in week eight of a participant's hospital admission.

Table 3

Procedure for data collection (*N* = 98)

Interview	Day of Admission Interview Occurred	Measures Administered
1	1 or 2	Demographics; IRAOS; PAS; FES; SCID; Checklist of Psychotic Symptoms; TLFB; Urine Screen; BPRS; DBR
2	4 or 5	BPRS; DBR
3	8 or 9	BPRS; DBR
4	15 or 16	BPRS; DBR
5	22 or 23	BPRS; DBR
6	29 or 30	BPRS; DBR
7	36 or 37	BPRS; DBR
8	43 or 44	BPRS; DBR
9	50 or 51	BPRS; DBR

Ethical approval for this study was given by the Griffith University Research Ethics Committee, the Princess Alexandra Hospital Research Ethics Committee, and the West Moreton Health Service District Human Research Ethics Committee.

Data screening

Data was screened using the statistical program of SPSS for Windows, version 12.01 (SPSS Inc, 2003). Data ranges were observed for each variable and confirmed to be valid. Prior to analyses, variables were screened for missing data, normality of distribution, and outliers.

Missing data

The majority of measures consisted of structured or semi-structured interviews, and any missing data at the time of interview was subsequently obtained from hospital chart notes. The self-report FES was the only measure in the initial battery of tests that was associated with missing data. However, if an incomplete

questionnaire was returned, the interviewer subsequently provided further clarification and support (face-to-face) so that completion of the questionnaire occurred prior to re-submission. The FES was completed in full by 65 (66.33%) of the total sample and this portion of data provided the basis for FES analyses. Of the 33 participants who did not complete the measure, 11 (33.33%) refused participation and 22 (66.66%) were discharged prior to returning the measure.

Given that one-third of the sample (33.67%) did not complete the FES, completers and non-completers of the FES were compared on age, gender and recent substance use (yes or no). An independent samples *t*-test found no significant differences between completers and non-completers on age, $t(96) = 1.95$, *ns*. Chi-square analyses found no significant differences between the two groups on gender, χ^2 (1, $N = 98$) = 0.82, *ns* or recent substance use χ^2 (1, $N = 98$) = 3.15, *ns*.

With respect to data collected on a weekly basis during a patient's hospital admission, the statistical method employed (multi-level modelling) legitimately accounted for missing occasions of measurement and other missing data by providing estimates of statistical parameters based on the data from existing time points. Thus, it was possible to compare users and non-users on their predicted mean scores for each symptom dimension at week eight of admission (i.e., Interview 9), even though not all participants completed nine interviews. Analyses of the current study relied on the Maximum Likelihood approach to missing data, which has been identified by Schafer and Graham (2002) as the least biased method, and is preferable to traditional approaches such as Complete Case Analysis and Last Value Carried Forward.

Normality of data

Five dependent variables were screened for skewness and kurtosis: the four BPRS subscales (positive symptoms, negative symptoms, mania symptoms, and depression-anxiety symptoms) and the total score on the DBR scale (disturbed behaviour) (refer to Table I1 in Appendix I). Results indicated that the mania symptoms and disturbed behaviour variables were moderately positively skewed, suggesting that greater numbers of participants scored at the lower end of both scales. In order to test the influence of skew, analyses were performed using both square-root transformations and non-transformed data for the two variables in question. Given that transformations made no difference to results, the non-transformed raw data for the five dependent variables were used in all subsequent analyses (Tabachnick & Fidell, 2001).

Examination of the substance use variables (days of amphetamine use in the last 30 and days of cannabis use in the last 30) showed that amphetamine use was highly positively skewed, while cannabis use displayed a bimodal pattern of distribution (refer to Figures J1 and J2 in Appendix J). These distributions can be expected in a clinical sample of psychotic inpatients that consist of both substance users and non-users. Given these distribution patterns, the variables were dichotomised (amphetamine use in 30 days prior to admission = AmpPos vs. no amphetamine use in the 30 days prior to admission = AmpNeg; cannabis use in the last 30 days = CanPos vs. no cannabis use in the 30 days prior to admission = CanNeg) in the ANOVA's and MLM analyses whereby the aim was to compare users of each substance with their respective non-users. Users of *both* substances in the 30 days prior to admission (AmpCanPos) were compared to participants who had

not used both substances in the 30 days prior to admission (AmpCanNeg).

Outliers

Apart from one male participant who was subsequently excluded from analyses due to his inability to provide significant identifying or historical information, no univariate outliers were identified in the five dependent variables of positive symptoms, negative symptoms, mania symptoms, depression-anxiety symptoms, and disturbed behaviour. The definition for outliers proposed by Tabachnick and Fidell (2001) was adopted, which identifies cases lying 3.29 standard deviations away from the mean as outliers.

Data analyses

There were two primary components to the analysis of this study. First, the characteristics of the total sample and then the groups according to substance use were analysed with the statistical program of SPSS for Windows, version 12.01 (SPSS Inc, 2003). Characteristics of the total sample were examined with descriptive analyses. Several variables were then further analysed with the sample divided into groups that reflected recent substance use. In accordance with study aims and data distribution patterns, the sample was categorised into the following groups for analyses of continuous data: amphetamine use in the 30 days prior to admission (AmpPos; $n = 38$) vs. no amphetamine use in the 30 days prior to admission (AmpNeg; $n = 60$) and cannabis use in the 30 days prior to admission (CanPos; $n = 60$) vs. no cannabis use in the 30 days prior to admission (CanNeg; $n = 38$). A series of 2 (AmpPos vs. AmpNeg) x 2 (CanPos vs. CanNeg) between-subjects analyses of variance (ANOVA) were conducted to determine the differences between these groups on age, DUP, premorbid adjustment and family environment.

Importantly, the interaction effect of having recently used both amphetamines and cannabis (AmpCanPos; *n* = 30) in the 30 days prior to admission was also examined.

In order to maintain a 2-way table in the chi-square analyses of categorical dependent variables (gender, history of psychosis in immediate family, family history of other mental disorders, and differences in type of psychotic symptoms experienced), the independent variables were combined into a single four-group variable: AmpONLY (*n* = 8), CanONLY (*n* = 30), Amphet + Cannabis Use (*n* = 30), No Use (*n* = 30). Given the difference in group size of AmpONLY, a cautionary note is warranted with respect to all chi-square results.

In the second phase of analyses, the impact of amphetamine and/or cannabis use on positive symptoms, negative symptoms, mania symptoms, depression-anxiety symptoms, and disturbed behaviour was analysed using multi-level modelling (MLM) and the statistical program of MLwiN version 2.02r (Rasbash, Steele, Browne, & Prosser, 2005). AmpPos (*n* = 38) was compared to AmpNeg (*n* = 60), CanPos (*n* = 60) was compared to CanNeg (*n* = 38), and AmpCanPos (*n* = 30) was compared to AmpCanNeg (*n* = 68). MLM takes into consideration the hierarchical nature of data, which in the current study, consisted of repeated measurements nested within individuals belonging to either the substance using or non-using groups. The current analysis was conducted across two levels. Level-1 corresponded to variation across time in the outcome measure which is demonstrated by trajectories. Level-2 corresponded to variation across persons in their specific trajectories.

In the current study, the trajectories were linear and analyses were conducted so that results consisted of an intercept at admission (the predicted mean of the outcome variable at admission), a slope (the predicted average rate of change in the

outcome variable across time), and an intercept at Interview 9 (the predicted mean of the outcome variable at week eight of hospitalisation). A linear (versus curvilinear) measure of change was adopted in the MLM analyses based on there being fewer participants who had completed five or more interviews in total (refer to Table 4 in the Results section). Four measurement occasions are required across the total sample in order to estimate linear slope and intercept as a random effect, whereas a curvilinear measure of change requires at least five (but usually more) time points (Singer & Willett, 2003).

Results

Recruitment rate

Of a possible 222 patients admitted with psychosis, mental health staff referred 174 to the study (refer to Figure 1). The reasons for non-referral of the remaining 48 patients were as follows: patient refused to meet with staff and/or interviewer in order to discuss study (n = 6), patient was not accessible during first 24 hours of admission (n = 18), or admission was less than 24 hours due to transfer or clinical reasons (n = 24). Of the 174 patients referred, 133 were eligible to participate in the study, while the remaining patients did not fulfil inclusion criteria based on age (n = 4), diagnosis (n = 2), number of previous psychotic episodes and/or psychiatric history exceeding three years (n = 35). Written informed consent was obtained from 99 patients, one of whom was unable to provide significant identifying or historical information to staff or interviewer due to deteriorating mental state and was subsequently excluded from the study.

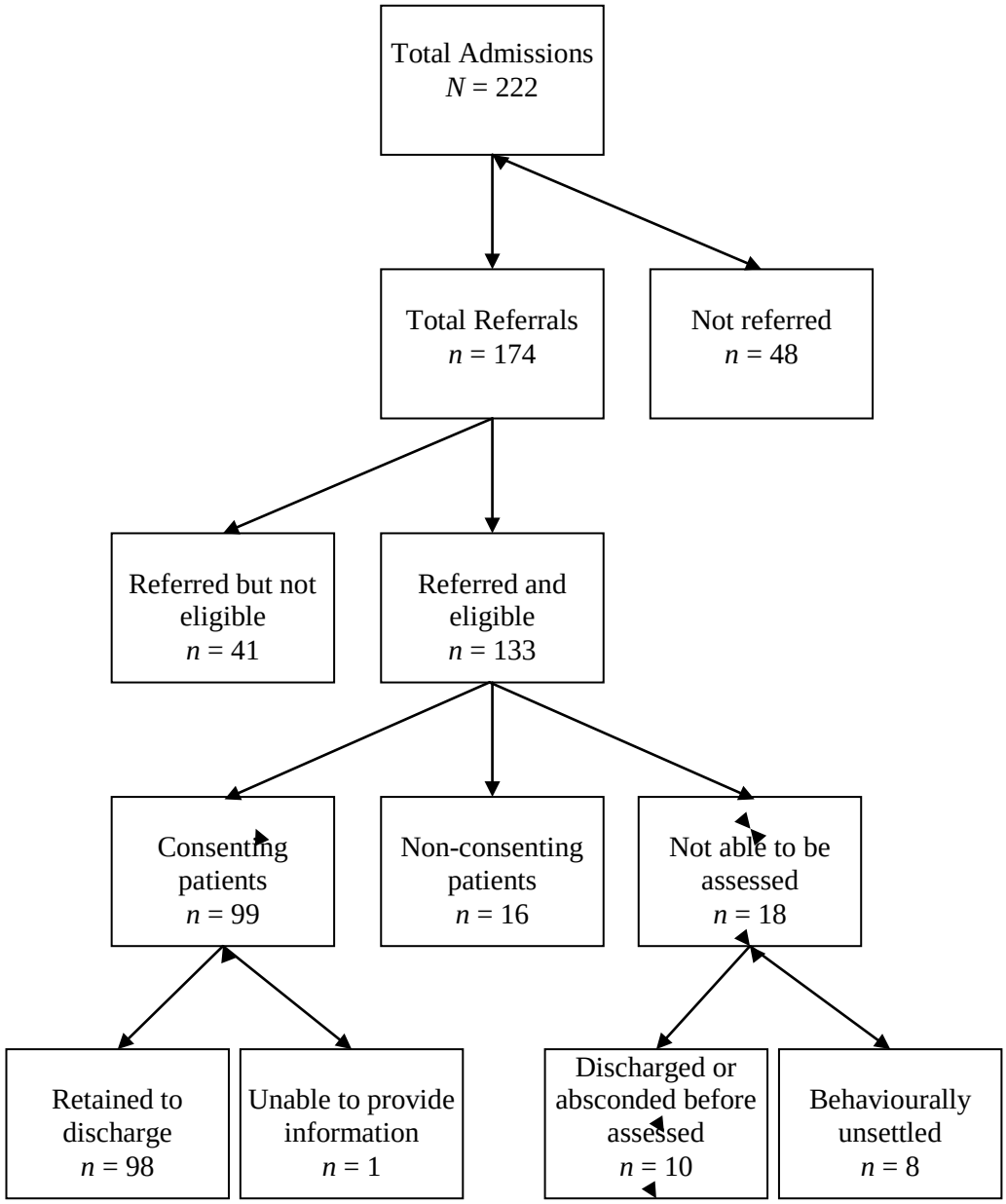

Figure 1. Recruitment rate

Number of interviews completed by participants

Due to varying lengths of hospital stay, participants differed in the number of interviews they completed (refer to Table 4).

Table 4

Total number of interviews completed (*N* = 98)

Total Number of Interviews	Participants
1	14 (14.3)
2	13 (13.3)
3	24 (24.5)
4	23 (23.5)
5	11 (11.2)
6	3 (3.1)
7	4 (4.1)
9	6 (6.1)

Note. Percentages in parentheses. No participants completed a total of eight interviews.

Interrater reliability of the BPRS

Approximately one-fifth of the sample (21.4%) was randomly chosen to be rated concurrently on the BPRS by the principal interviewer and a second interviewer (an experienced Nurse Unit Manager) as a measure of interrater reliability. Intraclass correlation coefficients were excellent for all four BPRS subscales (positive symptoms = .97, negative symptoms = .97, mania symptoms = .96, and depression-anxiety symptoms = .99).

Participant characteristics

Demographics

The sample was predominantly male (refer to Table 5 for a summary of demographics). There was a significant difference between the mean age of men at

25.73 years (*SD* = 7.02) and women at 33.28 years (*SD* = 10.45), $t(96) = 4.06$, $p < .001$. There were no gender differences in the remaining demographic variables. The majority of the sample was single and most participants lived with either their family of origin or their own family (partner and/or children). Nearly three quarters of participants were unemployed and receiving government assisted incomes, while half had completed educational studies to the end of Year 10. Australian non-Aboriginal people represented the majority of the sample.

The continuous variable of age was further analysed according to recent substance use by performing a 2 (AmpPos vs. AmpNeg) x 2 (CanPos vs. CanNeg) between-subjects ANOVA. There were no significant main effects found for either AmpPos $F(3,94) = 2.66$, *ns* or CanPos $F(3,94) = 3.19$, *ns* on age. Likewise, no significant interaction effect was found on this variable for AmpCanPos $F(3,94) = .64$, *ns*. Chi-square analyses on the categorical variable of gender found that the AmpONLY, CanONLY, Amphet + Cannabis Use, and No Use groups were not significantly different, χ^2 (3, $N = 98$) = 1.13, *ns*.

Table 4

Demographics

Variable	Total Sample (N = 98)	Substance Users (n = 68)	Non-Users (n = 30)
Male	73 (74.5)	51 (75.0)	22 (73.3)
Marital Status			
Single	67 (68.4)	47 (69.1)	20 (66.7)
Married / Defacto	16 (16.3)	11 (16.2)	5 (16.7)
Separated / Divorced / Widowed	15 (15.3)	10 (14.7)	5 (16.7)
Living Circumstances			
Family	71 (72.4)	51 (75.0)	20 (66.7)
Share Accommodation	18 (18.4)	12 (17.6)	6 (20.0)
Alone	5 (5.1)	2 (2.9)	3 (10.0)
Itinerant	4 (4.1)	3 (4.4)	1 (3.3)
Employment Circumstances			
Unemployed	71 (72.4)	50 (73.5)	21 (70.0)
Employed/Student	27 (27.6)	18 (26.5)	9 (30.0)
Education $\leq$ Year 10	50 (50.0)	34 (50.0)	15 (50.0)
Ethnic Identity			
Australian Non-Aboriginal	77 (78.6)	55 (80.9)	22 (73.3)
Other	8 (8.7)	4 (5.9)	4 (13.3)
New Zealand	7 (7.2)	3 (1.5)	4 (13.3)
Australian Aboriginal	5 (5.1)	6 (8.8)	-

Note. Percentages in parentheses.

Psychiatric history and family variables

The majority of the sample were referred to hospital either by a family member (n = 34; 34.7%) or the Police (n = 32; 32.7%), while 16 (16.3%) self-referred. Emergency services (n = 7; 7.1%), General Practitioners and other medical/health professionals (n = 4; 4.1%), community mental health services/professionals (n = 3; 3.1%), and other mental health facilities (n = 2; 2.0%)

made up the remaining portion of referral sources. The mean DUP for the current admission was 25.0 weeks (*SD* = 20.1). Over half of the sample (*n* = 56; 57.1%) reported having received outpatient mental health care prior to the current admission and 65 (66.3%) were presenting with their first psychotic episode. Of the total sample, 13 (13.3%) identified an immediate family member (parent or sibling) with psychosis. Other diagnosed mental health disorders within the family (parent, sibling, grandparent, aunt/uncle) were identified by 27 (27.6%) participants, the majority (*n* = 20; 74.1%) of which consisted of depressive disorders.

