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STIMULANT USE DISORDERS AND PSYCHOSIS

Prevalence, correlates and impacts

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Abstract

BACKGROUND

Stimulants such as amphetamine, methamphetamine, cocaine and ecstasy are the most widely used illicit drugs after cannabis, and may influence the onset and course of psychosis. However, evidence about stimulant misuse in people with psychotic disorders is limited, because stimulant use is usually preceded by cannabis use, and both are associated with other personal and social risk factors. Therefore even large clinical studies of people with psychosis have often not examined the impacts of stimulants separately from those of cannabis. Epidemiological approaches, using population surveys and administrative health datasets, provide an additional method for studying the associations and impacts of stimulant drug misuse in people with psychosis.

AIMS

This research addresses three questions. First, what is the prevalence of stimulant use disorders in people with psychosis? Second, what are the correlates of stimulant use disorders in people with psychosis, and how do they compare with people with psychosis who do not use stimulants? Third do stimulant use disorders influence the course of illness for people with psychosis?

METHODS

The research examines three overlapping groups. Part 1 examines the rate and correlates of stimulant disorders in the Australian population, using data from the 2007 Australian National Survey of Mental Health and Wellbeing. Part 2 focuses on early psychosis, examining people admitted with psychosis to hospitals in New South Wales (NSW, population 7.2 million) over a 13 year period. It comprises three studies, examining (i) whether admission to hospital with psychoses is influenced by variations in stimulant availability in the NSW community, (ii) the prevalence and correlates of stimulant use disorders in people with a first admission for psychosis and (iii) the relationship between stimulant misuse and hospital readmission over two years. Part 3 examines enduring psychosis, using data from NSW hospital and community mental health services. It investigates the impact of stimulant use disorders on (i) diagnostic stability and progression to a diagnosis of schizophrenia and (ii) service use and social outcomes in

people with schizophrenia. All studies measured and controlled for comorbid cannabis use disorders and potential personal and social confounders.

RESULTS

In the Australian population, the lifetime prevalence of stimulant disorders was 3.3%, and 12-month prevalence was 0.6%, equating to more than 97,000 Australians. Stimulant use disorders were most common in people with other risk factors for developing psychosis, including younger age, male gender, a family history of psychosis, earlier and more frequent use of cannabis, anxiety and depressive symptoms, and subclinical psychotic symptoms.

Quarterly variations in amphetamine availability accounted for 50% of variation in the rate of admission for stimulant induced psychosis. People with first admission psychoses had stimulant use disorders at a rate more than ten times that of the age-matched Australian population. Stimulant use disorders were associated with diagnoses of brief and drug induced psychoses. Cannabis and stimulant disorders at first admission did not predict readmission, whereas prior admissions with stimulant disorders did. The associations of stimulant use disorders differed from those of cannabis use disorders.

In the five years following admission for psychosis, comorbid stimulant use disorders were associated with diagnostic instability, reduced likelihood of diagnostic progression to schizophrenia and increased likelihood of revision of an initial diagnosis of schizophrenia to other conditions. By contrast, comorbid cannabis use disorders increased the likelihood of progression to schizophrenia.

Fourteen percent (14%) of people admitted to hospital with diagnoses of schizophrenia had comorbid stimulant use disorders, and these were associated with physical health comorbidities, social dislocation and frequent use of mental health and emergency services. More than 80% of those with stimulant use disorders also had cannabis disorders: the risks of cannabis and stimulants appeared additive in this group.

CONCLUSIONS

In the Australian population and in Australians with psychosis, the rate of stimulant disorders is consistent with that reported from the US but higher than for many other developed countries. Around one in seven Australians with psychosis also has a stimulant use disorder, a rate at least ten times that of the general population. Because stimulants

may precipitate or worsen acute psychotic symptoms, this suggests that they contribute to the overall burden of psychosis in Australia.

The associations of stimulant use disorders are distinct from those of cannabis use disorders. For people with early psychosis, stimulant disorders are associated with initial diagnoses of brief and drug-induced psychosis, lower rates of ongoing contact with specialist mental health services and lower rates of transition to a final diagnosis of schizophrenia. These findings are consistent with developmental and dimensional models of psychosis: stimulants are potent precipitants of acute psychotic symptoms and may therefore trigger psychotic symptoms in people with less personal vulnerability to the development of schizophrenia. An implication for clinical services is that stimulant-associated psychoses mark an important window of opportunity. Young people with stimulant-associated psychoses may have positive outcomes if they are supported in managing their substance use early in their illness. However, ongoing substance use is associated with high rates of relapse and readmission. For those people with schizophrenia, ongoing stimulant use disorders are associated with significant harms and frequent service use. More research is needed to identify effective interventions for this group.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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Publications during candidature

Peer reviewed publications

Sara, G., P. Burgess, M. G. Harris, G. Malhi and H. Whiteford (2011). Stimulant Use And Stimulant Disorders In Australia: Findings From The National Survey Of Mental Health And Wellbeing. Medical Journal of Australia 195: 607-610.

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List of abbreviations used in the thesis

ABS	Australian Bureau of Statistics
ANOVA	Analysis of Variance
ARIA	Accessibility Remoteness Index of Australia
ATS	Amphetamine-type stimulants
CAMHS	Child and Adolescent Mental Health Service
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CURF	Confidentialised Unit Record File
DALY	Disability Adjusted Life Year
DIP	Diagnostic Interview for Psychosis
DSM	Diagnostic and Statistical Manual of Mental Diseases
ECA	Epidemiological Catchment Area Survey
ED	Emergency Department
GP	General Practitioner
HIE	Health Information Exchange
HIV	Human Immunodeficiency Virus
HoNOS	Health of the Nation Outcome Scales
HR	Hazard Ratio
ICD	International Classification of Diseases
IRSD	Index of Relative Socioeconomic Disadvantage
LSD	Lysergic acid diethylamide
MDMA	Methylene-dioxy-methamphetamine (Ecstasy)
MTP	Methamphetamine Treatment Project
NDSHDS	National Drug Strategy Household Drug Survey
NFA	No Fixed Address
NOS	Not Otherwise Specified
NPV	Negative Predictive Value
NSMHWB	National Survey of Mental Health and Wellbeing
NSW	New South Wales
OR	Odds Ratio
PABAK	Prevalence and Bias Adjusted Kappa
PECC	Psychiatric Emergency Care Centre

PPV	Positive Predictive Value
ROC	Receiver Operator Characteristics
RSE	Relative Standard Error
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SD	Standard Deviation
SE	Standard Error
SEIFA	Socio-Economic Indices for Areas
SHIP	Survey of High Impact Psychosis
SLA	Statistical Local Area
SPSS	Statistical Package for the Social Sciences
STRIDE	System to Retrieve Information from Drug Evidence
SUPI	State Unique Patient Identifier
THC	delta-9 tetrahydrocannabinol
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

PART 1

STIMULANTS AND PSYCHOSIS: BACKGROUND AND RATIONALE

1: Introduction

Overview

A substantial minority of young Australians use stimulants such as methamphetamine. Some of those who are the heaviest users experience psychotic symptoms of sufficient severity or duration that they require mental health care. For these young people, few things could be more frightening. The vignette that follows describes a common situation in the Australian health system. Its details are a de-identified composite drawn from many individuals.

> *At 11pm on a Monday night, in the Emergency Department of a busy outer metropolitan hospital, two mental health clinicians are speaking with a distressed young man. Tim recently turned 20. He studies computing at a nearby technical college and lives with his mother and 17 year old sister. That evening Tim's mother returned from work to find him frightened and angry. He told her that he had discovered a surveillance system, with wireless cameras hidden in smoke detectors in their ceiling. She tried to calm him, but Tim grabbed a large kitchen knife, saying that he needed to protect them all. She called local police.*
>
> *It was difficult for Tim to give the clinicians a clear history. He paced around the ED interview room. His words and thoughts tumbled over each other; he was afraid for his family, they were being watched, he had seen videos on the internet which he was sure were of his mother and sister, some neighbours had recently moved in and installed a satellite dish, he wanted to go home and confront them.*
>
> *Tim's mother gave the clinicians more details. She described a shy young man with a small circle of close friends. His main interests were computers and online gaming, and he had become increasingly interested in electronic music. Tim had been in the middle of his class academically, and never quite sure what direction he wanted to take in life. His first year at technical college had seemed promising; he had enjoyed his studies and passed all but one of his courses. His mother was pleased when he started attending some live music events and parties with some new friends. Over the summer break he had seemed a little bored and down. His mother hoped that things would improve when his second year of studies resumed, however in the few months since then she had become increasingly worried. She had twice found him smoking cannabis at home. He often stayed out all night with*

friends on weekends, and seemed tired and irritable for the first half of the week. He had started missing some days at college and often seemed worried or forgetful.

Tim's parents had separated when he was seven. His father lived in a nearby regional town; he saw him rarely but enjoyed their contact. Tim's mother described his father as a heavy drinker who had periods of depression and mood swings for which he never accepted care. Tim's paternal grandmother had been hospitalised with a post-partum psychosis.

Tim's sister tearfully tells her mother that Tim has been using methamphetamine and ecstasy on most weekends. He had made her promise not to tell anyone.

It is likely that Tim is experiencing a first episode of psychosis and that stimulant drugs have played a part in its onset. Many other personal, developmental, family and social factors are also likely to have interacted to bring Tim to this point at this time. In the months and years that follow, Tim's story may unfold in many different ways.

This research examines the relationship between stimulants and psychosis from the perspective of specialist mental health services. It focuses on severe drug use, examining the role of stimulant abuse and dependence rather than recreational use. It also focuses on psychotic syndromes, enduring constellations of symptoms and signs of psychosis lasting days, weeks or longer, rather than on brief or transient psychotic symptoms. It is in this area, where significant drug use and psychotic syndromes overlap, that many young people like Tim experience great harm and disruption. However it also where knowledge is most limited and where clinicians and services often struggle to discern what role the drug use has played and to deliver effective care.

The goal of this research is to inform mental health care, service planning and policy. We should aim to prevent situations like Tim's. When they do occur, we should provide the most effective care possible, so that Tim has the best possible chance of going on to live the life that he wants to live, unburdened by psychosis.

This research is in three parts. The first examines stimulant disorders in the general population, the second examines stimulant disorders in persons with early psychosis and the third examines stimulant disorders in persons with enduring psychoses such as schizophrenia.

Part 1 looks “upstream” of a presentation such as Tim’s to examine stimulant abuse and dependence in the Australian population. It asks: how common is stimulant misuse in Australia? Who misuses stimulants? How do the risk factors for stimulant use differ from those for cannabis and other drugs? Are stimulant disorders more common in people with other risk factors for psychosis? Answering these questions helps to understand how different levels of exposure to stimulants interact with other risk factors. It provides essential context, allowing us to understand whether correlates of stimulant disorders in people with psychosis are specific to psychosis or instead reflect correlates of use in the broader population.

Part 2 examines situations like Tim’s, people with first episode psychosis. How common is this problem? Who is affected? Are these presentations more common at times of greater drug availability? Does initial or ongoing use of stimulants influence the early course of Tim’s illness and the likelihood that he will require future admissions? Answers to these questions may help to inform clinical care, service planning and public policy.

Part 3 looks “downstream” from this first psychosis episode. There are many possible paths for a young person like Tim. This may be a traumatic but one-off event, the first of several episodes, or the beginning of an enduring psychotic illness such as schizophrenia. Current models of psychosis emphasise the evolving nature of psychotic disorders, the opportunities for intervention and the positive outcomes for many when intervention is successful. The research presented here asks whether people with stimulant disorders and psychosis are more or less likely to develop ongoing psychoses such as schizophrenia. Does ceasing stimulant use change these outcomes? What are the outcomes for people with schizophrenia who continue to use stimulants? Answering these questions helps to identify whether stimulants play a role as a potentially malleable risk factor in the development of psychosis, and whether they contribute to the overall burden of psychosis.

This research uses an epidemiological approach. Part 1 examines data from the Australian National Survey of Mental Health and Wellbeing, a survey of common mental health and substance use problems in the Australian population. Parts 2 and 3 use data from health services for the population of New South Wales (NSW) between 1990 and 2013. The relationship between stimulant disorders and psychosis is likely to be influenced by many personal, social and illness-related factors. In particular, stimulants cannot be considered in isolation from other drugs. Cannabis is the most widely abused illicit drug in young

Australians, and most people who use stimulants also use cannabis. Epidemiological approaches have the potential to complement clinical studies in trying to disentangle the complex relationships between use of these illicit drugs and the development of psychoses.

This introduction briefly summarises some background regarding current views on the aetiology and course of psychosis, the role of substance abuse in psychosis and the reasons for specific concern about the impact of stimulants in people with psychosis. Chapter 2 to 9 comprise a series of linked peer-reviewed published papers. Chapter 2 systematically reviews the rate and correlates of stimulant use disorders in people with psychosis. Chapters 3 to 9 examine stimulant use and disorder in three groups: the Australian population (Chapters 3, 4), people with early psychosis (Chapters 5 to 7) and people with ongoing psychosis (Chapters 8, 9). Chapter 10 summarises findings across these three groups and considers their possible implications.

Stimulant drugs

Stimulant drugs are a family of substances which produce physiological states of increased arousal and subjective states of increased mood, energy and attention (National Drug Research Institute, 2007). They include amphetamine, methamphetamine, methylene-dioxy-methamphetamine (MDMA or “ecstasy”) and cocaine. All act on dopamine pathways, and shared mechanisms are likely to underlie some of their shared effects (Barr et al., 2006) . However, there are also important differences between these substances which may be relevant to understanding any associations with or impacts on psychosis.

Amphetamine and methamphetamine are synthetic compounds produced in various forms including a powdered or tablet form (often known as “speed”), concentrated paste or liquid form (“base”) and a higher purity, crystalline form (“ice”) (Degenhardt et al., 2008c). Amphetamines are small molecules with a close structural affinity to brain amines and in particular to dopamine. They increase the availability and activity of dopamine and other neurotransmitters through several mechanisms, including: increased release from synaptic vesicles; blockage of membrane re-uptake; reduced membrane dopamine transport; inhibited activity of metabolizing enzymes such as monoamine oxidase, and; increased dopamine synthesis (Barr et al., 2006). As well as acute chemical effects, there is evidence that repeated amphetamine exposure may produce ongoing chemical and

structural changes (neurotoxicity) lasting for months or longer (Barr et al., 2006; Hanson et al., 2004).

Methylene-dioxy-methamphetamine (MDMA) or “ecstasy” shares many of the properties of methamphetamine, and is often grouped with amphetamine and methamphetamines in a broader category of “Amphetamine-type stimulants” (United Nations Office on Drugs and Crime, 2011a). In addition to stimulant effects, ecstasy may also produce hallucinogenic actions (Barr et al., 2006; National Drug Research Institute, 2007), which may be related to actions in serotonin pathways (Schenk, 2011; Seger, 2010). Ecstasy has often been associated with patterns of less frequent use (Agar and Reisinger, 2004), and there is debate as to whether it produces a true dependence syndrome (Degenhardt et al., 2010a).

Cocaine is a plant-derived compound. It is a larger and more structurally complex molecule than amphetamine-type stimulant drugs, and has a shorter half-life: 1-3 hours compared with 8-13 hours for methamphetamine (Barr et al., 2006). It acts to increase the levels of dopamine within the synapses by blocking mono-amine reuptake, but has less effect on intracellular dopamine levels than amphetamine-type stimulants, which may indicate a lower potential to cause neurotoxic effects (Seger, 2010). Cocaine’s powerful subjective effects and short half-life may contribute to psychological dependence, and it may be associated with a higher risk of dependence when compared to amphetamine-type stimulants (Degenhardt and Hall, 2012a; Agar and Reisinger, 2004).

Stimulant drugs: global prevalence and impacts

Globally, stimulants are the most widely abused illicit drugs after cannabis (United Nations Office on Drugs and Crime, 2011a). In recent decades amphetamine-type stimulants (ATS) have overtaken cocaine as the most widely used stimulant drugs, and ATS seizures and ATS use now exceed those of opiates (United Nations Office on Drugs and Crime, 2011a; United Nations Office on Drugs and Crime, 2011b; Degenhardt and Hall, 2012a). Over the last two decades stimulant use has increased in North America (Degenhardt et al., 2008a), Europe (Davies and Ditton, 1990) and South East Asia (McKetin et al., 2008).

In 2012 it was estimated that between 13 million and 56 million people globally had used ATS drugs in the preceding 12 months (Degenhardt and Hall, 2012a), representing between 0.3% and 1.3% of adults. This rate is slightly lower than that estimated for

cannabis (0.3% – 1.3%) but higher than that for cocaine (0.3% – 0.5%) or opiates (0.3% – 0.5%) (Degenhardt and Hall, 2012a).

Serious consequences of substance use are typically associated with severe or dependent use. The Global Burden of Disease study estimated that in 2010, more than 24 million people globally were dependent on stimulants, with most (17 million) being dependent on amphetamines (Degenhardt et al., 2014). This equated to an estimated point prevalence of amphetamine dependence of 0.25% (0.22% – 0.28%) and of cocaine dependence of 0.10% (0.09% – 0.11%). Globally, the 12-month prevalence of amphetamine dependence has been estimated to be 0.1% – 0.7%, slightly lower than that of cannabis (0.1% – 1.5%) and consistent with that of opiates (0.1% – 0.8%) (Degenhardt and Hall, 2012a).

There are significant regional differences in the type of stimulant used in the general population. Cocaine use is estimated to be more common in North America (Degenhardt et al., 2008b), while amphetamine use is more common in Oceania (United Nations Office on Drugs and Crime, 2011a; Degenhardt et al., 2008c; Degenhardt and Hall, 2012a). Amphetamine is more widely used than methamphetamine in Europe and Scandinavia (Griffiths et al., 2008), but there are some significant differences between individual countries (United Nations Office on Drugs and Crime, 2011a). South East Asia has been described as the “global hub” of methamphetamine production and use (McKetin et al., 2008), accounting for more than 60% of global methamphetamine seizures and more than half of the world’s methamphetamine users. In South East Asia, Australia and New Zealand, methamphetamine has been the most widely used stimulant, however there has also been a recent increase in the usage of MDMA (Australian Institute of Health and Welfare, 2008; Degenhardt et al., 2009b).

These regional differences in stimulant use are also reflected in estimates for stimulant dependence. The Global Burden of Disease study reported higher rates of any stimulant dependence in North America, South East Asia and Australasia; cocaine was the main substance of dependence in North America, while amphetamine or methamphetamine dominated in Australasia and South East Asia (Degenhardt et al., 2014). Estimated patterns of burden due to stimulants mirrored those prevalence differences: overall amphetamines were estimated to account for 38 disability adjusted life years (DALYs) per 100,000 population, compared with 16 per 100,000 for cocaine. More than half of amphetamine-related DALYs were in Asia and Oceania, and nearly half of cocaine-related DALYs were in the Americas (Degenhardt et al., 2014).

Amphetamines have become an emerging problem in the USA: the RAND Corporation has estimated that in the USA in 2005 amphetamines accounted for nearly 900 deaths, the loss of more than 44,000 quality adjusted life years and an annual economic burden of approximately $US 23 billion. Health care comprised only a minority of amphetamine-related costs: the greatest costs were due to impacts on quality of life, premature death, policing and justice (Nicosia et al., 2009; Steinberg, 2009).

Stimulant use and dependence in Australia

In Australia, the National Drug Strategy Household Drug Survey (NDSHDS) has reported on rates of illicit drug use every three years since 1985, with data currently available to 2010 (Makkai and McAllister, 1998; Adhikari and Sumerill, 2000; Australian Institute of Health and Welfare, 2002; Australian Institute of Health and Welfare, 2005; Australian Institute of Health and Welfare, 2008; Australian Institute of Health and Welfare, 2011). Between 1998 and 2010 methamphetamine has been the most commonly used stimulant in Australia, with prevalence of lifetime use varying between 6% and 8%. The prevalence of recent (12-month) use of stimulant drugs has varied between 2% and 3% of the population. However self-reported use of both cocaine and ecstasy has increased steadily since 1995 and ecstasy use has overtaken methamphetamine use in the two most recent surveys, conducted in 2007 and 2010 (Australian Institute of Health and Welfare, 2011).

These surveys provide valuable information about stimulant use at a population level, but also have limitations. Population surveys of drug use may underestimate prevalence as they sample conventional households, under-represent drug use “hotspots” and high risk subgroups, and may be sensitive to the effect of stigma on self-report (McKetin et al., 2005). Data on individual drugs reflects the substances that individuals believe they have purchased and consumed, however drug seizure data often shows little relationship between the apparent and actual content of stimulant drugs. Many tablets sold as ecstasy contain little or no MDMA but include other stimulants such as methamphetamine, or a range of non-psycho-active substances (United Nations Office on Drugs and Crime, 2011a).

Several aspects of these estimates are relevant to the current research and to understanding any potential impact of stimulant use on psychosis in Australia. First, while the overall prevalence of stimulant use is low, this represents an estimate for the whole population aged over 14. In Australia as in other Western countries, stimulant use is most prevalent in males (Adlaf et al., 2005; Degenhardt et al., 2007b; Substance Use and

Mental Health Services Administration, 2010), especially in their late teens or twenties (Durell et al., 2008; Substance Use and Mental Health Services Administration, 2010; Wilkins et al., 2006), and this the population group who are also at highest risk for psychosis. In 2010, the rate of recent substance use in Australian males aged 20-29 ranged from 6.8% for methamphetamine to 11.4% for MDMA (Australian Institute of Health and Welfare, 2011). Stimulant use is also associated with other risk factors for psychiatric illness including social marginalisation, lower education, a family history of mental health or drug problems, prior anxiety and depressive symptoms and the use of other drugs (Russell et al., 2008; Degenhardt et al., 2007b; Degenhardt et al., 2007c; Degenhardt et al., 2008c; Degenhardt et al., 2009b). This concentration of use implies that stimulants may have potentially greater effects than their 2-3% population prevalence may suggest, precisely because their rate of use is highest in people who are most vulnerable to psychosis. Chapter 2 will review the rate of stimulant abuse and dependence in people with psychosis, and examine whether this rate is higher in Australia than in other comparable countries.

Second, the changing patterns of stimulant use, changing fashions in the particular type of stimulant drug used and inherent inaccuracy in individual's self-report of the type of drug used mean that it is important to examine all stimulant drugs (amphetamine, cocaine, ecstasy) rather than limit investigation to only one of these drugs.

Third, serious drug-related harms are most likely to occur in conjunction with more frequent or dependent use, higher potency forms and riskier routes of administration such as intravenous injection (Degenhardt et al., 2008c). Therefore when examining stimulant-related harms such as psychosis, estimates of dependent use or abuse are more relevant than estimates of use. In Australia the prevalence of dependent stimulant use has been estimated by indirect (benchmark/multiplier) methods (McKetin et al., 2005). Among persons aged 15-49 years these methods produce an estimated 12-month prevalence of monthly amphetamine use of 1.0%, and dependent amphetamine use of 0.7%. Chapter 3 of this thesis aims to supplement these estimates with direct estimates of stimulant abuse and dependence drawn from a national household survey.

Dependent stimulant use is associated with serious health harms such as cardiovascular and cerebrovascular disease, infection with hepatitis, HIV or other blood borne viruses, and psychiatric symptoms (Darke et al., 2008). Amongst the most serious of the psychiatric symptoms is psychosis.

The impact of psychosis

Before considering the specific relationship between stimulant use and psychosis, this section briefly reviews evidence regarding the impact and nature of psychosis. Psychotic disorders are “a diverse group of illnesses that have their origins in abnormal brain function and are characterised by fundamental distortions of thinking, perception and emotional response” (Morgan et al., 2011).

Psychoses have been called the “most mysterious and costly of illnesses” (van Os and Kapur, 2009). They may cause distress and disability due to a diverse range of positive psychotic symptoms, negative symptoms, cognitive impairments and disturbances of affect, behaviour and social functioning. They have a substantial adverse impact on affected individuals, their families, health systems and society because they are often disabling conditions which commence early in life: more than three quarters of incident cases occur before the age of 30 (Kessler et al., 2007; Morgan et al., 2011). Treatments are only partly effective. It has been estimated that current treatments, even if optimally delivered, can only avert 22% of the burden of schizophrenia (Andrews et al., 2004).

The World Health Report estimated that schizophrenia and bipolar disorder together account for at least 5% of total disability for people aged 15-44 (World Health Organisation 2001). The Global Burden of Disease study has estimated that schizophrenia and bipolar disorder together account for around 14% of the total mental health-related disability (Whiteford et al., 2013). Psychosis accounts for more than 1% of total Australian health expenditure and is estimated to cost Australian society Aus$ 4.9 billion annually (Neil et al., 2014).

There is increasing evidence that effective interventions in early psychosis may influence the course of illness (McGorry, 2010; Gafoor et al., 2010; Addington and Addington, 2009; Birchwood et al., 2000). A significant proportion of people with established psychoses such as schizophrenia may also have positive symptomatic and functional outcomes (Leamy et al., 2011 ; Warner, 2009). It is therefore critical to understand the factors that may influence the onset and course of psychosis, especially those that might lead to opportunities for prevention or intervention and thus lead to better outcomes. Psychoactive substances such as cannabis and stimulants are one such potentially remediable factor.

Current models of psychosis

Psychoses are seen as neurodevelopmental disorders in which genes and early environment interact to produce abnormalities in brain structure and function, manifesting at critical stages of brain development such as adolescence (Weinberger, 1987; DeLisi, 1997; Keshavan, 1999). Psychoses have a significant genetic component: up to 80% of variation in the illness may be heritable (Keshavan et al., 2011), however genetic influences appear to involve small effects from large numbers of candidate genes (Mitchell and Porteous, 2011; Insel, 2010) and concordance in monozygotic twins is no more than 50% (Insel, 2010).

Genetic susceptibility to psychoses appears to be shared with a broad range of other neurological and psychiatric conditions (Jacka and Berk, 2014). These interact with environmental exposures occurring either in intrauterine development (such as hypoxia or maternal influenza), during adolescent brain development, or both; “the model that emerges is of an early insult, a latent period then emergence of psychosis in late adolescence or early development” (p189) (Insel, 2010). Abnormalities in dopamine pathways appear to play a role, particularly in positive psychotic symptoms (Insel, 2010). Dopamine has been described as “the wind of the psychotic fire” (Laruelle and Abi-Dargham, 1999), and all effective antipsychotics block dopamine D2 receptors (Keshavan et al., 2011).

Three emerging themes in understanding psychosis are relevant to studying the interaction between psychotic conditions and substances. First, the traditional Kraepelinian dichotomy of schizophrenia and manic-depressive psychosis has come under sustained attack (Tandon et al., 2009; Cuthbert and Insel, 2010). Psychoses are increasingly seen as heterogenous and overlapping syndromes rather than specific diseases. It has been argued that “schizophrenia is perhaps best seen as a category, such as cancer, epilepsy, or dementia” (p 260) (Silverstein et al., 2014). Indeed there have been calls for the term “schizophrenia” to be replaced (Henderson and Malhi, 2014).

Dimensional models of psychoses have been proposed instead of the categorical model (van Os and Kapur, 2009). DSM-5 includes a proposed set of psychosis descriptors with eight dimensions; hallucinations, delusions, disorganised speech, abnormal motor behaviour, negative symptoms, cognitive impairment, depression and mania (Heckers et al., 2013; Barch et al., 2013). This heterogeneity implies that when studying substance use in psychosis it is important to take a broad, multi-diagnostic approach rather than to limit study to a specific disorder such as schizophrenia.

Second, there is heterogeneity not only cross-sectionally in symptoms, but longitudinally in the ways in which psychotic disorders develop over time. Insel (Insel, 2010) has said "perhaps the most fundamental change from re-conceptualizing schizophrenia as a neurodevelopmental disorder is the notion of trajectory of illness" (p 190). There is increasing recognition that sub-syndromal psychotic symptoms are common in healthy populations, and that psychotic disorders may emerge initially as brief, transient or poorly differentiated clinical syndromes before evolving into more clearly defined illnesses. A spectrum model (van Os and Kapur, 2009) has been proposed whereby up to 10-20% of the population may have a broad vulnerability to psychosis, and 2-3% have a lifetime prevalence of a "complex multi-dimensional psychotic syndrome" which includes episodes of brief psychotic syndromes. A further subset (0.5 – 1% of the population) have a severe vulnerability expressed as schizophrenia.

Clinical staging models for psychosis have been developed, for example Yung and McGorry (Yung and McGorry, 2007; McGorry, 2010) have proposed a five-stage model ranging from at-risk and prodromal states to severe and enduring psychosis. This view of psychosis is relevant to studying substance comorbidity. It suggests the need to study individuals at different stages of psychosis and to assess whether the associations of substance use are specific to that stage or reflect a broader pattern also found in other stages. It is also important to assess whether substance use increases the likelihood of progression through different stages of psychosis.

Third, there is increasing evidence that genetic and neurodevelopmental factors interact with the social environment to influence the development of psychosis. Urban location, migration and marginalised or minority status are consistently and independently associated with psychosis (van Os et al., 2010; McGrath, 2007; McGrath et al., 2004; Bourque et al., 2011). Possible explanations for these associations include the impact of trauma, social marginalisation and "social defeat" (van Os et al., 2010; Krabbendam et al., 2014), perhaps mediated through stress-related mechanisms (Jacka and Berk, 2014).

These findings also have implications for the study of comorbid substance use in psychosis, since many of these risk factors for psychosis are also risk factors for substance use and other psychiatric syndromes (Jacka and Berk, 2014). Therefore studies of substance use in psychosis should ideally measure common risk factors which may potentially confound the relationship between substances and psychosis, such as urban location, migrant status and disadvantage.

Substance comorbidity in psychosis

Substance misuse is common throughout all stages of psychosis. It occurs in up to half of people with first episode psychosis (Wisdom et al., 2011; Green et al., 2005; Addington and Addington, 2007; Wade et al., 2005; Grech et al., 2005; Archie et al., 2007) and schizophrenia (Regier et al., 1990; Kavanagh et al., 2004; Moore et al., 2012b). People with psychosis use cannabis at least ten times more frequently than the general population of the same age (Green et al., 2005; Koskinen et al., 2010; Degenhardt and Hall, 2012b).

Debate continues about the nature of the association between various types of substance use and psychosis and the reasons for elevated rates of substance use in people with psychosis. The critical issue for the current research is that, regardless of the mechanisms involved, substance use is associated with clinically significant changes in the symptoms, course and outcome of psychosis.

Substance use is associated with earlier onset of psychosis (Foti et al., 2010; Large et al., 2011; Compton et al., 2009), and greater severity of positive psychotic symptoms both in early psychosis (Wade et al., 2007; González-Pinto et al., 2011; Sorbara et al., 2003; Grech et al., 2005) and in chronic psychotic disorders (Foti et al., 2010; van Os et al., 2002). People with psychosis who also use substances are less likely to continue their medication (van Rossum et al., 2009; Faridi et al., 2012; Wade et al., 2007) and less likely to remain engaged with follow-up care (Miller et al., 2009; Stowkowy et al., 2012). They are more likely to experience relapse or readmission (Hides et al., 2006; Sorbara et al., 2003; Wade et al., 2006a; Strakowski et al., 2007; Linszen et al., 1994) and involuntary hospitalisation (Opsal et al., 2011). They are more likely to have a continuous course of illness (Bertelsen et al., 2009) with lower rates of remission and recovery (Lambert et al., 2005; Petersen et al., 2008) and reduced function in social and other domains (Chouljian et al., 1995; Wade et al., 2007; González-Pinto et al., 2011; Menezes et al., 2009; Faber et al., 2012).

Conversely, following a first psychotic episode in young people, cessation of drug use is associated with better outcomes, increased remission and reduced rates of relapse (Wade et al., 2007; Gonzalez-Pinto et al., 2008; Strakowski et al., 2007; Baeza et al., 2009; Lambert et al., 2005).

The strength of the association between substance use and the symptoms, course and outcome of psychosis demonstrate the importance of further research in this area. The

level of suffering, disability and cost caused by psychosis is substantial. Understanding factors which may worsen psychosis or influence its course may lead to more effective prevention and care. At the point of first contact with mental health services, many of the risk factors for negative outcome in psychosis (such as genetic vulnerability, gender, early developmental exposures, childhood social functioning, age of psychosis onset and duration of untreated illness) are fixed and hence not amenable to intervention. Substance use is one of the few risk factors for the development of a more chronic psychosis which can be modified after a first psychosis presentation, along with adherence to care and the effectiveness of interventions and social support provided.

Cannabis and psychosis

Some of the studies cited above have examined the relationships between psychosis and the misuse of any substance. Many have specifically examined the role of cannabis use or abuse. Cannabis is the most widely used illicit drug, with international comparisons suggesting lifetime rates of cannabis use between 5% and 40% (Degenhardt et al., 2008b). Cannabis use is illegal in Australia but around 9% of Australians report using cannabis in the last twelve months, and around 33% report lifetime cannabis use (Australian Institute of Health and Welfare, 2008).

There is ongoing debate about the nature of the link between cannabis and psychosis. Cannabis has a number of active constituents, including delta-9 tetrahydrocannabinol (THC) and cannabidiols (Paparelli et al., 2011). THC seems primarily responsible for the impact on positive psychotic symptoms (Di Forti et al., 2009), perhaps through actions on dopamine pathways (Kuepper et al., 2010). The sensitivity to these effects may be subject to genetic variation (Genetic Risk Outcome in Psychosis Investigators, 2011; Henquet et al., 2008). Therefore cannabis may precipitate psychosis in vulnerable individuals (Degenhardt and Hall, 2006; Hall and Degenhardt, 2011) by interacting with other risk factors as a “component cause” (D'Souza et al., 2009). It may also cause a modest increase in the risk of developing schizophrenia in people without genetic vulnerability (Hall and Degenhardt, 2011). It has been estimated that around 8% of the population risk for psychosis can be attributed to cannabis (Thirthalli and Benegal, 2006), and that regular cannabis use is associated with a two- to three-fold increase in the relative risk of developing schizophrenia (Tandon et al., 2008; Hall and Degenhardt, 2011).

Different substances have different pharmacological actions, so it is likely that they may have different effects on the symptoms and course of psychosis. Stimulants have the

potential to worsen psychotic symptoms: their effects on people with psychosis may be different from or additive to those of cannabis. However the evidence regarding their impact in people with psychotic disorders is more limited than for cannabis.

The overlap between cannabis and stimulant use disorders

A critical issue for the current research is the substantial overlap between stimulant use and cannabis use. Between 80% and 100% of people with psychosis who use stimulants also report concurrent cannabis use (Wade et al., 2005; Tosato et al., 2013; Arndt et al., 1992; Baeza et al., 2009; Barrigon et al., 2010; Bersani et al., 2002; Brown, 1998; Dekker et al., 2012; Archie et al., 2007).

Cannabis use not only accompanies stimulant use, it typically precedes it, in a so-called "gateway" pattern (Degenhardt et al., 2009a). In the US National Comorbidity Study Replication, more than 96% of drug users used cannabis before using other illicit drugs (Degenhardt et al., 2009a). The second Australian national survey of psychosis found that more than 98% of people with psychosis who used stimulants had previously used cannabis (Power et al., 2014). In cohort studies cannabis use is one of the strongest predictors of later stimulant use (Degenhardt et al., 2007c). Therefore it is not possible to examine the effects of stimulant use disorders in people with psychosis without also considering and controlling for possible associations and impacts of cannabis.

Because of this overlap, studies examining "pure" stimulant use (i.e. without comorbid cannabis use) are rare. They have mainly been limited to two types of study. First, some studies have examined clinical samples of people seeking treatment for specific problems of amphetamine dependence. This includes a group of studies from the UCLA Methamphetamine Treatment Project (MTP), a randomised trial of clinical interventions for methamphetamine dependence conducted over 8 sites in California and other US states (Glasner-Edwards et al., 2010a; Glasner-Edwards et al., 2008b; Rawson et al., 2004; Glasner-Edwards et al., 2010b; Glasner-Edwards et al., 2009; Gonzales et al., 2011; Glasner-Edwards et al., 2008a; Zweben et al., 2004). The MTP recruited more than 1000 people meeting DSM-IV criteria for methamphetamine dependence (Zweben et al., 2004), and is the largest trial of clinical intervention for this condition. It has provided very valuable information on treatment, which is discussed further in Chapter 10. However the requirements of a treatment trial limit the extent to which the MTP can be used to understand the prevalence or impact of stimulant use disorders in people with serious mental health disorders such as psychoses. Follow up studies of the MTP cohort showed

that nearly half of those followed up had significant psychopathology, including significant rates of depression, anxiety, and antisocial personality disorder (Glasner-Edwards et al., 2010b; Glasner-Edwards et al., 2008a; Glasner-Edwards et al., 2009; Glasner-Edwards et al., 2010a). Significant rates of psychotic experiences were also described: at three-year follow up 4.9% had a current psychotic disorder (Glasner-Edwards et al., 2010b) and 13% met criteria for a past psychotic disorder (Glasner-Edwards et al., 2008b). However, the MTP excluded participants initially meeting DSM-IV criteria for dependence on any other substance (such as alcohol or cannabis) or having other psychiatric conditions requiring immediate care or precluding a focus on treatment of methamphetamine dependence. People with language or intellectual difficulties, or with significant social instability were also excluded (Zweben et al., 2004), in order to ensure that people were able to participate fully and safely in treatment. As a result, those followed up at three years were predominately white, female, aged over 30, college-educated and employed (Glasner-Edwards et al., 2010b) . This makes it difficult to generalise to the clinical situations typically encountered in acute mental health services.

Second, there is a substantial literature from Japan, Thailand and Taiwan examining psychotic syndromes in methamphetamine users. South East Asian countries have high rates of methamphetamine use (McKetin et al., 2008) and researchers from these countries have contributed many of the studies examining the familial, genetic and pharmacological characteristics of methamphetamine-related psychoses (Bousman et al., 2009). Most of these studies use a diagnostic construct of “Methamphetamine Psychosis”, which is seen as including both acute and transient psychotic states (Kittirattanapaiboon et al., 2010) and psychosis which persists or recurs despite abstinence from stimulants (Sato et al., 1992; Suzuki et al., 2006; Yamamoto et al., 2007; Yui et al., 2000a).

Most Western psychiatrists would diagnose enduring psychotic states which continued after cessation of drug use as schizophrenia or related psychoses. However these authors distinguish chronic methamphetamine psychosis from schizophrenia on the basis of (i) a strict application of the exclusion criterion for substance abuse within the DSM criteria for schizophrenia and (ii) findings that persons with chronic or recurrent stimulant psychosis have fewer negative symptoms than persons with chronic schizophrenia (Tomiyama, 1990; Yeh et al., 2001; Yui et al., 2000b). Within contemporary views of schizophrenia, the absence of negative symptoms is not an exclusion criterion for diagnosis. Studies comparing chronic “methamphetamine psychosis” with schizophrenia find that the two conditions cannot be distinguished on the basis of their positive symptoms (Iwanami et al.,

1994b; Tomiyama, 1990), the factor structure of their symptoms (Srisurapanont et al., 2003), neurophysiological measures (Iwanami et al., 1994a) or response to treatment (Srisurapanont et al., 2001).

As well as these diagnostic differences, the patterns of drug use and the cultural, health service and legal context of drug use also differ substantially between Asian and Western countries. Cannabis use is less frequent in Asian countries than Western countries (United Nations Office on Drugs and Crime, 2011b), and this is reflected in different patterns of drug use in clinical populations (Colfax et al., 2010) . For example a Taiwanese case-control study of adolescent amphetamine users found no cannabis use but a high proportion of comorbid betel-nut abuse (Yen and Chong, 2006). A study of more than 300 Taiwanese adults in detention with amphetamine abuse found less than 1% also used cannabis (Lin et al., 2004). In a Japanese cohort, less than half of injecting stimulant users had a lifetime history of cannabis use (Matsumoto et al., 2002). Therefore, while these studies provide important insights into possible mechanisms underlying psychosis in methamphetamine use, it is difficult to generalise from these studies to understand the correlates or impacts of stimulant use in people with psychosis who misuse amphetamines in combination with cannabis and other substances, such as are commonly encountered in North American, English and Australian mental health systems.

The overlap between cannabis and stimulants described in this section creates a significant methodological challenge for understanding the relationship between stimulants and psychosis. If the majority of people with psychosis who use stimulants also use cannabis, it is very difficult to separate the associations and impacts of stimulants from those of cannabis. Even very large clinical studies may not have sufficient statistical power to examine stimulant drugs. For example, several recent clinical studies have reported on samples of more than 300 young people with first episode psychoses (Petersen et al., 2007; Wobrock et al., 2013; Van Mastrigt et al., 2004; Lambert et al., 2005; Larsen et al., 2006). However, none have reported on the characteristics of those young people who used stimulants.