The mean overall score on the PAS for the total sample was 0.42 (*SD* = 0.20). The mean scores on the subscales were as follows: early adolescence = 0.38 (*SD* = 0.22), late adolescence = 0.40 (*SD* = 0.25), adulthood = 0.46 (*SD* = 0.27), and the general subscale = 0.44 (*SD* = 0.20). Using a cut-off score of $\geq$ 0.50, approximately a third of the sample scored in the unhealthy range for each of the subscales (overall score *n* = 33 [33.7%]; early adolescent subscale *n* = 31 [31.6%]; late adolescent subscale *n* = 33 [33.7%]; adulthood subscale *n* = 39 [39.8%]; and the general subscale *n* = 36 [36.7%]).

Further analyses on continuous variables using 2 x 2 between-subjects ANOVA found there were no significant main effects for AmpPos on DUP $F(3,94) = .09$, *ns*; the PAS overall score $F(3,94) = .27$, *ns*; the four PAS subscale scores (early adolescent $F(3,94) = .23$, *ns*; late adolescent $F(3,94) = 1.63$, *ns*; adulthood $F(3,89) = .57$, *ns*; general $F(3,94) = 1.31$, *ns*); or any of the four FES subscale scores (cohesion $F(3,62) = .28$, *ns*; expressiveness $F(3,62) = .45$, *ns*; conflict $F(3,62) = .28$, *ns*; control $F(3,62) = .10$, *ns*).

Likewise, there were no significant main effects for CanPos on DUP F(3,94) = .78, *ns*; the PAS overall score F(3,94) = 1.12, *ns*; the four PAS subscale scores (early adolescent F(3,94) = .55, *ns*; late adolescent F(3,94) = .07, *ns*; adulthood F(3,89) = 1.67, *ns*; general F(3,94) = 1.79, *ns*); or any of the four FES subscale scores (cohesion F(3,62) = .11, *ns*; expressiveness F(3,62) = .71, *ns*; conflict F(3,62) = .28, *ns*; control F(3,62) = .98, *ns*).

There were also no significant interaction effects for AmpCanPos on DUP F(3,94) = 2.51, *ns*; the PAS overall score F(3,94) = .53, *ns*; the four PAS subscale scores (early adolescent F(3,94) = .67, *ns*; late adolescent F(3,94) = .85, *ns*; adulthood F(3,89) = .17, *ns*; general F(3,94) = .01, *ns*); or any of the four FES subscale scores (cohesion F(3,62) = .66, *ns*; expressiveness F(3,62) = .82, *ns*; conflict F(3,62) = 1.29, *ns*; control F(3,62) = 1.55, *ns*).

Chi-square analyses found no significant differences between the groups of AmpONLY, CanONLY, Amphet + Cannabis Use and No Use on the categorical variables of positive history of psychosis in immediate family χ^2 (3, N = 98) = 4.06, *ns* and positive family history of other mental health disorders χ^2 (3, N = 98) = 5.78, *ns*.

Nature of psychotic symptoms

More than two-thirds of participants experienced auditory hallucinations, while less than half experienced visual hallucinations (refer to Table 6 for details). Other types of hallucinations (tactile, olfactory, and gustatory) were experienced at considerably lower rates. Persecutory delusions were reported by most of the sample. Approximately one-half of the sample experienced delusions of reference

and one-quarter experienced delusions of grandiosity. The negative symptoms of avolition/apathy and flat affect were observed in slightly more than one-third of participants.

Further analyses were conducted in order to compare the four groups on the presence of these psychotic symptoms. Due to minimal occurrences of some symptom types within some or all of the four groups, further analyses were only possible for a portion of the symptoms from the checklist. These results will now be presented. Chi-square analyses found no differences between the groups of AmpONLY, CanONLY, Amphet + Cannabis Use and No Use on the symptoms of auditory hallucinations χ^2 (3, N = 98) = 2.65, *ns* or visual hallucinations χ^2 (3, N = 98) = 2.35, *ns*. These groups were also comparable on persecutory delusions χ^2 (3, N = 98) = 6.48, *ns* and delusions of reference χ^2 (3, N = 98) = 2.01, *ns*. Finally, no significant differences were found between the four groups on either of the negative symptoms of avolition/apathy χ^2 (3, N = 98) = 7.08, *ns* or flat affect χ^2 (3, N = 98) = 5.95, *ns*.

Table 5

Nature of psychotic symptoms (N = 98)

Symptom	Participants
Hallucinations	
Auditory	71 (72.4)
Visual	41 (41.8)
Tactile	17 (17.3)
Olfactory	10 (10.2)
Gustatory	9 (9.2)
Delusions	
Persecutory	89 (90.8)
Of Reference	52 (53.1)
Grandiosity	25 (25.5)
Of Mind Reading	30 (30.6)
Of Being Controlled	29 (29.6)
Somatic	22 (22.4)
Religious	21 (21.4)
Of Guilt	14 (14.3)
Of Jealousy	8 (8.2)
Thought Broadcasting	12 (12.2)
Thought Insertion	11 (11.2)
Thought Withdrawal	5 (5.1)
Negative Symptoms	
Avolition/Apathy	35 (35.7)
Flat Affect	35 (35.7)
Inappropriate Affect	9 (9.2)
Other	
Derealisation	12 (12.2)
Depersonalisation	12 (12.2)
Catatonic Motor Behaviour	6 (6.1)
Odd Speech	26 (26.5)
Disorganised Speech	39 (39.8)
Disorganised Behaviour	47 (48.0)

Note. Percentages in parentheses.

Substance use

Recent illicit drug use was widely reported by participants (refer to Table 7). Cannabis, alcohol, and amphetamines were identified as the most common

substances used in the 30 days prior to admission.

Table 6

Substance use characteristics of total sample in the last 30 days (N = 98)

Substance	Any Use	Daily or Almost Daily[a] Use	No Use
Cannabis	60 (61.2)	38 (38.8)	38 (38.8)
Alcohol	63 (64.3)	20 (20.4)	35 (35.7)
Amphetamines	38 (38.8)	10 (10.2)	60 (61.2)
Heroin	2 (2.0)	1 (1.0)	96 (98.0)
Ecstasy	2 (2.0)	0 (0.0)	96 (98.0)
Cocaine	1 (1.0)	0 (0.0)	97 (99.0)

Note. [a] = ≥ 25 days. Percentages in parentheses.

Of the total sample, 70 (71.4%) reported amphetamine use and 86 (87.8%) reported cannabis use at least once in their lifetime. With respect to recent use (i.e., the 30 days prior to admission), more than one-third of participants had used amphetamines and more than half had used cannabis. Classifying these groups further, 8 (8.2%) participants had used amphetamines only, 30 (30.6%) had used cannabis only, a further 30 (30.6%) had used both amphetamines and cannabis, and 30 (30.6%) had not used any illicit substance. The mean number of days of amphetamine use (in the 30 days prior to admission) by the amphetamine only group was 14.7 (*SD* = 10.6), while the mean number of days for the cannabis only group during this time period was 22.3 (*SD* = 10.7).

Regarding route of amphetamine administration, 29 (76.3%) identified injecting as their primary route, 7 (18.4%) identified swallowing, 1 (2.6%) identified snorting, and 1 (2.6%) identified smoking as the main route of use. Of those

participants who had used amphetamines, 24 (63.2%) reported crystal methamphetamine as their primary substance.

Seventy participants (71.4%) agreed to provide a urine sample for screening at admission. Of this group, 13 (18.6%) obtained a positive result for amphetamine use, and all 13 (100%) of these participants gave positive verbal reports of amphetamine use in the seven days prior to admission. Ten (14.3%) participants self-reported amphetamine use in the seven days prior to admission but obtained a negative urine drug screen (UDS) result for this substance. Regarding cannabis use, 38 (54.3%) of those who provided a urine sample obtained a positive result, and 32 (84.2%) of these gave positive verbal reports of cannabis use in the seven days prior to admission. Eight (11.4%) participants gave a verbal report of cannabis use in the seven days prior to admission but obtained a negative UDS result. Given that less than three-quarters of the sample provided a urine sample for screening, and that a sizeable portion of participants self-reported amphetamine or cannabis use but obtained a negative UDS, participants' self-report was used to classify substance use status.

Prescribed medication

Fifty-seven participants (58.2%) had been prescribed antipsychotic medication prior to the current admission, and 11 (19.3%) of these reported daily compliance with this medication in the 30 days prior to admission.

The most commonly prescribed antipsychotic medications within the first 48-hours of admission were Risperidone (n = 48; 48.9%), Olanzapine (n = 29; 29.6%) and Amisulpride (n = 10; 10.2%). These medications are all categorised as

atypicals, which can be loosely defined as relatively selective for D_2 receptors and causing fewer extra-pyramidal side-effects, in addition to potentially impacting upon negative symptomatology (Taylor, Paton, Kerwin, 2003).

A 2 (AmpPos vs. AmpNeg) x 2 (CanPos vs. CanNeg) between-subjects ANOVA was performed on the antipsychotic medication dose (converted to chlorpromazine equivalents in milligrams) prescribed at admission. There were no significant main effects for AmpPos $F(3,85) = .61$, *ns* or CanPos $F(3,85) = 2.13$, *ns* on antipsychotic medication. Likewise, there was no significant interaction effect for AmpCanPos $F(3,85) = .00$, *ns* on this variable at admission.

Diazepam was the most common benzodiazepine prescribed at admission (*n* = 19; 19.4%). A 2 (AmpPos vs. AmpNeg) x 2 (CanPos vs. CanNeg) between-subjects ANOVA was performed on the benzodiazepine dose (converted to diazepam equivalents in milligrams) prescribed at admission. There were no significant main effects for AmpPos $F(3,16) = 1.06$, *ns* or CanPos $F(3,16) = .92$, *ns* on the dose of benzodiazepine. Similarly, there was no significant interaction effect found for AmpCanPos $F(3,16) = 1.53$, *ns* on this variable at admission.

Severity of sample psychopathology

As an indication of illness severity, the total BPRS score was calculated for the total sample ($M = 64.3$, $SD = 12.3$). A 2 (AmpPos vs. AmpNeg) x 2 (CanPos vs. CanNeg) between-subjects ANOVA was then performed to compare total BPRS scores between substance-using and non-using groups. No significant main effects were found for AmpPos $F(3,94) = .32$, *ns* or CanPos $F(3, 94) = .32$, *ns*. There was also no significant interaction effect found for AmpCanPos $F(3, 94) = .47$, *ns*. While

substance users and non-users were not significantly different from each other, it is worth noting the scores for AmpPos (*M* = 65.5, *SD* = 10.2), CanPos (*M* = 65.5, *SD* = 10.7), and AmpCanPos (*M* = 65.1, *SD* = 14.3) were all in the "severe" range (score > 65), while non-users of amphetamines or cannabis were in the "moderate" range (score = 35 – 65).

The impact of amphetamines and cannabis on symptoms and behaviour

The approach used in the series of MLM analyses was to look first at the impact of amphetamine use (AmpPos vs. AmpNeg), then the impact of cannabis use (CanPos vs. CanNeg), and finally, the interaction term where the combined effect of using both amphetamines and cannabis (AmpCanPos) was examined. Refer to Appendix K for specific examples of the MLM analysis output for the symptom dimensions of positive symptoms and disturbed behaviour. Table 8 summarises MLM analysis output for all symptom dimensions. Using an Excel 2006 program, MLM analysis output was then collated to produce Figures 2 to 16.

Table 7

Summary of MLM analysis results

Variables	AmpPos (*n* = 38)			AmpNeg (*n* = 60)			CanPos (*n* = 60)			CanNeg (*n* = 38)			AmpCanPos (*n* = 30)		
	Admit	Slope	Week 8	Admit	Slope	Week 8	Admit	Slope	Week 8	Admit	Slope	Week 8	Admit	Slope	Week 8
Positive Symptoms	19.61 (1.10)	-3.23 (0.48)	-6.20 (3.64)	19.07 (0.69)	-2.57 (0.29)	-1.47 (2.20)	19.65 (1.10)	-3.23** (0.44)	-6.23** (3.36)	18.66 (0.86)	-2.10 (0.34)	1.87 (2.59)	18.47 (2.50)	-1.39 (1.02)	7.36 (7.91)
Negative Symptoms	6.94** (0.77)	-0.56 (0.23)	2.45 (1.61)	8.82 (0.48)	-0.68 (0.14)	3.35 (0.98)	7.20** (0.76)	-0.75 (0.22)	1.25** (1.45)	9.49 (0.59)	-0.44 (0.17)	5.95 (1.11)	13.19 (1.68)	-0.37 (0.50)	10.20 (3.32)
Mania Symptoms	16.66** (1.37)	-2.25* (0.45)	-1.36 (2.99)	12.83 (0.85)	-1.35 (0.28)	2.05 (1.81)	16.11*** (1.34)	-2.07* (0.45)	-0.41 (2.92)	11.49 (1.05)	-1.12 (0.34)	2.57 (2.25)	7.20 (2.98)	-1.77 (0.95)	-6.96 (6.20)
Depression -Anxiety Symptoms	10.62 (1.01)	-1.04 (0.31)	2.30 (1.87)	11.34 (0.63)	-1.47 (0.19)	-0.46 (1.13)	11.14 (1.01)	-1.36 (0.31)	0.13 (0.83)	10.94 (0.79)	-1.22 (0.24)	1.21 (1.41)	13.25 (2.29)	1.71 (0.70)	-0.41 (4.18)
Disturbed Behaviour	2.57*** (0.30)	-0.68** (0.11)	-2.85* (0.65)	1.19 (0.19)	-0.33 (0.07)	-1.47 (0.40)	2.01* (0.32)	-0.59** (0.10)	-2.68** (0.58)	1.28 (0.25)	-0.28 (0.08)	-0.96 (0.42)	0.25 (0.66)	-0.18 (0.20)	-1.19 (1.14)

Note. Admit = Predicted intercept (score) at admission. Slope = Predicted rate of symptom/behaviour change across time points. Week 8 = Predicted intercept (score) at week 8 of admission. *p values* represent significance of difference of AmpPos, CanPos, AmpCanPos from their respective non-using groups. *p<.05. **p<.01. ***p=.001. Negative values at Week 8 are predicted intercepts based on the fitted linear model, rather than actual negative scores. In the interest of space and in light of no significant findings, AmpCanNeg (*n* = 68) results are not reported. Standard errors are provided in parentheses.

Positive psychotic symptoms

No significant differences were found between AmpPos and AmpNeg with respect to their mean positive symptom scores at admission or their predicted mean scores for positive symptoms at Interview 9. No significant difference in slope indicated that the two groups were also comparable in the rate at which their positive symptoms abated during hospitalisation. Refer to Figure 2.

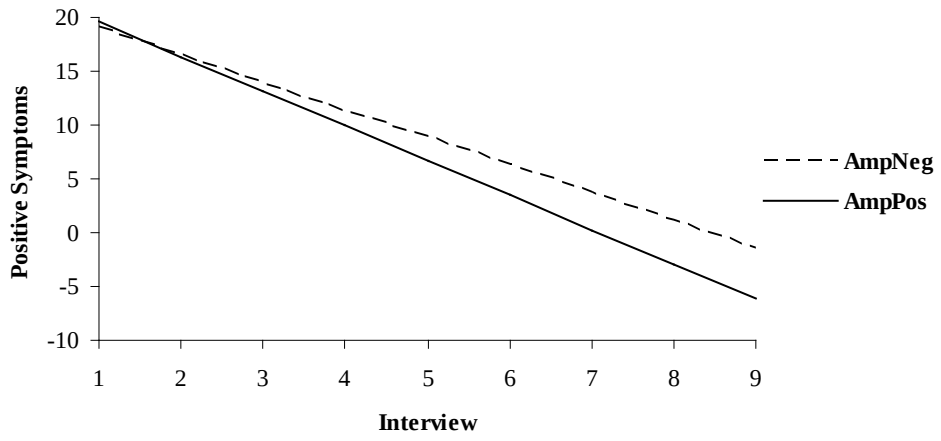

Figure 2. Predicted positive symptom scores and amphetamine use

CanPos did not differ significantly from CanNeg on positive symptom scores at admission. However, CanPos was associated with a significantly more rapid abatement of positive symptoms during hospitalisation than CanNeg. CanPos was also associated with significantly less severe positive symptoms at Interview 9 than CanNeg. Refer to Figure 3.

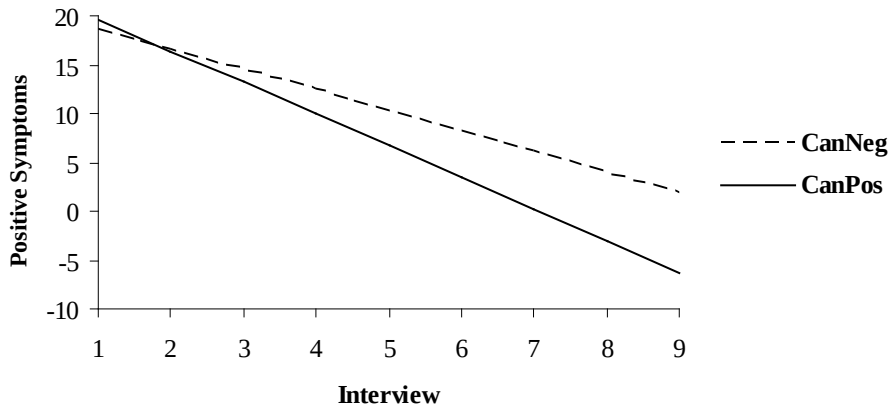

Figure 3. Predicted positive symptom scores and cannabis use

AmpCanPos was not significantly different from the AmpCanNeg group with respect to positive symptom ratings at admission or on predicted mean scores at Interview 9. There was also no significant difference found between the groups on the slope, indicating a comparable rate of positive symptom reduction during hospitalisation. Refer to Figure 4.

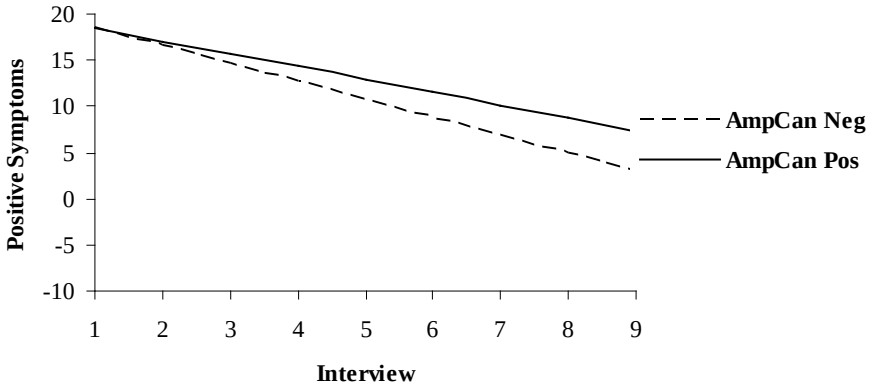

Figure 4. Predicted positive symptom scores and amphetamine + cannabis use

Negative psychotic symptoms

AmpPos was associated with significantly less severe negative symptoms than AmpNeg at admission. However, there was no difference between AmpPos and AmpNeg regarding the abatement of negative symptoms during hospitalisation, and these groups were not significantly different on the severity of negative symptoms at Interview 9. Refer to Figure 5.

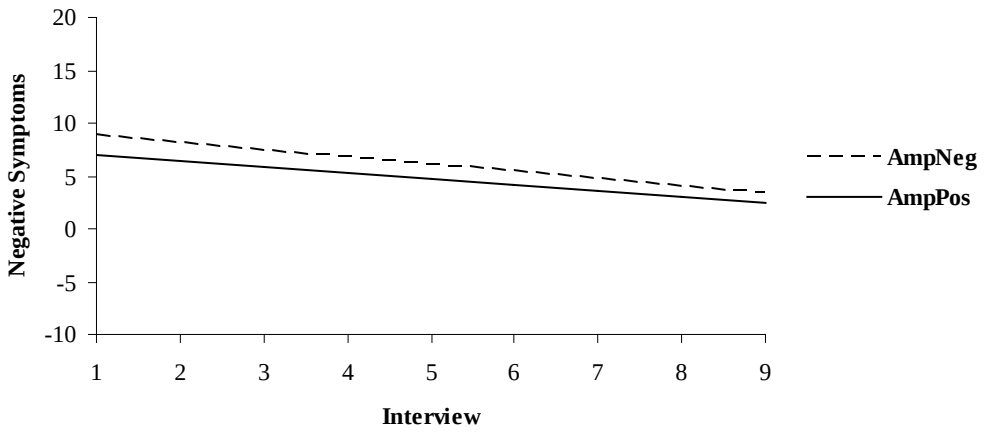

Figure 5. Predicted negative symptom scores and amphetamine use

The CanPos group obtained significantly lower negative symptom scores than CanNeg both at admission and at Interview 9. However, the two groups were comparable in slope, indicating a similar rate of negative symptom abatement during hospitalisation. Refer to Figure 6.

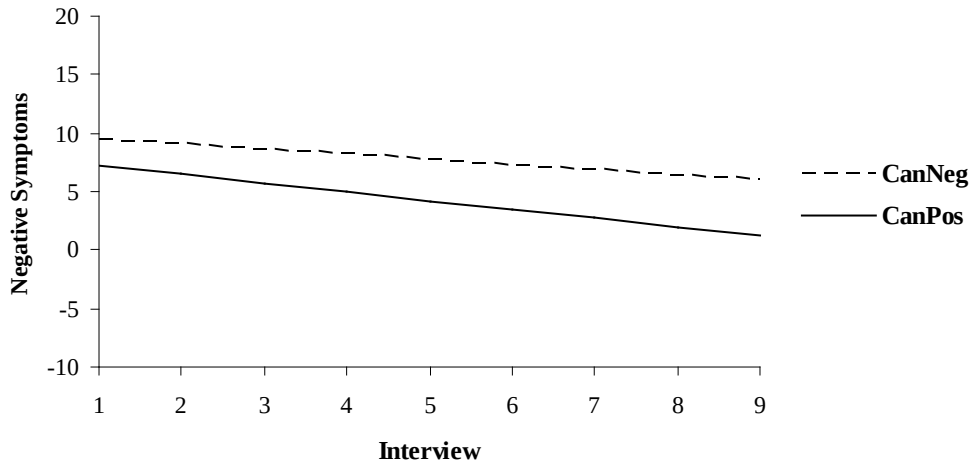

Figure 6. Predicted negative symptom scores and cannabis use

AmpCanPos was not significantly different to the AmpCanNeg group with respect to negative symptom ratings at admission or at Interview 9. There was also no difference between the groups in the abatement of negative symptoms during hospitalisation. Refer to Figure 7.

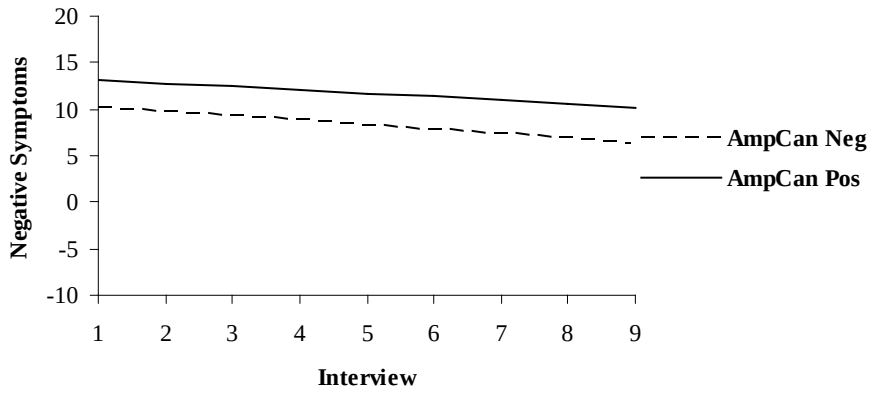

Figure 7. Predicted negative symptom scores and amphetamine + cannabis use

Mania symptoms

AmpPos scored significantly higher than AmpNeg on mania symptoms at admission. Mania symptoms also abated significantly more rapidly for the AmpPos group than they did for the AmpNeg group during hospitalisation. However, the predicted difference between the two groups at Interview 9 did not reach significance. Refer to Figure 8.

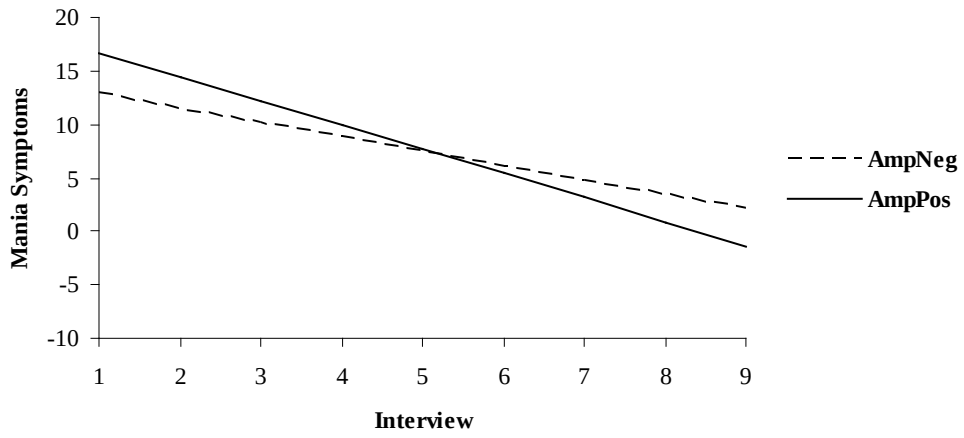

Figure 8. Predicted mania scores and amphetamine use

The CanPos group scored significantly higher than the CanNeg group on the mania subscale at admission. These symptoms also abated significantly faster for the CanPos group during hospitalisation. However, the groups were comparable in the severity of mania symptoms at Interview 9. Refer to Figure 9.

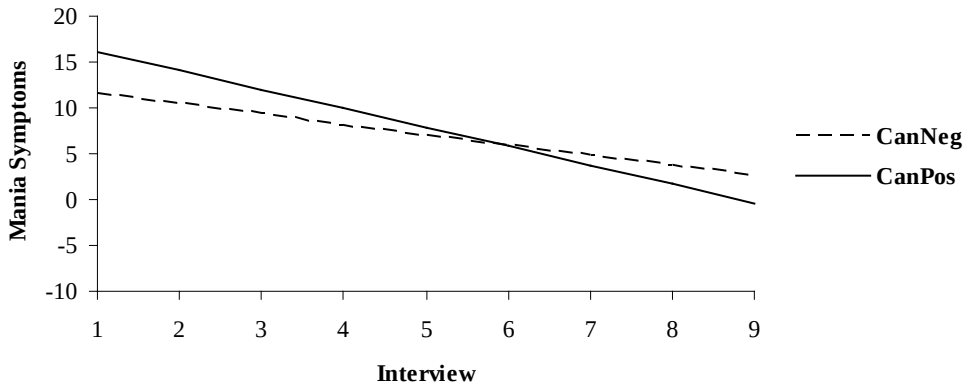

Figure 9. Predicted mania scores and cannabis use

There were no significant differences between the AmpCanPos group and the AmpCanNeg group regarding the severity of mania symptoms at admission or at Interview 9. There was also no significant difference in slope, indicating a similar abatement of mania symptoms during hospitalisation. Refer to Figure 10.

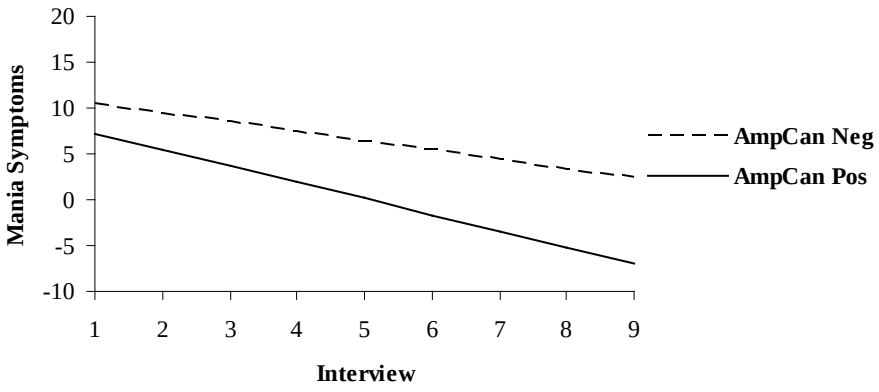

Figure 10. Predicted mania scores and amphetamine + cannabis use

Depression-anxiety symptoms

AmpPos demonstrated no significant difference from AmpNeg with respect to the severity of depression-anxiety symptoms at admission or at Interview 9. Furthermore, no significant differences were found between these groups on the abatement of depression-anxiety symptoms during hospitalisation. Refer to Figure 11.

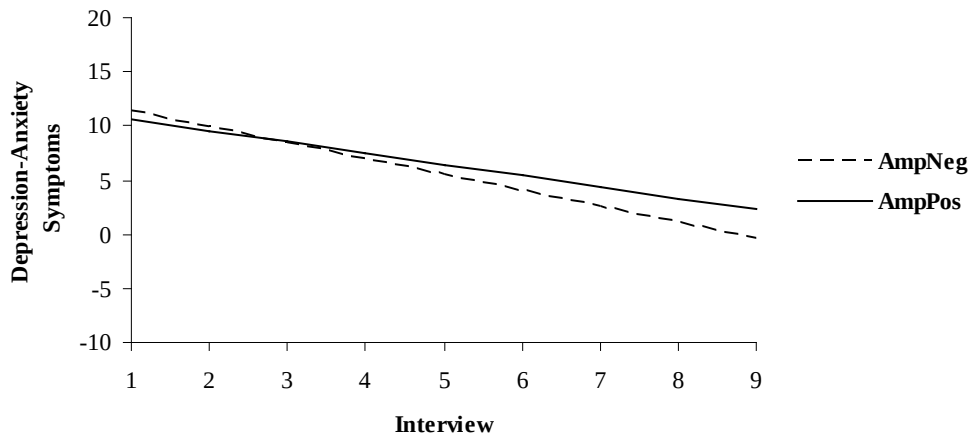

Figure 11. Predicted depression-anxiety scores and amphetamine use

Likewise, CanPos was not significantly different to CanNeg regarding depression-anxiety symptoms either at admission or at Interview 9. There was also no significant difference between the groups on the abatement of these symptoms during hospitalisation. Refer to Figure 12.

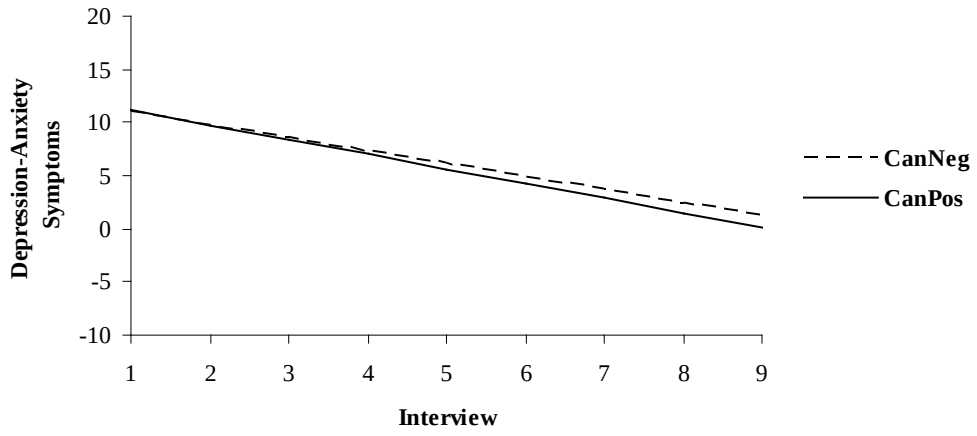

Figure 12. Predicted depression-anxiety scores and cannabis use

There were no differences between the AmpCanPos group and the AmpCanNeg group regarding symptoms of depression-anxiety at admission or at Interview 9. Again, there were no differences between the groups in the rate at which these symptoms abated during hospitalisation. Refer to Figure 13.