Stimulants and psychosis

The first clinical descriptions of psychosis associated with amphetamine abuse appeared in the 1930s, within five years of the commercialisation of amphetamines (Angrist et al., 1974; Curran et al., 2004). Connell's seminal 1958 Maudsley Monograph (Connell, 1958) described 200 cases of amphetamine-related psychosis. Since that time, it has become

clear that amphetamine abuse may trigger psychotic experiences and states (Angrist et al., 1974; Caplehorn, 1990; Harris and Batki, 2000; McKetin et al., 2006b; Curran et al., 2004; Darke et al., 2008). Amphetamine-related psychoses have therefore been studied as important phenomena in their own right and also as a possible model for understanding the mechanisms of psychosis and the development of schizophrenia (Hermens et al., 2009; Machiyama, 1992; Sato et al., 1992; Snyder, 1973).

The evidence that stimulants may precipitate or worsen psychotic symptoms comes from several types of study. First, in experimental challenges, high dose amphetamines can induce acute reversible psychotic symptoms in volunteer subjects who do not have any apparent vulnerability to psychosis (Angrist et al., 1974; Griffith et al., 1972).

Second, there are high rates of brief and transient psychotic symptoms reported by recreational stimulant users. Hall (Hall et al., 1996) examined 301 recreational amphetamine users: around 60% reported brief hallucinations or paranoia following stimulant use, compared with less than 20% who reported such symptoms prior to their first amphetamine use. In another large sample of recreational stimulant users, three quarters reported at least one psychotic symptom over a 12-month period, and nearly one quarter reported at least one clinically significant psychotic symptom (18% after excluding a people with a diagnosis of psychotic disorders) (McKetin et al., 2006b). Amongst homeless youth in Canada, more than half of methamphetamine users reported auditory hallucinations, a significantly higher rate than in other vulnerable young people (Martin et al., 2006). It has been estimated that recreational amphetamine users have a more than ten-fold increase in psychotic symptoms compared with general population (McKetin et al., 2006b) and up to a threefold increase in risk of psychotic symptoms compared to other young people (McKetin et al., 2010). These symptoms are dose-related, being associated with more frequent use, use of high potency forms (Hall et al., 1996), dependent use (McKetin et al., 2006b), or use in combination with other drugs (McKetin et al., 2010).

Third, regular amphetamine use is associated with hospital admission for brief psychotic syndromes such as drug-induced psychosis. A study of Australian hospital admission data suggested that amphetamine users had a significantly higher risk of admission to hospital for psychosis than cannabis users, and that this risk increased with age: for drug users aged over 30, the estimated risk of hospital admission with drug-induced psychosis was more than eight times higher for amphetamine users than for cannabis users (Degenhardt et al., 2007d).

Fourth, amphetamines increase psychotic symptoms in people with schizophrenia and other psychotic disorders (Lieberman et al., 1990; Angrist et al., 1980). Curran (Curran et al., 2004) reviewed 26 studies which reported on experimental amphetamine challenge in persons with schizophrenia. These found an increase in positive psychotic symptoms (such as hallucinations), especially for those who were already experiencing hallucinations: 28% of persons in remission at the time of the challenge experienced a recurrence of psychotic symptoms, and 51% of people with current symptoms deteriorated.

Fifth, the evidence reviewed above provides a plausible theoretical link between stimulant use and worsening of psychotic symptoms. Stimulants act to increase synaptic dopamine, and increased dopamine activity is particularly associated with positive psychotic symptoms (Insel, 2010; Di Forti et al., 2009). In experimental challenges, psychotic symptoms are associated with increased levels of the dopamine metabolite homovanillic acid (Angrist et al., 1974; Angrist and Gershon, 1974) and are blocked by the antipsychotic haloperidol, a dopamine receptor blocker (Angrist et al., 1974). Animal studies also provide indirect support for this link: amphetamine administration in rats and primates produces abnormalities of motor activity and behaviour which have some parallels to psychosis and which are also blocked by administration of haloperidol (Curran et al., 2004; Sato et al., 1992; Ujike, 2002).

Summary

This introduction has highlighted issues relevant to the design of the studies presented in this thesis, rather than attempting to systematically review all the evidence on the relationship between psychosis and stimulants or other substances. In summary, the key issues relevant to the design of the current research are:

Psychosis is a significant problem and it is important to understand any factors that might help to prevent its onset or modify its course. Substance disorders are one such factor, and are amongst the few risk factors which may be amenable to modification at the time of a person's first contact with mental health services.

Psychoses are increasingly seen as a heterogeneous spectrum of disorders which evolve through clinical stages and are influenced by social as well as personal and genetic factors. In understanding possible impacts of substance abuse on psychosis at a population level it is important to take a broad, multi-diagnostic and multi-stage approach

and to measure and control for personal and social factors such as age, gender, urban location, migration and disadvantage which may confound the relationships between psychosis and substances.

Most research on substance comorbidity in psychosis has focused on cannabis because it is the most commonly used drug both in the population and in people with psychosis. However stimulant use is also common and there are good reasons to be concerned about the potential role of stimulants in precipitating or worsening psychosis.

Studies of transient psychotic symptoms in recreational stimulant users have provided very important evidence about the relationship between stimulants and psychosis. However in understanding severe or enduring harms, it is important to complement these studies by examining (i) more severe and enduring psychotic syndromes and (ii) more severe or dependent stimulant use.

Evidence about the impact of stimulants on the onset and progression of psychotic disorders is limited, in part because of the substantial overlap of stimulants with cannabis disorders. This means that studies of very large samples are required in order to examine the effects of stimulants separately from those of cannabis. It also implies that any examination of stimulants in psychosis should also measure and control for concurrent cannabis use.

A role for epidemiological approaches?

This combination of challenges means that an epidemiological approach using linked data sets may be of particular value in examining the relationship between stimulants and psychosis. Using large, representative, population-based datasets it may be possible to measure many relevant confounding factors and to have sufficient scale and power to examine these complex relationships. Two types of dataset are likely to be of relevance: (i) household surveys of drug or mental health problems and (ii) large administrative data collections or registers drawn from routine mental health service data.

Household surveys of substance and/or mental health problems have formed the basis for some of the evidence already reviewed above. Advantages of these surveys include their large scale, control over sampling, representativeness, and use of standardised measures to allow comparison between jurisdictions or over time. These studies are discussed further in Chapter 3. They include the US Epidemiological Catchment Area (ECA) study

(Regier et al., 1990), US National Comorbidity Survey (Kessler et al., 2001) and its 2001-2003 replication (Degenhardt et al., 2007a), International Consortium on Psychiatric Epidemiology (Vega et al., 2002), WHO World Mental Health Survey Initiative studies (Gureje et al., 2006; Jacobi et al., 2004; Lee et al., 2007; Stein et al., 2008), UK National Substance Use Survey (Coulthardt et al., 2002) and New Zealand Mental Health (Wells et al., 2006) and National Drug Surveys (Wilkins and Sweetsur, 2008). Many of these studies include estimates of stimulant use. However, few measure stimulant dependence, and even fewer measure psychotic symptoms or syndromes. Using data from the early 1980's the ECA study (Regier et al., 1990) reported a lifetime prevalence of amphetamine dependence or abuse of 1.7%. Since that time, no population study has reported on rates of stimulant dependence diagnosed according to standardised diagnostic criteria.

Health service data collections provide a second source of epidemiological data. The low prevalence of psychotic disorders makes them difficult to study in household surveys. However, most people living with psychotic illnesses have contact with health services (Jablensky et al., 2000; Morgan et al., 2011) and therefore health service data may be particularly helpful in research into psychotic disorders (Morgan and Jablensky, 2010; Byrne et al., 2005). As well as traditional case registers there is increasing scope to derive this information from electronic health records and administrative databases (Perera et al., 2009).

Three studies using population-level health service data demonstrate the particular potential for this approach in examining stimulant disorders in psychosis. Degenhardt and colleagues (Degenhardt et al., 2007d) examined data for all Australian hospital admissions over the decade to 2004 and calculated admission rates for cannabis and amphetamine-induced psychoses. They estimated that amphetamine users had a greater risk of admission with drug-induced psychosis than cannabis users and that this difference in risk increased with age. Callaghan and colleagues (Callaghan et al., 2012) used hospital discharge records from California to identify 42,412 people with methamphetamine-related conditions. Their risk of a later diagnosis of schizophrenia was significantly greater than matched controls with no substance disorders or with cocaine, alcohol and opioid disorders but similar to the risk for those with cannabis disorders. Niemi-Pynttari and colleagues (Niemi-Pynttari et al., 2013) used the Finnish Hospital Discharge Register to examine 18,478 people with diagnoses of drug-induced psychosis. They found that people with diagnoses of stimulant-induced psychosis had lower risk of receiving a later diagnosis of schizophrenia than people with a cannabis-induced psychosis. These last two studies

are currently the only published studies examining whether cannabis and stimulant disorders are associated with different risks of progression to a diagnosis of schizophrenia. The differing findings of these studies underline the need for further examination of this issue.

Epidemiological approaches can complement clinical studies, but also have important limitations. They are powerful tools for identifying candidate risk factors, and contributing to hypotheses about the causes and development of psychosis (McGrath, 2007), but cannot by themselves demonstrate causation (McGrath, 2008).

The current research

This research examines the relationship between stimulant dependence and psychotic disorders. It examines the rate and correlates of stimulant disorders in people with psychosis, and the potential impact of stimulant disorders on progression to successive stages of psychosis. The specific research questions that are addressed are summarised at Figure 1.1.

The research uses epidemiological approaches. Chapters 3 and 4 use data from a national household survey, the second Australian National Survey of Mental Health and Wellbeing (NSMHWB), (Slade et al., 2009). This nationally representative household survey was conducted in 2007 by the Australian Bureau of Statistics (ABS). It collected data on common mental disorders and substance use disorders using standardised diagnostic criteria. The survey also collected data on other personal and family risk factors for psychosis, and included screening questions on psychotic symptoms and experiences.

Chapters 5 to 9 use health service administrative data for state-operated hospital admission and community mental health contacts for the state of New South Wales (NSW), Australia. The organisation of Australian health services means that state-operated services have primary responsibility for the care of psychosis, and therefore this data includes most people with psychotic disorders in a population of more than 7 million people over a period of more than ten years.

The design of each component study will be described within each chapter. However, all studies were designed to address the specific methodological issues described in this introduction. They focus on severe stimulant use, including people with diagnoses of stimulant abuse or dependence. They focus on psychotic syndromes rather than

symptoms, and take a broad, multi-diagnostic approach including brief, atypical and drug-induced psychoses, affective psychoses and schizophrenia. They consider different stages of psychosis, and separately examine the prevalence, correlates and impacts of stimulant disorders in the general population, in early psychosis and in enduring psychoses such as schizophrenia. They measure rates of cannabis use disorders, and seek to control for the effects of cannabis disorders and to assess the additive effects of cannabis and stimulants on psychosis outcomes. They measure personal and social factors which may confound the relationship between stimulants and psychosis (age, sex, migration, urban location, social disadvantage) and seek to control for these where relevant.

All studies examined stimulant disorders as a group, combining amphetamine, methamphetamine, MDMA and cocaine into a single “stimulant” category. The principal reason for combining stimulant drugs in this way us that most of the data sources used in this research do not consistently or reliably distinguish individual stimulant drugs. Chapter 2 reviews studies examining rates of stimulant use in people with psychosis: up to a third of such studies report on stimulant use as a combined category rather than reporting on specific stimulant drugs. Chapters 3 and 4 examine data from Australia’s National Survey of Mental Health and Wellbeing (NSMHWB). That survey asks about individual stimulant drugs when quantifying substance use. However, it combines stimulant drugs when examining abuse, dependence and impacts, reporting only on a combined “stimulant” category. Chapters 5 to 9 examine administrative data from NSW hospital and community mental health services, using ICD-10 diagnoses recorded by mental health clinicians and medical records coders. Diagnostic precision is an important limiting factor in using large administrative datasets (Morgan and Jablensky, 2010; Mortensen, 1995) and focusing on broader diagnostic groupings may be one strategy for limiting this imprecision. ICD-10 distinguishes cocaine disorders (F14.x) from other stimulant disorders (F15.x), and allows the option of coding specifically for methamphetamine-related disorders at the second decimal place (F15.x1). However in practice, clinicians and coders rarely use the lowest levels of coding. Specific diagnostic codes for methamphetamine disorders are rarely entered and could not be used to consistently distinguish methamphetamine use disorders from other stimulant disorders (such as MDMA use disorders). While ICD-10 distinguishes cocaine-related disorders from other stimulant disorders, cocaine disorders were hypothesised to be less frequent in Australian mental health services, and anecdotal feedback from Australian clinicians was that many are likely to document terms such as “stimulant abuse” when seeing people with cocaine abuse.

Two further factors contribute to the decision to consider stimulant drugs as a broader group. First, there are significant regional differences in the type of stimulant used, with cocaine being the most widely used stimulant in North America and amphetamine-related stimulants dominating in Australia and South East Asia (United Nations Office on Drugs and Crime, 2011a; Degenhardt et al., 2008c; Degenhardt and Hall, 2012a). Therefore when comparing data globally, differences between individual stimulant drugs may also be confounded by other regional differences. Second, individuals often use more than one type of stimulant drug. In particular ecstasy use often overlaps with amphetamine and other drug use (Degenhardt et al., 2009b; Kinner et al., 2008; Keyes et al., 2008). Therefore attempting to distinguish between specific stimulant drugs would require research designs which compared at least four groups of people with stimulant use disorders; (i) those with cocaine use disorders (ii) those with methamphetamine or ecstasy use disorders (iii) those with multiple stimulant use disorders and (iv) those with unspecified stimulant use disorder. All planned analyses in these studies aimed to examine the overlap of stimulant use disorders with cannabis disorders and to compare these with people with no substance disorders. Adding four or more subcategories of stimulant disorder would add substantially to the complexity of planned analyses, while reducing their statistical power. Because a large proportion of people would be likely to be in mixed or unspecified stimulant disorder groups, this increase in complexity would be unlikely to be accompanied by additional explanatory power. Combining amphetamine, MDMA and cocaine use disorders into single stimulant use category does create limitations, and these are discussed further in Chapter 10.

LITERATURE REVIEW

n = *Chapter number.*

2	Internationally, what is the prevalence of stimulant use disorder in people with psychosis?
2	Are there regional or national differences in the prevalence of stimulant use disorders in people with psychosis?
2	What person or service factors are associated with variations in prevalence?

PART 1: THE AUSTRALIAN POPULATION

3	What is the prevalence of stimulant use disorders in the Australian population?
4	What are the characteristics of people with stimulant use disorders in Australia?
4	Are stimulant use disorders more common in people with other risk factors for psychosis?

PART 2: EARLY PSYCHOSIS

5	Is greater stimulant availability in the community associated with more frequent admission for psychosis?
6	What is the prevalence of stimulant use disorders in people with first admission psychosis?
6	What are the correlates of stimulant use disorders in people with first admission psychosis?
7	Are stimulant use disorders associated with readmission in the first two years of psychosis?

PART 3: SCHIZOPHRENIA

8	Are stimulant use disorders associated with increased risk of progression to schizophrenia over five years?
9	What is the prevalence of stimulant use disorders in people with schizophrenia?
9	What are the correlates of stimulant use disorders in people with schizophrenia?
9	In people with schizophrenia, are stimulant use disorders associated with frequent service use, physical health problems or housing instability?

Figure 1.1. Overview of research questions.

2: Stimulant use disorders in psychosis – a meta-analysis

This chapter is based on the manuscript: **Sara G, Large M, Matheson S, Burgess PM, Malhi G, Whiteford H, Hall W (2014). Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation.**

Australian and New Zealand Journal of Psychiatry. In press.

ABSTRACT

Objective

Stimulant abuse and dependence often complicate the care of people with psychotic disorders. This study systematically reviews prevalence estimates reported for stimulant abuse and dependence in people with psychotic disorders, and examines personal, clinical, regional and methodological factors which explain variation in these rates.

Methods

PsychINFO, EMBASE and MEDLINE (1946 - 2013) were searched systematically for studies reporting on stimulant drug use disorders in representative samples of people with psychotic disorders. Random effects models estimated the pooled rate of a stimulant use disorder, defined to include stimulant abuse and stimulant dependence. Study characteristics associated with heterogeneity in rates of stimulant use disorder were examined by subgroup analyses for categorical variables, by meta-regression for continuous independent variables and by multiple meta-regression.

Results

64 studies provided 68 estimates of lifetime or recent stimulant use disorders in 22,500 people with psychosis. The pooled rate of stimulant use disorder was 8.9% (95% CI 7.4% - 10.5%). Higher rates of stimulant use disorders were reported in studies of affective psychosis, studies from inpatient settings, studies from the USA and Australia, and studies with higher rates of cannabis disorder; in multiple meta-regression analysis these factors

explained 68% of between-study variance. Rates of stimulant use disorder were stable over time, and unrelated to age, gender, stage of psychosis, type of stimulant drug or study methodology factors.

Conclusions

Reported rates of stimulant use disorder in people with psychosis are much higher than in the general population but vary widely and are associated with regional, service setting and clinical differences between studies. It is likely that stimulants contribute to the overall burden of psychosis, and that social and environmental factors combine with drug and illness-related factors to influence stimulant use in psychosis.

INTRODUCTION

Amphetamines, cocaine and other stimulants are the most widely used illicit drugs after cannabis in developed countries (United Nations Office on Drugs and Crime, 2011a). They are most commonly used by males in their late teens and early twenties, who are also the group most at risk for the development of psychotic disorders (Adlaf et al., 2005; Degenhardt et al., 2007b; Durell et al., 2008; Substance Use and Mental Health Services Administration, 2010; Wilkins et al., 2006). In 2007, around 3% of Australians, including more than 8% of men aged 16 to 29, met criteria for a lifetime stimulant use disorder (Sara et al., 2011a).

Stimulants may have harmful effects across the spectrum of psychotic disorders and, along with cannabis, may play a causal role in some episodes of psychosis (Sara, 2012). Many regular stimulant users report transient and dose-dependent psychotic symptoms (McKetin et al., 2006b). Stimulants can precipitate brief syndromes of drug-induced psychosis (Bramness et al., 2012; Crebbin et al., 2009), sometimes diagnosed as "methamphetamine psychosis" (Kittirattanapaiboon et al., 2010; Yui et al., 2000b). Stimulant exposure can worsen existing psychotic symptoms or precipitate relapse among people with established psychotic disorders such as schizophrenia (Curran et al., 2004). The effects of stimulants on psychosis are more common in people with patterns of severe or dependent stimulant use (McKetin et al., 2013; Chen et al., 2003), and stimulants such as methamphetamine may be more potent than cannabis in precipitating psychotic symptoms (McKetin et al., 2013). Therefore, knowing the rate of severe or dependent stimulant use in people with psychosis may help in understanding whether stimulant drugs contribute significantly to the overall burden of psychosis.

Studies of people with psychosis have reported rates of stimulant use disorder which range from below 4% (Compton et al., 2005; Hambrecht and Häfner, 1996; Martins and Gorelick, 2011) to more than 30% (Gearon and Bellack, 2000; Sevy et al., 1990). In a population cohort of people with a diagnosis of schizophrenia in NSW, 14% also had a diagnosis of a stimulant use disorder (Sara et al., 2014c). This wide variation between studies may reflect differences in the personal, clinical or social characteristics of the people with psychosis who were included in the study. Delineating these factors would help in understanding which groups of people with psychosis may be at greater risk of stimulant-related harms. There are also significant regional differences in stimulant use in the general population (United Nations Office on Drugs and Crime, 2011a; Agar and

Reisinger, 2004; Degenhardt et al., 2008c). If stimulants contribute to the overall burden of psychosis then stimulant use disorders in people with psychosis may be more common in regions where stimulant use is also more common in the general population. Rates of stimulant use may also be influenced by the subtype or stage of psychosis; several studies of people with a first episode of schizophrenia-spectrum or affective psychosis have reported rates of stimulant use or dependence between 15% and 30% (Hides et al., 2006; Mauri et al., 2006; Rabinowitz et al., 1998; Ruiz-Veguilla et al., 2009; Sara et al., 2013; Wade et al., 2005). Cannabis use often precedes or accompanies stimulant use (Degenhardt et al., 2009a; Power et al., 2014) and cannabis disorders are one of the strongest predictors of later stimulant disorder (Degenhardt et al., 2007c). Therefore in examining stimulant use disorders it is also important to measure and control for cannabis use disorders.

The wide between-study variation in rates of stimulant use disorder in people with psychosis may also be due to methodological differences between studies: rates of stimulant use disorder are likely to be influenced by issues including the period examined (lifetime or recent stimulant use), the inclusion or exclusion of specific stimulant drugs (amphetamine, cocaine, ecstasy), or whether drug-induced psychoses were included or excluded.

The first aim of this study is to synthesize the results of primary research through meta-analysis, in order to derive a pooled estimate and range for the rate of stimulant use disorder in people with psychosis. The second aim of this study is to identify whether between-study variation in the rate of stimulant use disorder is systematically influenced by personal, clinical or social factors, or whether this heterogeneity is better explained by methodological differences between studies.

METHODS

The methods conformed to the guidelines for Meta-analysis of Observational Studies in Epidemiology (Stroup et al., 2000).

Data Sources

PsychINFO (1967 - 2013), EMBASE (1974 - 2013) and MEDLINE (1946 - 2013) were searched systematically for peer-reviewed English-language publications reporting rates of substance use in people with psychosis. To identify potential studies for examination in full

text, titles, abstracts and keywords were searched for “Schizophrenia OR Psychosis OR Psychotic OR Bipolar OR Mania OR Manic OR Prodrome OR Prodromal” AND “Substance OR Dual Diagnosis OR Drug Abuse OR Cannabis OR Amphetamine OR Methamphetamine OR Stimulant OR Cocaine”. The search strategy was broad, including any substance use disorder or cannabis disorder, because rates of stimulant use disorder are often reported as incidental findings without mention of stimulants in the study’s title, key words or abstract. The reference lists of identified studies and key literature reviews were hand-searched for further relevant studies.

Study selection and data extraction

Studies were included if they reported the recent or lifetime prevalence of stimulant use disorders in people with a diagnosed psychotic disorder. We accepted the diagnostic method used by the original study to identify and define stimulant use disorders and psychosis. Stimulant Use Disorders were defined to include DSM or ICD categories of abuse and dependence, or, where these were not applied, levels of use characterised by the original study as “abuse”, “problem use”, “severe use” or “harmful use”. Studies that reported stimulant use but did not report on rates of stimulant use disorder were excluded. Stimulants included unspecified stimulants or any specific stimulant drug identified through chemical or common names including amphetamine, methamphetamine, ice, cocaine/crack, or ecstasy/MDMA. Psychoses included commonly used diagnostic categories (schizophrenia, schizo-affective disorder, affective psychosis, brief, atypical and drug-induced psychoses) or prodromal states.

Studies were included if they described rates of stimulant use disorder in representative clinical populations of people with psychosis, such as successive admissions or referrals from a defined catchment area or population. We excluded studies whose sampling framework rendered them non-representative or were likely to systematically influence the estimated prevalence of substance use disorders, such as clinical samples from dual diagnosis programmes, groups with only drug-related psychoses (such as “methamphetamine psychosis”), studies where groups were selected to obtain matched samples of people with and without substance comorbidity, and studies excluding people with substance use or dependence. Some studies had inclusion or exclusion criteria which were ambiguous or had the potential to distort prevalence estimates, such as referrals from clinical services to specialist treatment trials or imaging studies. If the study authors explicitly excluded people with substance use disorders, then these studies were excluded

from this review. However, even where substance use disorders were not explicitly excluded, people with comorbid substance use disorders may have been less likely to be referred for these studies. Therefore these studies were flagged for subgroup analysis rather than being excluded. Some representative samples allowed the inclusion of people with drug-induced psychoses within a larger multi-diagnostic sample: these studies were included in this review, but were flagged for subgroup analysis. In order to reduce the probability of chance results from very small samples, we defined an arbitrary minimum sample size of 15 people.

Two authors selected the studies according to our inclusion criteria and extracted data independently. These authors were a psychiatrist (GS) and a psychologist (SM) who both had prior experience in data extraction for systematic reviews. Multiple published studies based on a single clinical sample were examined for possible overlap; a single estimate was obtained from the most complete study reporting on those participants. One published conference abstract was identified which included all relevant data and was not otherwise reported: this was included in the review. Differences between raters were resolved by a joint examination of papers.

Definition of outcome and moderator variables

The primary outcome measure was the rate of stimulant use disorder in each study, expressed as the number of people with stimulant use disorder divided by the number of participants with psychosis in the study. Recency of drug use was classed as either “Recent” (within previous 12 months) or “Lifetime” (greater than 12 months). Psychosis diagnoses were grouped into “Schizophrenia Spectrum” (including schizophrenia, schizoaffective disorder and schizophreniform psychoses), “Affective Psychoses” (bipolar disorder, psychotic depression), “Other Psychoses” (brief, atypical and drug-induced psychotic disorders), and “Mixed” (diagnostic subtype mixed or unspecified).A binary variable was constructed to indicate whether persons with substance-induced psychosis were included or excluded. Stage of psychosis was classed as “Prodromal” (including prodromal, pre-psychotic, ultra high risk or comparable states), “First Episode” (first episode psychosis, first hospitalisation or first contact with a specialist early psychosis service), “Established illness” (ongoing or chronic illness, diagnoses limited to schizophrenia only, contact with extended care or rehabilitation services) or “Mixed” (stage of illness mixed or not specified). Where reported, the rate of recent or lifetime cannabis use disorder was recorded. Where a study collected data over several years, the year of

collection was taken as the midpoint of the study period. Where year of collection was not reported, it was estimated by calculating the average time-lag between collection and publication for other studies in the review where this data was available, and subtracting this from the publication year. Country, location within country (urban, rural, mixed or unspecified) and service setting (inpatient, community, mixed or not specified) were recorded.

Data were extracted on study design and eight strength of reporting variables: the use of research interviews in (i) psychosis or (ii) substance disorder diagnosis; the use of standardised criteria (DSM or ICD) for (iii) psychosis or (iv) substance disorder; (v) the inclusion of biological assays (hair, urine or blood) in substance identification; (vi) missing demographic data for (sample average age or sex distribution); (vii) the use of an estimated year of collection and (viii) type of recruitment method (random/representative or non-random). A composite "strength of reporting" score was constructed by simple addition of these eight individual scores.

Meta-analysis

Analysis was conducted using Comprehensive Meta-analysis (CMA) Version 3, (Biostat, Inc, Englewood, New Jersey, USA). An a priori choice of a random effects model was made for all analyses because of significant variation in study design and populations. Where studies reported stimulant rates for mutually exclusive diagnostic groups, these were treated as subgroups and examined separately.

Subgroup analyses

The contribution of categorical study characteristics (e.g., type of stimulant, stage of psychosis) to between-study heterogeneity was assessed using Q-value statistics. The contribution of continuous variables (e.g., age, sex, year of publication, cannabis rate) to between-study heterogeneity was examined using a random effects (restricted maximum likelihood) meta-regression model. Continuous and categorical variables with univariate significance were examined together using a random effects (restricted maximum likelihood) meta-regression model, with Knapp-Hartung distribution. Categorical variables were examined and, where required, collapsed into fewer categories to ensure that no variable had a Variance Inflation Factor (VIF) greater than 3.

The effect of variations in strength of reporting was measured by subgroup analysis for individual strength of reporting variables and after splitting studies at the median of the

composite strength of reporting score. To investigate possible publication bias, a funnel (Egger's) plot of the main effect was examined for interaction between stimulant rate and standard error. Duval and Tweedie's "trim and fill" method (Duval and Tweedie, 2000) was used to examine the effect on the pooled effect rate of hypothetical missing studies.

RESULTS

Search Results

The search strategy identified 1,610 potentially relevant citations; 1,291 were excluded following abstract review and 255 were excluded after review in full text (Figure 2.1). The 64 remaining studies had a combined sample size of 22,500 people with psychosis (per sample mean 331; SD 1,195; range 40-9,919). They provided 68 estimates of stimulant use disorder rates, since some studies included estimates for more than one diagnostic group. Differences between raters were resolved for rates of stimulant use disorder (20 studies) and other study details (6 studies). Summary details for all included studies are provided as a supplementary table (Table 2.6) at the end of this chapter.

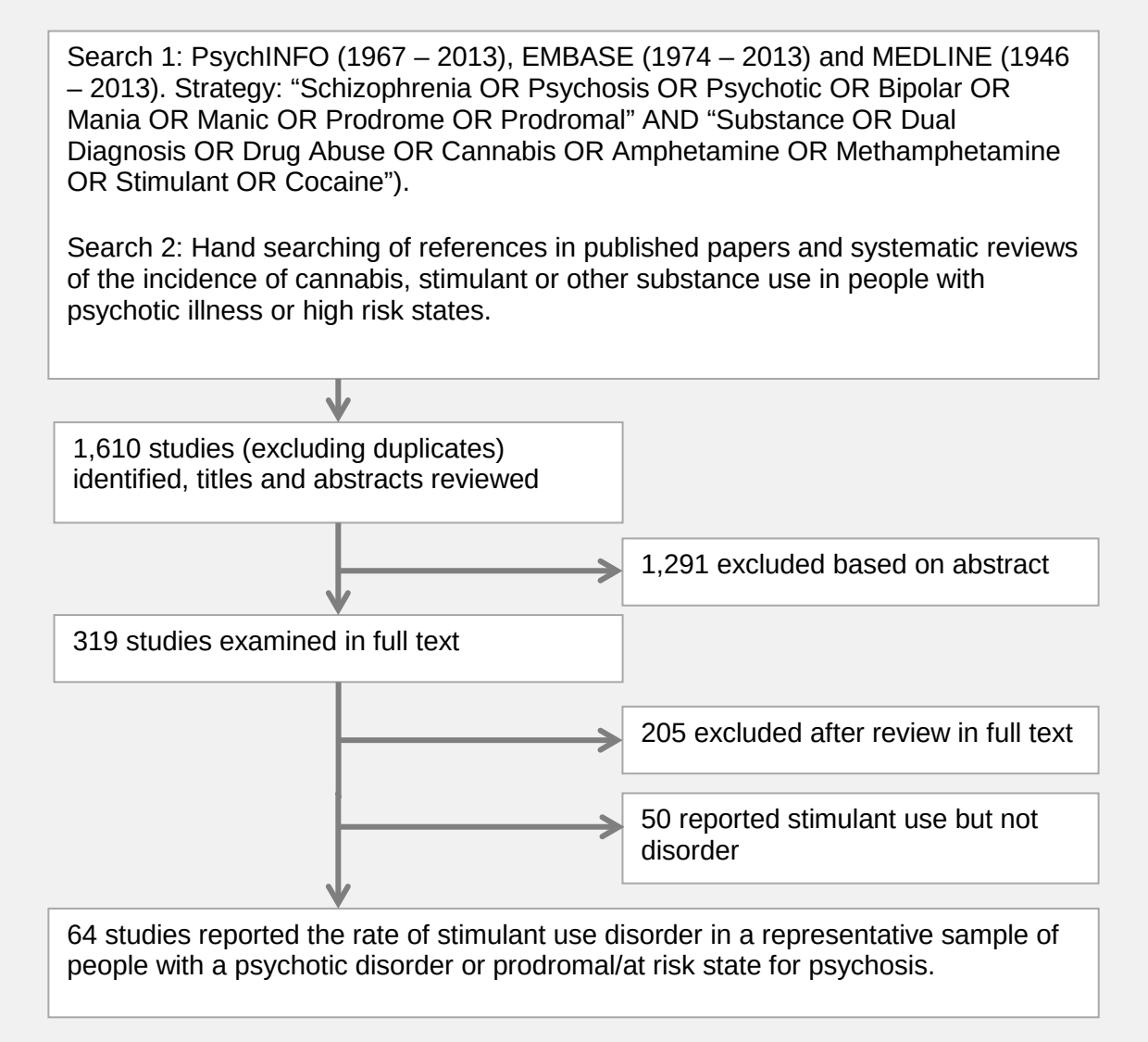

Figure 2.1. Search strategy

Meta-analysis of studies reporting stimulant use disorder

The pooled rate of recent or lifetime stimulant use disorder was 8.9% (95% confidence interval 7.4% - 10.5%, median 8.5%, interquartile range 4.0% - 15.9%). Between-study heterogeneity was assessed as high (I2 = 91.0%). The study with the lowest reported rate of stimulant use disorders (0.5%) described recent (12-month) substance abuse in 475 medication-free young people referred to an early psychosis service in Denmark (Petersen et al., 2007). The highest rate was reported by study examining 67 people attending a psychiatry outpatient service in an inner city mental health service in Baltimore, USA (Gearon and Bellack, 2000); 37.3% of that group had 12-month diagnosis of cocaine abuse or dependence.

Test of possible publication bias

Examination of the funnel plot showed asymmetry (Figure 2.1). The trim and fill method identified and removed 10 studies, producing a revised pooled estimate of 10.5% (95% CI 8.9% - 12.4%).

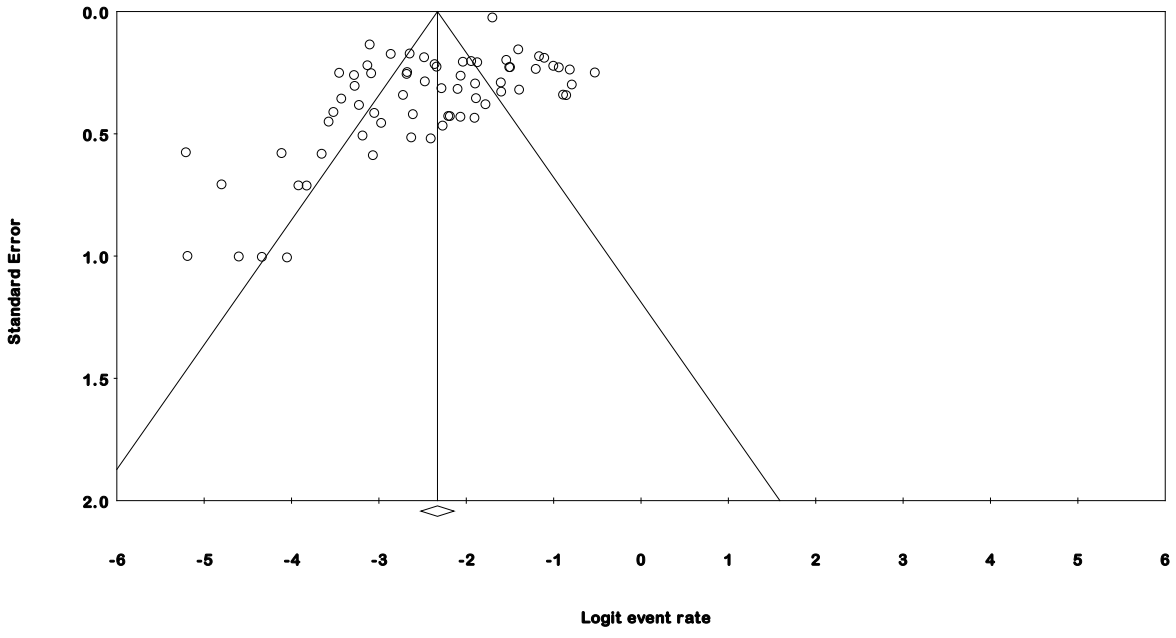

Figure 2.2. Funnel plot of standard error by logit event rate

Subgroup analyses

Subgroup analyses of clinical study characteristics are summarised in Table 2.1. The highest rates of recent or lifetime stimulant use disorder were reported in studies which examined affective psychosis (Miller and Tanenbaum, 1989; Mueser et al., 1992; Rabinowitz et al., 1998; Strakowski et al., 1996), having a pooled estimate of 15.2% (95% CI 6.9% - 30.2%). Studies of people with schizophrenia also reported higher rates of stimulant use disorder than studies of people with mixed or unspecified psychosis diagnoses. The pooled estimate of stimulant use disorder was non-significantly higher in studies examining lifetime rather than recent periods. The inclusion or exclusion of drug-induced psychosis, the stage of psychosis or the type of stimulant drug did not contribute to between-study heterogeneity.

The influence of service and setting factors is summarised in Table 2.2. Higher rates of stimulant use disorder were reported in studies from hospital settings than in studies from community or mixed settings. There were significant regional or national differences, with the highest rates of stimulant use disorder being reported by studies from the USA and Australia, and lower rates reported by studies from Western and Southern Europe, Scandinavia, the UK and Ireland. There were differences between regions in the type of stimulant drug examined: most studies from the USA (19 of 29 studies) reported cocaine use disorders, UK studies reported a mix of amphetamine (3 studies) and ecstasy use disorders (2 studies), European studies reported cocaine (7 studies) or unspecified stimulant use disorders (5 studies). Australian studies reported amphetamine/methamphetamine disorders (5 studies) or unspecified stimulant disorders (4 studies).

Table 2.1. Subgroup analysis, clinical and substance factors affecting prevalence of stimulant use disorder in psychosis.

			95% CI		Between sample heterogeneity				Between group heterogeneity		
Group	Studies	Event rate	Lower limit	Upper limit	Q	df	P	I^2	Q	df	P
Type of stimulant drug											
Amphetamine	14	8.4%	5.5%	12.5%	107.8	13	<0.001	87.9	1.5	3	0.692
Cocaine	32	8.6%	6.5%	11.4%	327.8	31	<0.001	90.5			
Ecstasy	2	4.7%	1.4%	14.9%	3.5	1	0.060	71.6			
Stimulants mixed/unspecified	20	9.7%	6.9%	13.4%	245.8	19	<0.001	92.3			
Period of estimate											
Lifetime (>12 months)	41	9.8%	7.7%	12.4%	315.6	40	<0.001	87.3	2.4	1	0.120
Recent (<12 months)	27	7.2%	5.2%	9.8%	416.9	26	<0.001	93.8			
Type of psychosis											
Schizophrenia spectrum	38	10.4%	8.1%	13.4%	316.3	37	<0.001	88.3	11.7	3	0.008
Affective psychosis	4	15.2%	6.9%	30.2%	10.9	3	0.012	72.6			
Other psychoses	4	10.4%	4.5%	22.0%	28.0	3	<0.001	89.3			
Mixed or unspecified	22	5.2%	3.6%	7.5%	373.1	21	<0.001	94.4			
Drug-induced psychosis											
Excluded from sample	53	8.8%	7.1%	10.8%	492.5	54	<0.001	89.0	0.0	1	0.961
Included in sample	15	8.7%	5.7%	12.9%	151.2	14	<0.001	90.7			
Stage of psychosis											
Early and prodromal psychosis	26	7.8%	5.7%	10.5%	290.6	25	<0.001	91.4	2.1	2	0.345
Established psychosis	28	8.6%	6.4%	11.4%	291.4	27	<0.001	90.7			
Mixed or unspecified	14	11.3%	7.5%	16.6%	101.6	13	<0.001	87.2			

Table 2.2. Subgroup analysis, service and setting factors affecting prevalence of stimulant use disorder in psychosis.

			95% CI		Between sample heterogeneity				Between group heterogeneity		
Group	Studies	Event rate	Lower limit	Upper limit	Q	df	P	I^2	Q	df	P
Type of service											
Hospital	27	13.9%	10.8%	17.7%	152.9	26	<0.001	83.0	20.1	3	<0.001
Community	13	7.6%	5.2%	10.9%	118.2	12	<0.001	89.9			
Mixed	24	6.4%	4.8%	8.5%	236.3	23	<0.001	90.3			
Other / unspecified	4	3.8%	0.9%	15.2%	11.1	3	0.011	73.1			
Location within country											
Urban	36	9.5%	7.3%	12.2%	349.8	36	<0.001	89.7	0.9	2	0.652
Mixed urban/rural	23	7.8%	5.7%	10.7%	317.2	23	<0.001	92.8			
Not specified	3	5.6%	2.2%	13.6%	9.3	2	0.009	78.5			
Country or region											
USA	29	11.9%	9.1%	15.3%	225.0	28	<0.001	87.6	17.4	6	0.008
UK	7	6.8%	3.8%	11.7%	57.8	6	<0.001	89.6			
Europe	10	8.3%	4.9%	13.5%	84.2	9	<0.001	89.3			
Scandinavia	5	4.7%	2.4%	9.3%	40.0	4	<0.001	90.0			
Australia	9	10.8%	6.8%	16.9%	85.2	8	<0.001	90.6			
Other	5	4.7%	2.3%	9.1%	14.7	4	0.005	72.8			

Meta-regression was used to examine whether individual continuous variables predicted differences between studies in the reported rate of stimulant use disorder (Table 2.3). Higher rates of stimulant use disorder were associated with higher rates of cannabis use disorder. Stimulant use disorder rates were not related to the average age or proportion of males in study samples. There was no significant change in stimulant use disorder rates over the period covered by the studies, from 1971 (McLellan and Druley, 1977) to 2009 (Sara et al., 2013).

Table 2.3. Univariate meta-regressions: *association of continuous variables with prevalence of stimulant use disorders in studies of people with psychosis.*

Variable	No of samples	Point estimate of slope	SE	95% CI Lower Limit	95% CI Upper limit	t	p
Average age of sample	61	0.003	0.020	-0.037	0.043	0.13	0.898
Percent of sample male	66	0.012	0.009	-0.005	0.029	1.39	0.170
Percent cannabis use/disorder	63	0.036	0.007	0.022	0.049	5.36	<0.001
Year of data collection	68	-0.027	0.017	-0.062	0.007	-1.58	0.118

Study methodology variables had little impact on estimated stimulant use disorder rates (Table 2.4). Studies with missing demographic (age or sex) data reported higher rates of substance use disorder. Studies which used biological assays to define recent substance use had a higher pooled estimate of stimulant use disorder rates than studies which did not use assays. Differing rates of stimulant use were not explained by whether studies used operational criteria or research interviews for defining psychosis or stimulant use disorder, or by a lower composite strength of reporting score.

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Table 2.4. Subgroup analysis, study methodology factors affecting prevalence of stimulant use and disorder in psychosis.

			95% CI		Between sample heterogeneity				Between group heterogeneity		
Group	Studies	Event rate	Lower limit	Upper limit	Q	df	P	I^2	Q	df	P
Sampling and selection											
Representative or random sample	59	9.1%	7.6%	11.0%	633.6	58	<0.001	90.8	0.6	1	0.431
Non-random sample	9	7.5%	4.6%	11.8%	60.7	8	<0.001	86.8			
Diagnostic criteria for psychosis											
DSM or ICD criteria used	57	9.3%	7.7%	11.2%	577.2	56	<0.001	90.3	0.4	1	0.516
Criteria not used or unclear	9	7.9%	4.9%	12.4%	86.6	8	<0.001	90.8			
Diagnostic criteria for stimulant disorder											
DSM or ICD criteria used	51	8.9%	7.3%	10.9%	532.4	50	<0.001	90.6	0.0	1	0.942
Criteria not used or unclear	17	8.8%	6.2%	12.3%	159.5	16	<0.001	90.0			
Psychosis diagnosis method											
Research diagnostic interview	40	7.7%	6.1%	9.9%	369.4	39	<0.001	89.4	2.4	1	0.120
Routine clinical diagnoses	28	10.4%	7.8%	13.7%	337.7	27	<0.001	92.0			
Substance diagnosis method											
Research diagnostic interview	38	8.2%	6.4%	10.5%	364.8	37	<0.001	89.9	0.6	1	0.429
Routine clinical diagnoses	30	9.5%	7.2%	12.5%	355.7	29	<0.001	91.8			
Substance estimate includes biological assay											
Uses assay (hair, urine etc)	12	13.1%	8.7%	19.3%	89.3	11	<0.001	87.7	4.3	1	0.038
No assay	56	8.1%	6.6%	9.8%	652.6	55	<0.001	91.6			
Sample demographic data complete											
Data complete	56	8.0%	6.6%	9.8%	658.3	55	<0.001	91.6	4.2	1	0.040
Sample age or sex missing	12	12.9%	8.6%	18.9%	82.6	11	<0.001	86.7			
Collection period data complete											
Period reported	38	9.6%	7.6%	12.0%	505.0	37	<0.001	92.7	1.1	1	0.285
Period estimated	30	7.8%	5.9%	10.4%	224.7	29	<0.001	87.1			
Composite strength of reporting score											
Below median	18	8.6%	6.1%	12.0%	185.4	17	<0.001	90.8	0.0	1	0.837
Median or higher	50	8.9%	7.3%	10.9%	510.7	49	<0.001	90.4			

Multiple meta-regression

Significant univariate predictors of between-study heterogeneity were examined by multiple meta-regression (Table 2.5). To avoid unacceptable inflation of variance, two categorical variables (region, service setting) were collapsed to a smaller number of categories. Five studies (8%) had no data for rates of cannabis use and were excluded from this analysis. The rate of cannabis use disorders was the strongest predictor of stimulant use disorder rates, accounting for 43% of between-study variance. After controlling for cannabis use disorders, the period of observation (lifetime or 12-month) and the type of psychosis diagnosis did not contribute to between-study heterogeneity. Significant differences between regions remained in the multivariate model. Higher rates of stimulant use disorder were reported in studies from the USA and Australia. The combined model explained 67% of between-study variance (Goodness of fit: Tau^2 = 0.8646, I^2 = 91.37%, Q = 718.81, df = 62, p = < 0.0001).

Table 2.5. Multiple meta-regression, predictors of variation in rate of stimulant use disorder in studies of people with psychosis.

				95% CI				
		Coefficient	SE	Lower	Upper	t	p	
Cannabis disorder rate [a]		0.034	0.006	0.022	0.046	5.500	0.000	
Hospital setting		0.443	0.192	0.057	0.829	2.300	0.025	
Psychosis diagnosis [b]								
	Affective psychosis	0.645	0.426	-0.208	1.499	1.520	0.135	F=2.24, df=3,53, p=0.094
	Schizophrenia	0.561	0.221	0.118	1.004	2.540	0.014	
	Other psychoses	0.472	0.462	-0.455	1.398	1.020	0.312	
Region [c]								
	USA	0.765	0.299	0.164	1.365	2.550	0.014	F=2.70, df=4,53, p=0.040
	Australia	0.572	0.385	-0.200	1.345	1.490	0.143	
	Europe [d]	0.111	0.323	-0.537	0.759	0.340	0.733	
	UK	0.454	0.362	-0.272	1.181	1.250	0.215	

Notes. (a) Reference group is mixed/unspecified psychosis. (b) Reference group is other countries, including studies from mixed or multiple countries, Canada, Israel and Morocco. Pooled estimates from Canada were significantly lower than those from the USA: grouping Canada with USA or examining separately resulted in unacceptable inflation of variance. (c) Includes studies from Belgium, Germany, Switzerland, France, Italy, Spain, Denmark and Sweden.

DISCUSSION

The first aim of this study was to estimate the rate and range of stimulant use disorders in people with psychosis. We found a pooled estimate (including recent and lifetime disorders) of 8.9% (95% CI 7.4% - 10.5%). Estimates varied widely between studies, and factors contributing to this variation are discussed below. The overall rate of stimulant use disorders in people with psychosis was substantially higher than estimated rates in the general population. The Global Burden of Disease study estimated the 12-month prevalence of amphetamine or cocaine use in the general population to be 0.3%-1.3% (Degenhardt and Hall, 2012b), and the point prevalence of stimulant dependence to be 0.10-0.25% (Degenhardt et al., 2014). The current study cannot directly demonstrate the effect of stimulants, however there is substantial evidence that stimulants may precipitate or worsen psychotic symptoms (Hermens et al., 2009; Curran et al., 2004).The high prevalence of stimulant use in people with psychosis therefore suggests that stimulants may make a significant contribution to the overall burden of psychosis.

The second aim of this study was to examine whether between-study variation in the rate of stimulant use disorder reflected factors that may be relevant to clinical care or health service planning, or was merely due to methodological differences between studies. There was very wide variation in rates of stimulant use disorder in people with psychosis: estimates ranged from 0.5% to 37.3%, with an interquartile range of 4.0% - 15.9%. We found that in a multiple meta-regression model, a combination of clinical and setting factors together accounted for nearly 70% of observed variation. Higher rates of stimulant use disorders were reported in studies with higher rates of cannabis disorder and studies from the USA and Australia. In univariate analyses higher rates were also reported in studies of affective psychosis and from inpatient settings. Studies which included biological assays in the diagnosis of substance disorders reported higher rates of stimulant use or disorder, but other study methodology factors such as the period examined (lifetime or recent), the inclusion or exclusion of drug-induced psychosis or the use of structured diagnostic interviews had little impact on reported rates of stimulant use disorder.

Cannabis use disorders were the strongest correlate of the prevalence of stimulant use disorders. A meta-analysis cannot examine whether cannabis and stimulant disorders co-exist in the same individuals, but evidence from many other sources demonstrates such overlap. In the Australian population, 73% of people with lifetime stimulant use disorders also had lifetime cannabis use disorders (Sara et al., 2012). In clinical studies, most

people with psychosis who used stimulants also used cannabis (Degenhardt et al., 2010b; Power et al., 2014; Sara et al., 2014c:). This is clinically significant because stimulants and cannabis may act synergistically in worsening psychotic symptoms (Paparelli et al., 2011).

Australian clinicians have expressed concern that stimulant abuse has contributed to increased demand for acute mental health services (Australian Senate Select Committee on Mental Health, 2006). We found that after controlling for differences in diagnostic mix and service setting, rates of stimulant use disorder in people with psychosis were higher in studies from Australia and the USA than in studies from the UK and Europe. Studies from the USA mainly reported cocaine use disorders and Australian studies mainly reported abuse of amphetamine-related stimulants. These findings mirror regional differences in stimulant use in the broader population: the Global Burden of Disease study (Degenhardt et al., 2014) found high rates of stimulant dependence in North America, South East Asia and Australasia, with cocaine being the main stimulant used in in North America and amphetamines being more prevalent in Australasia and South East Asia. This suggests that people with psychosis may be influenced by the same social and environmental drivers of drug use and choice as other people in their community. It also suggests that the impact of stimulant drugs on people with psychosis might be greater in the USA and Australia than in some other regions.

In univariate analyses, higher rates of stimulant use disorder were reported by studies of people with affective psychoses. There are several possible explanations for this finding. First, it is based on a small number of studies, and may be a chance finding or influenced by other characteristics of those studies. Second, people with affective psychoses may use stimulants as self-medication for experiences of depression or dysphoria (Mueser et al., 1998; Barch and Carter, 2005). Third, recent evidence suggests a strong relationship between affective disorders and psychotic experiences in the general population (van Os, 2014), and it is possible that stimulants and other substances interact with vulnerabilities to both mood disturbance and psychotic experience. Finally, substance use disorders can cause diagnostic uncertainty in psychosis (Mathias et al., 2008; Sara et al., 2014a) and it is possible that stimulant misuse causes overactivity or elation, contributing to misdiagnoses of an affective disorder. On the other hand, our findings are less consistent with “reward deficiency” models which focus on anhedonia, negative symptoms and antipsychotic medication as primary causes of stimulant and other substance comorbidity in psychosis (Blum et al., 1996; Bedard et al., 2013; Green et al., 1999). These would

predict higher rates of stimulant use disorder in studies of schizophrenia and in studies of established or chronic psychosis: we found that studies of schizophrenia reported lower rates than those of affective psychosis, and rates of stimulant use disorder did not differ between studies of early psychosis and those of established or chronic psychoses (Blum et al., 1996; Bedard et al., 2013; Green et al., 1999; van Os, 2014)

We did not find a significant change in the rate of stimulant use disorder in people with psychosis between 1974 and 2009. It is likely that this negative finding may have been due to the substantial between-study heterogeneity observed. However the finding is also consistent with the Global Burden of Disease study, which found no discernible increase in the prevalence of stimulant dependence in the general population between 1990 and 2010 (Degenhardt et al., 2014).

Finally, we also found higher rates of stimulant use disorder in studies of people in hospital settings than in community or mixed settings. This may reflect better detection and diagnosis of substance comorbidity in hospital settings, a greater level of severity and acuity in hospital settings, or selection of people more likely both to use substances and to require inpatient care (e.g., younger males or people with fewer personal or social supports). However, higher rates of stimulant use disorder in inpatient settings would also be consistent with stimulants playing a role in precipitating or worsening psychosis. We have previously found that admissions to NSW Mental health units with stimulant related psychosis occurred more often during periods of greater amphetamine availability (Sara et al., 2011b).

Limitations of the study

This study aimed to examine factors contributing to between-study variation in stimulant use disorder estimates, however the high degree of heterogeneity in these estimates is also a limitation of this study. Many of the pooled estimates in subgroup analyses had wide confidence intervals, and therefore some negative findings in this study may reflect type II error. For example, estimates of lifetime abuse of any drug would be expected to be higher than estimates of recent abuse: we found lifetime rates of stimulant use disorder were non-significantly higher than recent rates.

We found that rates of stimulant use disorder were low in studies with higher variance, suggesting that the pooled estimate of the rate of stimulant use disorder has not been inflated by publication bias. We excluded studies whose selection criteria appeared likely

to bias the estimated rate of stimulant or other drug use, and found that studies with potentially non-representative samples did not have systematically higher rates than those with more clearly representative samples. However there may have been other sources of selection or reporting bias in the studies included. All studies examined were in English, and there were more estimates and higher precision in estimates from English-speaking countries. There were few studies from many individual countries; lower estimates from those countries may reflect less complete capture of studies or systematic differences in studies from those countries published in English compared with other languages. Self-reported drug use may differ systematically between countries, and is likely to be underestimated in countries where drug use may lead to more serious criminal sanctions.

We examined stimulant use disorders as a group since few studies reported on stimulant abuse or dependence as separate disorders. The strong correlation between stimulant use disorders and cannabis use disorders also suggests that some of the univariate associations found may be non-specific associations of substance use disorder rather than specific associations of stimulant use disorder. As in any meta-analysis, the associations found are ecological associations, and may not be reflected in individuals.

CONCLUSIONS

People with psychosis abuse stimulants at much higher rates than the general community. The type of psychosis, service setting and country all affect estimates: higher rates of stimulant use disorder are reported in studies of affective psychosis, from inpatient settings or from the USA and Australia. Methodological factors contribute little to between-study variation in rates of stimulant use disorder. Increased rates of stimulant use disorder are not limited to younger people or earlier stages of psychosis, suggesting that stimulants may contribute to the burden of psychosis at all stages of illness, from early psychosis to established schizophrenia. Cannabis use disorders are the strongest correlate of stimulant use disorders in studies of people with psychosis. Further research is required to disentangle the adverse effects of stimulants and cannabis: clinical or population-based studies using very large samples are likely to be required.

Table 2.6: Details of included studies

Study	Country	Data year	Recency	Drug	Psychosis diagnosis	Psychosis stage	Num	Denom	Stim rate	Age	Male (%)	Cann rate
(Arndt et al., 1992)	USA	1986	Lifetime	Stimulant	Schizophrenia spectrum	Established	9	145	6.2%	31	71	19.3%
(Barbee et al., 1989)	USA	1983	Lifetime	Amphetamine	Schizophrenia spectrum	Mixed	6	53	11.3%		66	35.8%
(Barry et al., 1995)	USA	1989	Lifetime	Amphetamine	Mixed	Established	8	253	3.2%	44	51	15.8%
(Bersani et al., 2002)	Italy	1996	Lifetime	Stimulant	Schizophrenia spectrum	Established	23	125	18.4%	32	100	26.4%
(Brown, 1998)	England	1992	Recent	Amphetamine	Mixed	Established	3	185	1.6%		68	9.2%
(Buckley et al., 1994)	USA	1988	Lifetime	Cocaine	Schizophrenia spectrum	Established	3	118	2.5%	34	66	9.3%
(Cantor-Graae et al., 2001)	Sweden	1998	Lifetime	Amphetamine	Schizophrenia spectrum	Established	6	87	6.9%	48	62	17.2%
(Carr et al., 2009)	Canada	2002	Recent	Cocaine	Mixed	Early psychosis	2	243	0.8%	25	78	29.2%
(Chouljian et al., 1995)	USA	1987	Recent	Cocaine	Schizophrenia spectrum	Established	11	100	11.0%	27	81	11.0%
(Compton et al., 2005)	USA	1999	Lifetime	Cocaine	Schizophrenia spectrum	Mixed	16	248	6.5%	43	61	6.5%
(Condren et al., 2001)	Ireland	1995	Lifetime	Amphetamine	Schizophrenia spectrum	Established	13	99	13.1%	45	61	42.4%
(Coulston et al., 2007)	Australia	2001	Lifetime	Amphetamine	Schizophrenia spectrum	Established	6	59	10.2%	26	100	
(DeQuardo et al., 1994)	USA	1989	Lifetime	Cocaine	Schizophrenia spectrum	Established	3	67	4.5%	29	63	28.4%
(Dervaux et al., 2001)	France	1995	Lifetime	Cocaine	Schizophrenia spectrum	Established	1	100	1.0%	34	68	27.0%

Study	Country	Data year	Recency	Drug	Psychosis diagnosis	Psychosis stage	Num	Denom	Stim rate	Age	Male (%)	Cann rate
(Dixon et al., 1991)	USA	1988	Lifetime	Cocaine	Schizophrenia spectrum	Established	14	83	16.9%	31		31.3%
(Duke et al., 2001)	England	1990	Lifetime	Stimulant	Schizophrenia spectrum	Established	23	265	8.7%	50	53	19.2%
(El Omari et al., 2011)	Morocco	2005	Lifetime	Cocaine	Schizophrenia spectrum	Mixed	1	77	1.3%	32	72	35.1%
(Elangovan et al., 1993)	USA	1991	Recent	Cocaine	Schizophrenia spectrum	Mixed	4	48	8.3%	32	49	
(Elangovan et al., 1993)	USA	1991	Recent	Cocaine	Other psychoses	Mixed	12	40	30.0%	32	49	
(Farrelly et al., 2007)	Australia	2002	Recent	Stimulant	Mixed	Established	5	182	2.7%	31	68	11.0%
(Fowler et al., 1998)	Australia	1992	Lifetime	Amphetamine	Schizophrenia spectrum	Established	26	194	13.4%	36	72	36.1%
(Gearon and Bellack, 2000)	USA	1994	Recent	Cocaine	Schizophrenia spectrum	Established	25	67	37.3%	38	57	40.3%
(Green et al., 2004)	USA and Europe	1998	Lifetime	Cocaine	Mixed	Early psychosis	17	262	6.5%	23	82	28.2%
(Helseth et al., 2009)	Norway	2001	Recent	Stimulant	Mixed	Mixed	12	60	20.0%	28	58	30%
(Hides et al., 2006)	Australia	2000	Recent	Amphetamine	Mixed	Early psychosis	25	81	30.9%	24	73	70.4%
(Hides et al., 2009)	Australia	2005	Recent	Amphetamine	Mixed	Early psychosis	27	214	12.6%	20	66	37.4%
(Jimenez-Castro et al., 2010)	US, Mexico Guatemala Costa Rica	2003	Lifetime	Cocaine	Schizophrenia spectrum	Established	16	518	3.1%	38	66	11.6%
(Kamali et al., 2000)	Ireland	1994	Lifetime	Ecstasy	Mixed	Established	2	102	2.0%	38	67	16.7%

Study	Country	Data year	Recency	Drug	Psychosis diagnosis	Psychosis stage	Num	Denom	Stim rate	Age	Male (%)	Cann rate
(Kamali et al., 2009)	Ireland	2003	Lifetime	Ecstasy	Mixed	Early psychosis	13	166	7.8%	28	57	29.5%
(Katz et al., 1991)	Israel	2005	Lifetime	Stimulant	Schizophrenia spectrum	Mixed	21	237	8.9%		65	11.4%
(Khalsa et al., 1991)	USA	1989	Lifetime	Cocaine	Schizophrenia spectrum	Mixed	36	144	25.0%		96	
(Kwapil, 1996)	USA	1990	Lifetime	Cocaine	UHR/ Prodrome	UHR/ Prodrome	7	182	3.8%	30	48	7.7%
(Lambert et al., 2005)	Australia	1999	Recent	Amphetamine	Mixed	Early psychosis	34	625	5.4%	22	67	43.5%
(Larsen et al., 2006)	Norway, Denmark	1999	Recent	Amphetamine	Mixed	Early psychosis	11	300	3.7%	28	59	13.0%
(Linszen et al., 1994)	Netherlands	1988	Recent	Stimulant	Mixed	Early psychosis	2	93	2.2%	21	72	25.8%
(Margolese et al., 2004)	Canada	1998	Recent	Cocaine	Schizophrenia spectrum	Established	6	207	2.9%	39	58	8.2%
(Martins and Gorelick, 2011)	USA	2002	Lifetime	Cocaine	Schizophrenia spectrum	Mixed	30	386	7.8%			7.8%
(Mata et al., 2008)	Spain	2003	Lifetime	Cocaine	Schizophrenia spectrum	Early psychosis	6	132	4.5%	27	65	46.2%
(Mauri et al., 2006)	Italy	1997	Lifetime	Cocaine	Schizophrenia spectrum	Early psychosis	23	99	23.2%	28	62	67.7%
(McLellan and Druley, 1977)	USA	1971	Lifetime	Amphetamine	Schizophrenia spectrum	Established	16	141	11.3%	36	100	
(Miles et al., 2003)	England	2000	Recent	Stimulant	Mixed	Established	55	1271	4.3%	39	83	6.4%
(Miller et al., 1989)	USA	1983	Recent	Cocaine	Affective	Mixed	6	60	10.0%	37	28	8.3%

Study	Country	Data year	Recency	Drug	Psychosis diagnosis	Psychosis stage	Num	Denom	Stim rate	Age	Male (%)	Cann rate
(Miller and Tanenbaum, 1989)	USA	1987	Recent	Cocaine	Schizophrenia spectrum	Established	8	55	14.5%	28	100	23.6%
(Modestin et al., 2001)	Switzerland	1994	Recent	Cocaine	Schizophrenia spectrum	Established	35	525	6.7%	40	53	12.0%
(Mueser et al., 1992)	USA	1988	Lifetime	Stimulant	Schizophrenia spectrum	Established	38	159	23.9%	32	62	32.1%
(Mueser et al., 1992)	USA	1988	Lifetime	Stimulant	Affective	Established	12	41	29.3%	32	62	34.1%
(Petersen et al., 2007)	Denmark	1999	Recent	Stimulant	Mixed	Early psychosis	3	547	0.5%	26	59	12.1%
(Phillips et al., 2002)	Australia	1997	Recent	Stimulant	UHR/ Prodrome	UHR/ Prodrome	4	100	4.0%	19	49	18.0%
(Potvin et al., 2008)	Canada	2002	Recent	Cocaine	Mixed	Mixed	5	53	9.4%	34	74	35.8%
(Rabinowitz et al., 1998)	USA	1992	Lifetime	Stimulant	Schizophrenia spectrum	Early psychosis	26	224	11.6%		65	29.9%
(Rabinowitz et al., 1998)	USA	1992	Lifetime	Stimulant	Other psychoses	Early psychosis	11	65	16.9%		45	16.9%
(Rabinowitz et al., 1998)	USA	1992	Lifetime	Stimulant	Affective	Early psychosis	50	252	19.8%		50	28.2%
(Ringen et al., 2013)	Norway	2008	Recent	Stimulant	Schizophrenia spectrum	Established	16	364	4.4%	31	57	11.8%
(Ruiz-Veguilla et al., 2009)	Spain	2005	Lifetime	Cocaine	Schizophrenia spectrum	Early psychosis	26	92	28.3%	27	64	55.4%
(Sara et al., 2013)	Australia	2009	Recent	Stimulant	Mixed	Early psychosis	1542	9919	15.5%	23	66	29.9%
(Sevy et al., 1990)	USA	1984	Lifetime	Cocaine	Schizophrenia spectrum	Established	16	51	31.4%	33	94	51.0%

Study	Country	Data year	Recency	Drug	Psychosis diagnosis	Psychosis stage	Num	Denom	Stim rate	Age	Male (%)	Cann rate
(Sevy et al., 2001)	USA	1990	Lifetime	Stimulant	Schizophrenia spectrum	Early psychosis	11	118	9.3%	26	52	14.4%
(Shaner et al., 1993)	USA	1990	Recent	Cocaine	Schizophrenia spectrum	Mixed	27	100	27.0%	42	96	14.0%
(Siris et al., 1988)	USA	1982	Lifetime	Cocaine	Schizophrenia spectrum	Mixed	6	46	13.0%	32	52	34.8%
(Sorbara et al., 2003)	France	1997	Recent	Cocaine	Mixed	Early psychosis	1	58	1.7%	31	57	15.5%
(Steele et al., 2003)	Ireland, Scotland	1993	Lifetime	Amphetamine	Schizophrenia spectrum	Established	30	169	17.8%	36	88	42.6%
(Strakowski et al., 1993)	USA	1987	Recent	Cocaine	Mixed	Early psychosis	5	102	4.9%	30	49	6.9%
(Strakowski et al., 1994)	USA	1988	Lifetime	Cocaine	Mixed	Mixed	15	412	3.6%	34	63	12%
(Strakowski et al., 1996)	USA	1990	Lifetime	Cocaine	Affective	Early psychosis	4	59	6.8%	25	63	32%
(Veen et al., 2002)	Netherlands	1998	Recent	Amphetamine	Mixed	Early psychosis	1	179	0.6%	30	70	14.5%
(Wade et al., 2005)	Australia	1999	Lifetime	Stimulant	Mixed	Early psychosis	23	126	18.3%	22	71	63.5%
(Wobrock et al., 2009)	Germany	1998	Lifetime	Stimulant	Schizophrenia spectrum	Early psychosis	9	68	13.2%	27	66	45.6%
(Wobrock et al., 2013)	Europe	2004	Lifetime	Cocaine	Schizophrenia spectrum	Early psychosis	21	498	4.2%	25	63	23.1%

Notes. Data year: Year of data collection (midpoint if range specified, estimated from publication year if not provided - see Methods).Recency: Period of stimulant estimate – Lifetime or Recent (within last 12 months). Drug: Type of stimulant drug. “Amphetamine” includes methamphetamine. “Stimulant” recorded where specific drug not specified. Num: Numerator, number of study sample with stimulant use or disorder. Denom: Denominator, size of study sample. Stim rate: Numerator/Denominator. Age: Average age of study sample. Male (%): Percent of study sample male. Cann rate: Rate of cannabis disorder in sample for same period (lifetime or recent) as stimulant estimate.

PART 2

STIMULANT USE AND DISORDERS IN THE AUSTRALIAN POPULATION

3: Prevalence of stimulant disorders in Australia

This chapter is based on the publication: **Sara, G., P. Burgess, M. G. Harris, G. Malhi and H. Whiteford (2011). Stimulant use and stimulant disorders in Australia: findings from the National Survey of Mental Health And Wellbeing. Medical Journal of Australia 195 (10): 607-610.**

ABSTRACT

Objectives

To describe the prevalence of lifetime and 12-month stimulant use disorders in the Australian population, and to compare the prevalence estimates from a population survey with prevalence estimates derived using indirect methods.

Methods

Data were drawn from the National Survey of Mental Health and Wellbeing 2007, which sampled 8,841 residents of private dwellings in Australia in 2007. Interviews were conducted by lay interviewers using the Composite International Diagnostic Interview (CIDI). Main outcome measures were lifetime and 12-month rates of stimulant use and stimulant use disorders (abuse, dependence) diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).

Results

Lifetime prevalence of stimulant disorders was 3.3%, and 12-month prevalence was 0.6%, equating to more than 97,000 Australians. Nearly half of those who had used stimulants on more than five occasions met criteria for a lifetime disorder. More than 8% of men aged 16-29 met criteria for a lifetime stimulant use disorder. Prevalence estimates were consistent with recent estimates using indirect methods.

Conclusions

Stimulant use disorders affect a significant number of Australians, and are most common in the age groups at greatest risk for development of psychosis.

INTRODUCTION

Stimulant use in Australia has increased over the last two decades (Degenhardt et al., 2008c; Ministerial Council on Drug Strategy, 2008). Regular stimulant use may be associated with serious morbidity (Darke et al., 2008). A balanced policy and service response requires reliable data about stimulant use disorders in the general population. This study examines the prevalence of stimulant use disorders (including amphetamine-type stimulants, ecstasy and cocaine) in the Australian population in 2007.

Population surveys are the most frequent method for estimating rates of illicit drug use. The Australian National Drug Strategy Household Drug Survey (NDSHDS) has sampled persons aged 14 and over every three years from 1993 to 2007 (Australian Institute of Health and Welfare, 2008). Over this period, methamphetamine was the most commonly used stimulant, with prevalence of lifetime use averaging 7.4% (from 5.4% in 1993 to 9.1% in 2004). The NDSHDS 2007 reported a significant decline in lifetime amphetamine use, to 6.3%. The surveys report a steady increase in the lifetime use of ecstasy (3.1% in 1993, 8.9% in 2007) and cocaine (2.5% in 1993, 5.9% in 2007). Rates of recent (12-month) use were around one third of lifetime rates and followed a similar trend over time. Prevalence of recent methamphetamine use was 2.3% in 2007 (down from 3.7% in 1998). Recent ecstasy and cocaine use increased steadily to 2007 (ecstasy 3.5%, cocaine 1.6%).

Differences in methodology make direct comparison difficult, but rates of stimulant use in Australia appear consistent with or slightly higher than those reported in population surveys in the USA (Substance Use and Mental Health Services Administration, 2007; Substance Use and Mental Health Services Administration, 2010), Canada (Adlaf et al., 2005), UK (Coulthardt et al., 2002) and New Zealand (Wilkins and Sweetsur, 2008).

Harm associated with stimulant use does not affect all users. It is associated with higher frequency of use, higher potency forms and riskier routes of administration such as intravenous injection (Degenhardt et al., 2008c). Those stimulant users who have features of a stimulant use disorder (abuse or dependence) are at highest risk. Therefore "*we need to know the size of the population of dependent methamphetamine users in order to understand their impact on public health and order, and to estimate the services that are needed to reduce this impact"* (McKetin et al., 2005) (Page v).

Compared to estimates of stimulant use in the general population, less is known about rates of stimulant disorder. In the early 1980's the US Epidemiological Catchment Area

study (Regier et al., 1990) reported lifetime prevalence of Dependence/Abuse of amphetamine (1.7%) and cocaine (0.2%). However no recent population surveys have reported prevalence of stimulant dependence using standardised diagnostic criteria. The NHS National Substance Use Survey UK (Coulthardt et al., 2002) reported rates of "stimulant dependence" but this was based on a single positive answer to a screening questionnaire. Teesson (Teesson et al., 2006) examined the US National Comorbidity Survey (1990-96) and Australian National Survey of Mental Health and Wellbeing (NSMHWB) (1997), reporting 12-month prevalence of DSM-diagnosed stimulant disorders of 0.2% in the US and 0.5% in Australia. However to allow comparison of the two surveys, these figures excluded cocaine.

The 1990-1996 US National Comorbidity Survey (Kessler et al., 2001) and its 2001-2003 replication (Degenhardt et al., 2007a) reported only cocaine and prescription stimulants. The International Consortium on Psychiatric Epidemiology (Vega et al., 2002) reported lifetime use of cocaine and stimulants, but not rates of abuse or dependence. WHO World Mental Health Survey Initiative studies (Gureje et al., 2006; Jacobi et al., 2004; Lee et al., 2007; Stein et al., 2008) reported use of alcohol or any illicit drug but did not describe specific drug classes, or diagnoses of abuse or dependence. The New Zealand Mental Health Survey (Wells et al., 2006) and National Drug Survey (Wilkins and Sweetsur, 2008) did not report stimulant disorders.

In Australia the prevalence of stimulant disorders has been estimated by indirect methods. McKetin (McKetin et al., 2005) used multipliers from regular amphetamine users in Sydney and benchmark data for substance treatment, admissions and arrests in 2002/03. Among persons aged 15-49 years they estimated a 12-month prevalence of monthly amphetamine use of 1.0%, and dependent amphetamine use of 0.7%. They estimated that this represented more than 70 000 dependent amphetamine users, comparable to the number of dependent heroin users during the peak period of Australian heroin use in the late 1990s and early 2000s.

Both survey and indirect methods have limitations in estimating the prevalence of stimulant disorders. Population surveys may underestimate prevalence as they sample conventional households, under-represent “hotspots” and high risk subgroups, and may be sensitive to stigma (McKetin et al., 2005). Indirect methods use samples of identified substance users such as treatment populations. They may over-represent more disadvantaged users and under-represent employed users who are not in contact with treatment services. Rates of

help-seeking may differ by sex or cultural background (McKetin et al., 2005). Therefore, it is useful to compare prevalence estimates using both direct and indirect methods.

The 2007 NSMHWB (Slade et al., 2009) collected information on substance use and substance use disorders. It provides the only population data on stimulant (amphetamine, ecstasy and cocaine) use disorders in Australia diagnosed according to standardised diagnostic criteria. This study aims to describe the prevalence of lifetime and 12-month stimulant use and disorder in the Australian population, and to compare estimates from a population survey with previous estimates derived using indirect methods.

METHODS

National Survey of Mental Health and Wellbeing

The 2007 NSMHWB was a nationally representative household survey conducted in 2007 by the Australian Bureau of Statistics (ABS). Slade (Slade et al., 2009) provides a detailed description of its methodology. The population in scope was usual residents of private dwellings in Australia, aged 16 to 85 years. A stratified, multi-stage probability sample of dwellings (excluding very remote areas) was selected by the ABS. Interviewers used household composition questions to identify eligible adults in each household. One person in each household was randomly selected to be interviewed. Younger (16-24 years) and older people (65-85 years) were oversampled. In total 8,841 respondents from 14,805 eligible households completed the interview (a response rate of 60%). Interviews were conducted in English by trained interviewers, and took an average of 90 minutes to complete.

Stimulant use variables

The NSMHWB asked about stimulant use in five categories: (i) Amphetamine/Speed, (ii) Methamphetamine/Base/Ice, (iii) Ecstasy, (iv) Cocaine and (v) Any stimulant. Lifetime stimulant use was assessed by asking whether respondents had used any of these drugs (i) at any time and (ii) more than five times in their lifetime. Respondents who reported lifetime stimulant use on more than five occasions were asked whether they had used any stimulant in the last 12 months.

Diagnostic variables

The NSMHWB used a modified Composite International Diagnostic Interview (CIDI). This provides lifetime and 12-month diagnoses of Stimulant Abuse and Stimulant Dependence. The NSMHWB reported ICD-10 and DSM-IV diagnoses. For consistency with recent studies of the prevalence of cannabis and other substances, DSM-IV criteria and hierarchy rules were used in this study.

Data analysis

Data from the 2007 NSMHWB Basic Confidentialised Unit Record File (CURF), April 2009 version (Australian Bureau of Statistics, 2009) were analysed using PASW Statistics v18 (SPSS Inc. 2009. PASW for Windows, Version 18. Chicago, SPSS Inc.) and Stata v11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, StataCorp LP). Data were weighted using the factors within the CURF which adjust for the differential probability of survey selection and for the age and sex distribution of the Australian population (Slade et al., 2009). Standard errors and 95% confidence intervals (CIs) were calculated using jackknife repeated replication to take account of the complex survey design.

Prevalence was calculated for the whole NSMHWB age range (16-85). For comparison with indirect estimates (McKetin et al., 2005) it was also calculated for persons aged 16-49 only. Following ABS conventions, estimates with a Relative Standard Error (RSE) of between 25% and 50% were considered possibly unreliable. Estimates with RSE greater than 50% were suppressed.

RESULTS

The prevalence of lifetime stimulant use was 12.2% (7.2% on more than five occasions) (Table 3.1). Amphetamine/speed was the most commonly used stimulant (9.3% any use, 5.4% more than five occasions), followed by Ecstasy (7.9%, 4.5%), Cocaine (5.2%, 2.8%) and Methamphetamine/Base/Ice (3.0%, 1.9%). Overall 12-month use of any stimulant was 3.9%.

Table 3.1. Lifetime use of individual stimulant drugs in Australia.

	Lifetime use		Lifetime use > 5 times	
	Rate per 100 (95% CI)		Rate per 100 (95% CI)	
Amphetamine/Speed	9.3	(8.6 – 10)	5.4	(4.7 - 6.1)
Methamphetamine/Base/Ice	3.0	(2.6 - 3.4)	1.9	(1.6 - 2.3)
Ecstasy	7.9	(7.1 - 8.7)	4.5	(3.9 - 5.2)
Cocaine	5.2	(4.5 - 5.9)	2.8	(2.2 - 3.4)
Any stimulant	12.2	(11.5 - 12.9)	7.2	(6.5 – 8.0)

Note: Rate per 100 population. Source: National Survey of Mental Health and Wellbeing 2007

The lifetime prevalence of DSM-IV stimulant disorders was 3.3% (Table 3.2), with abuse (1.9%) more common than dependence (1.4%). The 12-month prevalence of stimulant disorders was 0.61% (abuse 0.35%, dependence 0.26%). For persons aged 16-49 years, 12-month stimulant disorder rates were higher: any disorder 0.97%, abuse 0.55%, dependence 0.42%. Of the 7.2% of persons who had used stimulants on more than five occasions, 46% (3.3% of the population) met criteria for a lifetime stimulant use disorder.

Table 3.2. Lifetime and 12-month stimulant use and disorder in Australia.

	Lifetime		12-month		12-month (Persons 16-49 years)	
	Rate per 100 (95% CI)		Rate per 100 (95% CI)		Rate per 100 (95% CI)	
Abuse	1.93	(1.57 - 2.29)	0.35	(0.21 - 0.49)	0.55	(0.32 - 0.78)
Dependence	1.41	(0.92 - 1.91)	0.26	(0.12 - 0.41)	0.43	(0.19 - 0.66) †
Any stimulant disorder	3.34	(2.76 - 3.93)	0.61	(0.41 - 0.81)	0.97	(0.66 - 1.29)
Stimulant use, no disorder	3.90	(3.36 - 4.45)	3.30	(2.70 - 3.90)	-	

Note: Rate per 100 population, for persons 16-85 years and 12-month prevalence for persons 16-49 years, National Survey of Mental Health and Wellbeing 2007. † Relative standard error of estimate (RSE) between 25% and 50%: estimate may be unreliable

Table 3.3 shows the prevalence of stimulant disorders by age group and gender. Stimulant disorders were more common in males (lifetime 4.6%, 12-month 0.9%) than females (lifetime 2.1%, 12-month 0.3%). Stimulant disorders declined with age, with the highest rate in persons aged 16-29 (lifetime 7.0%, 12-month 1.6%). The highest prevalence rates were among males aged 16-29 (lifetime 8.4%, 12-month 2%). Estimates were unreliable for some groups with lower rates.

Table 3.3. Stimulant disorder prevalence, by gender and age-group.

	Female		Male		All Persons	
	Rate per 100 (95% CI)		Rate per 100 (95% CI)		Rate per 100 (95% CI)	
Lifetime stimulant disorder						
16-29	5.5	(3.7 - 7.3)	8.4	(4.7 - 12.1)	7.0	(4.9 - 9.2)
30-39	2.7	(1.3 - 4.0) †	7.2	(4.9 - 9.6)	4.9	(3.5 - 6.3)
40+	0.5	(0.2 - 0.7) †	2.1	(1.3 - 2.8)	1.3	(0.8 - 1.7)
All ages	2.1	(1.6 - 2.6)	4.6	(3.6 - 5.7)	3.3	(2.8 - 3.9)
12-month stimulant disorder						
16-29	1.1	(0.3 - 1.9) †	2.0	(1.0 – 3.0)	1.6	(1.0 - 2.2)
30-39	s		1.1	(0.1 - 2.1) †	0.7	(0.1 - 1.2) †
40+	s		s		s	
All ages	0.3	(0.1 - 0.5)	0.9	(0.6 - 1.3)	0.6	(0.4 - 0.8)

Note: Rate per 100 population Source: National Survey of Mental Health and Wellbeing 2007.
† Relative standard error of estimate (RSE) between 25 and 50%: estimate may be unreliable
s Estimate suppressed as RSE > 50%

DISCUSSION

This study provides the only current estimate of the prevalence of diagnosed stimulant disorders in a large population sample. We found that 12.2% of the Australian population aged over 16 have used illicit stimulants, and 7.2% have used on more than five occasions. Amphetamine and ecstasy were the most commonly used substances. Of those using stimulants more than five times, nearly half (3.3% of the population) met criteria for a lifetime DSM-IV stimulant abuse or dependence disorder. The lifetime prevalence of stimulant disorders was 3.3%. The 12-month prevalence of stimulant disorders was 0.61%, equating to more than 97,000 Australians.

These figures are consistent with those obtained using indirect estimation methods. McKetin (McKetin et al., 2005) used 2002/03 data to estimate prevalence of amphetamine dependence amongst 15-49 year olds as between 0.6% and 1.1%. For persons aged 16-49 years we found a 12-month prevalence of 0.97% (95% CI 0.66% -1.29%). A population survey may be expected to produce a lower prevalence estimate than indirect methods based on drug-using populations.

Stimulant use is more common in younger adults and men (Substance Use and Mental Health Services Administration, 2007; Adlaf et al., 2005; Australian Institute of Health and Welfare, 2008 ; Degenhardt et al., 2007b). We found a similar pattern for stimulant disorders. More than 8% of men aged 16-29 met criteria for a lifetime stimulant disorder.

Younger men are the group most vulnerable to the development of psychosis. This finding is of concern given that stimulants may interact with other risk factors in the development of psychosis.

Limitations

Population-based studies are likely to underestimate prevalence of the use of illicit drugs, for reasons discussed above. The NSMHWB was designed primarily for the study of high prevalence mental health and substance conditions. Disorders of relatively low prevalence such as stimulant use disorders are at the lower limits of resolution of the NSMHWB, especially when considering 12-month prevalence rates. This means that there are higher levels of uncertainty in the estimates of prevalence, particularly when examining subgroups by age or sex. The response rate for the 2007 survey was lower than in the previous (1997) NSMHWB, and this may have introduced a selection or sampling bias which may account for some differences from other surveys.