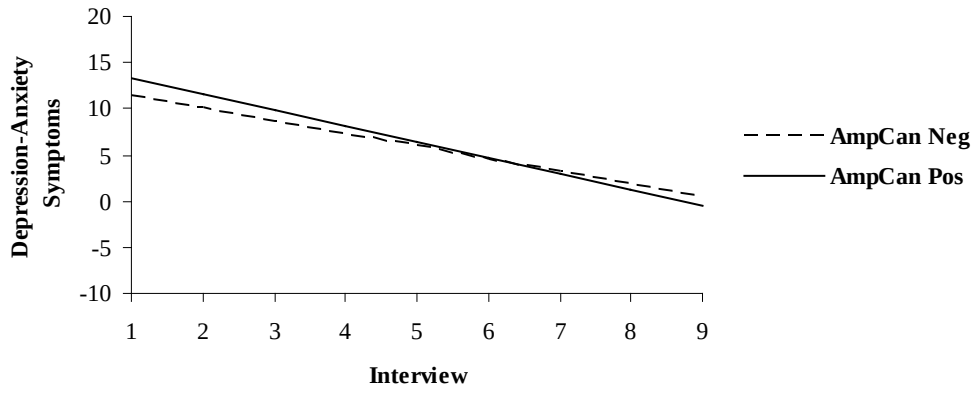

Figure 13. Predicted depression-anxiety scores and amphetamine + cannabis use

Disturbed behaviour

As measured by the DBR scale, the AmpPos group demonstrated significantly more disturbed behaviour than non-users at admission. However, these symptoms were found to abate significantly more rapidly for the AmpPos group than the AmpNeg group during hospitalisation. At Interview 9, AmpPos demonstrated significantly less disturbed behaviour than AmpNeg. Refer to Figure 14.

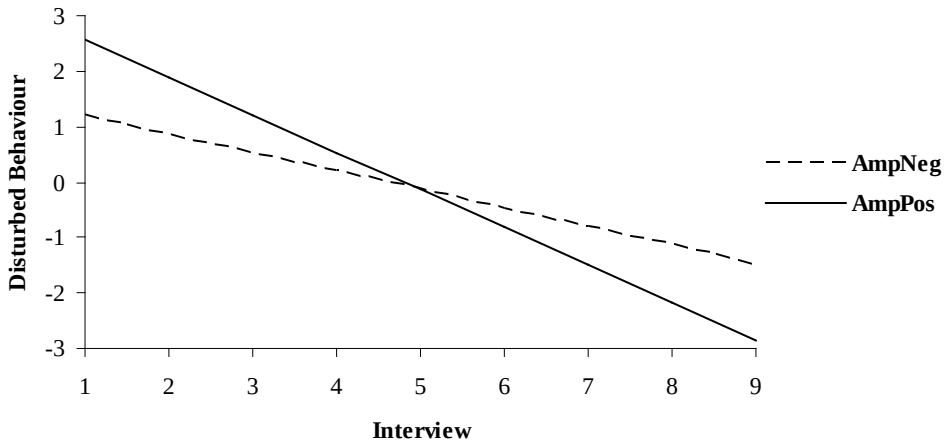

Figure 14. Predicted disturbed behaviour scores and amphetamine use

CanPos was associated with significantly more disturbed behaviour than CanNeg at admission. However, symptoms of disturbed behaviour abated significantly more rapidly for the CanPos group. Furthermore, the CanPos group demonstrated significantly less disturbed behaviour than the CanNeg group at Interview 9. Refer to Figure 15.

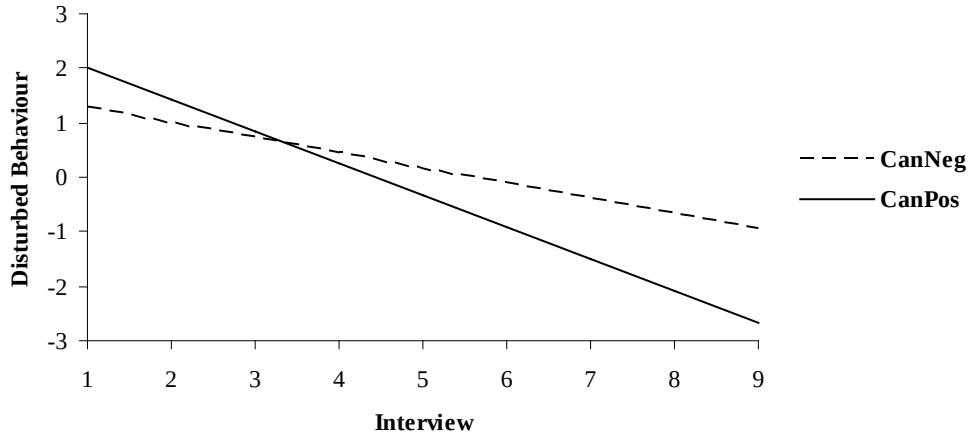

Figure 15. Predicted disturbed behaviour scores and cannabis use

The AmpCanPos group was not found to be significantly different to AmpCanNeg on the severity of disturbed behaviour at admission or at Interview 9. There was also no difference found between the groups with respect to the slope, demonstrating a comparable rate of reduction in disturbed behaviour during hospitalisation. Refer to Figure 16.

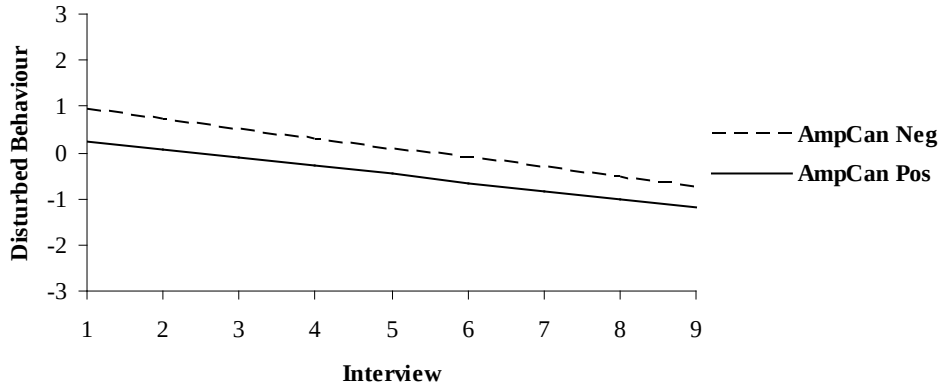

Figure 16. Predicted disturbed behaviour scores and amphetamine + cannabis use

Chapter 9. Discussion

The current research examined the impact of amphetamine and/or cannabis use on the severity and clinical course of symptoms and behaviour of 98 inpatients with early psychosis. Each participant's recent use (in the 30 days before admission) of amphetamines and/or cannabis was assessed, and users were compared to non-users on five symptom dimensions (positive symptoms, negative symptoms, mania symptoms, depression-anxiety symptoms, and disturbed behaviour). Comparisons were made between the groups on the severity of their symptoms and behaviour at admission to hospital and also at eight weeks post-admission. Changes in symptoms and behaviour were also tracked between these two time points, and were represented as linear trajectories that provided an indication of clinical course.

No significant differences were found between those who had used substances and those who had not on demographic, familial, or premorbid characteristics. The study then moved on to examine differences between the substance-using groups and their respective non-using groups on each of the symptom dimensions at admission. The key findings at admission were: (1) recent amphetamine use was associated with significantly less severe negative symptoms and significantly more severe symptoms of mania and disturbed behaviour; and (2) recent cannabis use was associated with significantly less severe negative symptoms and significantly more severe symptoms of mania and disturbed behaviour. Next, the groups were compared on clinical course during the first eight weeks of hospitalisation, with the major findings being: (1) amphetamine use was associated with a significantly faster reduction in mania symptoms and disturbed behaviour;

and (2) cannabis use was associated with a faster reduction in positive symptoms, mania symptoms, and disturbed behaviour. Finally, the groups were compared on the severity of their symptoms and behaviour at week eight of admission, finding: (1) amphetamine use was associated with significantly less severe disturbed behaviour; and (2) cannabis use was associated with significantly less severe positive symptoms, negative symptoms, and disturbed behaviour. Interestingly, substance use had no significant impact on depression-anxiety symptoms. Furthermore, the use of both amphetamines and cannabis demonstrated no influence (when compared to those who had not used both substances) on any of the symptom dimensions. These findings will now be discussed further, followed by a consideration of the contributions and limitations of the current study, future directions and clinical implications.

Participant characteristics of total sample

Total sample demographics were comparable to those of other early psychosis populations (e.g., Black et al., 2001; Garety et al., 2006; Preston et al., 2003; Verma, Subramaniam, Chong, & Kua, 2002), consisting of mostly single, unemployed males. Women were significantly older than men; a finding that was predictable based on the known epidemiology of schizophrenia and related psychoses (Hafner & an der Heiden, 1997; Kirkbride et al., 2006; Sajatovic, Donenwirth, Sultana, & Buckley, 2000; Zipursky, 2006). There were no other gender differences in the remaining demographic variables.

Further similarities with samples previously described in the literature were demonstrated with respect to family history of psychosis, severity of

psychopathology, and premorbid adjustment. For example, the percentage of people who reported a family history of psychosis (*n* = 13; 13%) was comparable to that reported by Bersani et al. (2002) (*n* = 20; 16%) and Sevy et al. (2001) (*n* = 11; 10%) in their studies of psychosis patients with co-occurring substance use. With respect to the severity of psychopathology, the total BPRS score of the current sample (*M* = 64.3, *SD* = 12.3) was in the 'moderate' range of severity (Barbato, D'Avanzo, Rocca, Amatulli, & Lampugnani, 2004), and was comparable to the mean BPRS score reported by Nash et al. (2004) in their study of early psychosis patients (*M* = 60.0, *SD* = 19.1). With respect to premorbid adjustment, the PAS scores of the current sample were more consistent with those of schizophrenia patients than normals (see Cannon-Spoor, Potkin, & Wyatt, 1982). It is interesting to note, however, that two-thirds of the current sample obtained mean scores that reflected a healthy premorbid adjustment. PAS scores for the current sample were lower (i.e., healthier) than those reported by Sevy et al. (2001). This may reflect a more clinically unwell sample in the Sevy et al. study, given that poorer premorbid adjustment has been linked to more severe psychotic symptom profiles (Addington, van Mastrigt, & Addington, 2003; Rabinowitz, De Smedt, Harvey, & Davidson, 2002). The PAS scores of the current sample and the Caton et al. (2005) study were more comparable, and participants of both studies also presented with less severe psychotic symptomatology as indicated by moderate scores on the BPRS and PANSS (respectively).

When compared to first-episode psychosis patients, the current sample presented with a relatively short DUP (*M* = 25 weeks, *SD* = 20.1). McGlashan

(1999) provided a summary of DUP estimates in first-episode psychosis samples, reporting that the average mean DUP across studies was between one and two years. However, a more recent study of first-episode patients reported a mean DUP of just over 12 weeks (Lambert et al., 2005), demonstrating the variances in this literature. The reasonably short DUP of the current sample may, in part, be explained by the severity of their mania symptoms (as will be reviewed later in this discussion). It has been suggested that mania symptoms are associated with a shorter DUP and more rapid hospital admission due to the intensity of these symptoms and their potential impact on others (Conus et al., 2006; Drake, Haley, Akhtar, & Lewis, 2000; Sipos, Harrison, Gunnell, Amin, & Singh, 2001). Interestingly, a study by Larsen and colleagues (2001) found that a shorter DUP in first-episode psychosis patients was associated with better premorbid adjustment, less severe psychosis (as demonstrated by lower positive and negative symptom scores on the PANSS), and higher levels of substance use. In line with the findings of Larsen and colleagues, these characteristics were all identified in the current sample (i.e., better premorbid adjustment, moderate severity of psychopathology on the BPRS, and high levels of substance use).

With respect to phenomenology, findings of this study were again consistent with those of previous research. Participants experienced notably more positive psychotic symptoms than negative psychotic symptoms. Delusions of persecution, auditory hallucinations, and delusions of reference were the most common positive symptoms experienced, with visual hallucinations being less frequently reported.

This profile is broadly similar to that of the amphetamine-induced psychosis sample studied by Chen et al. (2003).

While relatively less common, the negative psychotic symptoms of avolition/apathy and flat affect were reported by a substantial minority of the current sample (35.7% of participants for both symptom types). When considered alongside previous studies of amphetamine-induced psychosis patients, these rates of negative symptoms appear to be high. For example, avolition/apathy and flattened affect were reported by 15.2% and 17.6% respectively in the Chen et al. (2003) study. However, it is important to note that participants with psychosis (n = 174) in the Chen et al. (2003) study had a lifetime (versus current) history of amphetamine-induced psychosis and 72.4% of participants retrospectively reported their symptoms at the time of interview. The studies conducted by Harris and Batki (2000) and Srisurapanont et al. (2003) reported somewhat more comparable rates of negative psychotic symptoms (26% and 21.4% of participants respectively) to the current study. With respect to first-episode patients, Malla and Payne (2005) reported that negative symptoms typically manifest at a relatively low prevalence rate (usually within the range of 19% – 27%), but indicated that varying definitions and measurement methods make comparisons across studies difficult.

As expected, lifetime and recent use (30 days prior to admission) of amphetamines and cannabis in the current sample were both markedly higher than the general population. The 2004 NDSHS reported that lifetime and recent use (last month) of amphetamines in the Australian population was 9.1% and 1.3% (respectively) (Australian Institute of Health and Welfare, 2005a), compared to

71.4% and 38.8% (respectively) in the current sample. Lifetime and recent use of cannabis in the Australian population was found to be 33.6% and 6.7% (respectively) (Australian Institute of Health and Welfare, 2005a), compared to 87.8% and 61.2% (respectively) in the current sample. The strikingly high rate of substance use in the current sample (aged 18 – 65 years) becomes even more apparent when it is noted that the figures from the 2004 NDSHS represent all age groups 14 years and above. However, similarities in the rate of substance use have been found between the current sample and other Australian studies of early psychosis populations. For example, Preston et al. (2003) reported that 60% of early psychosis patients had used cannabis and 30% had used amphetamines/cocaine/ecstasy within the previous three months. Somewhat lower rates were reported in an epidemiological study of psychosis by Kavanagh et al. (2004), with 41% of participants reporting lifetime repeated use of cannabis and 18% reporting lifetime repeated use of amphetamines. Participants of the Kavanagh et al. (2004) study were predominantly outpatients with psychotic illnesses at varying stages of chronicity, which may partially explain the differences in rates of substance use.

Characteristics of substance users versus non-users

Substance users and non-users were comparable on a range of demographic characteristics and psychiatric history. No significant differences were found with respect to age, gender, family history of either psychosis or other mental health problems, or family of origin factors including conflict and control. These findings were consistent with many previous studies of substance-using psychosis patients (e.g., Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Kovasznay, 1991; Mikami

et al., 2003; Miller & Tannenbaum, 1989; Sevy, Kay, & Opler, 1990; Sevy et al., 2001), and support a review of first-episode psychosis studies provided by Malla and Payne (2005) that concluded there are few significant differences to be found between substance users and non-users.

Substance-using groups and non-users were also not statistically different on their total BPRS scores, indicating comparable levels of psychopathology across the groups. Likewise, no differences were found between substance users and non-users in relation to the type of psychotic symptoms (e.g., auditory hallucinations, delusions of persecution) most commonly experienced, although caution is warranted when interpreting these results due to differences in group sizes.

Given that there was some evidence in the existing literature that those with substance use and psychosis differed from those with psychosis alone on measures of premorbid adjustment and DUP, the current study also tested for group differences on these constructs. Substance-users and non-users were not found to differ on the subscale scores or total score of the PAS, which measures premorbid adjustment. This finding is disparate with a number of early studies (Arndt, Tyrrell, Flaum, & Andreasen, 1992; Breakey, Goodell, Lorenz, & McHugh, 1974; Ritzler, Strauss, Vanord, & Kokes, 1977) that used varying measures of premorbid adjustment. However, the current finding is consistent with the more recent studies conducted by Sevy et al. (2001) and Caton et al. (2005), which both used the PAS as a measure of premorbid adjustment. The former study found no significant differences between substance-using and non-using first-episode psychosis patients

and the latter found no significant differences between substance-induced psychosis patients and primary psychosis patients.

Consistent with recent studies conducted by Barnes et al. (2006) and Larsen et al. (2006), there was no significant difference between substance-users and non-users with respect to DUP. This lack of difference is likely to be at least partially due to the homogeneity of illness stage (i.e., early psychosis) across the sample.

There were also no differences between substance users and non-users with respect to dose of antipsychotic or benzodiazepine medications prescribed at admission, a finding consistent with earlier studies (e.g., Mikami et al., 2003; Negrete, Knapp, Douglas, & Smith, 1986; Rottanburg, Robins, Ben-Arie, Teggin, & Elk, 1982). This result was expected, given that the prescription of low-dose antipsychotic medications is considered 'best-practice' in the treatment of early psychosis patients (Lines, 2005; McGorry, 2002). Furthermore, it was reasonable to expect the prescription of similar doses of antipsychotic medication to both substance users and non-users at presentation to hospital given that no differences were found between the groups in severity of psychotic illness at this time (evidenced by comparable total BPRS scores).