Conclusions

More than 12% of Australians over 16 have used illicit stimulants. Of those using stimulants on more than five occasions, nearly one half meet criteria for a lifetime substance use disorder. While 12-month prevalence of stimulant disorders is less than 1%, this represents nearly 100 000 persons. Men aged 18-29 had the highest prevalence rates, with 8.4% having a lifetime stimulant disorder and 2.0% having a twelve-month disorder. It follows that stimulant use disorders are most common in those that are most vulnerable to the development of psychosis. Prevalence estimates obtained by this direct population survey are consistent with recent estimates using indirect methods.

4: Correlates of stimulant disorders in Australia

This chapter is based on the publication: **Sara, G., P. Burgess, M. G. Harris, G. Malhi, H. Whiteford and W. Hall (2012). Stimulant disorders: characteristics and correlates in an Australian population sample. Australian and New Zealand Journal of Psychiatry 46: 1165-1172.**

ABSTRACT

Objective

To describe the correlates of stimulant use disorders (abuse, dependence) in an Australian population sample, to compare the characteristics of stimulant users with and without stimulant disorders and to describe the patterns of service use and help-seeking in people with stimulant use disorders.

Method

Data were drawn from the 2007 National Survey of Mental Health and Wellbeing, which sampled 8,841 residents of private dwellings in Australia in 2007. Lifetime DSM-IV substance use and mental disorder diagnoses were obtained from interviews conducted by lay interviewers, using the Composite International Diagnostic Interview (CIDI). Socio-demographic, socio-economic and clinical correlates of stimulant use disorders were identified using binary logistic regression models. Stimulant users with and without stimulant use disorders were compared to non-stimulant users via multinomial logistic regression models.

Results

Compared to Australians without stimulant use disorder, people with stimulant use disorders were younger, more likely to be male, of non-heterosexual orientation and born in Australia, but were not more socially disadvantaged. Lifetime comorbidity rates were high: 79% of persons with stimulant use disorders had a lifetime alcohol use disorder, 73% a lifetime cannabis use disorder, and more than one third a lifetime mood or anxiety disorder. Stimulant use disorders were associated with a family history of substance use,

affective disorders and psychosis. One in five people with lifetime stimulant disorders had been imprisoned, homeless or hospitalised for substance or mental health problems, and 13% reported at least one symptom of psychosis. Nearly half had sought help for substance or mental health problems, primarily from general practitioners (GPs), psychologists or psychiatrists.

Conclusions

Stimulant use disorders in a representative population sample are associated with significant comorbidity and harm. Many persons with stimulant use disorders had sought care and found this helpful. There is scope for screening and intervention in this group.

INTRODUCTION

Stimulants may cause serious physical and mental health problems (Darke et al., 2008), more often in regular or dependent users than in those who use less frequently (McKetin et al., 2006a; Degenhardt et al., 2008c). In Australia the 12-month prevalence of stimulant use disorders (abuse or dependence) is estimated to be at least 0.6%-0.7% (McKetin et al., 2005; Sara et al., 2011a), a rate comparable to the prevalence of dependent heroin use at the height of Australia's heroin "epidemic" in the late 1990s (Hall et al., 2000). Understanding the characteristics and comorbidities of individuals with stimulant use disorders may assist in planning health system responses for this group.

The first aim of this study is to describe people with stimulant use disorders in a representative Australian population sample. Most descriptions of stimulant use disorders are based on treated or convenience samples such as injecting drug users or high risk populations. These studies find that stimulant use disorders are associated with very significant comorbidity. Dependent stimulant users are often dependent on other drugs, and have high rates of depression, anxiety, psychotic symptoms, suicidal ideation and suicide attempts (Glasner-Edwards et al., 2009; Kalechstein et al., 2000; Stafford and Burns, 2010; Wallace et al., 2009; Zweben et al., 2004; McKetin et al., 2010; McKetin et al., 2006b). Individuals with stimulant use disorders are significantly disabled or marginalised, with fewer years of education and significantly increased rates of unemployment, homelessness, criminal activity and imprisonment compared with those without stimulant use disorders (Copeland and Sorensen, 2001; Degenhardt et al., 2008c; Korte et al., 2011; Stafford and Burns, 2010; Zweben et al., 2004; Farrell et al., 1998). However treatment and convenience samples are likely to include a more severely dependent or disabled group, who may differ systematically from persons with stimulant use disorders in the general population.

Population surveys of drug use can complement studies based on treatment or convenience samples. Most population surveys report only on stimulant use, and do not apply diagnostic criteria for stimulant abuse or dependence. Surveys from the US, UK, Canada, Australia and New Zealand (Adlaf et al., 2005; Durell et al., 2008; Substance Use and Mental Health Services Administration, 2007; Substance Use and Mental Health Services Administration, 2010; Wilkins and Sweetsur, 2008) find that stimulant use is more common in men, peaks in the 20s, and is usually preceded by the use of other drugs, particularly cannabis. Australia's National Drug Strategy Household Survey (NDSHS)

found that stimulant use is usually infrequent; only 36% of those who had used any stimulant in the preceding year had done so monthly or more often. Few population surveys have examined regular stimulant users or those diagnosed with stimulant use disorders. The US National Epidemiological Survey of Alcohol and Related Conditions (Conway et al., 2006) found high rates of lifetime depressive disorders (51%) and anxiety disorders (39%) in individuals with amphetamine abuse or dependence.

The second aim of this study is to compare stimulant users who do not have stimulant use disorders with those who do. We have previously reported that nearly half (46%) of people who have used stimulants on more than five occasions met criteria for a lifetime stimulant use disorder (Sara et al., 2011a). For an individual, the vulnerability to develop abuse or dependence is likely to reflect a mix of genetic, psychological and environmental factors (Kendler et al., 2003; Yucel et al., 2007) along with drug-related factors (McKetin et al., 2006a). To our knowledge, no study has compared the personal, family and social correlates of persons with stimulant use disorders against those of stimulant users who do not have features of abuse or dependence.

The third aim of this study is to examine help-seeking in people with stimulant use disorders. Australians with substance use disorders seek help less often than people with other mental disorders, and rates of help seeking are lowest in younger adults and males (Burgess et al., 2009b), who are the group most likely to have stimulant use disorders. Understanding the extent of unmet need for treatment in this group may assist in identifying opportunities for prevention or intervention.

This study addresses these three aims by examining stimulant use disorders in the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB) (Australian Bureau of Statistics, 2008), which provided information about a representative sample of the Australian population. It collected diagnostic information on substance use and high prevalence mental disorders diagnosed using ICD-10 and DSM-IV criteria, along with information about personal and household characteristics and family history.

METHOD

Setting and participants

The 2007 NSMHWB was conducted by the Australian Bureau of Statistics (ABS) in late 2007. Respondents aged 16 to 85 years were identified from private dwellings selected by

the ABS using a stratified, multi-stage area sample. One individual was selected from the pool of eligible adults in each dwelling, using a randomising algorithm implemented by computer-assisted interview schedule, and invited to participate in an interview. Younger (16-24 years) and older people (65-85 years) were over-sampled to improve the reliability of estimates for these groups. The sampling process yielded 8,841 fully-responding households, a response rate of 60%.

Stimulant use variables

The 2007 NSMHWB reported the use of stimulant drugs in five categories: (i) Amphetamine/Speed, (ii) Methamphetamine/Base/Ice, (iii) Ecstasy, (iv) Cocaine and (v) Any stimulant (any of i – iv). For each of these drug types respondents were asked whether they had ever used; if so they were asked their age at first use and whether they had used more than five times in their lifetime. Persons who reported using any stimulant more than five times in their lifetime were asked whether they had done so in the last twelve months.

Diagnostic variables

The 2007 NSMHWB used a modified version of the Composite International Diagnostic Interview (CIDI) to provide lifetime and twelve month diagnoses of Stimulant Abuse and Stimulant Dependence. The derived variable “Any Stimulant Use Disorder” was positive if an individual met criteria for Stimulant Abuse or for Stimulant Dependence. NSMHWB did not report diagnoses of abuse or dependence for individual stimulants (e.g. methamphetamine, ecstasy, cocaine). DSM-IV criteria were used in this study.

Other variables

Variables from the NSMHWB measuring demographics, harms and service use were extracted and are listed in more detail in the results section below. Service use variables included help sought for any problem, not only specific help sought for stimulant or other substance use disorders.

Data analysis

Data from the 2007 NSMHWB Basic Confidentialised Unit Record File (CURF), April 2009 version (Australian Bureau of Statistics, 2009) were analysed using PASW Statistics v18 (SPSS Inc. 2009. PASW for Windows, Version 18. Chicago, SPSS Inc.) and Stata v11

(StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, StataCorp LP.). Data were weighted using factors within the CURF which adjust for the differential probability of survey selection and for the age and sex distribution of the Australian population. For all analyses standard errors and 95% confidence intervals (CIs) were calculated using jackknife repeated replication to take account of the complex survey design. Because of the low prevalence of stimulant use disorders in the past 12 months, analyses were conducted on correlates of lifetime stimulant use disorders only.

Analysis was conducted in two stages. Firstly, binary logistic regression was used to compare people with and without lifetime stimulant use disorders. Secondly, people without lifetime stimulant use disorders were divided into two groups; stimulant users and non-stimulant users. Multinomial logistic regression was then used to examine whether stimulant users with a lifetime disorder differed from stimulant users without disorder and from people who had never used stimulants.

For the first analysis, personal correlates and comorbidities of stimulant disorders were examined by comparing persons with a lifetime history of DSM-IV stimulant disorder against those with no stimulant disorder. Odds ratios and CIs were calculated using binary logistic regression analyses conducted separately for a range of potential predictors, which included demographic variables and lifetime mental health and substance (alcohol, cannabis) disorders. Lifetime harms were not included in the multivariate analysis, as these are consequences of rather than risk factors for stimulant use disorders. Where necessary, variables with low frequency values and high standard errors were dichotomised or categories were combined.

Multiple logistic regression was then performed using those variables with significant associations ($P<=0.05$) and acceptable standard errors of estimate in univariate associations. Multicollinearity was tested by examination of variance inflation factors and condition number. Highly collinear variables were removed to yield a final model with a condition number less than 30 and with no condition index loading more than 0.4 for more than one individual variable (Belsley, 1991).

The distributions of age at first reported use of alcohol, cannabis and stimulants were skewed and censored. Therefore we examined the proportion using each drug, and the median and interquartile range of age at first use.

In a second analysis, to examine differential risk factors for stimulant use and stimulant disorders, we separated persons without stimulant use disorders into two groups; stimulant users and stimulant non-users, as described above. This produced an outcome variable with three mutually exclusive categories; (i) non-users (lifetime stimulant use on five occasions or less), (ii) users without disorder (lifetime stimulant use but no stimulant use disorder) and (iii) users with disorder (lifetime stimulant use and stimulant use disorder). Multinomial logistic regression was used to compare these groups. Multicollinearity was tested using the approach described above. Because of high relative standard errors for many of the estimates, we limited the variables entered to those identified in the earlier multiple logistic regression. Odds ratios were considered to differ significantly from each other if their 95% confidence intervals did not overlap (Schenker and Gentleman, 2001).

To examine service use, persons with stimulant use disorders were compared with persons meeting criteria for any other lifetime DSM substance use disorder or mental health disorder. Lifetime rates of hospitalisation, consultation with health professionals and self-management were described.

Persons with stimulant disorders were also compared with those with other substance use disorders. Rates of seeking help for substance problems, and the perceived effectiveness of that help were described for those groups.

RESULTS

Associations with lifetime stimulant use disorders

263 of the 8,841 respondents to NSMHWB met criteria for a lifetime DSM stimulant use disorder, yielding a weighted prevalence estimate of 3.3% (CI 2.8% - 3.9%).

Table 4.1 describes the correlates of lifetime DSM-IV stimulant use disorders. Compared to Australians without stimulant use disorders, those with a stimulant use disorder were younger, 76% (CI 75%-76%) were under 30, and were more likely to be male (69%, CI 62%-76%). There were no significant associations between lifetime stimulant use disorders and education, household measures of income or disadvantage, or urban/rural location. Stimulant use disorders were more common in those who reported a non-heterosexual orientation (OR 3.8, CI 1.9 – 7.4) and less common in persons born outside Australia (OR 0.4, CI 0.3 – 0.8), but both estimates had a relative standard error (RSE) between 25% and 50% and so should be interpreted with caution.

Table 4.1. Associations of lifetime DSM-IV stimulant use disorder

	Proportion of persons with lifetime stimulant use disorder		Univariate comparisons		Multivariate comparisons	
	%	(95% CI)	OR	95% CI	OR	(95% CI)
Personal and Household						
Age < 30	75.6	75.0 - 76.2	3.4 **	2.2 - 5.3	3.0 **	1.9 - 4.8
Male gender	68.8	61.5 - 76.1	2.3 **	1.6 - 3.3	1.3	0.8 - 2.0
Not heterosexual	6.1	2.4 - 9.8	3.8 **	1.9 - 7.4 †	3.3 **	1.5 - 7.0 †
Country of birth non-Australia	14.6	8.0 - 21.2	0.4 **	0.3 - 0.8 †	0.9	0.5 - 1.5 †
Parent(s) born non-Australia	39.3	28.2 - 50.5	0.8	0.5 - 1.2		
Non-school qualification	43.9	33.4 - 54.4	0.9	0.6 - 1.5		
Major urban location	73.0	65.1 - 80.9	1.4	0.9 - 2.1		
Income						
Deciles 1-3 (low income)	24.5	16.6 - 32.3	0.9	0.6 - 1.5		
Deciles 4-7	19.4	13.4 - 25.5	0.7	0.5 - 1.1		
Disadvantage						
Deciles 1-3 (low disadvantage)	32.9	23.4 - 42.4	1.3	0.8 - 2.2 †		
Deciles 4-7	26.2	18.5 - 34.0	1.0	0.6 - 1.7 †		
Family History						
Alcohol or drug problem	31.7	23.1 - 40.3	2.7 **	1.8 - 4.0		
Anxiety disorder	30.6	21.8 - 39.3	1.8 *	1.2 - 2.6		
Depression	40.7	30.1 - 51.3	2.2 **	1.4 - 3.3		
Schizophrenia or Bipolar	20.2	12.7 - 27.6	2.1 **	1.3 - 3.4		
Comorbid substance disorders						
Alcohol	78.6	71.3 - 85.8	14.5	9.2 - 22.8	4.4 **	2.5 - 7.8 †
Cannabis	73.0	66.1 – 80.0	66.9	44.8 - 99.9	27.8 **	18.1 - 42.7
Comorbid mental disorders						
Any affective disorder	38.8	29.2 - 48.4	3.8 **	2.5 - 5.7	2.3 **	1.5 - 3.5
Bipolar disorder	9.4	5.1 - 13.7	9.7 **	5.6 - 16.8		
Depression	36.1	27.1 - 45.1	3.4 **	2.3 - 5.1		
Anxiety disorder	42.0	32.8 - 51.2	3.0 **	2.0 - 4.3		
Lifetime harms						
Ever homeless	21.9	13.9 - 29.9	11.5	7.0 - 19.0		
Ever in jail	17.2	10.8 - 23.5	10.7	6.5 - 17.7		
Suicide attempts	14.1	8.9 - 19.3	5.5 **	3.5 - 8.9		
Suicidal ideas	31.7	23.1 - 40.2	3.2 **	2.1 - 4.9		
Psychotic experiences	13.2	8.0 - 18.3	4.9 **	3.0 - 8.1 †		

Note: Comparison to persons with no lifetime stimulant use disorder .1: N = 263 of 8,841 respondents with lifetime stimulant disorder, weighted prevalence 3.3% (CI 2.8% - 3.9%), 2: Odds ratios from logistic regression where DV is presence/absence of any lifetime DSM-IV stimulant use disorder. 3: Comparison group for income is Decile 8-10 (highest income), and for disadvantage is Decile 1-3 (lowest disadvantage). Lifetime harms not included in multivariate comparisons. † Relative Standard Error (RSE) of estimate is between 25 and 50%: estimate may be unreliable. * $p < 0.05$. ** $p < 0.005$.

Lifetime stimulant use disorders were strongly associated with the diagnosis of another substance use disorder. Most people with lifetime stimulant use disorder also met criteria for lifetime alcohol use (79%, CI 71% - 86%) or cannabis use disorders (73%, CI 66%-80%). They had more than a 60-fold higher risk of cannabis use disorders (OR 67, CI 45-100) and more than a 10-fold higher risk for alcohol use disorders (OR 15, CI 9 – 23) than people without lifetime stimulant disorders.

More than one third of those with a lifetime stimulant use disorder also had a lifetime history of an affective disorder (39%, CI 29% - 48%) or anxiety disorder (42%, CI 33% - 51%). These rates were three to four times higher than rates in those without a lifetime stimulant use disorder.

There were associations between lifetime stimulant use disorder and self-reported family history of substance use or psychiatric problems. There was an approximately two-fold higher risk of stimulant dependence in those with a family history of alcohol and drug problems (OR 2.7, CI 1.8-4.0), depression (OR 2.2, CI 1.4-3.3) or anxiety (OR 1.8, CI 1.2 – 2.6).

The final multivariate logistic regression model identified five variables that retained significant associations with lifetime stimulant use disorder after controlling for other variables. When compared to persons with no lifetime stimulant disorder, the strongest predictor of a stimulant disorder was a lifetime history of cannabis use disorder (OR 27.8, CI 18.1 – 42.7). There were also smaller but still significant associations with lifetime alcohol use disorder (OR 4.4, CI 2.5 – 7.8), being under 30 years of age (OR 3.0, CI 1.9 – 4.8) and a history of any affective disorder (OR 2.3, CI 1.5 – 3.8). The association with non-heterosexual sexual orientation also remained after controlling for other variables (OR 3.3, CI 1.5 – 7.0) but the RSE of this estimate was between 25% and 50%. Family history variables were excluded from the final model because of their close co-variation with individual substance, mood and anxiety disorders.

Persons with a lifetime history of stimulant use disorder reported significant psychosocial harms. One in five reported having been in prison (OR 10.7, CI 6.5 – 17.7) or homeless (OR 11.5, CI 7.0 – 19.0, RSE 25-50%). Around one third (32%, CI 23%-40%) reported suicidal ideation and nearly half of these (14%, CI 9% - 19%) reported a suicide attempt.

Persons with stimulant disorders had increased rates of family history of schizophrenia or bipolar disorder (OR 2.1, CI 1.3 – 3.4) compared to those without stimulant disorders.

Thirteen percent (13%, CI 8% - 18%) reported one or more psychotic experiences on the NSMHWB psychosis screener, almost five times the rate of those without stimulant disorders (OR 4.9, CI 3.0 – 8.1, RSE 25%-50%).

Differentiating the correlates of stimulant use and lifetime stimulant use disorder

In the second set of analyses, multinomial logistic regression was used to compare the three outcome groups; (i) stimulant non-users, (ii) stimulant users without disorder and (iii) stimulant users with disorder. Table 4.2 shows the results of this regression; stimulant non-users were the comparison group and results for that group are not shown. Stimulant users without disorder comprised 322 of 8,841 NSMHWB respondents (weighted prevalence 3.9%, CI 3.4%-4.5%). They did not differ from stimulant users with disorders on age, gender, sexual orientation or in the proportion with comorbid affective, anxiety or alcohol use disorders. Only comorbid lifetime cannabis disorder distinguished between stimulant users without disorder (OR 3.8, CI 2.1 – 6.6) and stimulant users with disorder (OR 33.2, CI 21.4 – 51.6).

Table 4.2. Multivariate associations of stimulant use and disorder

	Stimulant users with no DSM disorder		**Stimulant users with DSM disorder**	
	OR	(95% CI)	OR	(95% CI)
Age <30	2.8 **	2.0 - 4.0	3.7 **	2.4 - 5.8
Male gender	1.3	1.0 - 1.8	1.3	0.8 - 2.1
Not heterosexual	3.7 **	2.2 - 6.3 †	4.3 **	2.1 - 8.8 †
Alcohol disorder	3.6 **	2.5 - 5.1	5.4 **	3.1 - 9.3 †
Cannabis disorder	3.8 **	2.1 - 6.6 †	33.2 **	21.4 - 51.6
Affective or anxiety disorder	1.9 **	1.4 - 2.6	2.5 **	1.6 - 3.9

Note: Multinomial Logistic Regression comparing stimulant users with and without lifetime DSM-IV stimulant use disorder (abuse, dependence) to a reference group with no lifetime stimulant use. Reference group is stimulant non-users, i.e. persons who have used stimulants less than five times in their lifetime. N = 322 of 8,841 respondents reported stimulant use with no DSM disorder, weighted prevalence 3.9% (CI 3.4%-4.5%). † Relative standard error of estimate between 25 and 50%: estimate may be unreliable. * $p < 0.05$, ** $p < 0.005$.

Table 4.3 summarises age at first drug use and rates of lifetime use of alcohol and cannabis. Rates of lifetime cannabis use were much higher for stimulant users, whether with disorder (86%, CI 80% - 92%) or without disorder (83%, CI 77% - 88%), when compared to stimulant non-users (14%, CI 13% - 15%). For all groups the median age at first drug use was youngest for alcohol, intermediate for cannabis and oldest for stimulants. Stimulant users (with or without disorder) had a lower median age of first use of alcohol and cannabis than stimulant non-users. Stimulant users with disorder had a

lower median age of first use of cannabis and stimulants than stimulant users without disorder.

Table 4.3. Age at first drug use and lifetime use of other drugs

	Alcohol	Cannabis	Stimulants
Age at first drug use	*Median years (Interquartile range)*		
Stimulant non-users	16 (14-18)	17 (16-19)	-
Stimulant users without	14 (13-16)	16 (15-18)	20 (18-23)
Stimulant users with disorder	14 (12-15)	15 (14-17)	18 (16-20)
Lifetime drug usage	*Proportion (95% CI)*		
Stimulant non-users	93.6% (92.9% - 94.4%)	14.2% (13.0% - 15.4%)	0.0%
Stimulant users without	93.2% (92.4% - 94.0%)	82.7% (77.3% - 88.2%)	100.0%
Stimulant users with disorder	99.8% (99.5% - 100.0%)	86.0% (80.3% - 91.7%)	100.0%

Service use

Table 4.4 shows rates of help-seeking and service use. It includes help sought by stimulant users for any problem (i.e. stimulant use or any other mental health or drug and alcohol problem). The comparison group is persons with any DSM mental health or substance disorder other than stimulant use disorder. Nearly one in five persons (19%, CI 11%-27%) with a lifetime stimulant use disorder reported having been hospitalised for a mental health or substance use condition, approximately twice the rate of persons with other lifetime disorders (10%, CI 8% - 11%).

Table 4.4. Treatment and service use by people with lifetime stimulant disorders.

	Other lifetime disorder		Lifetime stimulant use disorder	
	%	95% CI	%	95% CI
Hospitalisation				
Hospitalised for any mental health condition	9.5	7.9 - 11.1	19.2	11.5 - 27.0
Self-management				
Used internet for help or information	11.0	9.6 - 12.3	11.9	7.3 - 16.4
Self-help group	6.8	5.5 - 8.1	6.2	3.4 - 8.9
Telephone counselling	7.8	6.2 - 9.4	8.6	5.6 - 12
Consultations with health professionals				
Any professional consultation	47.5	44.9 - 50.1	57.5	48.9 - 69.5
Any mental health professional	32.2	30.1 - 34.3	40.1	27.0 - 53.2
General practitioner / primary care physician	38.1	35.4 - 40.8	45.7	35.1 - 56.3
Psychiatrist	15.8	13.8 - 17.8	19.6	13.6 - 25.6
Psychologist	20.3	18.4 - 22.2	23.4	16.3 - 30.6
Mental Health Nurse	3.5	2.6 - 4.5	6.2 †	2.9 - 9.5
Other general health professionals	7.5	5.8 - 9.1	10.4	5.5 - 15.4
Alternative therapists	3.8	2.9 - 4.8	7.2 †	2.7 - 11.6

Note: Compares people with lifetime DSM-IV stimulant use disorders to those with other lifetime DSM mental health disorders. †: RSE of estimate is between 25% and 50%, estimate may be unreliable

More than half of those with a lifetime stimulant use disorder (57%, CI 47%-68%) reported a professional consultation for a mental health or substance use problem. The most common contacts were with General Practitioners (GPs) (46%, CI 35% - 56%), followed by Psychologists (23%, CI 16%-31%) and Psychiatrists (20%, CI 14% - 26%). The type of professionals did not differ substantially between those with lifetime stimulant use disorders and those with other disorders. Those with lifetime stimulant use disorders reported similar rates of use of internet information or self-help sites (12%, 7%-16%) and telephone counselling services (9%, CI 6%-12%) as persons with other disorders.

Stimulant users with disorder had sought help for drug and alcohol problems more often than persons with other specific drug and alcohol use disorders: nearly half (47%, CI 37%-58%) of stimulant users with disorder had talked to a medical practitioner or other health professional about drug and alcohol problems, compared to 16% (CI 14% - 19%) of people with other alcohol or drug use disorders. Fifty eight percent (58%, CI 40% - 76%) of stimulant users with disorder who had sought help considered that treatment had been effective, compared with 36% (CI 26% - 44%) of those with other drug and alcohol problems. Only 6% (CI 3% -9 %) of those with lifetime stimulant use disorders had participated in self-help groups for alcohol and drug problems.

DISCUSSION

This study is the first to report the correlates of diagnosed stimulant use disorders from a large, representative Australian population sample. We found high rates of comorbidity and harm in this group. Around three quarters of those with stimulant use disorders also had lifetime alcohol or cannabis use disorders. Depressive and anxiety disorders were common, and the risk of any affective disorder was more than twice that of the general population after controlling for age, gender and other disorders. The risk of suicide attempts, homelessness and imprisonment were between five and ten times greater than for the general population. These findings are consistent with those reported in treatment and conveniences samples, and suggest that the high rates of comorbidity and harm found in treated samples are not solely due to selection issues. This study does not demonstrate any causal link: stimulant use disorders may be a cause of other problems (such as mood disturbance or legal problems), an effect of such problems, or part of a broader set of personal and social vulnerabilities.

As expected, lifetime stimulant use disorders were more common in younger adults and in men. They were less common in people born outside Australia but this was not significant after controlling for other variables. Contrary to a number of clinical and cohort studies (Akiyama, 2006; Degenhardt et al., 2007b; Degenhardt et al., 2007c; Durell et al., 2008; Russell et al., 2008; Degenhardt et al., 2008c), we did not find a significant social gradient in the prevalence of stimulant use disorders. This may reflect limitations in NSMHWB which are discussed below. However we note also that a recent analysis of the Australian National Drug Strategy Household Drug Survey (Roche et al., 2008) found that amphetamine use was almost twice as common in those in the paid workforce as those not in work. Therefore those at risk of harm from dependent stimulant use may also include a broader group, and prevention or treatment strategies may need to consider a more diverse range than high risk studies suggest.

There have been reports of increased rates of stimulant use in homosexual men in the US and UK (Bonell et al., 2010; Maxwell and Rutkowski, 2008). We found that stimulant disorders were more common in people reporting non-heterosexual sexual preference. This effect remained after controlling for other variables but was based on small numbers of individuals and so should be interpreted with caution. In this sample, people reporting non-heterosexual orientation were more likely to use stimulants, but had the same risk as other stimulant users of developing abuse or dependence.

The second aim of this study was to compare stimulant users who do not have stimulant use disorders with those who do have such disorders. We found few differences between stimulant users with and without stimulant use disorders. Only comorbid cannabis use and younger age of first use of cannabis and stimulants distinguished the two groups. This finding is consistent with recent evidence for the role of early cannabis use as a gateway to later use of other illicit drugs (Degenhardt et al., 2009a; Degenhardt et al., 2010b). It suggests that strategies for the prevention of stimulant use disorders need to be broad based.

In this population sample, individuals with stimulant use disorders were twice as likely to report a family history of Bipolar Disorder or Schizophrenia than those without stimulant use disorders. The precipitation or worsening of psychosis is one of the most serious harms associated with stimulant use disorders (Curran et al., 2004; Darke et al., 2008). Many risk factors interact in the development of psychosis (McGrath et al., 2004) and the role of stimulants should not be overstated. However for some individuals interactions

between genetic liability and substance abuse, including stimulants, may increase the risk of psychosis (McGorry et al., 2008). Our findings suggest that those with stimulant use disorders may be vulnerable not only due to exposure to substances but also due to a higher rate of family history of psychosis.

This study's third aim was to describe help-seeking and service use in people with stimulant disorders. Around half of those with a lifetime stimulant use disorder had sought help for a substance or mental health problem (although not necessarily for stimulant use). Most had done so by consulting a GP, a psychologist or psychiatrist. This suggests the importance of GPs and mental health professionals screening for comorbid stimulant use disorders. Intervention and information strategies often target internet and social media but only 12% of those with stimulant use disorder reported using those media for help or information. In this study people with stimulant disorders who sought care were more likely to report that this had been helpful than persons with other substance problems, underlining the opportunity for effective intervention in this group. The rate of help-seeking in those with lifetime stimulant disorders was higher than that reported from NSMHWB for people with any 12-month substance use disorder (24%) (Burgess et al., 2009b). These higher rates partly reflect differences between lifetime and 12-month measurement periods, but may also reflect the high rate of comorbid conditions in people with stimulant use disorders. Help-seeking is more common where substance use disorders are comorbid with other mental disorders (Burgess et al., 2009b).

This study has a number of limitations. First, the NSMHWB 2007 had a response rate of 60%. Respondents to population surveys are more likely to be older, female, better educated, healthier and less socially disadvantaged than non-respondents (Knudsen et al., 2010; Galea and Tracy, 2007). Rates of illicit drug use may be particularly understated by population health surveys which may not recruit from unconventional households, marginalised groups or drug "hotspots" (Degenhardt et al., 2011). The NSMHWB weights data for the age and gender distribution of the Australian population, but cannot correct for other sources of bias. These factors may contribute to the lack of association between stimulant use and measures of social disadvantage in this study.

Second, the NSMHWB was designed for the study of high prevalence conditions. Stimulant use disorders, being infrequent, are at the lower limit of the survey's resolution. Therefore we have focused on lifetime rather than twelve month disorder. This limits the conclusions which can be drawn. Persons with comorbid lifetime conditions cannot be

assumed to have had these disorders at the same time, or in any particular sequence. There was also insufficient power to allow examination of some potentially important issues, such as comparison of those with stimulant dependence and stimulant abuse separately. Furthermore, the NSMHWB did not report diagnoses of abuse or dependence for individual stimulant drugs. We therefore could not examine individual stimulant drugs, when there is evidence that personal correlates, harms and risks of dependence do differ amongst different types or forms of stimulants (Conway et al., 2006; Grant, 1995; McKetin et al., 2006a).

Conclusions

Australians who met criteria for lifetime DSM-IV stimulant use disorders in the NSMHWB had high rates of comorbid substance use, mood and anxiety disorders, suicide attempts, homelessness and imprisonment. These findings from a representative population sample underline findings from treatment and convenience samples that stimulant use disorders are associated with significant comorbidity and harm.

Only comorbid cannabis disorders and earlier drug use distinguished stimulant users without disorder from those with abuse or dependence. Many people with stimulant use disorders had sought help, especially from GPs and mental health professionals, and many had found treatment helpful. Therefore health professionals need to be made aware of the scope for intervention. Prevention of stimulant use disorders may require a broad focus on younger people at risk, including those with cannabis use disorders. Treatment for stimulant use disorders may also need to address comorbid substance use disorders, mood and anxiety disorders as well as broader vulnerabilities.

PART 3

STIMULANT USE DISORDERS IN EARLY PSYCHOSIS

5: The effect of stimulant availability on hospital admissions for psychosis

This chapter is based on the publication: **Sara, G., P. Burgess, G. Malhi and H. Whiteford (2011). Amphetamine availability and admissions for psychosis in New South Wales, 2001-2009. Australian and New Zealand Journal of Psychiatry 45(4): 317-324.**

ABSTRACT

Objective

Clinicians have raised concerns about the impact of amphetamines on demand for mental health services. However, evidence for this link is limited. This study explores whether changes in the availability of amphetamines in NSW in the last decade have been associated with variations in admission to mental health units for amphetamine related conditions and for psychoses more generally.

Method

The study examined admissions from community settings to NSW acute mental health units from 2000 to 2009. Quarterly rates of hospital admission with primary or comorbid diagnoses of stimulant use disorders, stimulant-induced psychoses and non-drug-related psychoses were compared to quarterly rates of criminal incidents of amphetamine possession and use, which provide an indirect measure of the community availability of amphetamines. Analysis was confounded by increases in mental health beds over the period. Linear regression predicted admission rates on the basis of amphetamine availability, adjusting for changing mental health bed numbers.

Results

Amphetamine availability and admissions for psychoses increased steadily from 2000 to a peak in early 2007, but have declined since. Regression models including both amphetamine availability and bed numbers predicted 34% of variation in stimulant use disorders admission rates and 50% of variation in stimulant induced psychosis admission rates. There was no significant effect of amphetamine availability on admissions for

schizophrenia and other non-drug-induced psychoses after controlling for changing bed numbers.

Conclusions

Increased amphetamine availability appears to have been one factor increasing demand for mental health admission in NSW over the last decade. However, there appears to have been a recent downward trend in both amphetamine availability and amphetamine-related admissions. Policies which reduce the community availability of amphetamines may result in reduced admissions for amphetamine related mental health conditions, including amphetamine-induced psychoses. Further research is needed regarding effects of amphetamine availability on admissions for schizophrenia.

BACKGROUND

Over the last decade Australian mental health services have experienced a significant increase in demand, especially for acute inpatient care (Department of Health and Ageing, 2007). Many mental health professionals have argued that increased use of amphetamines has been a significant driver of this demand (Australian Senate Select Committee on Mental Health, 2006).

Amphetamines are associated with physical and psychological harm (Darke et al., 2008). They may trigger episodes of acute psychosis in vulnerable individuals, and worsen symptoms in persons with pre-existing psychotic disorders (Curran et al., 2004; Hall and Degenhardt, 2006; Darke et al., 2008). However, Degenhardt and colleagues (Degenhardt et al., 2008c) have cautioned against overstatement of the extent of amphetamine related harm. They reviewed Australian drug use and health indicators to 2005-2006 and reported that health-related "indicators of meth/amphetamine-related harm did not show the dramatic increases that might have been expected given recent media attention, with indicators stabilising over the past few years" (p 250).

From 1993 to 2004 there was a five-fold increase in admissions to Australian hospitals with a primary diagnosis of drug-induced psychosis, increasing from 56 admissions per million population aged 10-49 to 253 admissions per million population (Degenhardt et al., 2007d). Amphetamine induced psychoses accounted for an increasing proportion of these admissions (55% in 2003-04, up from 41% five years earlier). There have been several reports of increased amphetamine-related presentations to hospital Emergency Departments (ED) (Fulde and Wodak, 2007; Gray et al., 2007). In New South Wales (NSW) the number of ED admissions for amphetamines and related substances increased 139% between 2002 and 2007 (Snowball et al., 2008). While proportionally large, these are increases from a low base rate, and specific amphetamine-related disorders remain a small percentage of overall mental health service or Emergency Department activity.

This study examines relationships between amphetamine availability and admissions for psychosis in NSW from 2000 to 2009. If amphetamines are a significant driver of changes in mental health service demand, then there should be a relationship between community availability of amphetamines and admissions for amphetamine-related mental health problems. Increased incidence of amphetamine-related episodes of psychosis is likely to result in increased admissions for psychosis. It is also likely to result in a change in the mix

of persons admitted to inpatient units, increasing the acuity of those units by increasing the proportion of admissions that are due to psychotic disorders.

Arrests for drug possession have been shown to be a valid measure of community drug availability (Rosenfeld and Decker, 1999), although they are likely to be influenced both by supply factors (fluctuations in drug availability) and policing factors (changes in police resources and focus). A recent study (Snowball et al., 2008) has shown a steady increase in amphetamine arrests in NSW over the last decade, and also shown that over this same period arrests for narcotics and amphetamines were strongly correlated with emergency department presentations for problems related specifically to these drugs.

We hypothesize that greater community availability of amphetamines will be associated with an increase in admissions for stimulant use disorders (abuse, dependence etc) and stimulant-induced psychoses. In addition amphetamine use may lead to exacerbations of illness in persons with schizophrenia or other psychotic disorders.

The diagnosis of specific drug-related conditions is often imprecise due to lack of recognition of the role played by specific drugs, or by systematic under-recording of secondary or co-morbid diagnoses even when they are clinically recognised. Therefore the current study also examines for a relationship between amphetamine availability and admissions for non-drug-related psychoses.

This study aims to add to the existing evidence in several ways. First, no published study has examined for a direct relationship between a measure of community amphetamine availability and admissions for mental health care. Second, Australian national hospital data collections include only a single “primary” diagnosis for each admission. A study using a large state-based data collection can also examine additional “secondary” or comorbid diagnosis. In routine mental health care, substance-related conditions are often recorded as secondary diagnoses, and therefore examination of these diagnoses may be more sensitive than examination of primary diagnoses alone. Third, the most recent publication of an Australian time series (Degenhardt et al., 2007d) examines hospital admissions from 1993 to 2004, and changes in both drug availability and admissions for psychosis that may have occurred since that time.

METHODS

Data sources

Aggregated data was obtained from routinely collected crime and health datasets, and was used with permission of the relevant data custodians. No data on individual admissions or arrests was obtained.

Amphetamine supply

Amphetamine supply data was provided by NSW Bureau of Crime Statistics. This comprises the total number of "criminal incidents" of amphetamine possession and/or use detected by or reported to NSW Police, and recorded in the NSW "COPS" database. "Criminal incidents" differ from arrests in that they also include cautions and persons diverted from court through use of infringement notices or youth justice conferences. Criminal incidents of amphetamine dealing and supply are not included in this analysis as these are smaller in number, more variable and are likely to be more influenced by policing rather than supply factors. It is also possible that substantial amphetamine seizures for possession or supply could be a cause of reduced community drug availability rather than a marker of increased availability.

Demand for mental health care

Mental Health admissions data was extracted from Inpatient Statistics Collection, NSW Health Information Exchange (HIE). It included all same day and overnight episodes of inpatient care where the person was aged 14 – 65 and admission occurred to a designated acute adult mental health unit in NSW. Specialist acute Child and Adolescent Mental Health Units (CAMHS) were not included because of difficulties in separation of mental health from general medical admissions at several hospital sites. The study focuses on admission for acute or emergency care from community settings where exposure to amphetamines may have been a risk factor and where the timing of admission to a mental health unit could be influenced by that exposure. Therefore the following were excluded: (i) psychogeriatric units, non-acute adult and non-acute CAMHS units; (ii) acute adult units with a specialist or tertiary role (e.g. forensic units, neuropsychiatry units, day programs and admissions for electro-convulsive therapy); (iii) admissions following transfer from another hospital, a nursing home or due to statistical type-change within a facility; and (iv) episodes where greater than one week elapsed between admission to hospital

and transfer to an acute mental health unit. Admissions to Psychiatric Emergency Care Centres (PECCs) were included.

Diagnosis

NSW Health inpatient data records primary and additional ICD-10 diagnoses for all inpatient episodes. ICD includes amphetamines within stimulant use disorders (F15). ICD-10 introduced coding of a 5th digit to specify methamphetamine within these disorders. However this additional coding was present in only a minority of records and has not been examined. Diagnosis codes were grouped into three broad diagnostic groupings: stimulant use disorders, stimulant-induced psychoses and non-drug-related psychoses (Table 5.1).

Table 5.1. Mapping of ICD diagnostic codes

Diagnoses	ICD-10 codes included
Stimulant use disorders	F15.0 to F15.99, excluding stimulant-related psychoses codes below
Stimulant-related psychoses	F15.5, F15.50, F15.51, F15.59, F15.7, F15.70, F15.71, F15.79
Non-drug-related psychoses	
Brief and acute psychoses	F23- F23.91
Schizophrenia and related psychoses	F20- F22.9
Schizoaffective disorder	F25-F25.9
Mania with psychosis	F30.2, F31.2
Other psychoses	F31.5, F32.3, F32.30, F32.31, F06.0, F06.1, F06.2, F28, F29

Note. ICD-9 diagnoses recorded in earlier years of this series have been mapped to corresponding ICD-10 codes.

For each admission, each diagnosis of interest was recorded as present if it occurred as either a primary or an additional diagnosis. The unit of counting was the hospital episode, not the diagnosis. More than one diagnosis of the same group was often made in a single episode: for example, many episodes recorded more than one diagnosis in the stimulant use disorders group (eg stimulant intoxication and stimulant dependence). These were counted as a single episode with amphetamine use disorders rather than as two episodes.

Time period and incident/admission rates

Monthly data for both sources was available from June 2000 to September 2009 inclusive. Monthly data was aggregated to produce quarterly rates. As quarters differ in length, amphetamine incident and admissions data were calculated using daily rates (quarterly total / days in quarter).

Over the period studied, there was a 34% increase in public mental health beds in NSW, increasing from 1861 beds in July 2000 to 2491 beds in July 2009 (NSW Health Department, 2009; NSW Health Department, 2002). Over the same period there has been an overall upward trend in amphetamine arrests in NSW

Statistical Analysis

The major independent variable (amphetamine possession) was examined to exclude seasonal effects: dummy variables were created for quarter (1-4) and sequence (1-37), and a linear regression calculated for predicted amphetamine possession over time. Variance on the distribution of residuals was analysed (one way ANOVA, factored by quarter). There were no significant differences between quarters ($F=0.17$, $df=36$, $p=0.916$). Therefore subsequent analyses did not consider possible seasonal effects.

Linear regression was conducted separately for each of the three major dependent variables: (i) admissions with stimulant use disorders, (ii) admissions with stimulant-related psychoses; and (iii) admission with non-drug related psychosis (i.e., schizophrenia, brief psychoses, schizoaffective disorders, mania).

Initial data analysis and descriptive statistics were conducted using PASW Statistics v18 (SPSS Inc. 2009. PASW for Windows, Version 18. Chicago, SPSS Inc.). Regression analyses were conducted using Stata v11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, StataCorp LP.).

RESULTS

Summary data

Data was obtained for 111 months (37 quarters) from July 2000 to September 2009. In this period there were 19,897 incidents of amphetamine possession or use recorded.

In the study period 187,161 admissions to acute mental health units met the inclusion criteria for the study, of which 90,296 (48%) included at least one primary or secondary diagnosis of psychosis. Diagnoses of non-drug-related psychoses (82,684, 44% of admissions) were more frequent than drug-related psychoses (10,167, 5% of admissions). There were 10,423 admissions with a stimulant use disorder recorded, comprising 5.6% of all admissions. There were 3,557 stimulant-induced psychoses recorded (1.9% of admissions). Table 5.2 summarises the main dependent and independent variables.

Table 5.2. Amphetamine possession and admissions.

	Distribution				Confidence Interval	
	Mean	SE	SD	Skewness	Lower (5%)	Upper (95%)
Amphetamine availability *(Possession incidents per day)*	5.99	0.005	1.04	0.56	5.98	6.00
Stimulant use disorders *(Admissions per day)*	3.11	0.004	0.69	-0.02	3.10	3.12
Stimulant-induced psychoses (*Admissions per day)*	1.07	0.003	0.33	0.34	1.07	1.07
Non-drug-related psychoses *(Admissions per day)*	24.80	0.011	2.23	-1.08	24.78	24.82

Trends over time

Figure 5.1 shows trends in amphetamine possessions and amphetamine-related admissions. Amphetamine possessions increased from 2002, peaking in the first quarter of 2007. There was an apparent steady decline after 2007. Stimulant-induced psychoses and stimulant use disorders appeared to follow a similar trend to amphetamine possessions, with an overall gradual increase from 2002 to 2007 but a consistent decline from a peak in early 2007; rates in the first three quarters of 2009 were between one third and one quarter of that recorded in late 2006 and early 2007.

Admissions for non-drug-related psychosis were more frequent and had less variability. They appeared to show a similar but less marked trend, with an apparent reduction of around 20% in admission rate from early 2007 to 2009 (Figure 5.2).

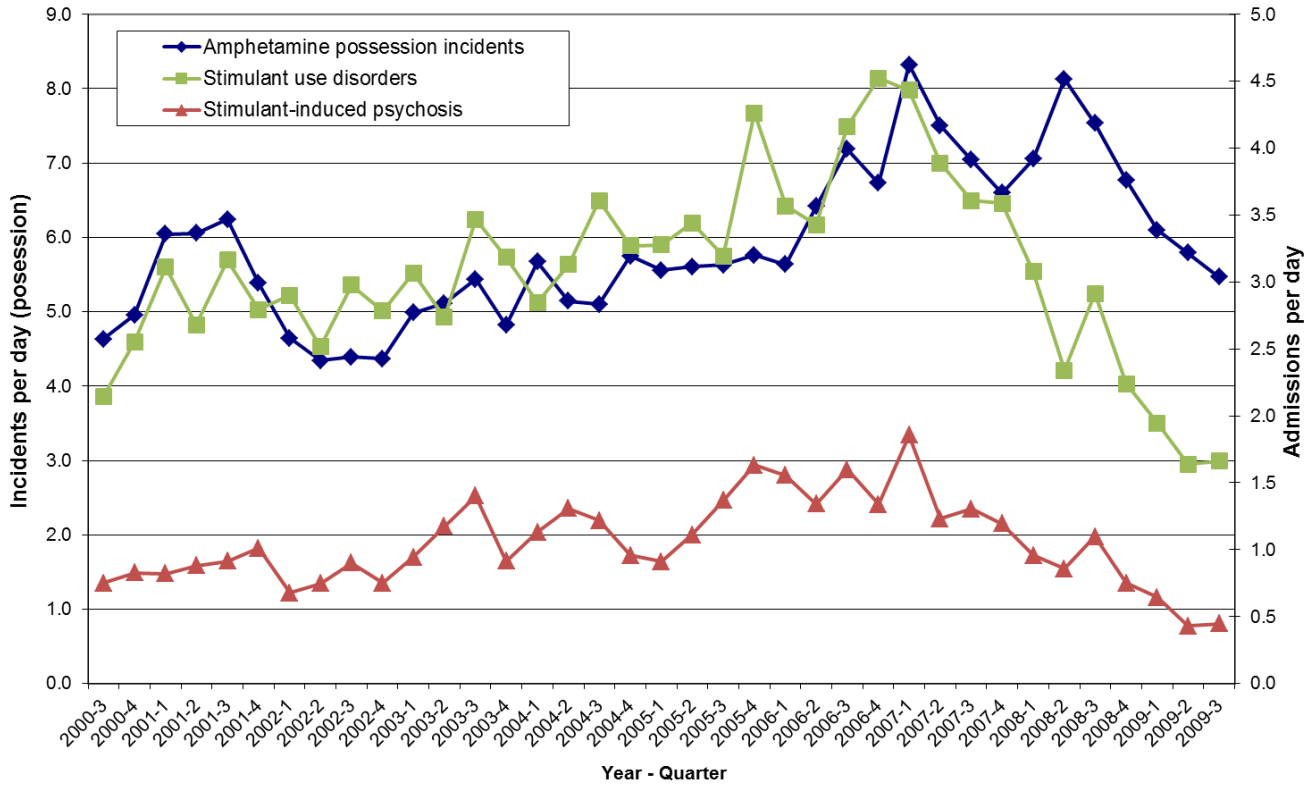

Figure 5.1. Amphetamine possessions and stimulant-related admissions, 2000-2009

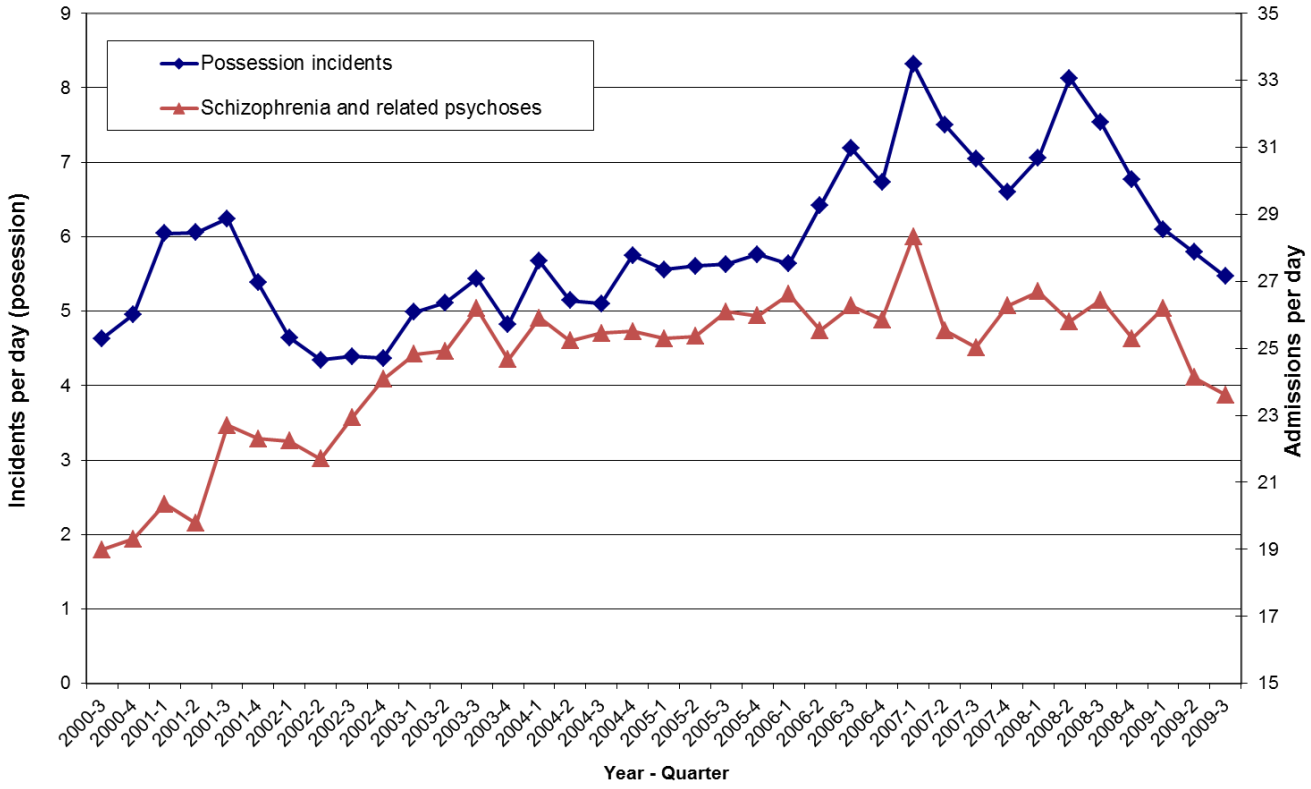

Figure 5.2. Amphetamine possessions and schizophrenia admissions, 2000-2009

Analysis of admission rates was complicated by an increase in acute mental health beds in NSW over the period being studied, largely due to the construction of new acute beds. For the acute units in scope for this study, average occupied beds rose steadily from 682 at the beginning of the period to 1114 in the third quarter of 2006 (Figure 5.3). The increase was not constant over the period examined: after late 2006 average occupied beds in the units included in this study levelled off, fluctuating between 1,114 and 1,069 occupied beds. A small proportion of this increase in occupied beds may also have been due to increasing occupancy of existing units.

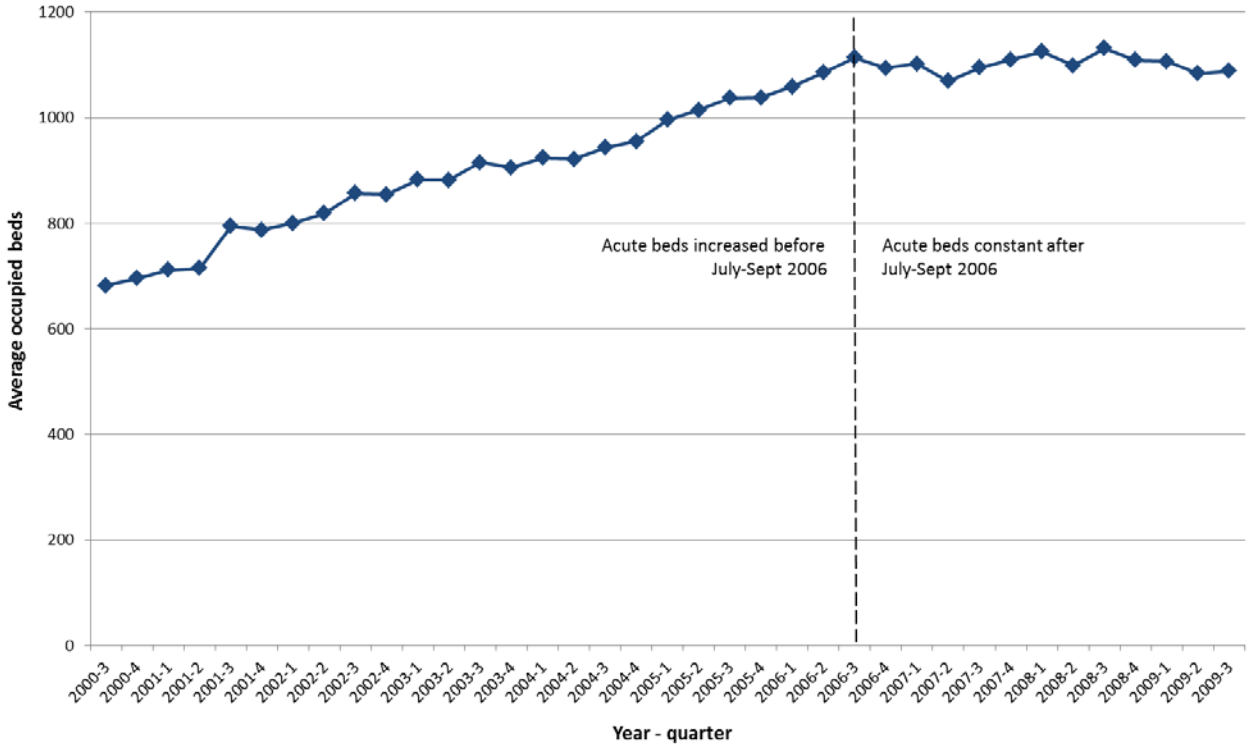

Figure 5.3. NSW acute mental health beds, 2000-2009.

As increasing bed numbers leads to increased admissions it is also possible that any increase in admissions for stimulant related disorders over the period may simply have reflected greater bed access rather than greater demand. Therefore analyses also included occupied bed days as a second dependent variable. As the increase in bed numbers was not linear, a “bed peak” dummy variable was also created, dividing the time series into a component prior to July-Sept 2006 where beds increased in a linear fashion and a component after that period where bed numbers were steady.

This analysis treated increased bed numbers as if they were independent of and preceded increased presentations and admissions. The relationship between bed numbers and admissions is of course likely to be complex and recursive: the increased construction of

beds in NSW during this decade was itself driven by community, consumer and clinician concerns about increased rates of admission and occupancy. However, for this analysis it was not possible to model the relationship in this way.

Association between possession and admissions

Linear regression was conducted separately for each of the three main dependent variables. The regression model included three variables: (i) amphetamine possession incidents per day, (ii) average occupied beds in in-scope units and (iii) a binary "bed peak" variable indicating whether the month examined was during or after the period of increasing bed numbers. Results of these regressions are summarised in Table 5.3.

Table 5.3. Relationship between amphetamine possession, beds and admissions.

	Coefficient	SE	t	P	95% CI (lower)	(upper)
Stimulant use disorders						
Amphetamine possessions	0.44	0.13	3.24	0.003	0.16	0.71
Average Beds	0.00	0.00	1.96	0.059	-0.00	0.00
Pre/post bed peak	-1.20	0.30	-3.9	<0.001	-1.82	-0.58
Constant	-0.93	0.93	-1.0	0.325	-2.81	0.96
Stimulant induced psychoses						
Amphetamine possessions	0.11	0.03	4.12	<0.001	0.06	0.17
Average Beds	0.00	0.00	2.9	0.007	0.00	0.00
Pre/post bed peak	-0.33	0.06	-5.4	<0.001	-0.46	-0.21
Constant	-0.09	0.19	-0.5	0.638	-0.47	0.29
Non-drug-induced psychoses						
Amphetamine possessions	592.10	419.35	1.41	0.167	-261.08	1445.28
Average Beds	26.68	3.05	8.76	<0.001	20.49	32.89
Pre/post bed peak	-3253.56	950.52	-3.42	0.002	-5187.40	-1319.72
Constant	-13016.15	2895.38	-4.50	<0.001	-18906.84	-7125.45

Admissions for stimulant-use disorders and stimulant-induced psychoses showed a significant association with incidents of amphetamine possession. These associations remained after adjustment for changes in bed numbers. The overall regression model, including possession rates and bed number/period variables accounted for 34% of variance in admissions for stimulant-use disorders ($F(3,33) = 7.28$, $p = 0.0007$, $R^2 = 0.398$, Adj $R^2 = 0.343$) and 50% of the variance in stimulant-induced psychoses ($F(3,33) = 13.17$, $p < 0.0001$, $R^2 = 0.545$, Adj $R^2 = 0.506$).

Examination of admissions for non-drug-related psychoses was complicated by the non-normal distribution of this variable. Of standard transformation options only a cubic transformation produced a distribution marginally suitable for regression (Chi-square of

original v transformed distribution=4.08, P=0.130). Using this transformation the combined regression model accounted for 77% of variation in admissions ($F(3,33) = 41.74$, $p < 0.0001$, $R^2 = 0.791$, Adj $R^2 = 0.773$), however amphetamine possession made a non-significant contribution to this model, and nearly all variance in admissions was accounted for by changes in bed numbers.

DISCUSSION

Summary of findings

In this NSW data, from 2000 to 2009, there was a relationship between amphetamine availability (as measured by police incidents of amphetamine possession) and admissions to acute mental health units for amphetamine use and amphetamine related psychoses. From 2000 to 2007 there was a steady increase in amphetamine possession incidents and in amphetamine-related admissions. Acute mental health beds also increased in this period, however the relationship between amphetamine availability (possession incidents) and amphetamine-related admissions remained when this bed increase was controlled for.

An unexpected finding was an apparent downward trend in both amphetamine availability and amphetamine-related admissions from a peak in the first quarter of 2007 to a low in late 2009. Over this period amphetamine possession incidents reduced by 33% (from 749 in Q1 2007 to 503 in Q3 2009), stimulant use disorders by 62% (from 399 to 153 admissions per quarter), stimulant related psychoses by 75% (from 167 to 41 admissions per quarter) and admissions for schizophrenia by 18% (from 1625 to 1334 admissions per quarter). Mental health bed numbers have remained stable during this period.

Limitations

The current study has the limitations of ecological studies in comparing two sets of aggregate, state level data (Wakefield, 2008), and we cannot demonstrate that the individuals who were admitted were exposed to stimulants, or that increased amphetamine availability and increased admissions occurred in the same geographical regions of NSW.

The study compares two imprecise measures. Amphetamine-related criminal incidents provide an indirect measure of community drug availability, but are clearly subject to influence from other factors. Diagnostic information collected from routine administrative collections reflects diagnoses made by many hundreds of clinicians using diverse diagnostic practices rather than structured diagnostic instruments. In considering

substance-related disorders in particular, the reliability of routine clinical diagnoses is limited, and there is frequent under-recognition and under-diagnosis of substance-related disorders in routine clinical practice. These factors clearly limit the conclusions that can be drawn from the current study. However, the imprecision of the available measures is likely to bias against finding an association in this study.

Both drug use and admissions may be influenced by broader social factors, including broad trends in economic activity and employment over the period being studied. Increased arrests for amphetamine possession due to increased police activity may result in increased detection and diversion of individuals with psychosis to mental health services by police. Therefore we cannot conclude that the association found between varying amphetamine availability and admissions is a causal one.

Both health and police data may have been influenced coincidentally by changes in practice and procedure or coding within their respective systems: there were changes to NSW Police resources and the introduction of new diversion and cautioning systems within NSW within this period. NSW Health services moved from ICD-9 to ICD-10 coding: the current study has mapped ICD-9 codes where present to equivalent ICD-10 codes, but these changes, or changes in NSW documentation requirements or source systems over the period, may have resulted in changes in diagnostic recording or coding.

Regarding the recent downward trend in criminal incidents and admissions, both sets of data are subject to underestimation for recent time periods and may be revised upwards as time elapses. Diagnosis in NSW Health data is not completed until after separation from hospital and following a further period required for coding and data entry: diagnosis completion may continue to increase for 3-6 months after the close of a period. Data for the current study were extracted approximately 4 months after the close of the last period being analysed, and so data for the last quarter may be underestimated by up to 5-10%. However, the decline since 2007 was steady and consistent, and the overall trend seen was unlikely to be an artefact of diagnostic coding delays.

The study sought to examine for a relationship between amphetamine availability and admission for non-drug-related psychoses including schizophrenia. The confounding effects of changing bed numbers over this period made it difficult to examine this question statistically. When comparing amphetamine availability with admissions for non-drug-related psychoses, including schizophrenia (Figure 5.2) there appeared to be similarities between these two data series: since early 2007 the reduction in overall admissions for

psychosis mirrored that for amphetamine-related disorders. If increased drug-related presentations for psychosis were themselves a driver for increases in bed numbers, our approach of adjusting for bed numbers as an independent variable may have prevented demonstration of an association. We think that the issue requires further study, examining a longer time-series of data for the period after bed numbers have stabilised. Even a minor impact of amphetamines on admission rates for schizophrenia and related psychoses may have significant personal and service impact; in the period studied there were approximately 10,000 admissions per year to acute mental health units with diagnoses of psychotic disorders, comprising 48% of all admissions to those units.

Conclusions

Within the limitations described above, increased amphetamine availability and use appear to have been one factor increasing demand for mental health admission in NSW over the last decade. Conversely, there appears to have been a significant downward trend in amphetamine availability and admissions for amphetamine-related disorders from early 2007 to the end of the study period (September 2009).

Policies and strategies which reduce the community availability of amphetamines may result in reduced admissions for amphetamine related mental health conditions, including amphetamine-induced psychoses. These psychoses result in significant trauma and morbidity, and for some vulnerable individuals may represent the first phase of a continuing or recurrent psychotic disorder. Therefore limiting community amphetamine availability may be one strategy contributing to the prevention of psychosis.

6: Prevalence and correlates of stimulant disorders in first episode psychosis

This chapter is based on the publication: **Sara, G., P. Burgess, G. Malhi, H. Whiteford and W. Hall (2013). Differences in associations between cannabis and stimulant disorders in first admission psychosis. Schizophrenia Research 147: 216-222.**

ABSTRACT

Background

Substance use in early psychosis is associated with male gender and earlier onset. Evidence about other correlates of substance use is less consistent. Stimulants (e.g. methamphetamine, cocaine) may precipitate psychosis. However the associations of stimulant disorders in early psychosis are difficult to examine because of lower prevalence and overlap with cannabis disorders.

Methods

Hospital records were used to identify 9919 persons aged 15-29 with a first hospital admission with psychosis in New South Wales (NSW), Australia. Correlates of illicit drug disorders, cannabis disorders and stimulant disorders were examined using univariate and multivariate logistic regression.

Results

Half of first psychosis admissions had comorbid substance diagnoses. Cannabis and stimulant disorders were increased more than ten-fold compared to the age-matched Australian population. Stimulant disorders were equally common in women and men and associated with urban location, social advantage and older age at first admission. Cannabis disorders were associated with male gender, younger age and non-metropolitan location. Diagnoses of drug-induced psychoses were more strongly associated with stimulants than with cannabis. Compared to people with cannabis diagnoses alone, those with both cannabis and stimulant disorders were older, more likely to have a diagnosis of drug-induced psychosis and more likely to have comorbid alcohol disorders.

Conclusions

Cannabis is the most commonly used substance in psychosis, and the associations of illicit drug use in psychoses are largely those of cannabis disorders. There are significant differences between the personal, socio-economic and diagnostic correlates of cannabis and stimulant disorders in young people with first admission psychosis.

INTRODUCTION

Substance use in psychosis is associated with male gender (Cantor-Graae et al., 2001; Crebbin et al., 2009; Rabinowitz et al., 1998; Wade et al., 2005) and earlier onset (Cantor-Graae et al., 2001; Compton et al., 2011; Wade et al., 2005; Large et al., 2011). There are conflicting findings about associations between substance use and symptom severity, urban location, disadvantage, migration and diagnostic subtype (Rabinowitz et al., 1998; Sevy et al., 2001; Wade et al., 2005). Some studies report no relationship with diagnostic subtype (Wade et al., 2005; Wade et al., 2006a), some report more substance use in affective psychoses than in other psychosis subtypes (Rabinowitz et al., 1998) while others report more substance use in non-affective psychoses (Cantwell et al., 1999).

More than one in five young people with psychosis may abuse stimulants (Wade et al., 2005; Rabinowitz et al., 1998; Genetic Risk Outcome in Psychosis Investigators, 2011). Amphetamines stimulate dopamine activity (Hermens et al., 2009) and can trigger psychotic symptoms in healthy volunteers (Angrist et al., 1974), recreational drug users (McKetin et al., 2006b) and people with psychotic disorders (Curran et al., 2004). The effects of amphetamines and other stimulants on people with psychosis may be different from or additive to those of cannabis. However, most persons who use stimulants have also used cannabis. Therefore even very large studies of young people with psychosis have not had sufficient power to examine the correlates of stimulant disorders and to assess whether they differ from those of cannabis disorders.

Using a large, population-based dataset it may be possible to examine a range of possible associations of substance use disorders in early psychosis, and to have sufficient power to examine the associations of stimulant use disorders while controlling for comorbid cannabis disorders. This study identified all first admissions with psychosis for young people aged 15-29 in the state of New South Wales (NSW), Australia, over a seven year period.

METHOD

The study was approved by the NSW Population and Health Services Research Ethics Committee. NSW had an estimated population of 7.27 million persons in 2012, 1.47 million (20%) of whom were aged 15-29 (Centre for Epidemiology and Evidence, 2012).

First admissions with psychosis

Admissions to NSW state operated hospitals were examined using the NSW Health Information Exchange. The first admission per individual was identified.

Inclusion criteria were (i) the person's first psychosis admission occurred during the study period (July 2005 to June 2012) and (ii) age 15 - 29 at that admission. Psychosis was identified by ICD-10 diagnosis codes. Drug-induced and affective psychoses were included. Where episodes had multiple psychosis codes a single psychosis diagnosis was derived using the following diagnostic hierarchy: schizophrenia, delusional disorder, schizoaffective disorder, affective psychosis, brief psychosis, drug induced psychosis and atypical/unspecified psychosis.

The period July 2000 to June 2005 served as a baseline for identification of incident cases. We excluded (i) persons with admissions for psychosis in the baseline period, (ii) same-day admissions, (iii) residents of another country or Australian state/territory, (iv) Organic Psychosis and (v) Schizotypal Disorder.

Individual substance disorders

Substance disorders were identified by diagnosis codes for abuse, dependence, intoxication or poisoning by alcohol or illicit drugs. Drug induced psychoses were counted as both psychosis and substance use disorder. Amphetamines and cocaine were grouped into a single stimulant category. All individual substance diagnoses were recorded; polydrug disorder was recorded only where this was specifically diagnosed.

Overlap between cannabis, stimulants and other drug disorders

A composite "Illicit Drug Use Group" variable was created based on the presence of cannabis and/or stimulant diagnoses. This had five mutually exclusive categories; (i) No illicit drug diagnoses, (ii) Cannabis, (iii) Stimulants, (iv) Cannabis plus Stimulants or (v) Other/ Polydrug only. Some persons in groups (ii) - (iv) had additional substance diagnoses, including opiate or hallucinogen disorders, however the "Other/Polydrug only" category was applied only where the person had neither cannabis nor stimulant diagnoses.

Personal variables

Migration status was based on country of birth recorded at index admission. Rurality and disadvantage measures were based on Australian Bureau of Statistics reference data for the statistical local area of residence at index admission.

Binary variables were constructed indicating whether persons had prior hospital admissions with non-psychotic mental health or substance disorders, or prior recorded contact with a NSW public community mental health team. Persons were defined as having acute entry into care if they had no prior hospital or community care for mental health or substance disorders, or only had community mental health contacts in the 7 days preceding their first admission with psychosis.

Analysis

Analyses were conducted using SPSS v20 (IBM Corporation, 2011) and Stata v11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, StataCorp LP). Demographic variables and substance disorder prevalence were compared to NSW population rates. Twelve month prevalence rates of substance disorders in the Australian population aged 15-29 were estimated from the Australian National Survey of Mental Health and Wellbeing, 2007, using methods described elsewhere (Australian Bureau of Statistics, 2009; Slade et al., 2009; Sara et al., 2011a).

Associations of illicit drug use were examined in two stages. First, univariate Odds Ratios and 95% CIs were calculated using binary logistic regression analyses conducted separately for candidate demographic, diagnostic and prior care variables, with the presence of any illicit drug diagnosis as the binary dependent variable. Multiple logistic regression was then performed entering all variables with significant univariate associations (P<=0.05) and including alcohol use disorders as a covariate.

Second, the associations of cannabis and stimulants with these independent variables were examined using multinomial logistic regression, with the five-category “Illicit Drug Use Group” as the dependent variable. The first category (No illicit drug use) was the reference group. Possible confounding effects of hallucinogen or polydrug diagnoses were examined by sensitivity analysis.

Multicollinearity for all regressions was tested by examination of variance inflation factors and condition index, achieving a final condition index less than 30 and no condition index loading more than 0.4 for more than one individual variable (Belsley, 1991).

Mean age at first admission for different drug types was compared using one-way ANOVA, with post hoc testing using Tukey's Honestly Significant Difference test.

RESULTS

We identified 9,919 individuals who met the study criteria. Two thirds (66%) were male (Table 6.1). The most common diagnoses at first admission were schizophrenia or delusional disorder (35%), drug induced psychosis (22%), affective psychosis (13%) and atypical or unspecified psychosis (13%).

Table 6.1. Sample characteristics, people with first psychosis admissions (n = 9,919).

	N	% [a]
Gender		
Male	6,529	65.8%
Age		
15-19	2,390	24.1%
20-24	3,732	37.6%
25-29	3,797	38.3%
Psychosis subtype at first episode [d]		
Schizophrenia and Delusional Disorder	3,434	34.6%
Schizoaffective	463	4.7%
Affective Psychosis	1,293	13.0%
Brief Psychosis	1,244	12.5%
Drug induced psychosis	2,193	22.1%
Other/Atypical/NOS	1,292	13.0%
Comorbid substance diagnoses [e]		
Any substance diagnosis	4,951	49.9%
Alcohol	1,352	13.6%
Sedative	104	1.0%
Any illicit drug diagnosis	4,570	46.1%
Illicit drug diagnosis group		
Cannabis	2,107	21.2%
Cannabis & stimulants	857	8.6%
Stimulants	685	6.9%
Other drug / polydrug only	921	9.3%
Care prior to first psychosis admission		
Previous hospital admissions	3,556	35.9%
Previous community mental health care	6,498	65.5%
Acute entry to care [f]	4,882	49.2%

Note. (a) Percentages are of non-missing data. (b) Country of birth data missing for 267 (2.7%). (c) Area of residence missing for 372 (3.8%). (d) Single psychosis diagnosis per person, hierarchy rule applied in order listed. (e) Multiple substance diagnoses per person, no hierarchy rule. (f) No prior mental health admissions and not more than 7 days of community mental health care prior to first psychosis admission.

Half of the group had a comorbid substance use disorder (Figure 6.1), especially cannabis (30%), stimulant (16%) and alcohol (14%) disorders. Cannabis and stimulant disorders overlapped; 857 persons had both cannabis and stimulant diagnoses, representing 29% of 2964 persons with cannabis diagnoses and 56% of 1542 persons with stimulant diagnoses. The Other/Polydrug group (n=921) included 752 persons with a diagnosis of polydrug disorder without specifying other individual substances, hence the estimates for specific individual drugs are under-estimates.

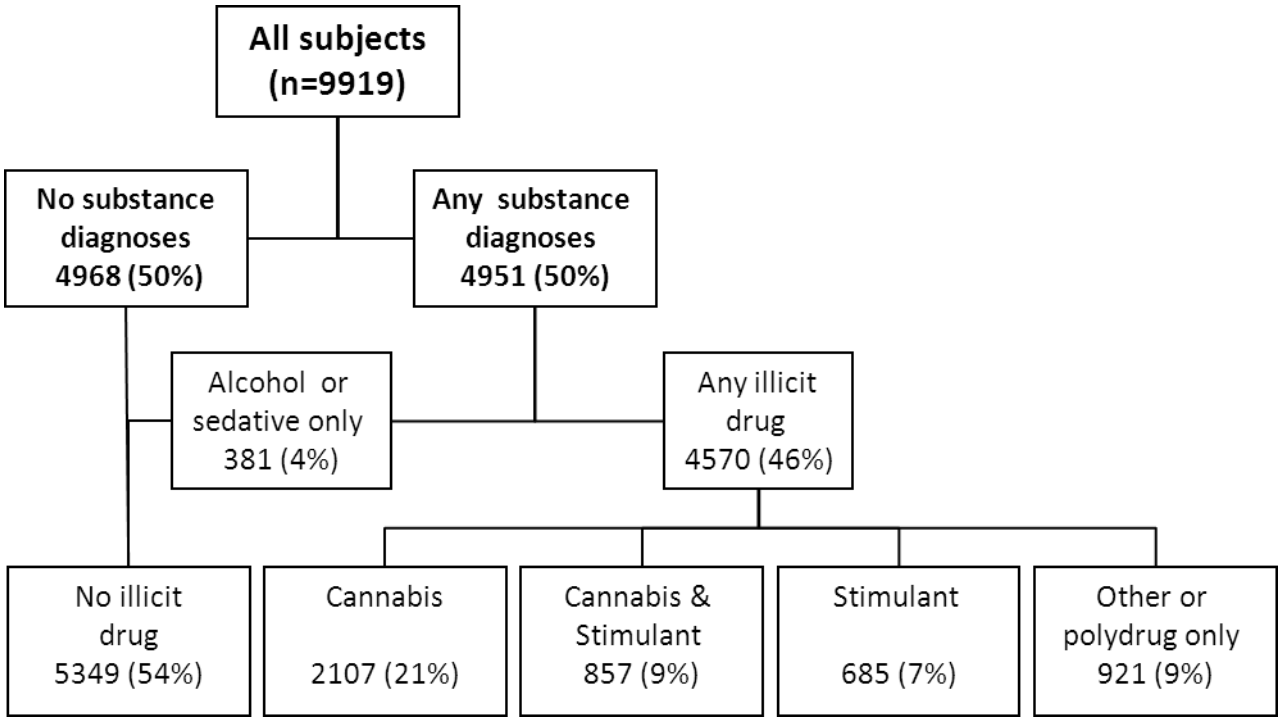

Figure 6.1. Comorbid drug diagnoses in persons aged 15-29 with first admission psychosis, *showing derivation of drug use group based on cannabis and stimulant use. 2964 (30%) persons had a cannabis diagnosis and 1542 (16%) had a stimulant diagnosis. All percentages are of total sample (n=9,919).*

By comparison with the aged-matched NSW population young people with first admissions for psychosis were more likely to be male, to be migrants, to reside in more disadvantaged areas and to live outside of major cities (Table 6.2). Young people admitted with psychosis had nearly eight times the odds of having a substance use disorder compared to the Australian population of the same age. There was a greatly increased rate of cannabis disorders and, to a slightly lesser degree, of stimulant disorders when compared to the age matched population. Alcohol disorders were moderately increased. Confidence intervals for these three estimates did not overlap, indicating that these differences were significant (Schenker and Gentleman, 2001).

Table 6.2. People with first admission psychosis compared to NSW population.

	First admission psychosis	NSW Population 15-29	Odds Ratio
	n = 9,919	n = 1,451,029	(95% CI)
Personal characteristics			
Male gender	65.8%	49.6%	1.90 (1.82 - 1.98)
Born outside Australia	19.8%	17.7%	1.15 (1.09 - 1.21)
Most disadvantaged 40%	45.6%	37.6%	1.39 (1.33 - 1.44)
Regional/remote residence	42.1%	40.5%	1.07 (1.03 - 1.11)
Substance use disorders [a]			
Any substance disorder	49.9%	11.1%	7.95 (7.64 - 8.27)
Alcohol disorder	13.6%	9.7%	1.47 (1.39 - 1.56)
Cannabis disorder	29.9%	2.5%	16.76 (16.03 - 17.52)
Stimulant disorder	15.5%	1.5%	11.85 (11.20 - 12.53)

Note: (a) Population rates for substance use disorders are rates for 12-month Abuse/Dependence for the Australian population, from the National Survey of Mental Health and Wellbeing 2007.

Table 6.3 shows univariate and multivariate associations of illicit substance disorders. Comorbid substance use was associated with male gender, younger age, being born in Australia and non-metropolitan residence. The association with younger age was less marked in the multivariate model. There was no univariate association with disadvantage or acute entry to care; these variables were excluded from multivariate analysis. Comorbid substance diagnoses were more prevalent in Schizophrenia (36%), Schizoaffective Disorder (31%) and Brief Psychoses (29%) than in Affective Psychoses (25%). Comorbid illicit substance diagnoses were by definition most common in persons with drug-induced psychosis. A small group (n=54) had diagnoses of drug-induced psychosis with alcohol or sedative diagnoses only but no illicit drug diagnoses. These may reflect alcohol-induced hallucinoses, delirium, or incomplete coding of comorbid substances. As they are small in number, these subjects have not been excluded.

Examining the composite “Illicit Drug Use Group” variable with multinomial logistic regression, the correlates of cannabis and stimulant disorders differed significantly (Table 6.4). Cannabis disorders declined with age, and were associated with male gender and rural location but not social disadvantage. By contrast, stimulant disorders increased with age, were unrelated to gender or rural location and were more common in less disadvantaged areas. Stimulant disorders were associated with a greater likelihood of acute entry into mental health care. Compared to people with cannabis diagnoses alone, those with both cannabis and stimulant disorders were older, more likely to have a diagnosis of drug-induced psychosis and more likely to have comorbid alcohol disorders.

Table 6.3. Associations of any illicit drug use disorder in first admission psychosis

		No comorbid illicit drug disorder	Comorbid Illicit drug disorder	Univariate	Multivariate
		n = 5,349 (53.9%)	n = 4,570 (46.1%)	OR (95% CI)	OR (95% CI)
Age group	15-19	1,242 (52.0%)	1,148 (48.0%)	1.24 (1.11 - 1.37)	1.13 (0.99 - 1.29)
	20-24	1,935 (51.8%)	1,797 (48.2%)	1.24 (1.13 - 1.36)	1.20 (1.07 - 1.35)
	25-29	2,172 (57.2%)	1,625 (42.8%)	1.00 [a]	1.00 [a]
Sex	Female	2,167 (63.9%)	1,223 (36.1%)	1.00 [a]	1.00 [a]
	Male	3,182 (48.7%)	3,347 (51.3%)	1.86 (1.71 - 2.03)	1.80 (1.61 - 2.02)
Migration status	Born in Australia	3,867 (50.0%)	3,872 (50.0%)	2.34 (2.10 - 2.61)	1.89 (1.64 - 2.18)
	Not born in Australia	1,340 (70.0%)	573 (30.0%)	1.00 [a]	1.00 [a]
Urban location	Major cities	3,208 (58.1%)	2,316 (41.9%)	1.00 [a]	1.00 [a]
	Regional and remote	1,971 (49.0%)	2,052 (51.0%)	1.44 (1.33 - 1.56)	1.20 (1.08 - 1.33)
Disadvantage	Least disadvantaged	2,821 (54.3%)	2,377 (45.7%)	1.00 [a]	-
	Most disadvantaged	2,358 (54.2%)	1,991 (45.8%)	1.00 (0.92 - 1.09)	-
Acute entry into care	No	2,755 (54.7%)	2,282 (45.3%)	1.00 [a]	-
	Yes	2,594 (53.1%)	2,288 (46.9%)	1.06 (0.98 - 1.15)	-
Diagnosis	Affective psychosis	964 (74.6%)	329 (25.4%)	1.00 [a]	1.00 [a]
	Schizophrenia	2,192 (63.8%)	1,242 (36.2%)	1.66 (1.44 - 1.92)	1.50 (1.29 - 1.76)
	Schizoaffective	321 (69.3%)	142 (30.7%)	1.30 (1.03 - 1.64)	1.25 (0.97 - 1.61)
	Brief	883 (71.0%)	361 (29.0%)	1.20 (1.01 - 1.43)	1.24 (1.03 - 1.50)
	Drug induced	54 (2.5%) [b]	2,139 (97.5%)	116.06 (86.18 - 156.30)	107.80 (79.39 - 146.37)
	Other / NOS	935 (72.4%)	357 (27.6%)	1.12 (0.94 - 1.33)	1.08 (0.90 - 1.31)

Note: (a) Reference groups for regression analysis (b) 54 subjects with a diagnosis of drug-induced psychosis had alcohol or sedative use disorders as the only recorded substance diagnoses.