The impact of substance use on the severity and clinical course of symptoms and behaviour

The large majority of studies that have examined the impact of substance use on the severity and clinical course of psychotic symptoms and behaviour have done so by assessing their samples at admission and again at discharge. The current study followed suit with respect to the comparison of substance users and non-users on the

severity of symptoms and disturbed behaviour at admission. However, one of the major contributions of the current research was that the clinical course of symptoms was also monitored for the first eight weeks of hospitalisation. This data was then analysed using the statistical method of MLM, which provided linear trajectories representing the rate of change in symptoms and behaviour across time. MLM also allowed for the substance-using and non-using groups to be compared on their predicted mean scores of each symptom dimension at week eight of hospitalisation, even though some patients were discharged prior to this assessment point. This is a novel approach to the examination of how amphetamines and cannabis impact upon psychosis, thus, the existing literature provides few studies for comparison. With this in mind, the findings with respect to each of the substances and their synergistic impact upon positive symptoms, negative symptoms, mania symptoms, depression-anxiety symptoms, and disturbed behaviour will now be discussed.

Amphetamines

Amphetamine use in the 30 days prior to admission had no significant impact on the severity of positive symptoms or depression-anxiety symptoms either at admission or eight weeks later. Not surprisingly, there was also no association between amphetamine use and the rate at which positive symptoms or depression-anxiety symptoms abated during hospitalisation. The symptom dimensions that did differentiate between the groups were negative symptoms, mania symptoms, and disturbed behaviour. Compared to non-users, amphetamine users experienced significantly less severe negative symptoms at admission. They presented with significantly more severe symptoms of mania at admission and they exhibited a

significantly faster reduction in these symptoms during hospitalisation. Recent amphetamine use also had a strong impact on behaviour. Users presented with significantly more disturbed behaviour, but went on to demonstrate a more rapid abatement of these symptoms during hospitalisation and their scores were significantly lower than non- users at week eight.

Descriptive studies of amphetamine use and psychosis present a profile that consists of high scores on measures of positive symptoms and relatively low scores on measures of negative symptoms (e.g., Chen et al., 2003; Iwanami et al., 1994). However, few studies have included a comparison group of non-users. Tomiyama (1990) included non-users in their study of amphetamine-induced psychosis, which in line with the current study, reported no significant difference in positive symptoms between methamphetamine users and non-users at baseline, but significantly less severe negative symptoms for the using group. It is interesting to note that both the current study and the one conducted by Tomiyama (1990) ensured that all participants were in a similar phase of their psychotic illness. The current study focussed on early phase psychosis while the sample in Tomiyama's study consisted of chronic patients. Mikami et al. (2003) also incorporated a non-using comparison group in their study. They reported significantly lower scores on both positive and negative symptoms for their amphetamine-using group. It is notable that the substance-using group in the Mikami et al. (2003) study had a significantly shorter DUP than the non-using group and their sample included both outpatients and inpatients. Thus, the Mikami et al. (2003) sample may in fact be a less pathological group than the current sample of inpatients.

There have been a number of studies that have focussed on substance-users as a general category of patients and compared them to a non-using control group. As in the current study, Sevy et al. (2001) and Rabinowitz et al. (1998) found that substance users and non-users with early psychosis did not differ on positive symptoms or depressive symptoms, again highlighting the importance of controlling for illness chronicity. To varying degrees, several other studies (that did not control for stage of illness) also found similarities between substance-users and non-users on these symptom dimensions at baseline assessment. Scheller-Gilkey et al. (2002) found no differences on positive or anxiety symptoms, Dixon et al. (1991) found no differences on positive or depression-anxiety symptoms, and Ries et al. (2000) found no differences on positive or depression symptoms. However, contrasting findings were evident in at least two studies. Scheller-Gilkey et al. (2002) found significantly higher scores for depression in the substance-using group on the Modified Hamilton Rating Scale for Depression. Interestingly, Kovasznay (1993) identified significantly higher ratings of depression-anxiety in the substance-using group on the BPRS, but no differences between the groups on the Hamilton Rating Scale for Depression. It is difficult to reconcile these particular findings from two very different population groups and settings.

With respect to negative symptoms at admission, some of these same studies (i.e., Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Scheller-Gilkey, Thomas, Woolwine, & Miller, 2002) obtained dissimilar results to the current study, finding no differences between substance-using and non-using groups. However, the studies that focussed on early psychosis (Caton et al., 2005; Kovasznay et al., 1993) found

that substance use was associated with less severe negative symptoms in early psychosis, as did the current study. Using meta-analytic methods, Talamo et al. (2006) also found in their examination of nine studies that substance users with schizophrenia obtained significantly lower negative symptom scores on the PANSS than non-users with schizophrenia. As commonly mentioned in the literature, this finding may be due to the substance-using group specifically seeking out substances that alleviate negative symptoms (Mueser, Drake, & Wallach, 1998; Talamo et al., 2006). Mueser and colleagues (1998) proposed several models of comorbidity between substance use and psychosis, with one of them being the secondary substance use model. This model is based on the premise of self-medication, whereby psychotic patients attempt to ease their symptoms (primarily negative symptoms) and/or prescribed medication side-effects with substances. With this in mind, it is then reasonable to consider that the amphetamine-using participants of the current sample may have lower negative symptoms at admission because they had been successfully self-medicating prior to hospitalisation. However, a particularly important point to mention here is that a growing body of research has found little robust support for this hypothesis overall (see overview by Hides, Lubman, & Dawe, 2004). An alternative possibility is that the subgroup of people who are able to successfully locate and purchase substances may be less impaired socially and emotionally, thus explaining their lower negative symptom scores (Arndt, Tyrrell, Flaum, & Andreasen, 1992; Mueser et al., 1990; Talamo et al., 2006; van Ammers, Sellman, & Mulder, 1997). Despite differences across studies, what does remain

reasonably clear is the consistency in findings relating to positive symptoms and negative symptoms when stage of psychotic illness is controlled.

We now turn to the finding of non-significant differences between groups within the current study population on positive, negative, mania, and depression-anxiety symptoms at week eight of admission. Dixon et al. (1991) reported some comparable findings, with substance users and non-users demonstrating similar scores of depression-anxiety and activation at discharge[4]. However, the Dixon group reported significantly less severe positive (thought disorder and paranoia-suspiciousness) and negative symptoms in their substance-using group at discharge; a finding comparable to the cannabis-using group of the current study but not the amphetamine-using group. Ries et al. (2000) also reported similar rates of depression and elevated mood in their substance-using and non-using groups at discharge[5]. However, this research group found that the substance-users experienced significantly less severe positive symptoms (hallucinations and delusions) than non-users at discharge. Differences between the findings (specific to amphetamine users) of the current study and those of Dixon et al. (1991) and Ries et al. (2000) may be at least partially attributable to the following factors: (1) the average length of time to the discharge assessment (i.e., approximately two weeks) in the Ries et al. (2000) study was comparatively short; (2) neither study assessed the impact of specific

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[4] The mean length of hospital stay was 47.4 days (*SD* = 25.7) for the using group and 61.1 days (*SD* = 54.4) for the non-using group.

[5] The mean length of hospital stay for the total sample was 15.4 days (*SD* = 10.7).

classes of substance on symptoms; and (3) neither of the studies controlled for chronicity of psychotic illness.

With respect to the impact amphetamines have on the severity of mania at admission and the clinical course of these symptoms across time, the current findings support those of several earlier studies that have linked amphetamine use with increased symptoms of mania (e.g., Hall, Hando, Darke, & Ross, 1996; Harris & Batki, 2000; Silverstone, Pukhovsky, & Rotzinger, 1998; Vollenweider, Maguire, Leenders, Mathys, & Angst, 1998). Although not specifically tested here, it would be reasonable to suggest that the pattern of symptom presentation and abatement for mania found in the current study supports earlier claims that mania symptoms are an acute and transient response to intoxication by amphetamines (Brown, Suppes, Adinoff, & Thomas, 2001; Clark et al., 2000; Meredith, Jaffe, Ang-Lee, & Saxon, 2005). Thus, recent users are likely to present with significantly more severe symptoms of mania while intoxicated with amphetamines, but these symptoms abate rapidly as the substance is excreted from the body. This explanation is strengthened by the previous finding that meth/amphetamine levels in urine and plasma have demonstrated a significant association with increased mania-type symptoms (Batki & Harris, 2004).

Disturbed behaviours have also been previously linked to amphetamine use (e.g., Degenhardt & Topp, 2003; Hando, Topp, & Hall, 1997; Sommers & Baskin, 2006; Tominaga, Garcia, Dzierba, & Wong, 2004; Wright & Klee, 2001), although until now, it was unclear how amphetamine users with psychosis differed from non-users with psychosis on this symptom dimension. The current study demonstrated

significant differences in disturbed behaviour at admission, during hospitalisation, and at the eight week assessment point. Previously, it has been suggested that more disturbed behaviour in the amphetamine-using population with psychosis is likely to be somewhat attributable to their propensity for more severe positive psychotic symptoms (Swanson et al., 2006). The current findings do not support this explanation, given that users and non-users were comparable in the severity of their positive symptoms. It is possible, however, that the more severe symptoms of mania in the substance-using group were in some way associated with the higher levels of disturbed behaviour in this group. Symptoms of mania have been linked to increased aggression/violence in previous research (e.g., Dean et al., 2006; Koen et al., 2004; Marken, Stanislav, Lacombe, & Pierce, 1992).

Cannabis

The use of cannabis in the 30 days prior to admission had an impact on all symptom dimensions except for depression-anxiety. Cannabis use was significantly associated with a faster reduction in positive symptoms during hospitalisation and significantly less severe positive symptoms at week eight; less severe negative symptoms at admission and at week eight; and more severe mania symptoms at admission, followed by a faster reduction in mania symptoms during hospitalisation. In a pattern similar to amphetamines, cannabis use was also associated with significantly more disturbed behaviour at admission, followed by a faster reduction in disturbed behaviour during hospitalisation and significantly less disturbed behaviour than non-users at week eight.

As in the current thesis, many earlier studies have found that positive symptoms did not differ between cannabis users and non-users at admission (Addington & Addington, 2007; Bersani, Orlandi, Kotzalidis, & Pancheri, 2002; Compton, Furman, & Kaslow, 2004; Peralta & Cuesta, 1992). Of interest, was the finding that cannabis users demonstrated a significantly more rapid reduction in their positive symptoms across time, leading to significantly less severe positive symptoms at week eight. These findings demonstrate similarities with those reported by Rottanburg et al. (1982), who found that cannabis users with early psychosis and their non-using counterparts presented with similar scores for positive symptoms (i.e., a range of delusions including delusions of persecution and grandiose delusions) on the PSE. Cannabis users then went on to demonstrate a significant reduction in these symptoms between the admission assessment and the follow-up assessment one week later, while the non-users experienced no significant reduction in these symptoms. The results of the current study suggest that a psychosis that occurs in the context of recent cannabis use is associated with a more benign clinical course for positive symptoms.

The findings pertaining to negative symptoms reflect the bulk of previous research on cannabis and psychosis, which generally reports that cannabis users experience significantly fewer negative symptoms at admission (Bersani, Orlandi, Kotzalidis, & Pancheri, 2002; Compton, Furman, & Kaslow, 2004; Potvin, Sepehry, & Stip, 2006; Rehman & Farooq, 2007) and at discharge (Dixon, Haas, Weiden, Sweeney, & Frances, 1991). Importantly though, the current study revealed that despite differences in the severity of negative symptoms at these time points, the

negative symptoms of both cannabis users and non-users followed a similar clinical course during the first eight weeks of hospitalisation.

Cannabis had a significant impact on the symptom dimension of mania at admission, with users presenting as markedly more manic. However, these symptoms abated more rapidly for the using group during hospitalisation. This symptom pattern is suggestive of an association with the intoxication phase of cannabis use, whereby the manic effects are only evident while the substance is in the body (e.g., Henquet, Krabbendam, de Graaf, Have, & van Os, 2006; Nunez & Gurpegui, 2002; Strakowski, DelBello, Fleck, & Arndt, 2000). An alternative explanation is that the symptoms of mania experienced by cannabis users respond better or faster to medication than do mania symptoms within the non-using group.

With respect to depression-anxiety, the findings of the current study support a large portion of previous literature that found no robust link between substance use in psychosis and increased symptoms of depression and/or anxiety (e.g., Baigent, Holme, & Hafner, 1995; Degenhardt et al., 2007; Dixon, Haas, Weiden, Sweeney, & Frances, 1991; Scheller-Gilkey, Thomas, Woolwine, & Miller, 2002).

The most striking result for cannabis was its association with disturbed behaviour. As was found for amphetamines, cannabis use was associated with significantly more disturbed behaviour at admission, and this group went on to experience a significantly faster reduction in disturbed behaviours during their hospitalisation, in addition to significantly less disturbed behaviour than non-users at week eight. Unlike amphetamines, however, cannabis use was not expected to be associated with significantly more disturbed behaviour at admission. Much of the

existing literature reports a non-significant relationship between cannabis use and aggression/violence/hostility (e.g., Dhossche, 1999; Hoaken & Stewart, 2003; Macleod et al., 2004; Myerscough & Taylor, 1986), although there exists some evidence of an association in other studies (e.g., Cuffel, Shumway, Chouljioa, & McDonald, 1994; Fulwiler, Grossman, Forbes, & Ruthazer, 1997). In explanation of the current findings, the association between cannabis and disturbed behaviour may be linked to the increased severity of mania symptoms at presentation, as was previously suggested in the discussion of amphetamines and disturbed behaviour. It may also be that the unlikely relationship between cannabis and more disturbed behaviour was the result of there being amphetamine-users (who commonly experience increased levels of aggression and violence) in the cannabis using group.

Alternatively, more disturbed behaviour at admission may reflect the early stages of withdrawal, which typically begin within 24 hours of cannabis cessation, and commonly involve irritability, tension, poor sleep patterns, and aggressive behaviour. Many patients will cease substance use in the first few days of hospital admission, if for no other reason than because they are under close and regular observation schedules by nursing staff. Thus, moderate to heavy substance users are likely to experience at least some withdrawal symptoms, which commonly include disturbed behaviours. A study by Hoaken and Stewart (2003) has previously demonstrated this link, finding that high levels of aggression were evident in cannabis-dependent participants during the first week of abstinence. It is reasonable to expect then that the disturbed behaviours would gradually resolve as the withdrawal process resolves. The finding of a significantly faster reduction in

disturbed behaviour during hospitalisation and significantly less disturbed behaviour by week eight further strengthens the proposal that the profile of this symptom dimension is linked to the stages of cannabis intoxication and withdrawal. This finding emphasises the need for clinicians to be familiar with the components of substance intoxication and withdrawal phases, and their impact on the severity of psychotic symptoms and behaviours.

Clearly not all possible confounding factors with respect to disturbed behaviour were controlled in the current study, however, it is important to note that demographics and family-of-origin conflict were not significantly different between users and non-users, thus removing these variables as potential contributors.

Amphetamines and cannabis

Polysubstance use has been previously linked to worse psychopathology (Marsden, Gossop, Stewart, Rolfe, & Farrell, 2000). For example, Cuffel et al. (1994) reported that polysubstance use (alcohol and cannabis) resulted in significantly more violent behaviour. It also seems reasonable to assume when both amphetamines and cannabis independently affect the severity of symptoms or behaviour, that the use of both substances together might have an increased impact on symptoms and behaviour. However, the current study found that users of both amphetamines and cannabis in the 30 days prior to admission did not experience more severe psychotic symptoms and behaviour than those who had not used both substances. Essentially, no synergistic effect was identified within the current sample. This may be partially explained by the finding that the independent use of amphetamines and cannabis demonstrated similar patterns of effect on several of the

symptom dimensions (e.g., mania and disturbed behaviour), thereby diluting the potential for any further synergistic effect to be found significant. It is also possible that while participants in the AmpCanPos group used both amphetamines and cannabis, they may have been primary users of only one or the other substance. For example, a person may have been placed in the AmpCanPos group even though they had used amphetamines daily and cannabis only twice weekly in the 30 days prior to admission. This area of research requires further exploration with particular attention being paid to the patterns of use for each substance used.

Contributions and limitations of the current study

Much of the previous literature examining the relationships between amphetamine and/or cannabis use, psychotic symptoms, and behaviour has been hampered by limitations such as a lack of homogeneity in the illness phase of participants, diagnostic inaccuracy, no control group of non-substance-users with psychosis, small sample size, poor control of confounding factors, and retrospective methodologies. The current study has attempted to address these limitations through sample selection criteria, methodological design, and statistical methods. With respect to sample, the current study examined only patients who were within the early phase ($\leq$ three previous episodes and < three years since initial psychosis diagnosis) of their psychotic illness. This criterion ensured that participants were all within a similar stage of their illness, thereby optimising comparability on symptom severity and course. It also controlled for problems associated with chronicity of psychotic illness (e.g., long-term neuroleptic use).