Table 6.4. Associations of specific drug use disorders in first admission psychosis

	Cannabis n=2107	**Cannabis and Stimulant** n=857	**Stimulant** n=685	**Other illicit drug / polydrug** n=921
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age group				
15-19	1.00 [a]	1.00 [a]	1.00 [a]	1.00 [a]
20-24	0.96 (0.83 - 1.11)	1.22 (0.98 - 1.51)	1.61 (1.23 - 2.10)	1.14 (0.92 - 1.42)
24-29	0.67 (0.57 - 0.78)	0.93 (0.74 - 1.16)	1.86 (1.43 - 2.42)	1.30 (1.05 - 1.61)
Person characteristics				
Male	2.09 (1.83 - 2.38)	1.89 (1.56 - 2.29)	1.09 (0.89 - 1.33)	1.53 (1.28 - 1.82)
Migrant	0.55 (0.46 - 0.65)	0.46 (0.36 - 0.60)	0.57 (0.44 - 0.74)	0.48 (0.38 - 0.60)
Urban location	0.67 (0.59 - 0.75)	0.84 (0.71 - 1.00)	1.17 (0.96 - 1.43)	1.32 (1.11 - 1.56)
Least disadvantaged	1.00 (0.88 - 1.12)	1.16 (0.98 - 1.38)	1.24 (1.02 - 1.50)	0.88 (0.75 - 1.03)
Psychosis diagnosis				
Affective Psychosis	1.00 [a]	1.00 [a]	1.00 [a]	1.00 [a]
Schizophrenia	1.13 (0.90 - 1.42)	0.95 (0.63 - 1.43)	0.79 (0.43 - 1.44)	1.18 (0.80 - 1.73)
Schizoaffective	1.25 (0.99 - 1.58)	1.33 (0.90 - 1.97)	1.25 (0.73 - 2.14)	1.07 (0.71 - 1.60)
Brief psychosis	1.04 (0.75 - 1.45)	1.31 (0.77 - 2.24)	2.21 (1.20 - 4.06)	1.47 (0.91 - 2.39)
Atypical / NOS	1.39 (1.14 - 1.69)	1.45 (1.04 - 2.01)	1.72 (1.11 - 2.68)	1.89 (1.38 - 2.60)
Drug induced psychosis [b]	63.53 (45.80 - 88.12)	139.14 (92.60 - 209.08)	287.91 (177.19 - 467.82)	129.34 (86.34 - 193.74)
Acute entry into care	1.11 (0.98 - 1.25)	1.31 (1.10 - 1.55)	1.33 (1.10 - 1.62)	0.76 (0.64 - 0.89)
Alcohol use disorder	3.49 (2.96 - 4.12)	5.25 (4.27 - 6.46)	2.51 (1.93 - 3.26)	2.13 (1.69 - 2.70)

Notes: (a) Reference group. (b) Comparison is with 54 persons with diagnoses of drug-induced psychosis associated with alcohol and sedatives.

Stimulants appeared more strongly associated than other drugs with diagnoses of Drug Induced Psychosis. Odds Ratios for these estimates were very high, being based on comparison with the small group with Drug-Induced Psychosis who had no illicit drug diagnosis. We conducted separate analyses using Cannabis Disorders and Stimulant Disorders as binary dependent variables, while controlling for the other drug as a covariate. Detailed results are not reported here, but the findings were consistent with that of the multinomial regression: persons with stimulant disorders had around twice the odds of having a diagnosis of Drug Induced Psychosis when compared to persons with cannabis disorders.

We examined the possible confounding impact of hallucinogen and polydrug diagnoses using sensitivity analysis. Multinomial logistic regression was repeated after excluding persons with these diagnoses. There was no change in the pattern of significant findings for cannabis or stimulant groups. Hallucinogen and polydrug diagnoses were more common in the “Cannabis and Stimulant” group, and when these were excluded there was no longer a significant association with age or atypical/unspecified psychosis for that group.

Age at first admission with psychosis differed by type of drug (Table 6.5). Average age at first admission was approximately one year younger for persons with cannabis disorders than for those with no comorbid drug use, and approximately one year older for those with stimulant use disorders.

Table 6.5. Age at first admission for psychosis, by type of drug used

	Persons	Mean (95% CI)
Cannabis alone	2,107	22.7 (22.5 - 22.9)
Cannabis and stimulants	857	23.1 (22.9 - 23.4)
No drug diagnosis	5,349	23.5 (23.4 - 23.6)
Polydrug, other drug	921	23.7 (23.4 - 23.9)
Stimulants alone	685	24.2 (23.9 - 24.4)

Note: One way ANOVA, $F = 26.2$ $p < 0.001$

DISCUSSION

We examined first admissions for psychosis in a representative population sample of 9,919 young people aged 15-29. Half had comorbid substance diagnoses. To our knowledge this is the largest reported series of first admission psychoses and the first to specifically examine the correlates of stimulant disorders.

Differences in Correlates of Cannabis and Stimulant Disorders

In NSW residents with first admission psychosis, comorbid substance disorders were associated with being younger, male and living in rural locations. Cannabis disorders were the most common substance comorbidity, and the associations of substance disorders are therefore largely those of cannabis disorders. By contrast, stimulant diagnoses were associated with older age, less social disadvantage and a more even gender balance. Cannabis and stimulant disorders were more common in atypical and drug-induced psychoses than in affective psychoses or schizophrenia.

Stimulant disorders appeared particularly associated with diagnoses of drug-induced psychosis. The validity of this diagnosis is often questioned (Mathias et al., 2008). Atypical, brief and drug-induced psychoses comprised nearly half of diagnoses in this study, but are frequently excluded from clinical studies (Compton et al., 2011; González-Pinto et al., 2011; Gonzalez-Pinto et al., 2008; Linszen et al., 1994; Sevy et al., 2001; Veen et al., 2004). This may underestimate the impact of cannabis and stimulants in young people admitted with psychosis. If these diagnoses are associated with more positive outcomes, then excluding them may also influence findings regarding course and outcome, and limit the generalizability of research findings to clinical settings where substance comorbidity and brief or atypical psychoses are common.

Notably, women were as likely as men to have stimulant diagnoses in this group, although stimulant disorders are four times more common in male than female Australians of this age (Sara et al., 2011a). This could suggest that stimulants are more likely to precipitate psychosis in women than in men. However, psychotic symptoms are unrelated to gender in recreational amphetamine users (McKetin et al., 2010) and are more common in male dependent stimulant users (Chen et al., 2003; Salo et al., 2011). Alternative explanations include that young women with psychotic symptoms and stimulant use are more likely to seek care, to be admitted when they do seek care or to have a comorbid stimulant diagnosis recognised and recorded.

Correlates of Drug Use Disorders in Psychosis

First admissions for psychosis were more common in disadvantaged areas, but comorbid substance diagnoses were not. Therefore the excess of psychosis in disadvantaged areas was not due to an excess of drug-related psychoses.

The excess of psychosis admissions amongst migrants is consistent with other reports (McGrath et al., 2004; Tandon et al., 2008). However, substance-related psychoses were around half as common in migrants as in those born in Australia, as also reported in an Australian clinical study (Wade et al., 2005).This may reflect lower rates of drug-use in migrant Australians. In population surveys, Australians whose main language is not English have much lower rates of use of alcohol, cannabis and stimulants than other Australians (Australian Institute of Health and Welfare, 2011). Alternative explanations include underreporting or poorer recognition of substance use in young people from differing cultural backgrounds.

Cannabis and stimulant disorders were more than ten times more frequent in young people with first admissions for psychosis than in young Australians of the same age. Alcohol disorders were only moderately increased. These findings are consistent with evidence that cannabis and stimulants play a causal role in psychosis (Hall and Degenhardt, 2011; Hermens et al., 2009). However this study does not demonstrate a causal link between individual substances and psychosis. We cannot identify whether substances precipitated psychosis, whether persons used substances for self-medication or whether other factors explained these associations.

We found that cannabis was more strongly associated with admission for psychosis than were stimulants, contrasting with findings that the risk of admission is higher for amphetamine users than for cannabis users (Degenhardt et al., 2007d). That study examined only diagnoses of drug-induced psychosis, and we found that stimulants were particularly associated with drug-induced psychoses.

Limitations

Diagnoses obtained from administrative data are less reliable than those made using standardised diagnostic instruments. Substance comorbidities may be particularly under-recorded in routine clinical data (Large et al., 2012). Rates of cannabis and stimulant use in our sample were nonetheless similar to those reported in clinical studies.

Some individuals in our cannabis and/or stimulant disorder groups also had comorbid diagnoses of alcohol, opiate or hallucinogen disorders. We have attempted to limit possible confounding effects of these other drugs by including alcohol diagnoses as a covariant and examining the effects of exclusion of individuals with hallucinogen or polydrug diagnoses. However, our drug use categories do not reflect completely “pure” users of cannabis or stimulants, and may include people with undiagnosed use of other substances.

This study examines only people admitted to hospital with psychosis. Studies from the UK (Sipos et al., 2001), Denmark (Petersen et al., 2005) and Australia (Wade et al., 2006c) found that more than 80% of people seen by specialist early psychosis services were admitted over the first 12 to 36 months of care. Those not admitted had longer duration of psychosis, less social disadvantage and greater likelihood of a manic psychosis (Sipos et al., 2001; Wade et al., 2006c; Compton et al., 2011), but did not differ in positive symptoms or likelihood of problem substance use (Wade et al., 2006c). Therefore studying only admitted persons is likely to have a modest impact on our findings.

Data on admissions to private hospitals were not available to us. In NSW, private hospitals are mainly located in advantaged urban areas. They do not provide involuntary care, and admit few young people with acute psychoses. In 2011 only 76 individuals aged 15-29 had a first or subsequent admission to a NSW private hospital with a diagnosis of psychosis (Morris-Yates, personal communication). By contrast there were 1,338 first admissions in our study group in that year. Exclusion of private hospitals is unlikely to explain our findings.

Conclusions

Stimulants and cannabis act through different chemical pathways and differ in their patterns of dependence and their clinical impacts. There are methodological challenges in separating the associations of stimulant use from those of cannabis use in young people with early psychosis. Examining a large population sample is one approach to these challenges. We have identified significant differences in age, gender, demographics and diagnosis between cannabis users and stimulant users admitted with psychosis. Our findings underline that substance comorbidity is so frequent in young people with psychosis that its identification and treatment should be a core component of their care. Strategies for comorbid stimulant disorders may need to include the needs of a slightly older and less disadvantaged group.

Future studies could examine the apparent relationship between stimulant disorders and diagnoses of brief or drug-induced psychoses, and whether these are associated with differences in outcome when compared with cannabis-associated psychoses.

7: Stimulant disorders and hospital readmission over two years following first psychosis admission

This chapter is based on the publication: **Sara, G., P. Burgess, G. Malhi, H. Whiteford and W. Hall (2014). Cannabis and stimulant disorders and readmissions 2 years after first episode psychosis. British Journal of Psychiatry. 204: 448-453.**

ABSTRACT

Background

Few studies have examined the impact of stimulant use on outcome in early psychosis. Ceasing substance use may lead to positive outcomes in psychosis.

Aims

To examine whether baseline cannabis or stimulant disorders and ongoing drug use predict readmission within two years of a first psychosis admission.

Methods

Predictors of readmission were examined with Cox Regression in 7269 people aged 15-29 with a first psychosis admission.

Results

Baseline cannabis and stimulant disorders did not predict readmission. A stimulant disorder diagnosis prior to index psychosis admission predicted readmission, but a prior cannabis disorder diagnosis did not. Ongoing problem drug use predicted readmission. The lowest rate of readmission occurred in people whose baseline drug problems were discontinued.

Conclusions

Prior admissions with stimulant disorder may be a negative prognostic sign in first episode psychosis. Drug use diagnoses at baseline may be a good prognostic sign if they are identified and controlled.

INTRODUCTION

Substance use may influence the onset and course of psychosis (Álvarez-Jiménez et al., 2011). Ongoing substance use is associated with negative outcomes (González-Pinto et al., 2011; Bertelsen et al., 2009; Wade et al., 2006b) but may also be a marker for other factors that affect prognosis, including younger age of onset and male gender (Wade et al., 2006b). Many young people with psychosis abuse stimulant drugs (Hides et al., 2006; Sara et al., 2013) however most of these young people also abuse cannabis (Degenhardt et al., 2010b), making it difficult to separate the effects of these two drugs. In a large Thai sample, more than half of first admissions with specific diagnoses of methamphetamine psychosis went on to have further episodes of psychosis (Kittirattanapaiboon et al., 2010). We are not aware of any study examining the relationship between stimulant disorders and outcome in young people with broadly diagnosed psychoses. Our study used a large population-based sample of people aged 15-29 with a first admission with psychosis. We examined readmission within two years as a measure of relapse or recurrence (Gleeson et al., 2010). Our first aim was to examine whether baseline cannabis or stimulant disorders predicted later readmission. Our second aim was to examine the impact of ongoing problem drug use on readmission.

METHODS

Setting and Participants

The study was approved by the NSW Population and Health Services Research Ethics Committee. NSW had an estimated resident population of 7.3 million persons in 2012, of which approximately 20% were aged 15-29 (Centre for Epidemiology and Evidence, 2012). Admissions to NSW state operated ("public") hospitals were linked using a unique health identifier.

Figure 7.1 summarises the study's method. For all persons with a diagnosis of psychosis, the first ever (index) hospital admission with psychosis was identified. People aged 15-29 whose index admission occurred within the study period (July 2005 to June 2010) were included. Exclusion criteria were: (i) admissions where the person was admitted and discharged on the same day; (ii) persons whose usual residence was another country or another Australian state; (iii) persons with organic psychosis or schizotypal disorder as the only psychosis diagnosis; (iv) persons whose index admission ended in death; and (v) persons not yet discharged 2 years after index admission.

The period July 2000 to June 2005 was used as a baseline period for determining incident cases. All subjects had no admissions with a psychosis diagnosis for at least five years prior to their index admission. Admissions in the baseline period for non-psychotic conditions (such as mood, anxiety, adjustment or substance disorders) were not excluded, as these conditions frequently precede psychosis (Yung and McGorry, 2007).

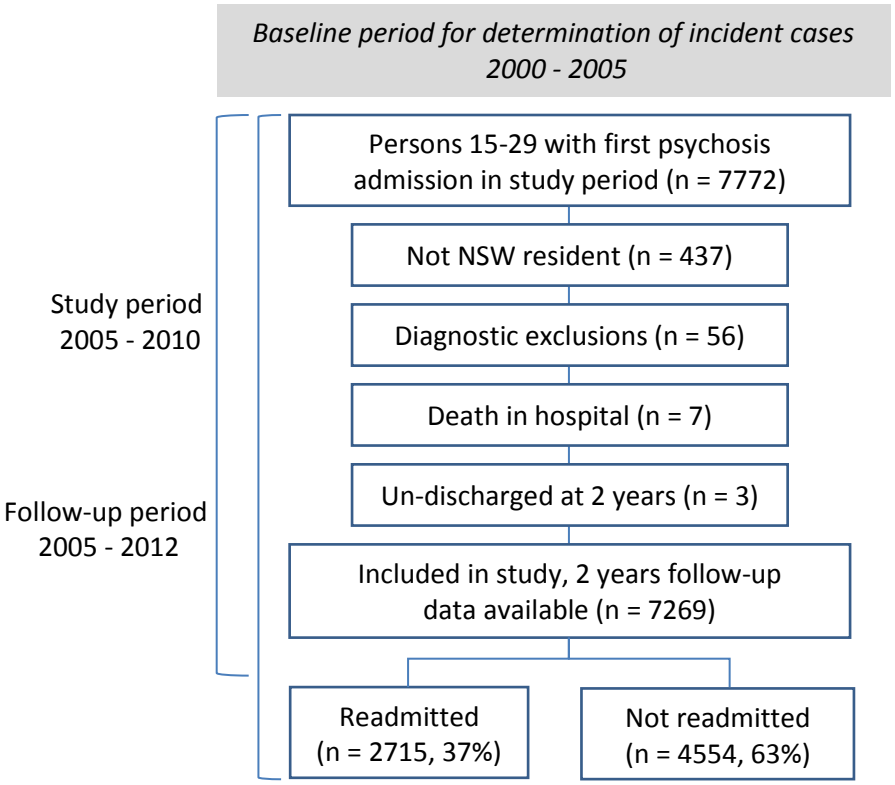

Figure 7.1. Overview of study method. Admissions to all NSW public hospitals, 2000 – 2012. Diagnostic exclusions: Schizotypal disorder (n=34), organic psychosis (n=22).

We identified readmissions to any NSW public hospital with a primary or additional diagnosis of psychosis within 2 years of discharge from the index psychosis admission. We excluded readmissions due to transfer between hospitals, or occurring on the day of discharge of the index admission. Readmission data were available to 30 June 2012.

Measures

Primary and additional diagnoses were made by the treating psychiatrist and extracted from clinical notes by medical records coders. Psychosis was defined by the presence of a primary or additional ICD-10 (National Centre for Classification in Health, 2010) diagnosis code for a psychotic disorder, including affective psychoses (mania or depression with

psychosis specified) and drug-induced psychosis. Substance related disorders were identified by diagnosis codes for abuse, dependence, intoxication or poisoning. Drug-induced psychoses were counted as both a psychosis and a substance use disorder. Amphetamines and cocaine were grouped into a single “stimulant” disorder category. All individual substance diagnoses were recorded; polydrug disorder was recorded only where this was specifically diagnosed (ICD code F19).

Binary variables were constructed to indicate prior hospital admissions with non-psychotic mental health conditions, cannabis disorders or stimulant disorders. Migration status was based on country of birth recorded at index admission. Australian Bureau of Statistics reference data for the statistical local area of residence at the index admission were used to obtain measures of rurality (Accessibility Remoteness Index of Australia, ARIA, www.abs.gov.au/websitedbs/d3310114.nsf/home/remoteness+structure) and disadvantage (Index of Relative Socio-Economic Disadvantage, IRSD, www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001).

A proxy measure of ongoing problem drug use was constructed for individuals who had contact with community mental health services or were re-hospitalised for any reason after their index admission. This proxy measure could not be constructed where a person had no further contact with NSW hospital or community services following their index admission. NSW inpatient and community mental health services collect diagnoses and periodic ratings using the Health of the Nation Outcome Scales (HoNOS) (Wing et al., 1998). Ratings are made by the treating clinician (case manager or psychiatrist). Ongoing drug problems were defined as present if, during the follow-up period, the person had either (i) any diagnosis of a substance use disorder in hospital or community records or (ii) at least one completed HoNOS with a score of 2 (“Loss of control of drinking or drug-taking”), 3 (“Marked craving or dependence”) or 4 (“Incapacitated by alcohol and drug problems”) on the HoNOS Problem Drinking or Drug-taking Scale (i.e., HoNOS Item 2) . HoNOS does not distinguish the type of substance used. A threshold score of 2 or more was chosen to define problem substance use, in keeping with expert clinician ratings of “clinically significant” problems on the HoNOS (Burgess et al., 2009a). Baseline and ongoing drug diagnosis and HoNOS measures were combined to create a composite variable with three possible values; No Drug Problem (baseline or ongoing), Drug Problem Ceased (drug diagnosis at index admission but no ongoing problem), Drug Problem Ongoing (drug problem in ongoing measure, with or without drug diagnosis at index admission).

Analysis

Statistical analyses were undertaken using Stata v11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX, StataCorp LP). Univariate Cox regressions were conducted on candidate variables. Proportional hazards assumptions were tested by visual examination of log-log survival plots and by testing for significant interactions when each variable was entered as a time-based covariate. Variables of interest, with univariate P <0.2, and which satisfied proportional hazards assumptions, were entered into a multivariate Cox regression. This model was stratified on local mental health service, because observations may have been correlated within health services due to local population or resource factors. Two variables failed proportional hazards assumptions and were therefore included as stratifiers rather than covariates: (i) admission to a non-specialised mental health unit and (ii) psychosis as a comorbid diagnosis rather than a primary diagnosis for the index admission. The distribution of deviance residuals was examined to identify multivariate outliers.

Differences between people with and without ongoing service contact were examined using binary logistic regression. The proxy measure of ongoing drug problems was analysed for the subset of subjects for whom the measure was available, using the same Cox Regression method described above.

RESULTS

There were 7,269 persons aged 15-29 who had a first admission in the study period (Table 7.1). Two-thirds (66%) were male and only 24% were aged under 20. The most common diagnoses at first admission were schizophrenia or delusional disorders (36%) and drug-induced psychosis (22%). Thirty percent had a comorbid cannabis disorder and 16% a comorbid stimulant disorder. One in six (16%) had prior admissions for mental health or substance-related problems but without a psychosis diagnosis. Thirty-seven percent of persons were readmitted with psychosis within two years. The risk of readmission was highest immediately following the index admission; 17% of subjects were readmitted within 90 days (representing 45% of those who were readmitted).

Table 7.1. Characteristics of the study group, first episode psychosis follow-up

	Number (%)	Readmitted % (95% CI)
Total	7,269 (100)	37 (37-37) [e]
Gender		
Male	4,810 (66)	39 (38-40)
Female	2,459 (34)	34 (32-35)
Age group		
15-19	1,736 (24)	42 (40-45)
20-24	2,718 (37)	37 (36-39)
25-29	2,815 (39)	34 (32-36)
Diagnosis		
Schizophrenia [a]	2,602 (36)	42 (40-44)
Schizoaffective	343 (5)	41 (35-48)
Affective psychosis [b]	939 (13)	28 (25-31)
Brief psychosis	919 (13)	38 (35-42)
Drug-induced psychosis	1,570 (22)	36 (33-38)
Other psychosis [c]	896 (12)	36 (33-40)
Baseline drug diagnoses		
Cannabis	2,197 (30)	41 (38-43)
Stimulants	1,162 (16)	38 (35-42)
Prior care		
Prior admissions [d]	1,177 (16)	42 (38-45)
Prior cannabis	645 (9)	41 (36-45)
Prior stimulants	372 (5)	46 (39-53)
Person		
Migrant	1,332 (18)	35 (32-38)
Rural residence	3,013 (41)	39 (37-41)
Most disadvantaged	3,183 (44)	39 (38-41)

Note: (a) Includes delusional disorder. (b) Mania or depression where psychosis specified. (c) Includes other non-organic psychosis (F28), Psychosis NOS (F29). (d) Prior admissions for mental health care but no prior psychosis diagnosis. (e) Readmission rate 37.35%, 95%CI 37.33% – 37.38%

Table 7.2 shows the results of univariate and multivariate Cox Regression. In univariate comparisons, readmission at two years was significantly more likely in males (HR 1.21, 95% CI 1.11-1.31) and in younger subjects. The highest rate of readmission (42%) was for people with an index diagnosis of schizophrenia. By comparison with schizophrenia, the risk of readmission was reduced in those with affective psychosis (HR 0.61, 95% CI 0.53-0.69), drug-induced psychosis (HR 0.83, 95% CI 0.75-0.92) and atypical psychosis (HR 0.85 95% CI 0.75-0.97). Cannabis disorders at index admission were associated with a greater risk of readmission (HR 1.15, 95% CI 1.06-1.25), but cannabis disorders prior to the index admission were not (HR 1.11, 95% CI 0.97-1.26). This pattern was reversed for stimulants: baseline stimulant disorders were unrelated to risk of readmission, but people

with an admission with stimulant disorders prior to their index admission had a higher risk of readmission (HR 1.30, 95% CI 1.11-1.51).

Table 7.2. Cox regression analysis - readmission within two years of first psychosis admission

		Univariate			Multivariate [f]	
	N	**HR**	**95% CI**	***P***	**HR**	**95% CI**
Gender (male)	4,810	1.21	1.11-1.31	<0.001	1.13	1.04-1.24
Age group						
15-19 [a]	1,736	1.00	-	<0.001	1.00	-
20-24	2,718	0.85	0.77-0.93		0.80	0.73-0.89
25-29	2,815	0.76	0.69-0.83		0.72	0.65-0.80
Diagnosis						
Schizophrenia [a b]	2,602	1.00	-	<0.001	1.00	-
Schizoaffective	343	0.98	0.82-1.17		1.01	0.84-1.21
Affective psychosis [c]	939	0.61	0.53-0.69		0.56	0.48-0.64
Brief psychosis	919	0.91	0.80-1.02		0.80	0.73-0.89
Drug-induced psychosis	1,570	0.83	0.75-0.92		1.13	1.04-1.24
Other psychosis [d]	896	0.85	0.75-0.97		0.81	0.71-0.92
Baseline drug diagnoses						
Cannabis	2,197	1.15	1.06-1.25	<0.001	1.06	0.97-1.16
Stimulants	1,162	1.05	0.95-1.16	NS [e]	1.02	0.90-1.14
Prior care						
Prior admissions	1,177	1.18	1.07-1.30	<0.001	1.22	1.08-1.37
Prior cannabis	645	1.11	0.97-1.26	NS	0.97	0.82-1.14
Prior stimulants	372	1.30	1.11-1.51	NS	1.36	1.12-1.66
Person						
Migrant	1,332	1.11	1.00-1.22	NS	1.04	0.93-1.16
Rural residence	3,013	1.10	1.02-1.19	NS	1.03	0.86-1.24
Most disadvantaged	3,183	1.13	1.04-1.22	<0.001	1.07	0.95-1.21

Notes: (a) Reference group. (b) Includes delusional disorder. (c) Mania or depression where psychosis specified. (d) Includes other non-organic psychosis (F28), Psychosis NOS (F29). (e) NS = Not significant ($p > 0.05$). (f) P for overall model <0.001

The results of multivariate analysis differed slightly: after controlling for other variables, affective, brief and atypical psychoses were associated with lower risk of readmission than schizophrenia, but drug-induced psychosis was associated with a higher risk (HR 1.13, 95% CI 1.04-1.24). Baseline cannabis disorder was no longer associated with readmission. Findings regarding stimulants were unchanged in the multivariate analysis: prior stimulant disorders predicted readmission (HR 1.36, 95% CI 1.12-1.66) but a baseline stimulant diagnosis did not. There was no relationship between readmission and migrant status, rural location or residing in more disadvantaged localities.

Examining multivariate outliers, 80 subjects (1.1%) had deviance residuals greater than 2.5 standard deviations (SD) but none greater than 3.0 SD. These subjects did not differ significantly from other subjects on age, gender, diagnosis group, rate of substance use or

year of admission, but they were more likely to have had their index admission outside a specialist mental health unit. Index admission occurred outside a specialised mental health unit for 1,068 persons (15% of the study group). These admissions were more common in rural hospitals, and were not excluded from the study in order to avoid systematic under-representation of rural residents. Sensitivity analysis was conducted by refitting the multivariate Cox regression model after removing this group; the risk of readmission for brief psychosis was slightly reduced, and now differed significantly from that for schizophrenia (HR 0.84, 95% CI 0.74-0.96) in the revised model. The model was otherwise unchanged.

Sensitivity analysis was conducted on the effects of different methods for dealing with tied observations within a Cox regression. There was no significant difference between exact and approximate methods; the results presented used the Efron approximation.

Thirty one percent (31%) of subjects had no further contact with NSW community mental health or inpatient services in the 2 years after their index admission, and therefore had no diagnostic or HoNOS information for ongoing care in the study period. People with no ongoing service contact were more likely to be younger, to have an index diagnosis of brief (OR 1.39, 95% CI 1.01 – 1.91), drug-induced (OR 1.27, 95% CI 1.02 – 1.58), or atypical/unspecified psychosis (OR 1.49, 95% CI 1.07 – 2.07) and to have had prior admissions with cannabis (OR 1.47, 95% CI 1.07 – 1.27) or stimulant (OR 1.50, 95% CI 1.01 – 1.21) diagnoses. They were less likely to have baseline cannabis diagnoses (OR 0.43, 95% CI 0.36 – 0.52) but did not differ from people with ongoing contact on gender, baseline stimulant use, urban/rural location or migration status.

Excluding people with no further contact with NSW Health services, the proxy measure of ongoing drug problems was available for 69% of the study group (4,993 persons). Their two year readmission rate (54%) was higher than for the study group as a whole, since the readmission rate for those with no further contact was, by definition, zero. Those with ongoing contact were divided into three groups; No Drug Problem (n=2,209), Drug Problem Ceased (n=866) and Drug Problem Ongoing (n=1,918). Figure 7.2 shows the cumulative readmission curve for these groups. The readmission rate was highest for the Drug Problem Ongoing group (66%, 95% CI 63%-69%), intermediate for those with No Drug Problem (50%, 95% CI 47% - 52%) and lowest for the Drug Problem Ceased group (40%, 95% CI 37% - 44%). This difference was significant (Wilcoxon/Breslow test, Chi-square = 147.92, $p<0.0001$). The proportional hazards assumption for Cox Regression

was not met: examination of the survival curves suggests that the reason for this was that the Drug Problem Ceased group had a lower rate of early readmission, but not of later readmission when compared with the No Drug Problem group. Sensitivity analysis, where people with an index diagnosis of drug-induced psychosis were excluded, did not change these results; readmission rates after exclusion of drug-induced psychosis were Drug Problem Ongoing 67% (95% CI 63% - 71%), No Drug Problem 50% (95% CI 48%-52%), Drug Problem Ceased 43% (95% CI 38%-48%).

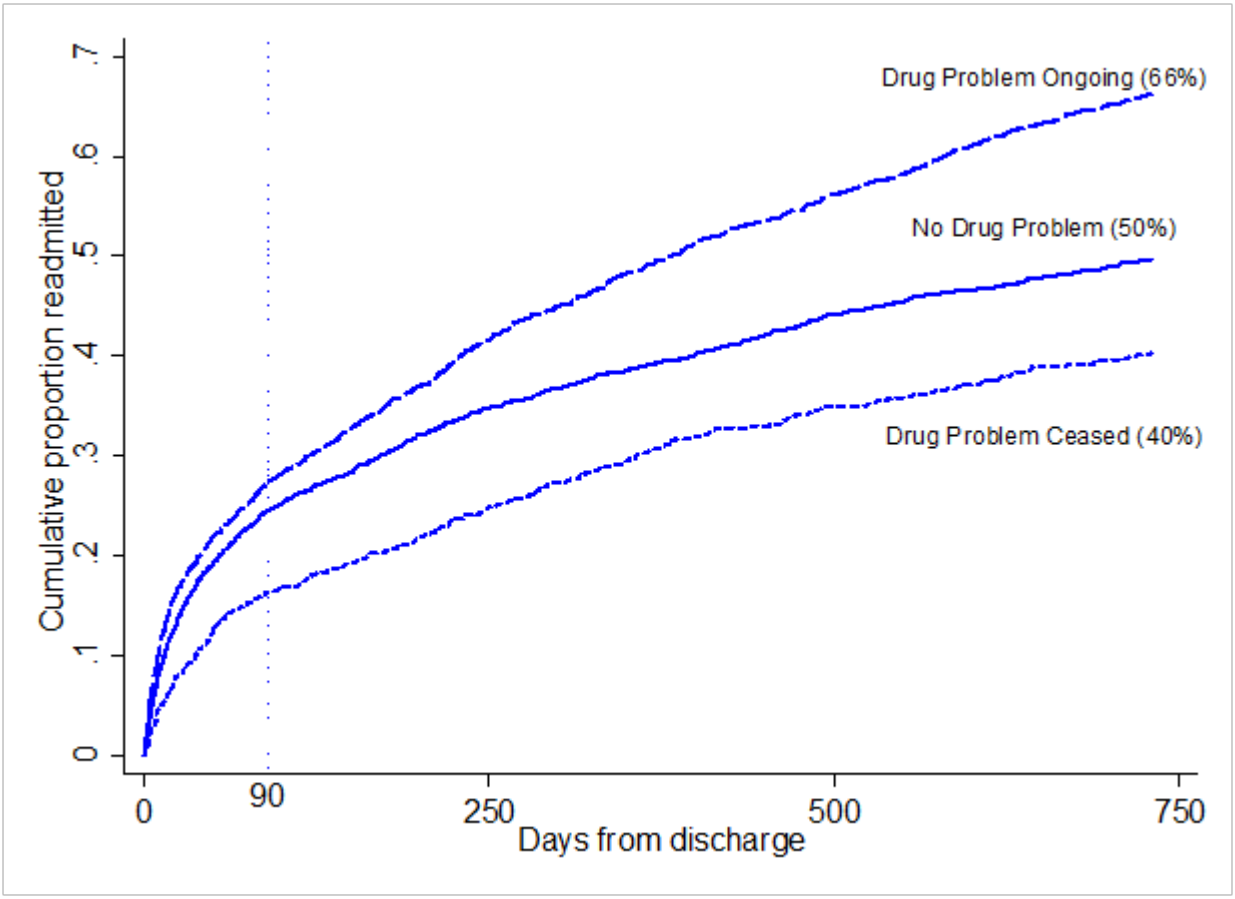

Figure 7.2. Readmission following first psychosis admission, by pattern of ongoing problem drug use. Results for 4,993 persons (69% of total sample) for whom a proxy measure of ongoing drug problems was available. Two year readmission rate for total sample: 37%.

DISCUSSION

It is clinically important to identify factors which predict outcome in first episode psychosis, and especially to identify prognostic factors which may be influenced by intervention. Some studies have found that substance use at psychosis onset predicts poorer outcomes (Malla et al., 2008; Addington et al., 2010). We have used health system data for a population of 7.3 million persons to examine the risk of readmission in young people following a first admission for psychosis. Neither cannabis nor stimulant diagnoses at baseline predicted readmission after controlling for age, gender and diagnostic subtype. Our findings are consistent with those suggesting that ongoing substance use is the more important issue (González-Pinto et al., 2011; Wade et al., 2006b; Bertelsen et al., 2009).

Cannabis disorders and readmission

We found univariate associations between baseline cannabis and outcome, however these were no longer significant after controlling for age, gender and diagnostic subtype. Our findings are consistent with studies reporting that baseline cannabis use did not predict poor outcome (Addington and Addington, 1998; González-Pinto et al., 2011). Some of the apparent association between baseline cannabis use and adverse outcome may be due to confounding of cannabis disorders with other factors which predict readmission, namely, being younger, male and having a primary diagnosis of schizophrenia. Baseline use of cannabis or other drugs may also be a predictor of ongoing drug use.

Stimulant disorders and readmission

Stimulant disorders at baseline were not associated with readmission, but hospital admissions with stimulant disorders prior to the index admission were. The finding is consistent with evidence that the risk of developing a drug-related psychosis after prolonged drug use is greater for stimulants than for cannabis (Degenhardt et al., 2007d), and with sensitisation models of the interaction between stimulant use and psychosis (Curran et al., 2004; Hermens et al., 2009). Prior stimulant-related admissions are likely be indicators of severe or enduring stimulant use, since most people with stimulant abuse or dependence are not admitted to hospital. Severe stimulant disorders may also be associated with abuse of a wider range of substances, including heavier or more sustained cannabis use. However the same association was not found for prior cannabis use disorders.

Ongoing drug use

We found that people with ongoing problem drug use had a rate of readmission nearly one third higher than people with no drug use. An association between ongoing drug use and poor outcome is not surprising, however our findings help to quantify the scale of this effect in a representative population-based sample, and underline the significant personal and health system impacts of ongoing drug use.

Conversely, we found that the best outcome (as measured by hospital readmission) occurred in people with baseline substance diagnoses but no ongoing substance use problems. Several studies have found that young people with psychosis who cease substance use have better outcomes than those who have never used substances (Strakowski et al., 2007; Baeza et al., 2009; Lambert et al., 2005). A recent meta-analysis of this issue concluded that further and larger studies were needed (Gupta et al., 2013). Our findings add further evidence on this issue.

An association between substance use and positive outcome in psychosis may seem counterintuitive, since substance use in people with psychosis is associated with negative prognostic factors including younger age, male gender and social disadvantage. However there is increasing evidence that comorbid drug use in psychosis is also associated with better neurocognitive performance, fewer negative symptoms, fewer neurological soft signs and more positive symptoms (Rabin et al., 2011; Yucel et al., 2012).

Three explanations have been proposed for these findings. First, cannabis may have direct neuroprotective effects (Yucel et al., 2012). Second, Meuser (Mueser et al., 1998) has proposed that this effect is mediated through social competence, whereby more "socially oriented patients with serious mental illness are more likely to come into contact with drugs and subsequently develop substance use disorder" (p726). Third, these findings may reflect varying degrees of personal vulnerability: psychosis in the absence of substance use is likely to reflect greater genetic or developmental diathesis in the person affected, whereas cannabis or other drugs may precipitate psychosis in individuals with less intrinsic vulnerability (Schnell et al., 2009; Loberg and Hugdahl, 2009). Our findings cannot distinguish between greater social competence and lesser personal vulnerability as explanations for positive outcome in former drug users with psychosis, and further research on this question is needed. The association between ongoing substance use and worse outcome is inconsistent with cannabis having a neuroprotective effect in psychosis.

Regardless of the mechanism, our findings underline an important and hopeful clinical message. Young people with a first episode psychosis and comorbid substance disorder may have the best outcomes, provided that substance disorder is properly managed.

Other findings

After controlling for other variables, the risk of readmission for people with an index diagnosis of drug-induced psychosis was higher than for those with an index diagnosis of schizophrenia. This is consistent with studies questioning the predictive validity of drug-induced psychosis diagnoses (Mathias et al., 2008; Crebbin et al., 2009). In a study of persons with diagnoses of cannabis-induced psychosis, nearly half were subsequently diagnosed with schizophrenia and 77% had further psychotic episodes (Arendt et al., 2005).

The association between ongoing problem drug use and readmission was not constant over time; cessation of problem drug use appeared to be associated with a reduced risk of early readmission (within 90 days of discharge from index admission). Early and late relapse or readmission may be influenced by different processes and risk factors (Durbin et al., 2007). This issue warrants further study.

Limitations

The scale and population coverage of administrative datasets can complement clinical studies by allowing an examination of issues such as stimulant abuse which may be otherwise confounded by other clinical or personal variables in smaller clinical samples. However routinely collected administrative data also have a number of limitations.

First, we have not captured all incident cases of psychosis in NSW because we have used hospitalisation data to define incidence. More than 80% of people seen by specialised early psychosis services are admitted early in their illness (Sipos et al., 2001; Petersen et al., 2005; Wade et al., 2006c). Those not admitted have longer duration of psychosis, less social disadvantage and greater likelihood of a manic psychosis (Sipos et al., 2001; Wade et al., 2006c; Compton et al., 2011), but do not differ in their prevalence of positive symptoms or the likelihood of problem substance use (Wade et al., 2006c). Our findings underestimate the total number of young people with psychosis, and our sample omitted some young people with better social support and/or a less acute onset.

Second, we did not have follow-up information on all study subjects. Thirty-one percent of subjects had neither a readmission to hospital nor a contact with NSW community mental health services during the follow-up period. These subjects were younger, more likely to have index diagnoses of brief, atypical and drug-induced psychoses and to have prior (but not baseline) cannabis and stimulant diagnoses. In the Australian health system, state operated mental health services care for most persons with psychosis. Loss of contact with specialised services may be a sign of resolution of symptoms and recovery from illness (Warner, 2009; Emsley et al., 2011). However people losing contact with specialised services may have equivalent rates of positive symptoms and substance use to those remaining in care (Stowkowy et al., 2012). We cannot know whether those with no follow-up had ongoing substance use or psychosis for which they did not seek care, or whether they sought care from services other than NSW public inpatient or community mental health services.

Third, we used hospital readmission as a measure of relapse. Lack of readmission does not equate with symptomatic or functional recovery, and many significant relapses of psychoses may be managed without readmission. We did not have a measure of the severity of psychotic symptoms nor of substance use. However hospital readmission remains the most widely used indicator of relapse in young people with psychosis (Gleeson et al., 2010), and a second hospital admission may be a very significant event for a young person and for their family.

Fourth we have examined admissions prior to the index psychosis admission with stimulant or cannabis diagnoses. Most people with substance use disorders (abuse or dependence) are not admitted to hospital with those disorders. Therefore this measure of prior substance disorder is likely to be of high specificity but low sensitivity.

Finally, our proxy measure of ongoing drug use was imprecise. It combined data from inpatient and community diagnoses with a clinician rating of problem substance use derived from the HoNOS. The HoNOS is not a diagnostic instrument and does not distinguish the type of drug used.

Conclusions

Cannabis or stimulant disorders at first admission with psychosis may not be negative prognostic signs. Young people with substance comorbidities may have both the best and worst of outcomes, depending on whether problematic substance use is discontinued. It is critical to screen and offer intervention for drug use in early psychoses. Admissions with stimulant disorder diagnoses prior to the first psychosis admission were associated with worse outcome. This suggests that it is important not only to identify current substance use at first admission with psychosis but also to obtain a detailed history of the type, severity and duration of past substance use.

PART 3

STIMULANTS AND ONGOING PSYCHOSIS

8: Stimulants, diagnostic stability and progression to schizophrenia over 2 – 5 years

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This chapter is based on the publication: **Sara, G., P. Burgess, G. Malhi, H. Whiteford and W. Hall (2014). The impact of cannabis and stimulant disorders on diagnostic stability in psychosis. Journal of Clinical Psychiatry. 75(4): 349-356.**

ABSTRACT

Background

Substance abuse adds to diagnostic uncertainty in psychosis and may increase the risk of transition from brief and affective psychoses to schizophrenia. This study examined whether comorbid substance disorder was associated with diagnostic instability and progression from other psychosis diagnoses to schizophrenia, and whether effects differed for cannabis and stimulant-related disorders.

Methods

We identified 24,306 individuals admitted to hospital with an ICD-10 psychosis diagnosis between 2000 and 2011. We examined agreement between initial diagnosis and final diagnosis over 2-5 years, and predictors of diagnostic change towards and away from a final diagnosis of schizophrenia.

Results

Nearly half (46%) of participants with initial brief, atypical or drug-induced psychoses were later diagnosed with schizophrenia. Persisting illicit drug disorders did not increase the likelihood of progression to schizophrenia (OR 0.97, 95% CI 0.89 – 1.04), but increased the likelihood of revision of index psychosis diagnosis away from schizophrenia (OR 1.55, 95% CI 1.40 – 1.71). Cannabis disorders predicted an increased likelihood of progression to schizophrenia (OR 1.12, 95% CI 1.01 – 1.24), while stimulant disorders predicted a

reduced likelihood (0.81, 95% CI 0.67 – 0.97). Stimulant disorders were associated with greater overall diagnostic instability.

Conclusions

Many people with initial diagnoses of brief and affective psychoses are later diagnosed with schizophrenia. Cannabis disorders are associated with diagnostic instability and greater likelihood of progression to schizophrenia. By contrast, comorbid stimulant disorders may be associated with better prognosis in psychosis, and it may be important to avoid premature closure on a diagnosis of schizophrenia when stimulant disorders are present.

INTRODUCTION

A person with psychosis may receive different diagnoses over time. “Diagnostic shifts” (Bromet et al., 2011) may reflect inter-rater variation, changes in available information, the evolution of illness or a combination of all of these (Bromet et al., 2011; Haahr et al., 2008). These shifts are of clinical relevance; the diagnosis first made by a person’s treating team may determine his or her subsequent care (Crebbin et al., 2009; Whitty et al., 2005) and may shape the expectations of the person, his or her family and treating clinicians.

Comorbid substance use is common in psychosis (Addington and Addington, 2007; Wade et al., 2005; Kavanagh et al., 2004; Moore et al., 2012a; Regier et al., 1990) and may contribute to diagnostic shifts in several ways. First, substance use creates clinical uncertainty; it is difficult to judge causation of psychosis when substance use persists (Mathias et al., 2008). Second, substance use may influence the course of psychosis. Substances may trigger recurrence of symptoms and relapse of illness (González-Pinto et al., 2011; Wade et al., 2006a; Wade et al., 2007; Sorbara et al., 2003; Bertelsen et al., 2009; Malla et al., 2008) and therefore may increase the likelihood of progression towards enduring psychoses such as schizophrenia. However, findings on this issue are conflicting; comorbid substance use in brief or affective psychoses has been associated with reduced (Schwartz et al., 2000; Bromet et al., 2011), increased (Whitty et al., 2005), or unchanged (Naz et al., 2003) likelihood of diagnostic shift to schizophrenia.

Cannabis and stimulants may differ in their effects on diagnostic stability. Cannabis interacts with personal vulnerabilities to increase the risk of developing schizophrenia (Hall and Degenhardt, 2011). Therefore persistent cannabis use is likely to predict a diagnostic trajectory from brief psychoses to schizophrenia. Amphetamine, cocaine and other stimulants are used in up to 30% of young people with psychosis (Hides et al., 2006; Sara et al., 2013). They are powerful dopamine agonists that can induce psychotic symptoms in healthy volunteers (Angrist et al., 1987), and whose effects may increase with repeated use due to sensitization (Hermens et al., 2009; Curran et al., 2004). Dopamine over-activity may play a role in schizophrenia (Keshavan et al., 2008; Laruelle and Abi-Dargham, 1999), therefore persistent stimulant use may be even more likely than persistent cannabis use to cause diagnostic progression from other psychoses to schizophrenia.

However, the only study that examined cannabis and stimulant induced psychoses separately found that 46% of people with cannabis-induced psychosis later received a diagnosis of schizophrenia, compared with only 30% of people with amphetamine-induced psychosis (Niemi-Pynttari et al., 2013). That study examined people with a specific diagnosis of substance-induced psychosis, and when multiple substances were related to the psychosis episode they were classed as “other or unknown” substances. It is important to know whether these findings can be generalized to other clinical situations that often involve a wide range of psychosis diagnoses and where cannabis and stimulant use often co-exist.

Our study examined admissions to mental health units in the state of New South Wales (NSW, population 7.2 million), Australia. This provided a population-based sample with sufficient power to examine diagnostic stability in brief psychoses (including brief, atypical and drug-induced psychoses) and affective psychoses (bipolar disorder and psychotic depression), and to examine the effects of cannabis and stimulant comorbidity separately and in combination. We focused on substance problems occurring during the follow up period rather than at the first (index) admission, because baseline substance problems have been shown to have a more limited effect on outcome in psychosis than ongoing substance use (González-Pinto et al., 2011; Sorbara et al., 2003; Wade et al., 2006a).

METHODS

Sample

Admissions of NSW residents to state operated (“public”) hospitals from 1 July 2000 to 30 June 2011 were screened. The first (index) admission with psychosis was identified for each person with the use of a unique person identifier (Figure 8.1). Participants were aged 18-50 years and had an index admission of more than one day’s duration to a designated mental health unit, with a primary or secondary diagnosis of psychosis. People whose index admissions were longer than 2 years or ended in death were excluded.

For each participant we identified all subsequent admissions for mental health care to NSW public hospitals, and all subsequent contacts with specialised community mental health services in the five years from the end of the index admission. Diagnostic stability was examined only in persons with at least two years of ongoing service contact, to avoid overestimating diagnostic agreement where the time between assessments was limited.

The study was approved by the NSW Population and Health Services Research Ethics Committee.

Psychosis diagnoses

New South Wales health services record diagnosis using the International Classification of Diseases Tenth Revision, Australian Modification (ICD-10-AM) (National Centre for Classification in Health, 2010). Hospital episodes with a primary or additional ICD-10 diagnosis of psychosis were grouped into (i) 'Schizophrenia', including schizophrenia (F20) and schizoaffective disorder (F25), (ii) 'Affective Psychoses', including bipolar disorder (F30, F31) and psychotic depression (F32.3, F32.30, F32.31, F33.3), and (iii) 'Other Psychoses', including acute and transient psychoses (F23), delusional disorders (F22, F24), other or unspecified psychosis (F28, F29) and drug-induced psychoses. Drug induced psychoses included ICD-10 substance codes (F10-F19) in which psychosis was specified (e.g. F10.5, F10.9). DSM-IV schizophreniform psychosis is classified with acute and transient psychoses in ICD-10. Organic psychoses and schizotypal disorder were excluded.

Index diagnosis was obtained from the first admission for each person. Final diagnosis was the mental health diagnosis at the end of the 2 to 5 year follow-up period in inpatient and community care episodes. When multiple diagnoses were recorded on the last date, priority was given to the diagnosis identified by the treating team as being primarily responsible for the episode of care. Final diagnoses of mental health conditions other than psychosis were grouped as "Non-psychotic conditions". Persons with no specific mental health diagnosis recorded in the study period were excluded from analysis.

Binary variables were created for schizophrenia or other psychosis diagnoses at index admission and during ongoing community-based care.

Substance diagnoses

Substance disorders were identified by primary or additional diagnosis codes for abuse, dependence, intoxication, poisoning by specific illicit drugs, or alcohol-related liver disease. Drug-induced psychoses counted as both a psychosis and a substance disorder. Amphetamines and cocaine were grouped as stimulant disorders. Opiate disorders included illicit opiates (e.g. heroin) and non-medical use of prescription opiates. Polydrug disorder was recorded only where specifically diagnosed (ICD code F19). We distinguished between substance disorders occurring only at the index admission, and

substance disorders occurring in the study period (i.e. at least one substance disorder diagnosis occurring subsequent to the index admission). Only substance diagnoses in the study period were examined in analyses of diagnostic stability.

A binary variable was constructed indicating the presence of any illicit drug diagnosis (cannabis, stimulant, hallucinogen, opiate or polydrug) during the study period (excluding the index admission). A composite “Illicit Drug Use Group” variable was created with five mutually exclusive categories: (i) No illicit drug diagnoses, (ii) Cannabis, (iii) Stimulants, (iv) Cannabis plus Stimulants, and (v) Other/Polydrug only. Some persons in groups (ii) – (iv) had additional substance diagnoses. People in the “Other/Polydrug only” category had only specific substance diagnoses (e.g. opiate disorders) or a polydrug diagnosis without indication of the substances involved, and no cannabis or stimulant diagnoses .

Other variables

Demographic variables were measured from index admission. Migration status was based on country of birth. Rurality and disadvantage measures were based on Australian Bureau of Statistics reference data for the area of residence, collapsed for rurality (major metropolitan vs. regional and rural residence) and disadvantage (most disadvantaged 40% of local areas vs. least disadvantaged 60%). Ongoing contact was defined as having at least one community mental health contact or admission to a mental health unit in the two to five years after discharge from the index admission.

Statistical analysis

Predictors of ongoing contact were examined using binary logistic regression. Univariate Odds Ratios (ORs) and 95% CIs were calculated separately for demographic, diagnostic and prior care variables. Multivariate analysis included all variables with significant univariate associations (P<=0.05). Multi-collinearity was assessed and collinear variables excluded (Belsley, 1991).

Index and final diagnoses were cross-tabulated, and overall diagnostic agreement was calculated as the percentage of persons with both index and final diagnosis in the same group. Diagnostic agreement was calculated separately for persons with and without comorbid substance diagnoses and compared using Pearson’s Chi-square test. For the binary Schizophrenia/No Schizophrenia variable, agreement between index and final

diagnosis was calculated using Cohen's kappa, calculated separately for persons with and without cannabis, stimulant and alcohol disorders.

Predictors of diagnostic change to or from schizophrenia were examined using binary logistic regression analyses, conducted separately for people with (i) schizophrenia and (ii) other psychoses at index admission. Within each group, two regression models were constructed. The first examined the effect of any illicit drug diagnosis, and the second examined the effects of cannabis and stimulants separately. Regression diagnostics were conducted as described above. Analyses were conducted using Stata v13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, StataCorp LP.).

RESULTS

After exclusions, an index psychosis admission was identified for 42,205 persons aged 18-50 years (Figure 8.1). Sixty percent were male (Table 8.1), and more than half were aged between 21 and 35. The most common diagnoses at index admission were schizophrenia (39%) and other (brief, atypical, drug-induced and unspecified) psychoses (33%). One third had comorbid illicit drug diagnoses at index admission, most commonly a cannabis disorder (22%) and/or stimulant disorder (11%). More than half of those with stimulant disorders also had cannabis disorder.

The rate and pattern of cannabis and stimulant disorders were similar for schizophrenia and affective psychoses (Table 8.2). Comorbid substance disorders were most common in brief, atypical and drug-induced psychoses.

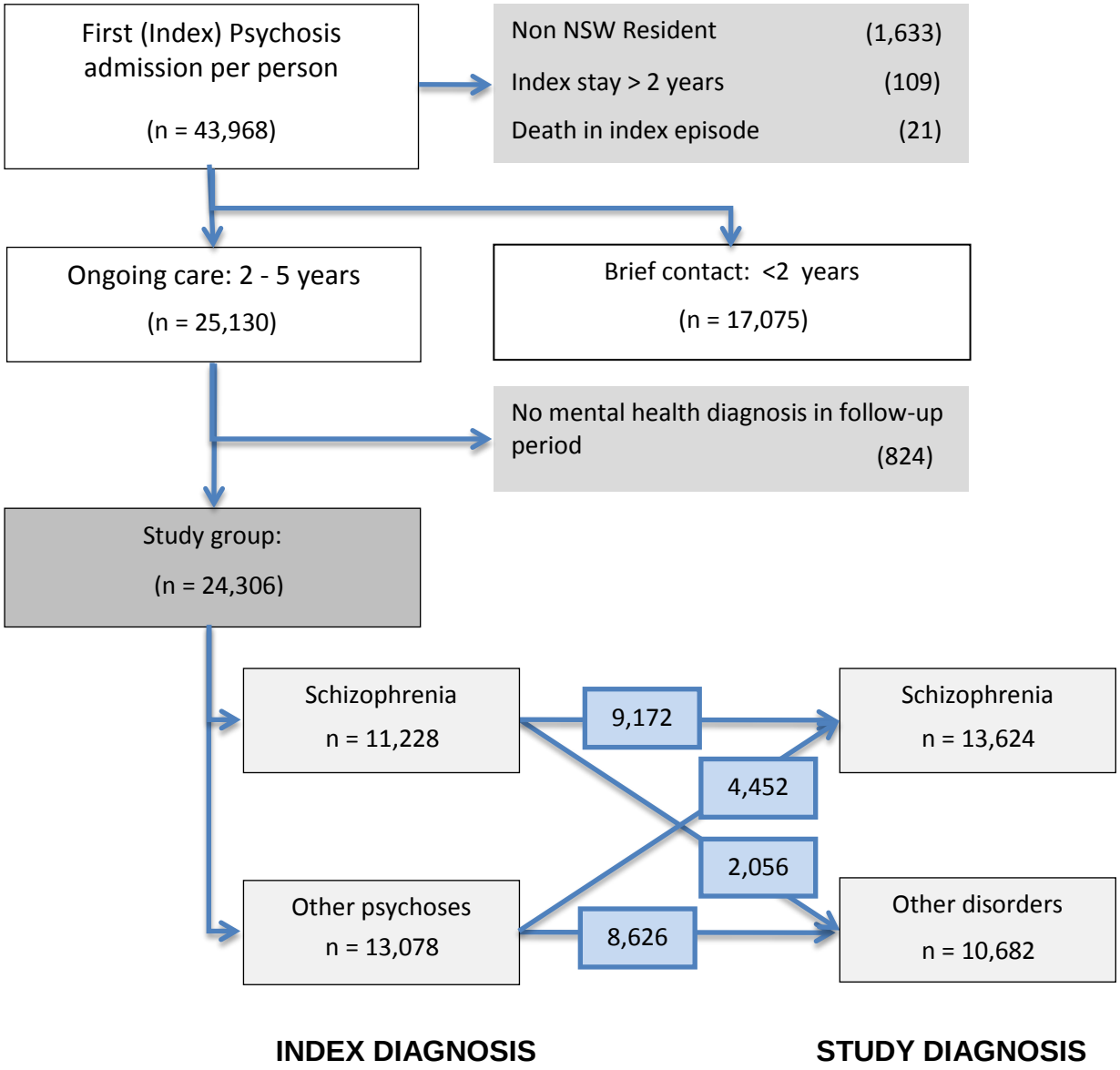

Figure 8.1. Overview of study method

Table 8.1. Characteristics of study sample and predictors of ongoing service contact over two to five years following an initial diagnosis of psychosis.

	All subjects n = 42,205 n (%)	**Brief contact (< 2 years)** n = 17,075 n (%)	**Ongoing contact (2-5 years)** n = 25,130 n (%)	**Odds of ongoing contact [a]** OR (95% CI)
Personal characteristics				
Age: mean (SD)	32.9 (8.9)	33.2 (8.9)	32.7 (8.9)	0.99 (0.99-0.99)*
Male	25,410 (60)	10,158 (60)	15,252 (61)	0.96 (0.91-1.00)
Migrant [b]	10,111 (25)	4,397 (27)	5,714 (24)	…
Regional and rural [b]	17,248 (43)	6,748 (42)	10,500 (43)	…
Most disadvantaged	16,657 (42)	6,382 (40)	10,275 (43)	1.08 (1.04-1.13)*
Psychosis Diagnoses [c]				
Schizophrenia	16,602 (39)	5,077 (30)	11,525 (46)	1.00
Affective psychoses	11,605 (28)	5,450 (32)	6,155 (25)	0.48 (0.45-0.50)*
Other psychoses	13,998 (33)	6,548 (38)	7,450 (30)	0.47 (0.45-0.50)*
Drug abuse/dependence [c]				
No illicit drugs	27,774 (66)	11,105 (65)	16,669 (66)	1.00
Cannabis	6,862 (16)	2,713 (16)	4,149 (17)	1.05 (0.99-1.11)
Cannabis + Stimulant	2,601 (6)	1,066 (6)	1,535 (6)	1.07 (0.98-1.17)
Stimulant	2,095 (5)	1,009 (6)	1,086 (4)	0.86 (0.78-0.94)*
Other / Polydrug only	2,873 (7)	1,182 (7)	1,691 (7)	1.02 (0.94-1.11)
Alcohol abuse/dependence [c]	5,628 (13)	2,284 (13)	3,344 (13)	1.05 (0.98-1.11)

Notes: (a) Odds ratios from multivariate logistic regression. (b) Migrant status and rurality excluded from regression due to collinearity with other variables. Country of birth data missing for 1648 persons (3.9%), Address data missing for 2124 persons (5.0%). Percentages of those with valid data (c) Psychosis and substance diagnoses at index admission. * p< 0.05.

Table 8.2. Psychosis type and substance disorder diagnoses in 42,205 people with an initial diagnosis of psychosis.

Index psychosis diagnosis	n	**Index substance diagnosis** Rate (95% Confidence Interval)		
		Any illicit drug	**Cannabis**	**Stimulant**
Schizophrenia	16,602	25.5% (24.8% - 26.1%)	17.8% (17.2% - 18.4%)	5.5% (5.2% - 5.9%)
Affective Psychoses / Bipolar	11,605	23.3% (22.5% - 24.1%)	16.9% (16.2% - 17.6%)	5.1% (4.7% - 5.5%)
Other psychoses	13,998	53.6% (52.8% - 54.4%)	32.5% (31.7% - 33.2%)	22.7% (22.0% - 23.4%)
Total	42,205	34.2% (33.7% - 34.6%)	22.4% (22.0% - 22.8%)	11.1% (10.8% - 11.4%)

Thirty-nine percent of subjects had two or fewer years of mental health service contact and were excluded from analysis of diagnostic stability. Ongoing contact was more likely in people who were younger, lived in disadvantaged areas and had index diagnoses of schizophrenia. Overall substance diagnoses at index admission did not predict ongoing contact however contact was less likely (OR 0.86, 95% CI 0.78 – 0.94) in people whose only substance comorbidity at index admission was a stimulant disorder.

Diagnoses at index admission were compared with diagnosis over the following two to five years (Table 8.3). Only 18% of those with an index diagnosis of brief, atypical or drug-induced psychosis retained a diagnosis within that group. Others were diagnosed with schizophrenia (46%), non-psychotic conditions (29%) and affective psychoses (7%). Index diagnoses of schizophrenia were stable: 82% retained that diagnosis in the study period.

Table 8.3: Comparison of index and final diagnosis over five years in 24,306 persons with an initial diagnosis of psychosis.

Index psychosis diagnosis	**Final diagnosis**				
	Schizophrenia	**Affective psychoses**	**Other psychoses**	**No psychosis**	**Total**
Schizophrenia	9,172 (82%)	370 (3%)	579 (5%)	1,107 (10%)	11,228 (100%)
Affective psychoses	1,196 (20%)	2,717 (46%)	245 (4%)	1,765 (30%)	5,923 (100%)
Other psychoses	3,256 (46%)	497 (7%)	1,302 (18%)	2,100 (29%)	7,155 (100%)
Total	13,624 (56%)	3,584 (15%)	2,126 (9%)	4,972 (21%)	24,306 (100%)

One third of people with ongoing service contact had at least one illicit substance diagnosis during the study period. Substance disorders predicted lower diagnostic stability. Index and final diagnoses agreed in 60% of persons without substance disorders but only in 47% of people with substance disorders ($\chi^2 = 423$, $p < 0.001$). Diagnostic agreement was lower for stimulant disorders (40% agreement between index and final diagnosis) than for cannabis disorders (47% agreement, $\chi^2 = 57$, $p < 0.001$). Stability between index and final diagnosis was also examined by measuring kappa for agreement between index and final diagnosis after grouping these into binary Schizophrenia/No Schizophrenia variables. Diagnostic stability was lower for those with comorbid stimulant disorders and cannabis disorders in the study period, compared with those with alcohol disorders in the study period (Figure 8.2).

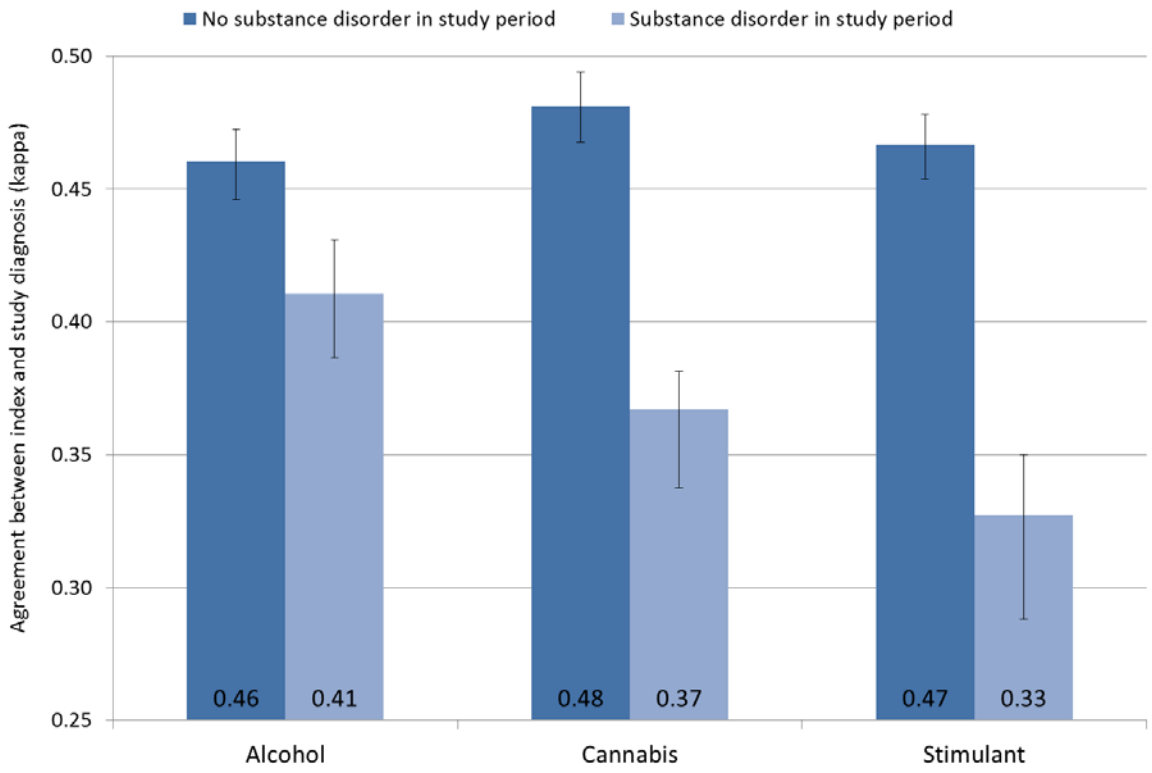

Figure 8.2. Comorbid substance disorders during study period and diagnostic stability: agreement (kappa) between index and final study diagnosis of schizophrenia or other psychosis in 24,306 persons over two to five years.

Table 8.4. Predictors of diagnostic change in 24,306 persons with an initial diagnosis of psychosis and 2-5 years of ongoing service contact.

	Diagnosis change to schizophrenia [a] (n = 4,452 of 13,078)		**Diagnosis change from schizophrenia [b]** (n=2,056 of 11,228)	
	Any substance disorder OR (95% CI) [c]	**Specific substance disorder** OR (95% CI) [d]	**Any substance disorder** OR (95% CI) [c]	**Specific substance disorder** OR (95% CI) [d]
Age	0.97 (0.97-0.98)*	0.97 (0.97-0.98)*	0.98 (0.98-0.99)*	0.98 (0.98-0.99)*
Male gender	1.69 (1.56-1.82)*	1.68 (1.55-1.81)*	0.65 (0.59-0.73)*	0.66 (0.59-0.73)*
Years in study	1.26 (1.19-1.33)*	1.26 (1.19-1.33)*	0.80 (0.75-0.86)*	0.81 (0.75-0.86)*
Substance disorders				
No illicit drugs	1.00	1.00	1.00	1.00
Any illicit drug	0.97 (0.89-1.04)	-	1.55 (1.40-1.71)*	-
Cannabis	-	1.12 (1.01-1.24)*	-	1.30 (1.13-1.49)*
Cannabis + Stimulant	-	0.99 (0.89-1.11)	-	1.66 (1.41-1.95)*
Stimulant	-	0.81 (0.67-0.97)*	-	2.21 (1.67-2.93)*
Other / Polydrug only	-	0.80 (0.71-0.90)*	-	1.67 (1.45-1.92)*

Note: (a) People with initial diagnoses of affective, brief, atypical or drug-induced psychosis. (b) People with initial diagnoses of schizophrenia. (c) Any substance disorder in study period. (d) Specific substance disorder in study period by type of substance. * p< 0.05.

Predictors of diagnostic change were examined separately for people with diagnoses of schizophrenia (n=11,228) or other psychoses (n=13,078) at index admission (Table 8.4). In people with initial diagnoses of affective, brief or atypical psychoses, male gender and longer duration of observation were associated with increased odds of diagnostic change to schizophrenia. Conversely, in people with initial diagnoses of schizophrenia, female gender was associated with diagnostic revision away from schizophrenia towards other diagnoses. Younger age was associated with diagnostic instability in both directions.

In people with initial diagnoses of affective, brief or atypical psychoses, illicit substance disorders during the study period were not associated with diagnostic change to schizophrenia after controlling for age, sex and duration of observation. However when examined separately, cannabis and stimulant disorders had significant but opposing effects: diagnostic change to schizophrenia was more likely with comorbid cannabis disorders (OR 1.12, 95% CI 1.01 – 1.24) and less likely with stimulant disorders (OR 0.81, 95% CI 0.67 – 0.97) or other drug disorders (OR 0.80, 95% CI 0.71 – 0.90) without cannabis disorders. Of people with an index diagnosis of affective or other psychoses and no substance diagnosis, 34.0% were later diagnosed with schizophrenia, compared with 36.6% of those with affective/other psychoses and ongoing cannabis disorders (Risk Difference 2.6%, Number Needed to Harm 39).

In people with initial diagnoses of schizophrenia, all comorbid substance disorders were associated with greater likelihood of diagnostic change towards other diagnoses. This effect was greatest for those with only stimulant disorders, least for those with only cannabis disorders and intermediate for those with both cannabis and stimulant disorders.

DISCUSSION

We examined diagnostic stability in 24,306 individuals two to five years after an admission for psychosis. More than 80% of initial diagnoses of brief, atypical or drug-induced psychoses were later revised, nearly half (46%) to schizophrenia. Index diagnoses of schizophrenia were more stable, but 18% were revised to other conditions over five years. The rate of diagnostic change in our sample was consistent with other studies that have found between 29% and 50% of people with brief or drug-induced psychoses later receive a diagnosis of schizophrenia (Arendt et al., 2005; Castagnini et al., 2008; Crebbin et al., 2009; Naz et al., 2003). Initial diagnoses of schizophrenia have been revised to other conditions in 8% of people at two years (Schwartz et al., 2000) and up to 21% of people at five years (Baca-Garcia et al., 2007) .

Our first aim was to examine whether comorbid substance disorders were associated with diagnostic instability. Nearly half of people with ongoing service contact had at least one comorbid illicit substance disorder. Considered together, ongoing substance disorders did not increase the likelihood of diagnostic progression from affective or other psychoses to schizophrenia. These findings are consistent with reports (Bromet et al., 2005; Schwartz et al., 2000) that substance use after a first psychosis admission predicts unchanged or reduced risk of a later schizophrenia diagnosis. However, we found that substance disorders were associated with diagnostic instability. In people with comorbid substance disorders, initial and final psychosis diagnoses agreed less than half of the time, because there was greater likelihood of revision of diagnosis away from index diagnoses of schizophrenia in people with substance disorders.

Our second aim was to examine whether cannabis and stimulant disorders differed in their associations with diagnostic change. We found that cannabis disorders had a modest association with diagnostic progression to schizophrenia; one additional person received this diagnosis for every 39 persons with an ongoing cannabis disorder diagnosis. In contrast, stimulant disorders were associated with diagnoses of briefer psychoses and with diagnostic change away from schizophrenia. These findings add to those of Niemi-Pynttari and colleagues (Niemi-Pynttari et al., 2013), who examined substance-induced psychoses. Together these studies underline the importance of examining cannabis and stimulants separately rather than grouping them together.

In people with comorbid diagnoses of both cannabis and stimulant disorders, an additive risk and an increase in the likelihood of developing a more chronic psychosis may be expected. However we found that people with both diagnoses had an intermediate risk of diagnostic transition to schizophrenia when compared to those with stimulant or cannabis diagnoses alone. There are a number of possible explanations for this finding, which warrant further research. If stimulants have greater potential than cannabis to trigger psychotic states then they may precipitate psychosis in individuals with a lower personal vulnerability to the development of schizophrenia. Persons with a first admission psychosis who also use stimulants may also have other factors associated with more positive outcomes, such as later age of drug use or psychosis onset, and a higher socio-economic status (Sara et al., 2013). It is also possible that stimulants and cannabis are associated with different responses to treatment. Stimulants act on the same dopamine pathways through which antipsychotic medications are thought to act (Hermens et al., 2009) , and so

antipsychotic medications may be more effective in stimulant-related psychoses. Psychoses associated with cannabis use may be less responsive to treatment because they involve abnormalities in other chemical pathways.

Limitations

The hospital data used do not have unique person identifiers prior to the start of the study period. Therefore we were unable to identify whether individuals had admissions prior to their index admission, and if so how many admissions they had. Older participants in our study are more likely to have had prior admissions, while for younger participants their index admission in the study period is more likely to have been their first ever hospital admission. Therefore age and stage of illness are likely to be confounded in our study.

We included only persons with at least two years of service contact. People with stimulant disorders and affective, brief, drug-induced and atypical psychoses were more likely to have brief contact and therefore be excluded from the study. People with no ongoing service contact are less likely to have had severe or enduring psychoses such as schizophrenia. Therefore, we may have underestimated any association between stimulant disorders and positive outcomes.

To obtain a population-wide sample, we used clinical diagnoses from administrative datasets. Routine diagnoses are less reliable than research diagnoses, and substance comorbidities may be particularly under-recorded (Large et al., 2012). In this study, the types of diagnoses, rates of substance comorbidity and patterns of diagnostic change were similar to those reported in clinical studies. However caution is needed in interpreting this study's conclusions and further evidence is required from clinical studies using more rigorous diagnoses.

We considered substance disorder diagnoses as a measure of ongoing substance problems. This measure is imprecise and cannot distinguish between different levels of duration or severity of substance disorder. Apparent differences between cannabis and stimulant groups in our study may have been due to the effects of different comorbidity with other drugs such as hallucinogens or opiates. However the rate of comorbid diagnoses with these substances was low.

We derived a single study diagnosis from the most recent diagnosis in the study period. This is one of several ways in which multiple diagnoses may be combined (Morgan and Jablensky, 2010). Our choice of method was based on testing of competing algorithms

against NSW administrative data and research diagnoses, as described in Appendix A (Sara et al., 2014d) .

Conclusions

Substance comorbidity is common in people with psychosis, and may contribute to diagnostic change by causing diagnostic uncertainty and by influencing the course of illness. Cannabis and stimulants differed in their impact on diagnostic change. Stimulant disorders were associated with diagnostic instability, a lower likelihood of change to schizophrenia, and greater likelihood of diagnostic revision away from schizophrenia. While many people with initial diagnoses of brief and affective psychoses may progress to a diagnosis of schizophrenia, it is important to avoid premature closure on a diagnosis of schizophrenia, particularly when stimulant disorders are present.

9: Prevalence and correlates of stimulant disorders in schizophrenia

This chapter is based on the publication: **Sara, G., P. Burgess, G. Malhi, H. Whiteford and W. Hall (2014). Stimulant and other substance use disorders in schizophrenia: prevalence, associations and impacts in a population sample Australian and New Zealand Journal of Psychiatry. 48: 1036-1047.**

ABSTRACT

Objectives

Stimulants may worsen psychotic symptoms but there is limited evidence about the impact of stimulant abuse in people with schizophrenia. This study examined the prevalence and correlates of stimulant and other drug disorders in a population-based sample of people with schizophrenia, examining associations with frequent service use, physical health comorbidities and accommodation instability.

Methods

New South Wales (NSW) hospital, community mental health and emergency department data were used to examine health service contact over five years in 13,624 people with a diagnosis of schizophrenia. Associations of stimulant disorders were examined with multinomial logistic regression, comparing people with no substance disorders to those with cannabis disorders, stimulant disorders or both.

Results

51% of people with schizophrenia had substance disorders, including 14% with stimulant disorders. Stimulant disorders were more common in young adults and in urban areas, less common in migrants, and unrelated to initial social disadvantage. More than 80% of those with stimulant disorders also had cannabis disorders. Service use and harms were most common in this group, including frequent mental health admissions (59%), frequent Emergency Department presentations (52%), admissions with injury or self-harm (44%),

infectious disease diagnoses (22%), multiple changes of residence (61%), movement to more disadvantaged locations (42%) and periods of homelessness (18%). People with stimulant disorders alone had higher rates of self-harm, infectious disease and non-mental-health admissions than people with cannabis disorders alone.

Conclusions

Stimulant disorders occur in people with schizophrenia and in first episode psychosis at rates more than ten times that of the broader population. Stimulant disorders are likely to worsen the burden of psychosis, and strategies are needed to engage and support the highly disadvantaged group of people with schizophrenia who have cannabis and stimulant disorders.

INTRODUCTION

Stimulants such as amphetamines, cocaine and ecstasy are the most widely used illicit drugs after cannabis (United Nations Office on Drugs and Crime, 2011a). There is increasing evidence that cannabis contributes to the onset and course of psychosis (Hall and Degenhardt, 2011; Santos et al., 2013), however there is less evidence about the impact of stimulant abuse on people with psychosis.

The pharmacology of stimulant drugs suggests a particular association with psychosis. Stimulants are powerful dopamine agonists, acting through a range of mechanisms to increase synaptic dopamine levels (Barr et al., 2006). These effects increase with repeated exposure due to a process of sensitization (Hermens et al., 2009; Curran et al., 2004). Dopamine over-activity may play a role in schizophrenia and other psychoses (Keshavan et al., 2008; Laruelle and Abi-Dargham, 1999), particularly in the development of positive psychotic symptoms (Paparelli et al., 2011).

Clinical and experimental studies demonstrate the potential for stimulants to worsen acute psychotic symptoms. High dose amphetamines can produce psychotic symptoms in healthy volunteers (Angrist et al., 1987; Griffith et al., 1972). Recreational stimulant users report high rates of transient psychotic symptoms which are related to the dose and frequency of stimulant use (McKetin et al., 2010; Hall et al., 1996). Amphetamines are associated with hospital admissions for brief, transient and drug-induced psychoses (Degenhardt et al., 2008c; Degenhardt et al., 2007d; Sara et al., 2013). Lieberman (Lieberman et al., 1984) found that transient increases in symptoms after stimulant challenge predicted later relapse of psychosis, and argued that ongoing stimulant use worsens the course of schizophrenia (Lieberman et al., 1990). Curran et al reviewed 26 studies of brief experimental methamphetamine challenge in people with schizophrenia (Curran et al., 2004) and found increased psychotic symptoms in more than half of those with current positive symptoms and nearly one third of those whose psychosis was in remission.

The current study builds on our earlier work examining stimulant use disorders in the Australian population (Sara et al., 2012) and in people with a first admission for psychosis (Sara et al., 2013). Those studies found that people with a first admission psychosis have a rate of stimulant disorders around ten times greater than other young Australians, and that the correlates of stimulant disorders differed from those of cannabis disorders, both in

the Australian population and in first episode psychosis. This study focuses specifically on people with diagnoses of schizophrenia, and has three aims.

Our first aim is to examine the rate of stimulant use disorders in people with schizophrenia. Many of the studies summarized above focus on brief or transient exposure to stimulants. Psychotic symptoms and other drug-related harms are especially associated with severe and dependent use (Degenhardt et al., 2014). Few studies have reported the rate of stimulant disorders in people with established diagnoses of schizophrenia. The Australian Survey of High Impact Psychosis (SHIP) found that 73% of people with schizophrenia or schizoaffective psychoses reported lifetime stimulant use, and 40% reported past year use (Moore et al., 2012b). The SHIP study, however, did not report rates of stimulant abuse or dependence. In three US studies, between 11% and 37% of people with schizophrenia had cocaine use disorders (Chouljian et al., 1995; Gearon and Bellack, 2000; Miller and Tanenbaum, 1989). Lower rates, ranging from 3% to 7%, have been reported in studies from Canada (Margolese et al., 2004) , Western Europe (Modestin et al., 2001) and Scandinavia (Ringen et al., 2013). However, all but one of these studies (Ringen et al., 2013) examined cocaine disorders. Rates of methamphetamine abuse and dependence are higher in Australia than in many other countries because methamphetamine is much more widely used in Australia than cocaine (Degenhardt et al., 2014) . Therefore current studies provide limited evidence about the scale of this problem in Australia.

The second aim of this study is to examine the correlates of stimulant disorders in people with schizophrenia. Knowing which people with schizophrenia have higher rates of stimulant disorders is important in understanding where any impact of stimulants may be felt most strongly. This knowledge may inform service planning, appropriate assessment and treatment. Most studies describing rates of stimulant use disorder in people with schizophrenia report this as a coincidental finding. To our knowledge no study has examined how people with schizophrenia who abuse stimulants differ from those who do not.

The third aim of this study is to examine the impact of stimulant use disorders in people with schizophrenia. If stimulants increase psychotic symptoms or precipitate relapse, then severe or ongoing use is likely to be associated with more chronic illness course, more frequent hospitalisation and greater service use. Long term stimulant use may also be associated with specific physical health consequences, in particular with cardiovascular disease and with infectious disease due to progression to intravenous methods of

administration (Darke et al., 2008; Degenhardt et al., 2008c; Darke et al., 1994). Dependent drug use may also be associated with disrupted social supports and marginalisation. In the Australian population, one in five people with a lifetime history of stimulant disorders have been homeless (Sara et al., 2012). Physical health comorbidities and unstable housing are both significant contributors to the overall burden of schizophrenia. Therefore people with schizophrenia who also abuse stimulants are likely to be especially vulnerable to these harms.

A major methodological challenge in studying stimulant use in psychosis is that most people with psychosis who use stimulants have also used cannabis. For example, amongst participants in SHIP, 98.4% of amphetamine users reported prior cannabis use (Power et al., 2014). Therefore even very large clinical studies have not had sufficient statistical power to separate the associations of stimulant use from those of cannabis. One strategy is to use a large, population-based dataset with sufficient scale to examine stimulant disorders while controlling for comorbid cannabis disorders.

Our study examines people admitted to hospital with psychosis in New South Wales (NSW) over an 11 year period. We examined people with at least two years of ongoing service contact, to ensure a sufficient period of observation to detect adverse outcomes that may be associated with stimulant disorders. We focused on ongoing substance problems rather than those recorded only at first contact, because many people cease substance use after a first psychosis episode, and it is ongoing use which appears to most adversely influence course and outcome in psychosis (González-Pinto et al., 2011; Sorbara et al., 2003; Wade et al., 2006a).

METHODS

The study was approved by the NSW Population and Health Services Research Ethics Committee.

Sample

Admissions of NSW residents to state operated (“public”) hospitals from 1 July 2000 to 30 June 2011 were screened. Potential participants were aged 18-50, had an index admission to a designated mental health unit that lasted more than one day, and had a primary or secondary diagnosis of psychosis. People whose index admissions were longer than two years (n=109) were excluded. For each potential participant we used a unique

statewide person identifier and examined the five year follow-up period from the end of their index hospitalization to identify (i) further admissions to NSW public hospitals for mental health or physical health care, (ii) contacts with specialised community mental health services and (iii) Emergency Department (ED) contacts. Study participants were selected who had a final diagnosis of schizophrenia and a minimum of two years of ongoing contact with inpatient or community mental health services.

Schizophrenia diagnosis

NSW health services record diagnosis using the International Classification of Diseases (ICD-10-AM) (National Centre for Classification in Health, 2010). Schizophrenia was defined by the presence of a primary or additional ICD-10 diagnosis code of schizophrenia (F20) or schizoaffective disorder (F25). Final diagnosis was the last recorded mental health diagnosis in the five year follow-up period, including both inpatient and community care episodes. Where multiple diagnoses were recorded on the last date, priority was given to the diagnosis identified by the treating team as responsible for the episode of care.

Substance diagnoses

Only substance diagnoses in the study period were examined (excluding the index admission). Substance disorders were identified by primary or additional diagnosis codes for abuse, dependence, drug-induced psychosis, intoxication or poisoning by specific illicit drugs. Amphetamine and cocaine disorders were grouped together as stimulant disorders. Polydrug disorder was recorded only where specifically diagnosed (ICD code F19). A binary variable was constructed indicating the presence of any illicit drug diagnosis during the study period. A composite “Illicit Drug Disorder Group” variable was created with five mutually exclusive categories: (i) No illicit drug disorder; (ii) Other/unspecified only; (iii) Cannabis; (iv) Stimulants; and (v) Cannabis plus Stimulants. Some people in cannabis and stimulant disorder groups had additional substance diagnoses. People in the “Other/unspecified” category had no cannabis or stimulant disorders but one of: a polydrug diagnosis without indication of the substances involved; a diagnosis of unspecified or mixed substance disorder or; a specific diagnosis of opiate or hallucinogen disorders.