A further contribution of this study was the consideration given to high levels of cannabis use in the sample. The study set out to focus on the impact of recent amphetamine use on psychosis, however, high rates of cannabis use (either independent of or concomitant with amphetamine use) meant that both substances required examination. This also provided an opportunity to study the synergistic effects of the two substances.

A final and particularly important strength of this study with respect to sample was the inclusion of a control group of psychotic patients who had not used substances. There is an immense literature that has examined the impact of amphetamines and cannabis on symptom severity and course. However, strikingly few studies have included a control group of non-users in their sample, thus obliging researchers to make inferences about the differences and similarities between the two groups.

There are three key methodological factors within this study that have enhanced the value of its findings. First, in an effort to avoid the potential problems associated with the misdiagnosis of a substance-induced psychosis versus a primary psychosis with co-occurring substance use, participants were categorised according to self-reported use of amphetamines/cannabis in the last 30 days. This approach has been successfully used by at least two other recent studies within the area (Degenhardt et al., 2007; Rehman & Farooq, 2007).

Second, this study examined several symptom dimensions associated with psychosis, namely positive symptoms, negative symptoms, mania symptoms, and depression-anxiety symptoms, in addition to disturbed behaviour. Many previous

studies have limited their focus to the positive and negative symptom profiles of patients with psychosis, despite a study by van Os et al. (1999) showing that a range of symptom dimensions are both relevant and independently influential with respect to psychotic illness course and outcome.

Third, symptom severity and clinical course were measured prospectively throughout the period of hospitalisation. Assessments of symptoms and behaviour occurred at frequent intervals (up to nine times in eight weeks), and unlike many earlier studies, did not rely exclusively on data from cross-sectional assessments at admission and discharge to determine symptom change.

With respect to statistical analyses, the use of MLM was a significant strength. This type of analysis made best use of a hierarchical data set that contained 'missing data' due to patients being discharged at varying times and thus completing different numbers of follow-up interviews. It also allowed for data to be represented by a linear trajectory, thereby providing evidence on the rate of symptom/behaviour change.

As with all research, this study also had several limitations that require consideration. First, reliance on self-reported substance use may not have captured all users in the relevant group. Although self-report has been identified as a highly valid measure of substance use (McPhillips et al., 1997; Selten et al., 2002; Weiss et al., 1998; Wolford et al., 1999), particularly at the intake assessment point (Buchan, Dennis, Tims, & Diamond, 2002; Harrison, 1997), the use of urine drug screening in a more systematic manner would have further increased confidence. Less than three-quarters of participants in the current study volunteered to provide a urine sample for

screening, therefore, it was necessary to rely solely on the self-report measure for the categorisation of participants as substance users or non-users. Fortunately, analyses comparing self-report and urine drug screen results showed that self-report was highly valid in the current study, particularly amongst amphetamine users.

Second, while it was considered beyond the scope of the current study, it is acknowledged that the targeted assessment of intoxication and withdrawal symptoms, in addition to the monitoring of ongoing substance use throughout hospitalisation may have contributed to our understanding of the findings. For example, Lambert and colleagues (2005) reported that persistent substance use post-discharge in a sample of first-episode psychosis patients (N = 643) was associated with poor remission rates across an 18-month period, highlighting the potential contribution of this variable to outcome. For the current study, the most accurate way to monitor substance use while an inpatient would have been twice-weekly urine drug screens. However, based on the financial limits of the study and the additional demands this process would have placed on the participants, it was decided not to incorporate this in to the data collection phase. At the very least, the current study provides clinicians with valuable information about the symptomatology and clinical course of psychosis during routine hospital care.

Third, this study would have benefited from the use of a standardised measure of disturbed behaviour. The Disturbed Behaviour Rating scale is not a standardised scale, but was chosen based on its specific development for the assessment of a broad range of disturbed behaviours (not just violent behaviour) in inpatients who were presenting with early psychosis. Importantly, it incorporated

responses from the participants themselves, interviewer observations, and collateral information from hospital medical charts which noted general behaviour, incident reports, etc. It was also able to be used as a repeated measure and was not lengthy. Given the lack of alternative standardised measures at the time of data collection that were able to assess a range of recent behaviours, this measure proved most relevant.

Finally, most participants of this study were discharged having completed four or fewer interviews. While MLM analyses were still able to make valid predictions under these circumstances, it is accepted that a considerably larger sample would have increased the sensitivity of these analyses. However, given the usual requirements of a doctoral thesis in addition to the complex and demanding methodology of the current study, it was decided reasonable to limit participants to approximately 100. An alternative method for improving sensitivity would have been to include only those participants who had completed all nine interviews. However, the primary problem with this approach is that it would have created a selection bias, and results would not have been generalisable to the bulk of the population (who require shorter hospital stays).

Clinical implications

The literature places much emphasis on the positive and negative psychotic symptoms associated with substance use and psychosis. These symptom dimensions also play an important role in the diagnostic processes of psychotic illness. However, the current study found that both the independent and synergistic effects of amphetamine and cannabis use were largely non-significant with respect to positive

symptoms, and little impact was evidenced on negative symptoms. No impact was demonstrated with respect to symptoms of depression-anxiety.

While empirical research often focuses on positive and negative symptoms, anecdotal reports from law enforcement and health professionals working with those people diagnosed with psychosis in the context of substance use are most frequently concerned with manic symptoms and aggressive behaviours. Interestingly, these anecdotal reports are supported by the findings of the current study, suggesting that our focus might be better placed on the symptoms of mania and disturbed behaviour, which were the most strongly affected by amphetamine use and cannabis use. There are implications for the individual, their family and community, and the health care system associated with these findings. For example, mania has been linked to greater impairment of the brain (Frey et al., 2006), in addition to increased social disability, increased hospital admissions, and longer hospital stays (Sipos, Harrison, Gunnell, Amin, & Singh, 2001; van Os et al., 1999). Both mania and disturbed behaviour also demonstrate an enormous potential to damage family and social relationships, affect employment, and increase the safety risk to the patient and others. They can also place barriers between the patient and health professionals/law enforcement, and frequently necessitate more invasive procedures from professionals in the management of these symptoms (e.g., the use of physical seclusion and/or restraint).

Fortunately, with the knowledge that amphetamine users and cannabis users are likely to present with increased symptoms of mania and disturbed behaviour, clinicians and researchers are able to plan their assessment and treatment processes

accordingly. For example, particular attention should be given to the substance use history of a patient presenting to hospital with early psychosis and a symptom profile marked by severe mania and disturbed behaviours. In the case of an inpatient admission, this symptom profile might also pre-empt a treatment plan that targets behaviour management and increased safety procedures (e.g., individual behavioural management programs, the designation of additional 'quiet' areas with low stimulation for the patient, the use of sedative medications, patient-specific safety plans etc.), particularly in the early weeks of hospitalisation. The patient, family, and staff might also be reliably informed of the prognostic features of these symptoms when associated with substance use, and be reassured of the likelihood that symptoms of mania and disturbed behaviour tend to abate rapidly, despite their severity at first presentation.

Another important application of these findings is their potential to be used in the psychoeducation phase of substance use treatment. For example, perceptions that polydrug use is the worst case scenario can be challenged with respect to psychotic symptoms and behaviour. Substance-using patients can be informed that if they develop a psychotic disorder, using either amphetamines or cannabis is at least equally problematic as the synergistic effects of using both substances.

Future directions

This study showed that amphetamine or cannabis use in the 30 days prior to hospital admission with an early psychosis had a limited impact on the severity and clinical course of positive symptoms and depression-anxiety symptoms. However, these substances were significantly influential with respect to the severity of negative

symptoms and the severity and clinical course of mania symptoms and disturbed behaviour during the first eight weeks of hospitalisation. These findings have generated a number of questions that might drive future research. First, it would be interesting to examine the clinical course of symptoms and behaviour beyond the first eight weeks of hospitalisation, to determine the period of time during which these differences persist.

Second, it would appear important to now consider the role that alcohol plays in the relationships examined here. The literature examining the links between alcohol use and psychosis is mixed, with some studies (Degenhardt, Hall, & Lynskey, 2001a; Thirthalli & Benegal, 2006; Tien & Anthony, 1990), but not all (e.g., Farrell et al., 2002), finding a significant association between the two. However, its high rate of use in both substance-using and clinical populations warrants its consideration as a contributing factor (Addington & Addington, 2007; Miles et al., 2003; Van Mastrigt, Addington, & Addington, 2004).

Third, this study substantiates the importance of considering a range of symptom dimensions in the examination of substance use and psychosis, thus encouraging the further examination of mania symptoms and disturbed behaviour in this group of patients.

A further issue for consideration here is the potential impact of substance use frequency and dose on outcome. While this was not the aim of the current thesis, it is acknowledged that further examination of this relationship would complement our understanding of the impact that recent substance use has on the severity and course of psychotic symptoms and behaviour. A recent study by Wade et al., (2007) found

that heavy substance use (versus mild or no use) was significantly associated with more severe positive symptoms (but not negative symptoms) at a 15-month followup in first-episode patients. The literature would benefit from a study of these variables in an inpatient sample similar to that of the current thesis, encompassing weekly assessments of symptom and behavioural change.

Finally, the importance of controlling for chronicity of illness was highlighted in this study, and it is a crucial factor for consideration when making comparisons between studies. Further exploration of the way that varying stages of psychotic illness impact upon the relationship between substance use and psychosis is clearly warranted.

Final conclusions

The use of amphetamines or cannabis in the 30 days prior to admission with an early psychosis has been found to have a largely non-significant impact on the severity and clinical course of positive symptoms and depression-anxiety symptoms. The recent use of these substances also demonstrated few significant effects on the severity and clinical course of negative symptoms. However, several significant differences were evident between substance users and non-users in the examination of mania symptoms and disturbed behaviour. Interestingly, amphetamine users and cannabis users demonstrated a similar profile of mania symptoms and disturbed behaviour, in that both groups presented with significantly more of these symptoms at admission, but they then abated rapidly over time. The synergistic impact of having recently used both amphetamines and cannabis in the 30 days prior to

admission was not found to be significant with respect to the severity and clinical course of symptoms/behaviour associated with psychosis.

These findings provide further evidence that psychotic patients who use amphetamines or cannabis can be distinguished from their non-using counterparts based on the severity and clinical course of some psychotic symptoms and behaviour. This is particularly important given the difficulties associated with the diagnosis of early psychosis in the context of substance use. It also highlights the benefits of assessing substance use histories in those presenting for admission, and how this information can enhance the treatment of these patients and the prognostic information available to carers and patients alike.

List of Abbreviations

Amphet + Cannabis Use	Amphetamine and cannabis use in 30 days prior to admission
AmpCanPos	Recent (30 days prior to admission) use of both amphetamines and cannabis
AmpCanNeg	Those who had not used both amphetamines and cannabis in the 30 days prior to admission
AmpNeg	No recent (30 days prior to admission) amphetamine use
AmpONLY	Amphetamine use only in 30 days prior to admission
AmpPos	Recent (30 days prior to admission) amphetamine use
BDI	Beck Depression Inventory
BPRS	Brief Psychiatric Rating Scale
CanNeg	No recent (30 days prior to admission) cannabis use
CanONLY	Cannabis use only in 30 days prior to admission
CanPos	Recent (30 days prior to admission) cannabis use
CHDS	Christchurch Health and Development Study
CIDI	Composite International Diagnostic Interview
DBR	Disturbed Behaviour Rating Scale
DIGS	Diagnostic Interview for Genetic Studies
DUP	Duration of Untreated Psychosis
FES	Family Environment Scale
GAF	Global Assessment of Functioning Scale
IRAOS	Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia
MLM	Multi-level Modelling
No Use	No use of amphetamines or cannabis in 30 days prior to admission
PAF	Psychiatric Assessment Form
PAS	Premorbid Adjustment Scale
PANSS	Positive and Negative Syndrome Scale
PRISM	Psychiatric Research Interview for Substance and Mental Disorders
PSE	Present State Examination

SADS	Schedule for Affective Disorders and Schizophrenia
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCID	Structured Clinical Interview for DSM-IV
SCL-90	Symptom Checklist 90
TLFB	Timeline Followback Method
UDS	Urine Drug Screening

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Appendix A Demographic information and IRAOS questions

Participant No.: _____ **Name:** _____

Date: _____ **Age:** _____ **Date of Birth:** _____

Address: _____

Phone: _____ **Gender:** Male □ Female □

Present Occupation: Student Pensioner Self-Employed Unemployed
Skilled Employee Unskilled Employee Other: _____

Occupation Activity Level: Part-Time Full-Time Casual N/A
Other: _____

Marital Status: Single Defacto Married Separated Divorced Widowed
Partnership

Current Living Arrangements ("Who do you currently live with?"):
Alone ; With Partner ; With own Family ; With Family of Origin ; Share Accommodation ;
Hostel / Boarding House ; Itinerant ; Other: _____

Number of Children: _____ **Ages of Children:** _____

Highest Level of Formal Education Obtained:
Primary School Year _____ ; Highschool Year – 8, 9, 10, 11, 12 ; Trade Qualification ;
TAFE ; Undergraduate University ; Postgraduate University ; Other _____

Ethnicity ("Which of the following ethnic groups do you describe yourself as belonging to?"):
Australian, non-Aboriginal
Australian, Aboriginal
Australian, South Sea Islander
Australian, Torres Strait Islander
New Zealander, non-Maori
New Zealander, Maori
Other, specify: _____
Don't Know □

Psychiatrist Diagnosis on admission: □ Confirmed

_____

_____

Hospital Admission Date: _____
Hospital Discharge Date: _____

Referred By: Self ; G.P. ; Community Based Mental Health Professional ; Family/Friend ; Police ; Emergency Services ; Other Mental Health Facility ; Other _____

Medication Compliance:
Compliant with medication in the 30 days prior to hospitalisation? YES / NO / NA
History of medication non-compliance? YES / NO / NA
Reason/s for non-compliance:_____

Urine Drug Screen: YES / NO Date: _____ Positive for: _____
_____

Previous Hospital Admissions:

	Hospital	Length of Stay	Diagnosis	Age
1.				
2.				
3.				

Outpatient Care:

	Type	Length of Care Period	Diagnosis	Age
1.				
2.				
3.				

Current Medication:

Name	Dose	Date	Once-off	PRN	Ongoing

Family Health:
Do you know of anyone else in your family (including mother, father, siblings, aunts, uncles, cousins, grandparents) who has had a *psychotic* illness?
NO / YES (circle)

If YES:

Family Member	Did they see a Doctor for the problem?	Have they been in hospital for the problem?	What diagnosis was given by the Doctor?

Do you know of anyone else in your family (including mother, father, siblings, aunts, uncles, cousins, grandparents) who has had *psychiatric troubles*?
NO / YES (circle)

If YES:

Family Member	Did they see a Doctor for the problem?	Have they been in hospital for the problem?	What diagnosis was given by the Doctor?

Onset of Current Episode:
When did the symptoms or troubles which led eventually to the present admission begin?
(mth & yr) _____How old were you? _____

List the complaints/symptoms associated with the current episode:

_____

_____

What was the very first thing you noticed as a sign of being unwell?

_____

_____

Prior to these symptoms or troubles beginning, did you feel well or was there some indication that your state was not totally normal?

_____

_____

For this episode, list date of first contact with a:
Medical Service mth yr
Psychiatric Service mth yr

Did you seek advice during the current episode from a non-medical service or counsellor?
NO / YES (specify): _____

Regarding this episode, how did your symptoms/difficulties begin?
1 = Acute/suddenly (from relatively symptom free/stable to unwell within 1-7 days)
2 = Subacute (across 1 – 4 weeks)
3 = Gradual/slow (slowly over a period of more than 1 mth)
4 = Gradual onset over period of between 1 and 6 mths
5 = Insidious onset over period of greater than 6 mths
9 = Unknown/not able to rate

Was there anything that triggered these symptoms? What do you think caused it?

_____

_____

Were you feeling stressed prior to this current episode? YES / NO

Indicators of Psychiatric Illness & Previous Episodes:
Were there any other episodes like the current one? (List number of occasions and dates): YES / NO (if No, cease interview here)

_____

_____

The very first time you became unwell, did other people also notice that you were behaving differently or unusually? YES / NO

Did they notice these differences before you did? YES / NO

When did the first sign of any emotional problems or difficulties occur?
(mth & yr) _____ How old were you at this time? _____

Did you go to hospital for treatment? _____

_____

Did you receive outpatient care? _____

_____

What was the very first symptom/sign you noticed in your first episode? _____

_____

What other symptoms or complaints did you notice regarding the very first time you were unwell? _____

_____

_____

How did your symptoms/difficulties begin regarding the first episode?
1 = Acute/suddenly (from relatively symptom free/stable to unwell within 1-7 days)
2 = Subacute (across 1 – 4 weeks)
3 = Gradual/slow (slowly over a period of more than 1 mth)
4 = Gradual onset over period of between 1 and 6 mths
5 = Insidious onset over period of greater than 6 mths
9 = Unknown/not able to rate

How long did the first episode last? _____

In between episodes, do you:
1 = Return to normal levels of complete wellness
2 = Have some experience of wellness but also some ongoing symptoms
3 = Do not have any normal levels of wellness

What do you think triggered the first episode? _____

_____

Were you feeling stressed at the time of your first episode? YES / NO

Appendix B Premorbid Adjustment Scale – Score sheet

Name: _____ Date: _____

12 – 15 Years

1. Sociability and Withdrawal
   0 1 2 3 4 5 6
2. Peer Relationships
   0 1 2 3 4 5 6
3. Scholastic Performance
   0 1 2 3 4 5 6
4. Adaptation to School
   0 1 2 3 4 5 6
5. Social-Sexual Aspects of Life During Early Adolescence
   0 1 2 3 4 5 6

Total Score= _____ Possible Score=_____
Subscale Rating=_____ (Rating = Total Score / Possible Score)

16 – 18 Years

1. Sociability and Withdrawal
   0 1 2 3 4 5 6
2. Peer Relationships
   0 1 2 3 4 5 6
3. Scholastic Performance
   0 1 2 3 4 5 6
4. Adaptation to School
   0 1 2 3 4 5 6
5. Social-Sexual Aspects of Life During Early Adolescence
   0 1 2 3 4 5 6

Total Score= _____ Possible Score=_____
Subscale Rating=_____ (Rating = Total Score / Possible Score)

PAS Score Sheet (cont'd)

19 Years and Above

1. Sociability and Withdrawal
   0 1 2 3 4 5 6
2. Peer Relationships
   0 1 2 3 4 5 6
3. Aspects of Adult Social-Sexual Life
   (a) 0 1 1 2 2 3
   (b) 2 3 4 5 6
   (c) 0 1 3 4 5 6

Total Score= _____ Possible Score=_____
Subscale Rating=_____ (Rating = Total Score / Possible Score)

General

1. Education
   0 1 2 3 4 5 6
2. Employment/Schooling Pre-Hospitalisation
   0 1 2 3 4 5 6
3. Changes in Employment/Schooling
   0 1 2 3 4 5 6
4. Frequency of Changes
   0 1 2 3 4 5 6
5. Independence
   0 2 4 6
6. GAF
   0 2 4 6
7. Social-Personal Adjustment
   0 1 2 3 4 5 6
8. Interest in Life
   0 2 4 6
9. Energy Level
   0 2 4 6

Total Score= _____ Possible Score=_____
Subscale Rating=_____ (Rating = Total Score / Possible Score)

Overall Score=_____
[Overall Score is an average of the subscale ratings]

Appendix C Family Environment Scale

Instructions:

There are 36 statements in this questionnaire. They are statements about families. You are to decide which of these statements are true of ***your family of origin*** and which are false. Answer each question by circling either TRUE *or* FALSE. If you think the statement is true or mostly true of your family, circle TRUE. If you think the statement is false or mostly false of your family, circle FALSE.

You may feel that some of the statements are true for some family members and false for others. Circle TRUE if the statement is true for most members. Circle FALSE if the statement is false for most members. If the members are evenly divided, decide what is the stronger overall impression and answer accordingly. Remember, we would like to know what your family seems like to *you*. So *do not* try to figure out how other members see your family, but *do* give us your general impression of your family for each statement.

Please turn over to complete questionnaire.

FES (cont'd)

Name: _____ Date: _____

Question	**Circle True or False**
1. Family members really help and support one another	T or F
2. Family members often keep their feelings to themselves	T or F
3. We fight a lot in our family	T or F
4. Family members are rarely ordered around	T or F
5. We often seem to be killing time at home	T or F
6. We say anything we want to around home	T or F
7. Family members rarely become openly angry	T or F
8. There are very few rules to follow in our family	T or F
9. We put a lot of energy into what we do at home	T or F
10. It's hard to "blow off steam" at home without upsetting somebody	T or F
11. Family members sometimes get so angry they throw things	T or F
12. There is one family member who makes most of the decisions	T or F
13. There is a feeling of togetherness in our family	T or F
14. We tell each other about our personal problems	T or F
15. Family members hardly ever lose their tempers	T or F
16. There are set ways of doing things at home	T or F
17. We rarely volunteer when something has to be done at home	T or F
18. If we feel like doing something on the spur of the moment we often just pick up and go	T or F
19. Family members often criticise each other	T or F
20. There is a strong emphasis on following rules in our family	T or F
21. Family members really back each other up	T or F
22. Someone usually gets upset if you complain in our family	T or F
23. Family members sometimes hit each other	T or F
24. Everyone has an equal say in family decisions	T or F
25. There is very little group spirit in our family	T or F
26. Money and paying bills is openly talked about in our family	T or F
27. If there's a disagreement in our family, we try hard to smooth things over and keep the peace	T or F
28. We can do whatever we want to in our family	T or F
29. We really get along well with each other	T or F
30. We are usually careful about what we say to each other	T or F
31. Family members often try to one-up or out-do each other	T or F
32. Rules are pretty inflexible in our household	T or F
33. There is plenty of time and attention for everyone in our family	T or F
34. There are a lot of spontaneous discussions in our family	T or F
35. In our family, we believe you don't ever get anywhere by raising your voice	T or F
36. You can't get away with much in our family	T or F

Appendix D Checklist of Psychotic Symptoms

Circle yes or no**:**

Delusions:	
Persecution	**Y or N**
Grandiosity	**Y or N**
Of Reference	**Y or N**
Of Mind Reading	**Y or N**
Of Being Controlled	**Y or N**
Somatic	**Y or N**
Religious	**Y or N**
Of Guilt	**Y or N**
Of Jealousy	**Y or N**
Thought Broadcasting	**Y or N**
Thought Insertion	**Y or N**
Thought Withdrawal	**Y or N**
Hallucinations:	
Auditory	**Y or N**
Tactile	**Y or N**
Olfactory	**Y or N**
Visual	**Y or N**
Gustatory	**Y or N**
Negative Symptoms:	
Avolition/Apathy	**Y or N**
Flat Affect	**Y or N**
Inappropriate Affect	**Y or N**
Other:	
Derealisation	**Y or N**
Depersonalisation	**Y or N**
Catatonic Motor Behaviour	**Y or N**
Odd Speech	**Y or N**
Disorganised Speech	**Y or N**
Disorganised Behaviour	**Y or N**

(Chen et al., 2003)

Appendix E 30 Day Timeline Followback

Name:_____ Date:_____

INSTRUCTIONS: Try to recall any substances you have used during the last month. Record any events (birthdays, parties, pay days, etc.) on the calendar to help you remember. List the substance **type, quantity, frequency** and the **route of administration** (eg., injecting, snorting, smoking). NOTE: Specific attention to amphetamine use is required. Other names include Ice, Fast, Speed, Go-ee. Comes as base (weight = points) or powder (weight = grams). 1 point (of base) = 1 gram (of powder) in purity. Price of either 1 point or 1 gram varies between $50 and $100.

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
MONDAY	**TUESDAY**	**WEDNESDAY**	**THURSDAY**	**FRIDAY**	**SATURDAY**	**SUNDAY**
MONDAY	**TUESDAY**	**WEDNESDAY**	**THURSDAY**	**FRIDAY**	**SATURDAY**	**SUNDAY**
MONDAY	**TUESDAY**	**WEDNESDAY**	**THURSDAY**	**FRIDAY**	**SATURDAY**	**SUNDAY**
DAY _____	**DAY _____**					

TLFB (cont'd)
Drug and Alcohol Use History:

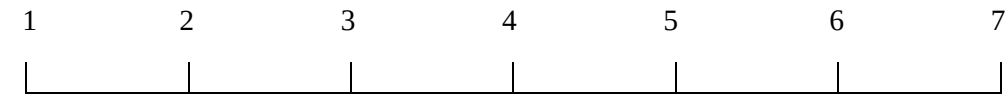
	Type	**Route**	**Frequency during regular use**	**Amount during regular use**
Cannabis: Marijuana, THC, Hash, other				
Stimulants: amphetamine, speed, crystal meth, ice, Ritalin, dexadrine, other				
Cocaine: crack, intranasal, IV, freebase, speedball, other				
Opioids: Heroin, Morphine, Methadone, opium, codeine, other				
Hallucinogens or PCP: LSD, mushies, PCP, MDMA, ecstasy, other				
Sedatives-hypnotics-anxiolytics: valium, Quaalude, seconal, xanax, barbiturates, other				
Drugs you sniff (eg., glue, petrol)				
Beer Beverages				
Wine Beverages				
Spirit Beverages				
Other				

Appendix F Brief Psychiatric Rating Scale (BPRS)

Score Sheet

Name: Date:
Rater Name: Location:

INSTRUCTIONS
This form consists of 24 symptom constructs, each to be rated on a 7-point scale of severity ranging from 'not present' to 'extremely severe'. If a specific symptom is not rated, mark 'NA' (not assessed). Circle the number headed by the term that best describes the patient's present condition.



not present very mild mild moderate moderately severe severe extremely severe

1.	Somatic concern	NA	1	2	3	4	5	6	7
2.	Anxiety	NA	1	2	3	4	5	6	7
3.	Depression	NA	1	2	3	4	5	6	7
4.	Suicidality	NA	1	2	3	4	5	6	7
5.	Guilt	NA	1	2	3	4	5	6	7
6.	Hostility	NA	1	2	3	4	5	6	7
7.	Elated mood	NA	1	2	3	4	5	6	7
8.	Grandiosity	NA	1	2	3	4	5	6	7
9.	Suspiciousness	NA	1	2	3	4	5	6	7
10.	Hallucinations	NA	1	2	3	4	5	6	7
11.	Unusual thought content	NA	1	2	3	4	5	6	7
12.	Bizarre behaviour	NA	1	2	3	4	5	6	7
13.	Self-neglect	NA	1	2	3	4	5	6	7
14.	Disorientation	NA	1	2	3	4	5	6	7
15.	Conceptual disorganisation	NA	1	2	3	4	5	6	7
16.	Blunted affect	NA	1	2	3	4	5	6	7
17.	Emotional withdrawal	NA	1	2	3	4	5	6	7
18.	Motor retardation	NA	1	2	3	4	5	6	7
19.	Tension	NA	1	2	3	4	5	6	7
20.	Uncooperativeness	NA	1	2	3	4	5	6	7
21.	Excitement	NA	1	2	3	4	5	6	7
22.	Distractibility	NA	1	2	3	4	5	6	7
23.	Motor hyperactivity	NA	1	2	3	4	5	6	7
24.	Mannerisms and posturing	NA	1	2	3	4	5	6	7

Appendix G Disturbed Behaviour Rating Scale

Name: _____ Date: _____

Rate behaviour exhibited in the last 48 hours.

1. Behaviour potentially threatening to life of patient: Includes attempted suicide or self-harm. For example, attempted hanging, head-banging, wrist-cutting, self-poisoning, drug overdose, and/or other violent/aggressive behaviours towards self.
   Specify behaviour: _____

2	1	0	□
Repeatedly	Once or Twice	None at All	Ratings Unobtainable

2. Behaviour potentially threatening to lives of others: Includes violent and aggressive behaviours affecting (or with the potential to affect) the health of staff, fellow patients or hospital visitors.
   Specify behaviour: _____

2	1	0	□
Repeatedly	Once or Twice	None at All	Ratings Unobtainable

3. Inappropriate or bizarre sexual behaviour: Includes explicit behaviour such as genital exposure or socially inappropriate behaviours of a sexual or indecent nature such as walking around the hospital ward dressed in underwear only. Specify behaviour:
   _____

2	1	0	□
Repeatedly	Once or Twice	None at All	Ratings Unobtainable

4. Behaviour damaging to property: Includes behaviour that is harmful or destructive to materialistic items or property belonging to the individual or others. For example, breaking windows or furniture.
   Specify behaviour: _____

2	1	0	□
Repeatedly	Once or Twice	None at All	Ratings Unobtainable

5. Bizarre or inappropriate behaviour not classified above: Includes any type of unusual or inappropriate behaviours that cannot be categorized elsewhere such as the patient believing they are a cat or dog, or absconding from the health care facility for reasons related to delusional content.
   Specify behaviour: _____

2	1	0	□
Repeatedly	Once or Twice	None at All	Ratings Unobtainable

Appendix H Information Sheet and Consent Form

INFORMATION SHEET

Project Title: An investigation of amphetamine use and psychological health

Researcher: Dr Sharon Dawe. Ph: (07) 3875 3371

Aims: Some people who attend psychiatric hospitals for help with psychological problems may also use substances. It is unclear what effect substance use has on psychological problems. In this study we would like to talk to people who have used drugs before coming into hospital and also people who have not had any experience or minimal experience of drug use.

Procedure: In this study we would like to ask you about your personal history, use of drugs and thinking style. If you agree, we would interview you up to nine times while you are in hospital, and possibly after you have left hospital to discuss your recovery. The first interview will take around 50 minutes and the following ones should only take around 30 minutes. Sometimes people with psychological problems may have difficulties remembering the exact dates of events leading up to their admission. In order to overcome this problem we may need to access your file about the events leading up to your admission. Signing this form gives us permission to interview you, to access your medical record, and to contact you at a later date (by telephone and/or mail) regarding your recovery if required.

Right to Withdraw: Your participation in this study is completely voluntary and you may withdraw at any time. Choosing not to take part or withdrawing will not affect your treatment at this hospital in any way. You may have a friend or relative present when the study is explained.

Confidentiality: All information you give will be kept confidential unless the researcher is ordered by a court of law to release the information or it is felt that there is a risk of serious harm to yourself or others. You will be assigned a number so that your name will not be connected to your responses. You will not be asked about other illegal activities apart from drug use and the information you provide the researcher will not be reported to your treatment provider or authorities.

If you have any questions during or after the interviews we are more than happy to provide you with answers and feedback. Call Sharon Dawe on 3875 3371. The secretary of the hospital research ethics committee may be contacted on 3240 5856. If you have any complaints concerning the manner in which the research project is conducted it may be given to the researcher, or, if an independent person is preferred, either:

1. University's Research Ethics Office, Office for Research, Bray Centre Griffith University, Kessels Road, Nathan, Qld 4111, telephone (07) 3875 6618; or
2. Pro Vice-Chancellor (Administration), Bray Centre, Griffith University, Kessels Road, Nathan, Qld 4111, telephone (07) 3875 7343

Griffith University acknowledges and thanks you for your time to support its research initiatives.

CONSENT FORM
Project Title: An investigation of amphetamine use and psychological health

If you agree to take part in the study we ask that you sign this form. If you have any questions at any stage of the assessment we are happy to provide you with answers and feedback.

I have read the above and I agree to participate in the above study and give my consent freely. I understand that the project will be carried out as described in the information statement, a copy of which I have retained. I have been given the opportunity to have a friend or relative present while the study is being explained. I realise that whether or not I decide to participate is my decision and will not affect my treatment. I also realise that I can withdraw from the project at any time and that I do not have to give any reasons for withdrawing. I have had all questions answered to my satisfaction.

Participant Name: ……..

…… ……
Signature Date

…… ……
Researcher Date

…… ……
Witness Date

Appendix I Normality of data

Table I1

Normality of dependent variables

Variables	Skew	Skew Standard Error	Skew Result	Kurtosis	Kurtosis Standard Error	Kurtosis Result
Positive Symptoms	-.065	.244	.270	-.382	.483	.889
Negative Symptoms	.745	.244	3.05	-.465	.483	.981
Mania Symptoms	.872	.244	3.57***	.041	.483	.291
Depression-Anxiety Symptoms	.558	.244	2.29	-.166	.483	.586
Disturbed Behaviour	1.020	.244	4.18***	.793	.483	1.281

Note. ***$p > .001$.

Appendix J Histograms of amphetamine use and cannabis use in the last 30 days

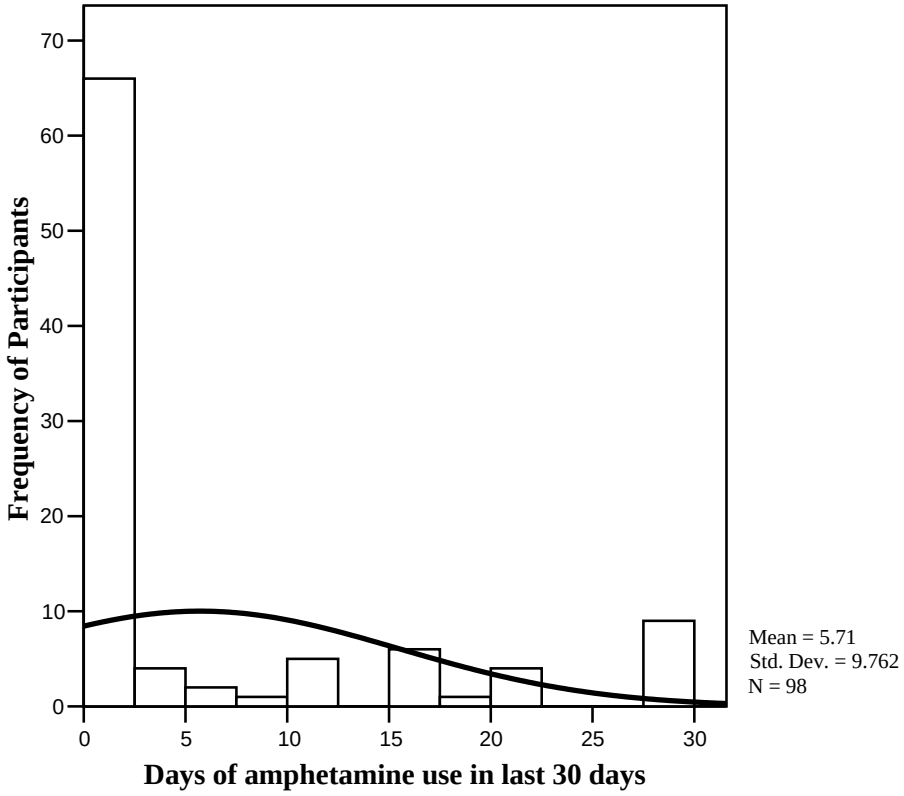


Figure J1. Days of amphetamine use in the last 30 days

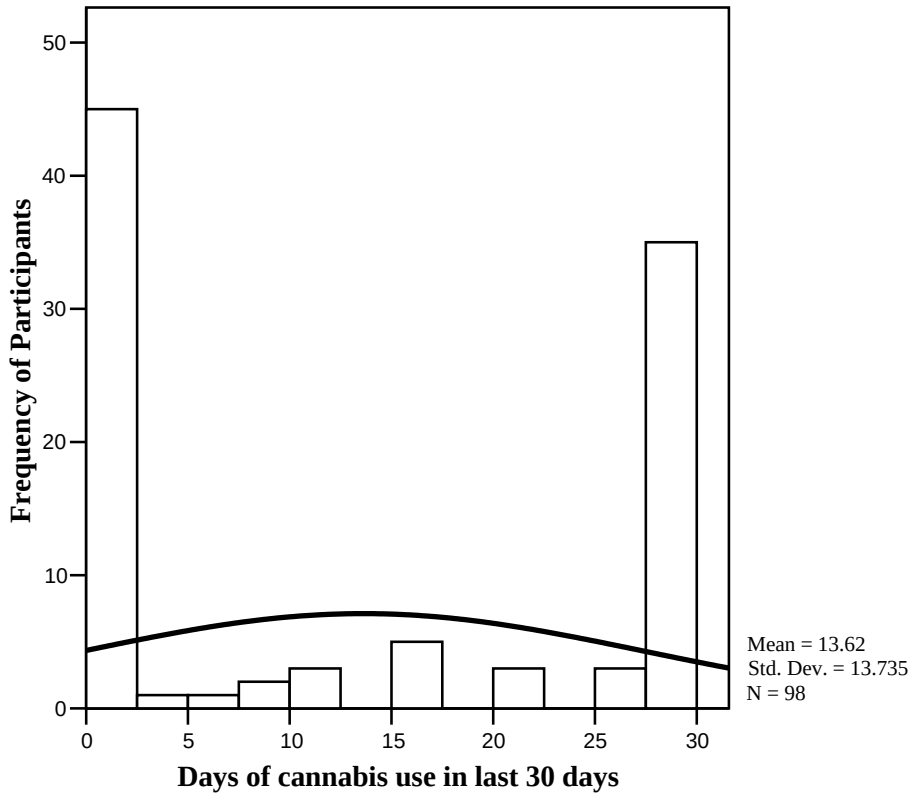


Figure J2. Days of cannabis use in the last 30 days

Appendix K Examples of MLM analyses output

Positive symptom analyses for admission and clinical course

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$
$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons}$$
$$\beta_{0ij} = 15.963(0.474) + u_{0j} + e_{0ij}$$

$$\begin{bmatrix} u_{0j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 14.515(3.155) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 21.986(1.937) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 2193.245(351 of 361 cases in use)

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$
$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + -1.775(0.129)\text{occasion}_{ij}$$
$$\beta_{0ij} = 18.402(0.551) + u_{0j} + e_{0ij}$$

$$\begin{bmatrix} u_{0j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 22.283(3.819) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 12.199(1.082) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 2061.658(351 of 361 cases in use)

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij}$$

$$\beta_{0ij} = 19.276(0.539) + u_{0j} + e_{0ij}$$

$$\beta_{1j} = -2.808(0.232) + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 23.944(4.082) & \\ -1.886(1.294) & 2.778(0.673) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 6.220(0.656) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1983.958(351 of 361 cases in use)

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij} + 0.544(1.104)\text{amp30day}_{j} + -0.659(0.477)\text{amp30day.occasion}_{ij}$$

$$\beta_{0ij} = 19.065(0.686) + u_{0j} + e_{0ij}$$

$$\beta_{1j} = -2.567(0.289) + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 23.838(4.065) & \\ -1.664(1.271) & 2.680(0.656) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 6.201(0.653) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1982.084(351 of 361 cases in use)

$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$

$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij} + 0.984(1.095)\text{can30day}_{j} + \text{-}1.135(0.438)\text{can30day.occasion}_{ij}$

$\beta_{0ij} = 18.661(0.855) + u_{0j} + e_{0ij}$

$\beta_{1j} = \text{-}2.099(0.337) + u_{1j}$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 23.399(4.018) & \\ \text{-}1.236(1.178) & 2.171(0.569) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 6.394(0.669) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1978.100(351 of 361 cases in use)

$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$

$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij} + 0.357(2.095)\text{amp30day}_{j} + \text{-}0.751(0.853)\text{amp30day.occasion}_{ij} +$
$0.944(1.365)\text{can30day}_{j} + \text{-}1.191(0.546)\text{can30day.occasion}_{ij} +$
$\text{-}0.111(2.503)\text{amp30day.can30day}_{j} + 0.575(1.023)\text{occasion.amp30day.can30day}_{ij}$

$\beta_{0ij} = 18.582(0.963) + u_{0j} + e_{0ij}$

$\beta_{1j} = \text{-}1.963(0.379) + u_{1j}$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 23.463(4.021) & \\ \text{-}1.250(1.188) & 2.234(0.579) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 6.321(0.662) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1977.231(351 of 361 cases in use)

Positive symptom analyses for Interview 9

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$
$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \text{-1.775(0.129)occdischarge}_{ij}$$
$$\beta_{0ij} = 4.201(1.001) + u_{0j} + e_{0ij}$$

$$\begin{bmatrix} u_{0j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} 22.283(3.819) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e) \ :\ \Omega_e = \begin{bmatrix} 12.199(1.082) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 2061.658(351 of 361 cases in use)

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$
$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij}$$
$$\beta_{0ij} = \text{-3.187(1.765)} + u_{0j} + e_{0ij}$$
$$\beta_{1j} = \text{-2.808(0.232)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} 171.545(38.134) & \\ 20.336(4.929) & 2.778(0.673) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e) \ :\ \Omega_e = \begin{bmatrix} 6.220(0.656) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1983.957(351 of 361 cases in use)

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij} + \text{-4.727(3.639)amp30day}_{j} + \text{-0.659(0.477)amp30day.occdischarge}_{ij}$$

$$\beta_{0ij} = \text{-1.469(2.200)} + u_{0j} + e_{0ij}$$

$$\beta_{1j} = \text{-2.567(0.289)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} \text{168.750(37.582)} & \\ \text{19.778(4.825)} & \text{2.680(0.656)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} \text{6.201(0.653)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1982.084(351 of 361 cases in use)

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{bprsps}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij} + \text{-8.095(3.361)can30day}_{j} + \text{-1.135(0.438)can30day.occdischarge}_{ij}$$

$$\beta_{0ij} = \text{1.866(2.589)} + u_{0j} + e_{0ij}$$

$$\beta_{1j} = \text{-2.099(0.337)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} \text{142.568(33.090)} & \\ \text{16.132(4.198)} & \text{2.171(0.569)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} \text{6.395(0.669)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1978.099(351 of 361 cases in use)

$$\text{bprsps}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\begin{aligned}\text{bprsps}_{ij} = {} & \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij} + \text{-5.644(6.626)amp30day}_{j} + \\ & \text{-0.750(0.853)amp30day.occdischarge}_{ij} + \text{-8.586(4.180)can30day}_{j} + \\ & \text{-1.191(0.545)can30day.occdischarge}_{ij} + \text{4.480(7.911)amp30day.can30day}_{j} + \\ & \text{0.574(1.023)amp30day.can30day.occdischarge}_{ij}\end{aligned}$$

$$\beta_{0ij} = \text{2.877(2.905)} + u_{0j} + e_{0ij}$$

$$\beta_{1j} = \text{-1.963(0.379)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} \text{146.261(33.664)} & \\ \text{16.598(4.269)} & \text{2.231(0.578)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} \text{6.324(0.663)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1977.231(351 of 361 cases in use)

$\text{dbrtot}_{ij} \sim \text{N}(XB, \Omega)$

$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons}$

$\beta_{0ij} = 1.013(0.097) + u_{0j} + e_{0ij}$

$\left[u_{0j}\right] \sim \text{N}(0, \Omega_u) : \Omega_u = \left[0.326(0.133)\right]$

$\left[e_{0ij}\right] \sim \text{N}(0, \Omega_e) : \Omega_e = \left[1.960(0.171)\right]$

*-2*loglikelihood(IGLS Deviance)* = 1276.402(351 of 361 cases in use)

$\text{dbrtot}_{ij} \sim \text{N}(XB, \Omega)$

$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \text{-0.397(0.042)occasion}_{ij}$

$\beta_{0ij} = 1.636(0.117) + u_{0j} + e_{0ij}$

$\left[u_{0j}\right] \sim \text{N}(0, \Omega_u) : \Omega_u = \left[0.477(0.135)\right]$

$\left[e_{0ij}\right] \sim \text{N}(0, \Omega_e) : \Omega_e = \left[1.451(0.128)\right]$

*-2*loglikelihood(IGLS Deviance)* = 1199.340(351 of 361 cases in use)

$$\text{dbrtot}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij}$$

$$\beta_{0ij} = 1.725(0.161) + u_{0j} + e_{0ij}$$

$$\beta_{1j} = -0.469(0.056) + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 1.915(0.364) & \\ -0.511(0.114) & 0.152(0.040) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 0.934(0.091) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1140.271(351 of 361 cases in use)

$$\text{dbrtot}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij} + 1.381(0.299)\text{amp30day}_{j} + -0.345(0.109)\text{amp30day.occasion}_{ij}$$

$$\beta_{0ij} = 1.190(0.186) + u_{0j} + e_{0ij}$$

$$\beta_{1j} = -0.333(0.068) + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 1.466(0.300) & \\ -0.400(0.098) & 0.124(0.036) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 0.935(0.091) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1120.172(351 of 361 cases in use)

$\text{dbrtot}_{ij} \sim \text{N}(XB, \Omega)$

$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij} + 0.729(0.316)\text{can30day}_{j} + -0.306(0.101)\text{occasion.can30day}_{ij}$

$\beta_{0ij} = 1.277(0.245) + u_{0j} + e_{0ij}$

$\beta_{1j} = -0.279(0.075) + u_{1j}$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 1.722(0.335) & \\ -0.417(0.098) & 0.110(0.032) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 0.950(0.091) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1132.322(351 of 361 cases in use)

$\text{dbrtot}_{ij} \sim \text{N}(XB, \Omega)$

$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occasion}_{ij} + 1.766(0.548)\text{amp30day}_{j} + -0.325(0.157)\text{amp30day.occasion}_{ij} +$
$0.535(0.359)\text{can30day}_{j} + -0.216(0.120)\text{occasion.can30day}_{ij} +$
$-0.660(0.657)\text{amp30day.can30day}_{j} + 0.027(0.203)\text{occasion.amp30day.can30day}_{ij}$

$\beta_{0ij} = 0.910(0.251) + u_{0j} + e_{0ij}$

$\beta_{1j} = -0.207(0.079) + u_{1j}$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} 1.324(0.279) & \\ -0.316(0.082) & 0.082(0.027) \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} 0.959(0.091) \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1112.906(351 of 361 cases in use)

Disturbed behaviour analyses for Interview 9

$$\text{dbrtot}_{ij} \sim \text{N}(XB,\ \Omega)$$
$$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \text{-0.397(0.042)occdischarge}_{ij}$$
$$\beta_{0ij} = \text{-1.540(0.288)} + u_{0j} + e_{0ij}$$

$$\begin{bmatrix} u_{0j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} \text{0.477(0.135)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e) \ :\ \Omega_e = \begin{bmatrix} \text{1.451(0.128)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1199.340(351 of 361 cases in use)

$$\text{dbrtot}_{ij} \sim \text{N}(XB,\ \Omega)$$
$$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij}$$
$$\beta_{0ij} = \text{-2.031(0.325)} + u_{0j} + e_{0ij}$$
$$\beta_{1j} = \text{-0.469(0.056)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u) \ :\ \Omega_u = \begin{bmatrix} \text{3.467(1.217)} & \\ \text{0.705(0.219)} & \text{0.152(0.040)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e) \ :\ \Omega_e = \begin{bmatrix} \text{0.934(0.091)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1140.271(351 of 361 cases in use)

$$\text{dbrtot}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij} + \text{-1.379(0.652)amp30day}_{j} + \text{-0.345(0.109)amp30day.occdischarge}_{ij}$$

$$\beta_{0ij} = \text{-1.471(0.404)} + u_{0j} + e_{0ij}$$

$$\beta_{1j} = \text{-0.333(0.068)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} \text{3.013(1.134)} & \\ \text{0.593(0.200)} & \text{0.124(0.036)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} \text{0.935(0.091)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1120.172(351 of 361 cases in use)

$$\text{dbrtot}_{ij} \sim \text{N}(XB,\ \Omega)$$

$$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij} + \text{-1.720(0.580)can30day}_{j} + \text{-0.306(0.101)can30day.occdischarge}_{ij}$$

$$\beta_{0ij} = \text{-0.960(0.415)} + u_{0j} + e_{0ij}$$

$$\beta_{1j} = \text{-0.280(0.075)} + u_{1j}$$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} \text{2.135(0.899)} & \\ \text{0.469(0.168)} & \text{0.111(0.032)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} \text{0.949(0.091)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1132.322(351 of 361 cases in use)

$\text{dbrtot}_{ij} \sim \text{N}(XB, \Omega)$

$\text{dbrtot}_{ij} = \beta_{0ij}\text{cons} + \beta_{1j}\text{occdischarge}_{ij} + \text{-0.832(0.843)amp30day}_{j} +$
$\text{-0.325(0.157)amp30day.occdischarge}_{ij} + \text{-1.196(0.704)can30day}_{j} +$
$\text{-0.216(0.120)can30day.occdischarge}_{ij} + \text{-0.443(1.144)amp30day.can30day}_{j} +$
$\text{0.027(0.203)occdischarge.amp30day.can30day}_{ij}$

$\beta_{0ij} = \text{-0.750(0.450)} + u_{0j} + e_{0ij}$

$\beta_{1j} = \text{-0.207(0.079)} + u_{1j}$

$$\begin{bmatrix} u_{0j} \\ u_{1j} \end{bmatrix} \sim \text{N}(0,\ \Omega_u)\ :\ \Omega_u = \begin{bmatrix} \text{1.521(0.742)} & \\ \text{0.341(0.139)} & \text{0.082(0.027)} \end{bmatrix}$$

$$\begin{bmatrix} e_{0ij} \end{bmatrix} \sim \text{N}(0,\ \Omega_e)\ :\ \Omega_e = \begin{bmatrix} \text{0.959(0.091)} \end{bmatrix}$$

*-2*loglikelihood(IGLS Deviance)* = 1112.907(351 of 361 cases in use)