Demographic variables

Age, sex, country of birth and location of residence were recorded from the index admission. Migration status was derived from country of birth. The statistical local area

(SLA) of residence was linked to Australian Bureau of Statistics reference data to obtain (i) a measure of rurality, the Accessibility Remoteness Index of Australia (ARIA, www.abs.gov.au/websitedbs/d3310114.nsf/home/remoteness+structure) and (ii) a measure of disadvantage, the Index of Relative Socio-Economic Disadvantage (IRSD, www.abs.gov.au/ausstats/abs@.nsf/mf/2033.0.55.001).

Service use variables

Four measures of contact with NSW health services over the 5 year follow-up period were derived: (i) mental health admissions (hospital admissions with at least one day of specialist mental health care); (ii) other admissions (hospital admissions with no specialist mental health care); (iii) ED presentations, and; (iv) community mental health contacts. A community mental health contact is a single visit with any NSW specialist ambulatory or community mental health service. Where a person sees more than one clinician during that visit, this is recorded as a single contact. A person may have more than one contact per day if they have repeated visits or are seen by more than one team or service. No data were obtained from private hospital admissions, private psychiatrists or primary care services. Community mental health contacts were converted to a rate (community contacts per 100 days) and the denominator for this rate adjusted to remove days spent in hospital during the study period.

Service use variables were anticipated to be highly skewed. For each of the four service use types a binary “frequent service use” variable was created by splitting at the 75th percentile.

Physical comorbidities

We created binary variables for the presence of three physical health conditions which may have particular associations with stimulant abuse or dependence: (i) self-harm and injury (ICD-10 codes S00- T88); (ii) infectious diseases (A00-B99); and (iii) cardiovascular diseases (I00-I99). These were coded as present if the person had at least one primary or additional diagnosis code for these conditions during the study period, in either inpatient or community mental health data.

Accommodation instability

Three proxy measures of accommodation instability were derived. First, we examined accommodation type at each hospital admission, and set a “Homeless period” flag if a

person had at least one admission with an accommodation type indicating homelessness (i.e., homeless, public place, homeless person's shelter, refuge, boarding house or hostel). Second, we recorded the number of different residential locations (SLAs) per person in the study period and set a "Multiple locations" flag for people in the top quartile of this distribution. Third, we calculated the average index of socio-economic disadvantage (IRSD) for each person's residential locations during the study period and set a "Move towards disadvantage" flag if this was higher than the IRSD of their residential location at index admission. IRSD cannot be calculated where a person has no address recorded.

Statistical analysis

All analyses were conducted using Stata v13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, StataCorp LP.). Means and standard deviations were calculated for continuous variables. Frequencies were described for categorical variables. For service use variables and residential locations, cut points were calculated at the 75th percentile to create binary variables.

The predictors of the presence and type of substance comorbidity were examined using multinomial logistic regression, with the composite five-level "Illicit Drug Disorder Group" as the categorical dependent variable and people with no illicit drug disorder as the reference category. All candidate variables were entered in a multivariate analysis. Multi-collinearity was assessed to exclude collinear variables if required (Belsley, 1991). Odds Ratios and 95% CIs were calculated.

The associations of drug type with service use, physical comorbidity and accommodation instability were described, reporting means and standard deviations for continuous variables, and frequencies with associated 95% confidence intervals for categorical variables. The association of these factors with drug type was examined using multinomial logistic regression. Regressions were conducted separately for each of the ten binary outcome variables as a dependent variable, entering age, sex and illicit drug disorder group as independent variables.

Sensitivity analyses were conducted on three issues by repeating all regressions after exclusion of three groups of participants. First, to examine for the effect of diagnostic imprecision, people who did not have a diagnosis of schizophrenia at both index admission and final contact were excluded. Second, to assess the effects of right-censoring of participants, the subset of people with more than two but less than five years of follow-up

were excluded. Third, to examine the effect of overlap between participants in this study and those in our earlier studies of first admission psychosis, members of the latter group were excluded.

RESULTS

We identified 13,624 people with a diagnosis of schizophrenia who met the study criteria (Table 9.1). Their average age was 32.6, three quarters were aged 40 or below and two-thirds were male. Migrant status and urban/rural distribution mirrored that of the overall NSW population. Only 13.5% had addresses in the least disadvantaged quintile of NSW local areas, while 22.3% resided in the most disadvantaged quintile. However a further 4.2% of people had no recorded address at their index admission and some of these people were likely to have been homeless and resident in more disadvantaged areas.

Substance use disorders were common; more than half (51.5%) of people had at least one primary or comorbid substance disorder diagnosis during the study period. The most common specific substance diagnoses were of cannabis (29.0%), alcohol (25.7%) and stimulant (13.9%) disorders. Many people had multiple substance diagnoses in the study period; 38.6% of people with cannabis disorders also had stimulant disorders and 80.2% of people with stimulant disorders also had cannabis disorders. A further 12.0% of persons had illicit substance disorder diagnoses involving neither cannabis nor stimulants; most of these people had polydrug or unspecified substance disorder diagnoses where an individual substance was not identified. Mixed or unspecified substance diagnoses were more common in community mental health records than inpatient records. Examining participants aged 18-29 only, 20.8% had at least one stimulant disorder diagnosis.

Predictors of the presence and type of substance disorder were examined with multinomial logistic regression (Table 9.2). Tests for multi-collinearity did not require the exclusion of any variables. The odds of having any substance disorder were highest in younger people. In the “Cannabis” or “Cannabis and Stimulant” groups there was a steady decline in odds of disorder with increasing age, while for those in the “Stimulant” group the odds of disorder were highest in those aged between 21 and 30. Membership of the “Cannabis and Stimulant” group was very strongly associated with being younger than 25.

Table 9.1. Characteristics of study sample, people with a schizophrenia diagnosis. 13,624 people aged 18-50 who were admitted to NSW hospitals and had subsequent contact with hospital or community mental health services over five years.

	N	%
Age [a]		
Mean (SD)	32.6 (8.8)	-
Median (Interquartile range)	32 (25 - 40)	-
Person characteristics [a]		
Male	9,121	66.9
Migrant [b]	3,268	25.0
Rurality [a]		
Major cities	7,671	58.8
Inner regional	3,894	29.8
Outer regional and remote	1,487	11.4
Disadvantage [a]		
Quintile 1 (least disadvantaged)	1,844	13.5
Quintile 2	2,732	20.1
Quintile 3	2,680	19.7
Quintile 4	2,764	20.3
Quintile 5 (most disadvantaged)	3,032	22.3
Unknown or no fixed address	572	4.2
Comorbid substance disorder [c d]		
Any substance diagnosis	7,022	51.5
Alcohol	3,495	25.7
Any illicit drug	5,952	43.7
Cannabis	3,946	29.0
Stimulant	1,897	13.9
Hallucinogen	143	1.0
Illicit drug disorder group [e]		
Cannabis	2,424	17.8
Stimulant	375	2.8
Cannabis and Stimulant	1,522	11.2
Other/Mixed/Unspecified [f]	1,631	12.0

Notes: (a) Person details as recorded at index (first) hospital admission. (b) Country of birth data missing for 541 persons (4.1%). (c) Substance diagnoses during study period, excluding index admission. (d) Total exceeds 100% as individuals may have more than one substance diagnosis recorded. (e) Excludes alcohol disorders; total with any illicit drug disorder = 5,952. (f) Unspecified includes Polydrug diagnoses. Other includes specific diagnoses of opiate or hallucinogen disorders.

Table 9.2. Predictors of the presence and type of substance disorder over five years in people with schizophrenia (n=13,624). Multinomial logistic regression, separating those with any comorbid illicit substance diagnosis into four mutually exclusive substance disorder groups and comparing them to a reference group of people with schizophrenia but no substance disorder.

	SUBSTANCE DISORDER GROUP [a]			
	Other or unspecified OR (95% CI)	**Cannabis** OR (95% CI)	**Stimulant** OR (95% CI)	**Cannabis & stimulant** OR (95% CI)
Age group				
18-20	1.8 (1.4 - 2.4)***	5.9 (4.6 - 7.7)***	4.6 (2.2 - 9.9)***	16.8 (10.6 - 26.3)***
21-25	1.7 (1.4 - 2.2)***	4.8 (3.8 - 6.0)***	7.3 (3.8 - 14.2)***	16.6 (10.8 - 25.6)***
26-30	1.6 (1.3 - 2.0)***	3.3 (2.6 - 4.2)***	6.7 (3.5 - 13.0)***	10.1 (6.5 - 15.6)***
31-35	1.5 (1.2 - 1.9)***	2.4 (1.9 - 3.0)***	4.7 (2.4 - 9.1)***	6.5 (4.2 - 10.1)***
36-40	1.0 (0.8 - 1.3)	2.0 (1.6 - 2.6)***	3.4 (1.7 - 6.7)***	3.7 (2.4 - 5.8)***
41-45	1.2 (0.9 - 1.5)	1.5 (1.1 - 1.9)**	1.6 (0.8 - 3.5)	2.0 (1.2 - 3.2)*
46-50	1.0	1.0	1.0	1.0
Male gender	1.8 (1.6 - 2.0)***	2.2 (2.0 - 2.5)***	1.6 (1.2 - 2.0)***	2.1 (1.9 - 2.5)***
Migrant	0.6 (0.5 - 0.7)***	0.6 (0.6 - 0.7)***	0.6 (0.4 - 0.8)***	0.6 (0.5 - 0.7)***
Regional and rural location [b]	1.1 (1.0 - 1.3)*	1.5 (1.4 - 1.7)***	0.7 (0.5 - 0.9)**	1.4 (1.2 - 1.6)***
Most disadvantaged [c]	0.9 (0.8 - 1.0)	1.1 (1.0 - 1.2)	1.1 (0.8 - 1.3)	0.9 (0.8 - 1.0)

Notes: * p<0.05. ** p<0.005. *** p<0.0005. (a) Substance disorder diagnoses during study period, excluding index admission. (b) ARIA codes for inner regional, outer regional, rural and remote. (c) Address in most disadvantaged two quintiles of NSW local areas.

Compared to the reference group (people with schizophrenia but no drug disorder in the study period), all substance diagnoses were more likely in males, but slightly less skewed towards males in the “Stimulant” group (OR 1.6, 95% CI 1.2 – 2.0) than in the “Cannabis” (OR 2.2, 95% CI 2.0 – 2.5) or other drug groups. Cannabis and stimulant disorders differed in their distribution within the state: cannabis disorders were more likely in regional and rural areas; stimulant disorders were more likely in metropolitan areas. All substance disorders were significantly less common in people with schizophrenia born outside Australia, and substance disorders were not associated with residence in more disadvantaged local areas.

Selected indicators of service use, physical health diagnoses and housing instability (Table 9.3, Figure 9.1) showed a similar pattern: rates were lowest for those with no substance disorders, slightly higher in people with only mixed or unspecified substance disorders, then progressively higher in “Cannabis”, “Stimulant” and “Cannabis and Stimulant” groups. The only exceptions to this pattern were (i) the odds of having a cardiovascular disease diagnosis were elevated only in the “Stimulant” and “Cannabis and Stimulant” disorder groups, and (ii) the percent of persons with any period of homelessness was higher in people with mixed or unspecified substance disorders than in the “Cannabis” group.

We used multinomial logistic regressions to examine the relationship between drug disorder group and indicators of frequent service use, physical health diagnoses and housing instability, after controlling for age and gender. Analyses were conducted separately for each binary indicator of service use or harm (Table 9.4). Substance disorders predicted greater service contact for all measures. The odds of being a frequent service user were highest in the “Cannabis and Stimulant” group, especially for mental health admissions (OR 8.9, 95% CI 7.9 – 10.1). The odds of self-harm, injury or infectious disease diagnoses increased more than three-fold in the “Stimulant” group and more than fourfold in the “Cannabis and Stimulant” group. Measures of housing instability showed a similar pattern, with substantially increased risk of any homeless episode (OR 3.5, 95% CI 2.9 – 4.2) and multiple changes of address (OR 5.0, 95% CI 4.5 – 5.7) in the “Cannabis and Stimulant” group.

Table 9.3. Service use, physical health diagnoses and housing stability by substance disorder group, showing average rate for continuous variables and frequency and 95% confidence intervals for categorical variables

	SUBSTANCE DISORDER GROUP					
	No illicit drug	**Other or unspecified**	**Cannabis**	**Stimulant**	**Cannabis and**	**Total**
Characteristics						
Number	7,672	1,631	2,424	375	1,522	13,624
Average age (SD)	35 (9)	32 (9)	30 (8)	30 (7)	28 (7)	33 (9)
Percent male (95% CI)	59 (58 - 60)	74 (71 - 76)	79 (77 - 80)	73 (69 - 78)	79 (77 - 81)	67 (66 - 68)
Rate of service use (Mean, SD)						
Mental health admissions	2.2 (3.0)	2.7 (3.7)	4.4 (4.0)	4.3 (3.7)	6.9 (5.8)	3.2 (4.0)
Other admissions	0.6 (1.9)	1.2 (3.3)	1.2 (2.6)	1.5 (2.3)	1.9 (3.8)	1.0 (2.5)
Community contacts per 100 days [a]	9.9 (13.0)	15.8 (21.3)	12.6 (14.6)	11.2 (13.0)	13.5 (14.3)	11.5 (14.8)
ED presentations	3.4 (13.5)	6.0 (16.3)	6.3 (12.2)	8.3 (12.7)	11.1 (19.9)	5.2 (14.7)
Service use in top quartile (%, 95% CI)						
Frequent mental health admissions [b]	14 (13 - 15)	19 (17 - 21)	35 (33 - 36)	37 (33 - 42)	59 (56 - 61)	24 (23 - 24)
Frequent community mental health contacts [c]	21 (20 - 22)	32 (30 - 34)	29 (28 - 31)	26 (22 - 31)	34 (32 - 37)	25 (25 - 26)
Frequent Emergency Department presentations [d]	16 (15 - 17)	26 (24 - 28)	33 (31 - 34)	38 (33 - 43)	52 (49 - 54)	25 (24 - 26)
Physical health diagnoses (%, 95% CI)						
Self-harm and injury [e]	16 (15 - 17)	26 (24 - 28)	30 (28 - 31)	38 (33 - 43)	44 (41 - 46)	23 (23 - 24)
Cardiac disease [f]	9 (8 - 10)	8 (7 - 10)	8 (7 - 9)	12 (9 - 16)	10 (9 - 12)	9 (8 - 9)
Infectious disease [g]	7 (6 - 8)	11 (9 - 12)	12 (11 - 13)	18 (15 - 23)	22 (20 - 24)	10 (10 - 11)
Housing instability (%, 95% CI)						
Any homeless period [h]	5 (5 - 6)	16 (14 - 18)	10 (9 - 12)	16 (13 - 20)	18 (16 - 20)	10 (9 - 10)
Address in 3 or more areas	22 (21 - 22)	36 (33 - 38)	45 (43 - 47)	50 (45 - 55)	61 (59 - 64)	33 (32 - 33)
Move to more disadvantaged area [i]	24 (23 - 25)	32 (30 - 34)	37 (35 - 38)	37 (32 - 42)	42 (39 - 44)	30 (29 - 30)

Notes. (a) Rate corrected for days spent in hospital. (b) 5 or more mental health admissions. (c) 14 or more contacts per 100 days. (d) 6 or more Emergency Department presentations. (e) ICD-10 codes S00- T88. (f) ICD-10 codes A00-B99. (g) ICD-10 codes I00-I99. (h) Based on coding of accommodation type at hospital admission. (i) Average index of socio-economic disadvantage (IRSD) for locations of residence in study period higher than IRSD at first contact.

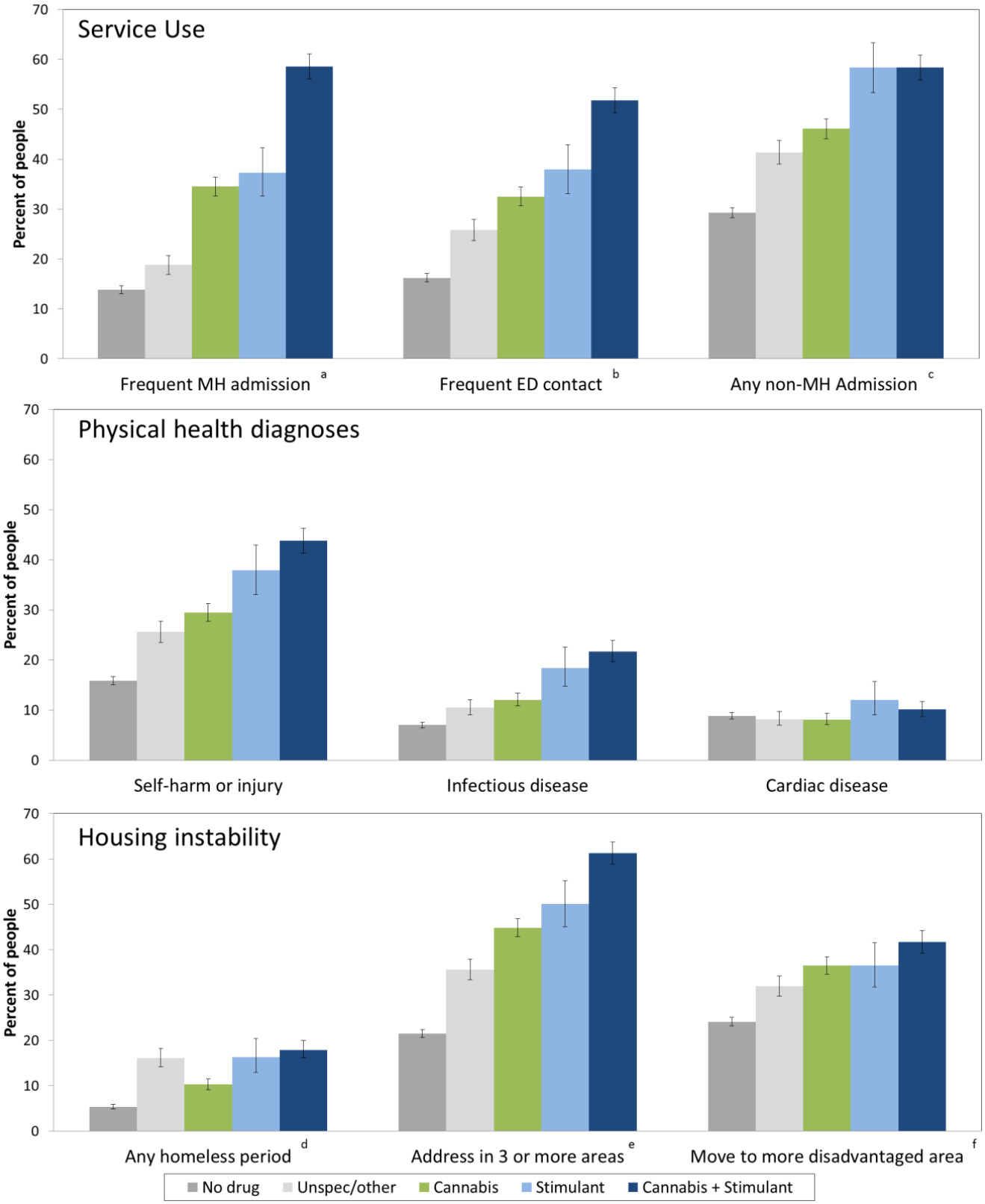

Figure 9.1. Service use, physical health diagnoses and housing stability in 13 624 people with schizophrenia over five years, grouped by type of illicit substance disorder in period: no illicit substance disorder (n=7,672), cannabis (2,424), cannabis and stimulant (1,522), stimulant (375) or other/unspecified substance only (1,631).

Table 9.4. Relationship between substance diagnosis group and selected harms over five years in people with schizophrenia (n=13,624). Multinomial logistic regressions conducted separately for each indicator of harm as an independent variable; reference group is people with no substance disorder. Age and sex are included as covariates in all regressions.

	SUBSTANCE DISORDER GROUP			
	Other or unspecified	**Cannabis**	**Stimulant**	**Cannabis and stimulant**
Frequent service use				
Frequent mental health admissions	1.5 (1.3 - 1.7)***	3.4 (3.0 - 3.8)***	3.8 (3.0 - 4.7)***	8.9 (7.9 - 10.1)***
Any non-mental health admission [a]	1.9 (1.7 - 2.1)***	2.4 (2.1 - 2.6)***	3.8 (3.1 - 4.7)***	4.0 (3.5 - 4.5)***
Frequent community mental health contacts	1.8 (1.6 - 2.0)***	1.5 (1.4 - 1.7)***	1.3 (1.0 - 1.6)*	1.9 (1.7 - 2.1)***
Frequent Emergency Department contacts	1.9 (1.7 - 2.1)***	2.6 (2.4 - 2.9)***	3.3 (2.7 - 4.1)***	5.9 (5.2 - 6.7)***
Physical diagnoses				
Self-harm and injury	1.9 (1.7 - 2.1)***	2.3 (2.1 - 2.6)***	3.3 (2.7 - 4.1)***	4.3 (3.8 - 4.9)***
Infectious disease	1.8 (1.5 - 2.1)***	2.2 (1.9 - 2.6)***	3.6 (2.7 - 4.8)***	4.9 (4.1 - 5.7)***
Cardiac disease	1.0 (0.8 - 1.3)	1.2 (1.0 - 1.4)	1.8 (1.3 - 2.5)***	1.7 (1.4 - 2.1)***
Housing instability				
Any homeless period	3.1 (2.6 - 3.8)***	1.8 (1.5 - 2.2)***	3.2 (2.4 - 4.4)***	3.5 (2.9 - 4.2)***
Address in 3 or more areas	1.9 (1.7 - 2.2)***	2.7 (2.4 - 3.0)***	3.4 (2.7 - 4.2)***	5.0 (4.5 - 5.7)***
Move to more disadvantaged area	1.4 (1.3 - 1.6)***	1.7 (1.5 - 1.9)***	1.7 (1.4 - 2.1)***	2.1 (1.9 - 2.4)***

Notes: * p<0.05. *** p<0.0005. (a) One or more hospital admissions with no mental health care.

The risk of frequent mental health admission, community mental health contact, change of local area and increase in IRSD all reduced with age, while cardiac disease, infectious disease and non-mental health admission increased with age. Self-harm or injury, infectious disease and frequent service use were more common in women, while housing instability was more common in men on all measures.

While the most substantial impacts were seen in the “Cannabis and Stimulant” group there were four indicators for which the “Stimulant” group had significantly higher rates than the “Cannabis” group, using the conservative test of non-overlapping confidence intervals (Schenker and Gentleman, 2001). These were non-mental health admissions, self-harm and injury, infectious disease and any period of homelessness. Three sensitivity analyses were conducted. First, all regressions were repeated including only the 9,172 participants (67% of total) who met the more specific diagnostic test of having a schizophrenia diagnosis at both index admission and final contact. The strength of most associations with cannabis and stimulant disorders was increased non-significantly in this subgroup but all regression models remained unchanged. Second, there were 1,709 right-censored participants (12.5%). They did not differ from non-censored participants on age or sex, but had lower rates of illicit drug diagnoses. Exclusion of this group resulted in a non-significant increase in the rates of service use and in the odds ratios reported in all regressions, but the findings of all regression models remained unchanged. Third, 1,618 participants (11.9%) in the current study had also been included in our previous studies of early psychosis during the first two years of their care. After excluding early psychosis participants, the remaining subjects were significantly older, more likely to be male and more likely to reside in metropolitan areas. However they did not differ in their rate of cannabis or stimulant use or the proportions using multiple substances. They had a slightly lower rate of ED presentations but they did not differ significantly on any other measure of service use, physical diagnosis or housing instability. All regression models remained unchanged after exclusion of this group

DISCUSSION

We followed people with a diagnosis of schizophrenia for five years after an index hospital admission. More than half had at least one comorbid substance use disorder. Because the group was defined by ongoing service contact it is unsurprising that many had further hospital admissions or emergency presentations, despite having a community mental health contact, on average, every ten days. We found substantial physical comorbidity and

housing instability; nearly one third lived in a more disadvantaged area at the end of the study period than at first contact; one quarter had further hospital admissions with self-harm or injury; and nearly one in ten had indicators of infectious disease, cardiovascular disease or homelessness. Our measures are drawn from routine administrative data, and are likely to under-estimate the prevalence of many of these outcomes. However even with limited sensitivity, these findings underline the challenges of substance misuse, physical ill-health and social dislocation which face many people with schizophrenia.

Our first aim was to estimate the rate of stimulant use disorders in people with schizophrenia. We estimated that 13.9% of this group (and 20.8% of those aged 18-29) had at least one stimulant disorder diagnosis. This is consistent with estimated rates of cocaine dependence in some US studies (Chouljian et al., 1995; Miller and Tanenbaum, 1989), and with the prevalence of stimulant disorders (15.5%) in people aged 15-29 with a first psychosis admission in NSW (Sara et al., 2013). The 12-month prevalence of stimulant abuse or dependence in Australians aged 16-49 is 0.97% (Sara et al., 2011a). While these population and clinical studies use different methodologies and are therefore not directly comparable, they suggest that stimulant disorders may be at least ten times more prevalent in people with early psychosis or schizophrenia than in the general population.

Our second aim was to describe the correlates of stimulant disorders. Like all substance disorders, stimulant disorders were more common in younger adults and males. By comparison with cannabis disorders, stimulant disorders were slightly more common in people in their mid and late 20s and were slightly less skewed towards males. Stimulant disorders were unrelated to social disadvantage (as measured by area of residence), were more common in urban areas and less common in people born outside Australia. These associations are consistent with those we have previously reported in the Australian population and in first admission psychosis in NSW. This suggests that the choice of illicit substance in people with psychosis is influenced by the same social and environmental factors that influence others. The much higher rate of use in psychosis may suggest that people with psychosis are more sensitive to these factors.

Our third aim was to describe the impacts of stimulant disorders on people with a diagnosis of schizophrenia. We found that all comorbid illicit substance disorders were associated with greater service use, more frequent physical comorbidities and greater housing instability. More than 80% of people with stimulant disorders also had cannabis

disorder diagnoses in the study period, and the risk of all harms was highest in this group. It is not surprising that physical health problems and unstable residence are more frequent in this group, but the strength of these associations was striking. After controlling for age and sex differences between groups, people with both cannabis and stimulant disorders were nearly nine times more likely to have frequent inpatient admissions, more than four times as likely to have admissions with self-harm/injury or infectious disease diagnoses, and more than three times as likely to have at least one period of homelessness, when compared to people with schizophrenia who did not have an illicit drug disorder.

An observational study of this type cannot demonstrate causation, or discriminate between several alternative explanations for these findings. First, it is possible that the association is partly an artifact of our method. We have extracted diagnoses from service data, therefore people with more service contacts have more opportunity to have multiple diagnoses recorded. More frequent service contact may have resulted in multiple substance diagnoses rather than vice versa. Similarly, people with comorbid physical health conditions may have been more likely to be admitted and therefore more likely to be included in our dataset. Second it is possible that multiple comorbid substance diagnoses are markers of complexity and disadvantage; younger people who are marginalized or socially dislocated are more likely to use multiple drugs, including stimulants (Degenhardt et al., 2007b). It is also possible that people with more severe psychotic illness use more substances in response to their illness, although support for the “self-medication” hypothesis in psychosis is increasingly limited (Kolliakou et al., 2013; Martins and Gorelick, 2011; Hall and Degenhardt, 2000). Third, cannabis and stimulants may have specific additive impacts in people with schizophrenia. Both have the potential to worsen psychotic symptoms and precipitate relapse, and together they may increase the likelihood of a more chronic course of illness. Recent speculations (Paparelli et al., 2011) suggest a role for endocannabinoid systems as well as dopaminergic pathways in the development of psychosis. Finally, it is likely that these social, personal and neurochemical factors interact in an iterative way; substance use may be both a contributor to and an effect of the psychological and social disruption associated with schizophrenia.

Regardless of the nature of the association, these findings identify a challenge for mental health services. The overlap between stimulants and cannabis in people with psychosis should be seen as a marker of significant risk, and a need for more focused clinical effort. Comorbid substance use is associated with worse outcome in early psychosis (Sorbara et

al., 2003; Wade et al., 2006a; Wade et al., 2007), however people who discontinue substance abuse may have more positive outcomes than non-substance-users (Baeza et al., 2009; Lambert et al., 2005; Sara et al., 2014b; Strakowski et al., 2007). Evidence for the effect of discontinuation of substance use in established psychosis is more limited (Gupta et al., 2013). Attempts to engage and offer effective treatment are critical, but our findings also point to one difficulty in this task; more than 60% of people with both cannabis and stimulant disorders lived in three or more locations over a five year period. This degree of mobility is likely to disrupt treatment networks as well as broader family and social supports for abstinence and adherence to care.

We also identified a small group of people with schizophrenia who had stimulant disorders but no cannabis disorders. This group had lower service use and fewer markers of physical or social harm than those with both cannabis and stimulant disorders. However when compared to people with cannabis disorders alone, they had higher rates of general hospital admission, self-harm or injury diagnoses, infectious disease diagnoses and homelessness. These findings are consistent with the physical health risks of stimulant use, particularly when used intravenously (Darke et al., 2008; Degenhardt et al., 2008c). This group was also more likely to live in urban areas. We have previously found the same regional association (an urban excess in stimulant disorders and a rural excess in cannabis disorders) in people with first admissions for psychosis (Sara and Burgess, 2012), and a trend towards greater urban prevalence of stimulant disorders in the Australian population (Sara et al., 2012).

Advantages and Limitations

This study uses data from public hospitals and specialist mental health services for a population of more than 7 million people over more than a decade. This provides a large, naturalistic, population-based sample with sufficient power to examine stimulant disorders while controlling for comorbid cannabis disorders and other potential confounders. However the use of administrative datasets involves a tradeoff between precision and statistical power, and our study has a number of limitations.

This study uses routine clinical diagnoses. Substance disorders may be particularly under-recorded in routine clinical records. Compounding this underestimation, around 12% of participants had diagnoses of polydrug or unspecified substance abuse; many will have had cannabis and stimulant disorders. However, this study uses diagnostic information

extracted from inpatient records by trained coders, and adopts a low threshold for recording a diagnosis (at least one substance diagnosis in the follow-up period). Therefore underestimation in this study may be modest. We found that 51% of participants had a substance use disorder, including 29% with a cannabis disorder and 13.9% with a stimulant use disorder. By comparison, the Australian Survey of High Impact Psychosis (Moore et al., 2012b) found that 35% of people with schizophrenia spectrum disorders reported cannabis use at least monthly in the previous 12 months, and 13.8% reported stimulant use at least monthly. A more significant limitation in our study may be that the quality of diagnostic information in this study is systematically poorer in community data, where diagnoses are recorded by clinicians rather than extracted by coders. Therefore apparent associations between substance use and hospital admission or physical health problems may merely reflect greater likelihood of accurate diagnosis in people admitted to hospital.

People included in this study are likely to have differed systematically from people with schizophrenia who were not included. We have included people with schizophrenia who had at least one hospital admission during an 11 year study period, and who had at least two years of contact with public inpatient or community mental health services following that admission. People with schizophrenia who had no hospital admissions, or admissions but no ongoing follow-up, are likely to have had a more stable course of illness and lower rates of substance use, physical health problems and housing instability. Therefore our findings should not be generalised to people with schizophrenia who do not have contact with specialist mental health services.

There is overlap between the dataset for the current study and that used in our previous studies, which examined the first two years of care in people aged 15-29 years with a first psychosis admission between 2005 and 2012. Some of that group had ongoing service contact over five years and a final diagnosis of schizophrenia. Sensitivity analysis demonstrated that removing those participants did not change the conclusions of this study. However the consistency of findings between the current study and our earlier studies may be partly due to overlapping participants.

Accommodation status codes and changes in address are imprecise measures of housing instability. Addresses and accommodation status codes are often inaccurate in routine clinical records. We used statistical local area codes to estimate social disadvantage, however people with psychoses may be living in disadvantaged individual circumstances

even within more affluent areas. Due to incomplete application of a unique person identifier to ED data, we are likely to have under-recorded ED presentations, especially where people attended multiple hospitals. Together these limitations add imprecision to our results, and are likely to lead to underestimation of associations between substance use disorders and poor outcomes in persons with psychoses.

Conclusions

Stimulant use disorders are as common in people with persistent forms of schizophrenia as in first episode psychosis. Both groups have rates of stimulant use disorders more than ten times that of the broader population. Most people with schizophrenia and stimulant disorders also have cannabis disorders, and they experience very high rates of service use, physical comorbidity and social dislocation. Stimulant use disorders are likely to contribute to the burden of chronic psychosis. Better strategies are needed to identify and treat comorbid substance use disorders in people with schizophrenia, especially cannabis and methamphetamine disorders.

PART 4

DISCUSSION AND CONCLUSIONS

10: Discussion

The research in this thesis has described the prevalence, correlates and impacts of stimulant use disorders in people with psychosis. These are important issues because psychotic disorders cause significant personal and social cost, and substance disorders are among the few modifiable factors affecting the outcome of psychosis. Stimulants such as amphetamines and cocaine have particular potential to affect psychotic symptoms, because of their specific dopaminergic actions.

Most stimulant users have also used cannabis, so it is difficult to separate the associations of stimulants from those of cannabis. Other personal and social factors such as age, gender, disadvantage, urban location and migrant status also confound the relationship between drug use and psychosis. Even very large clinical studies have not had usually had sufficient power to disentangle these effects. Exceptions have been studies conducted in South East Asian countries where stimulant use is common but cannabis use is rare, and in studies in developed countries of highly selected clinical samples receiving treatment for stimulant dependence in the absence of other drug comorbidity. It is difficult to generalise from these studies to the situations usually encountered by Australian mental health services where the use of multiple drugs is common.

The studies presented in this thesis have used an epidemiological approach. They used data from an Australian national household survey of mental health and substance disorders, and routinely collected health service data on persons treated for psychoses in a population of more than seven million people in the state of New South Wales. Together these provided representative data with sufficient statistical power to examine the impacts of stimulants in people with different diagnostic subtypes and at different stages of psychosis, while controlling for cannabis disorders and other confounders. The studies focused on the types of acute and severe clinical problems encountered by mental health services. They examined psychotic syndromes rather than brief or transient psychotic symptoms. They focused on stimulant abuse and dependence rather than stimulant use, because severe harms such as psychosis are more common in persons who have a history of more severe and longstanding drug use disorders.

This chapter summarises and integrates the findings of the studies presented in this thesis. First, it summarises the main findings of each study as they relate to the specific research questions outlined in Chapter 1. Second, it draws several broader conclusions

based on those findings. Third, it discusses the limitations of the studies, along with their strengths and their contribution to knowledge of this issue. Fourth, it discusses possible implications of these findings and how they fit with current models of psychosis and of the role of substance use in psychosis. Finally it considers possible implications for prevention, health service planning and clinical care.

FINDINGS FOR SPECIFIC RESEARCH QUESTIONS

Chapter 1 identified 14 specific research questions regarding the association of stimulant disorders with psychosis. The studies presented in chapters 2 to 9 of this thesis have been designed to address these questions. Several of these studies have examined more than one question, and some questions draw on findings from several studies or chapters.

Internationally, what is the prevalence of stimulant use disorder in people with psychosis?

Chapter 2 presented a meta-analysis of 61 studies examining 22,500 people with psychosis. It calculated a pooled estimate of any stimulant use disorder of 8.9% (95% confidence interval 7.4% - 10.5%).This is substantially higher than the estimated rate of stimulant dependence in the general population. The Global Burden of Disease study estimated the 12-month prevalence of amphetamine or cocaine use in the general population to be 0.3%-1.3% (Degenhardt and Hall, 2012b), and the point prevalence of stimulant dependence to be 0.10%-0.25% (Degenhardt et al., 2014). These population estimates have used different methods and cannot be compared directly to the estimates obtained from clinical studies. However they suggest that people with psychosis use and abuse stimulants at a much higher rate than the general population.

Are there regional or national differences in the prevalence of stimulant use disorders in people with psychosis?

The meta-analysis presented in Chapter 2 identified significant regional differences in the prevalence of stimulant use disorders in people with psychosis. The highest rates were reported in studies from the USA (11.9%, 95% CI 9.1% - 15.3%) and Australia (10.8%, 95% CI 6.8% - 16.9%). These were higher than rates in studies from the UK, Ireland, Europe and Scandinavia. The studies described in Chapters 6 and 9 provide additional estimates of the prevalence of stimulant disorders in Australians with first admission

psychosis or established diagnoses of schizophrenia. These are summarised further below.

The type of stimulant drug used in people with psychosis (cocaine, amphetamine) also varied by region. Studies from the USA and Western Europe reported higher rates of cocaine use disorder, while studies from the UK and Australia reported only methamphetamine or unspecified stimulant disorders. In people with psychotic disorders, regional differences in the rates of stimulant disorder and type of stimulant drug used mirrored regional differences in the broader population.

What person or service factors are associated with variations in prevalence?

The meta-analysis reported in Chapter 2 also examined the predictors of stimulant use disorder in studies of people with psychosis. There was substantial between-study variation in reported rates of stimulant use disorder, however 68% of this variation could be explained using multiple meta-regression. Higher rates of stimulant use disorder were predicted by higher rates of cannabis use or disorder, diagnoses of affective psychosis, and studies from inpatient settings as well as by the regional differences discussed above. Cannabis use disorder was the strongest single predictor of stimulant use disorder, explaining 43% of between-study variance.

Study methodology factors such as the period examined (lifetime or recent), the inclusion or exclusion of drug-induced psychosis or the type of diagnostic methods used had little impact on reported rates of stimulant use disorder.

The meta-analysis in Chapter 2 found no significant increase in the rate of stimulant use disorder in people with psychosis between 1971 and 2009. These findings are not consistent with clinical concerns that stimulant abuse has increased among new presentations for psychosis in Australia, or with the overall increase in stimulant-related mental health admissions reported in Chapter 5. This null finding may reflect the very high heterogeneity in stimulant use disorder estimates. Stimulant use disorders were unrelated to the stage of psychosis, being equally common in prodromal and early psychosis and in chronic schizophrenia. After controlling for other factors in multivariate analysis, there was no association of age or gender with rates of stimulant use disorder in psychosis

What is the prevalence of stimulant use disorders in the Australian population?

Chapter 3 used data from a national household survey, the 2007 Australian National Survey of Mental Health and Wellbeing (NSMHWB), to estimate the number of Australians with stimulant abuse or dependence diagnosed according to DSM-IV criteria. Stimulant use was reported by 12.2% of the adult population, and 7.2% of persons had used stimulants on more than five occasions.

For the Australian population aged 16-85, the lifetime prevalence of stimulant use disorder was estimated to be 3.3% (95% CI 2.8% - 3.9%). Just under half of these disorders (1.4%, 95% CI 0.9% - 1.9%) were stimulant dependence. Serious drug-related harms such as psychosis are more likely to be related to recent use: the 12-month prevalence of any stimulant disorder was 0.6% (95% CI 0.4% - 0.8%) and the 12-month prevalence of stimulant dependence was 0.3% (0.1% - 0.4%). While stimulant disorders were uncommon, they affected a significant number of individuals; these prevalence estimates equate to more than 97,000 Australians having experienced features of stimulant abuse or dependence in the past year.

Nearly half (46%) of people who reported having used stimulants on more than five occasions met criteria for a lifetime stimulant use disorder. This suggests that for stimulant drugs the window between use and harmful use is narrow.

What are the characteristics of people with stimulant use disorders in Australia?

Age and sex-specific prevalence rates for stimulant disorders were also reported in Chapter 3, using data from the Australian NSMHWB 2007. Stimulant use and psychosis were both more common in younger adults. For younger adults (aged 16-49) the 12-month prevalence of any stimulant disorder was 1.0% (95% CI 0.7% - 1.3%) and of stimulant dependence was 0.4% (95% CI 0.2% - 0.7%).

Stimulant disorders were two to three times more common in males than females. They declined with age, with the highest rate among persons younger than 29 years. The highest prevalence rates were among males aged 16 to 29 years (lifetime 8.4%, 12-month 2.0%).

Chapter 4 used data from the NSMHWB 2007 to describe the more detailed correlates of lifetime stimulant disorders. The strongest predictor of stimulant disorders was the use or abuse of other substances: 86% of people with a stimulant disorder reported prior use of

cannabis and 73% met criteria for a lifetime cannabis disorder (OR 67, 95% CI 0.45 – 1.00). People with stimulant disorders reported significantly earlier use of all drugs, and nearly 80% also had a history of lifetime alcohol or other drug use disorders.

In multivariate analyses controlling for age, gender and other factors, cannabis disorders (OR 28, 95% CI 18-43) and alcohol disorders (OR 4.4, 95% CI 2.5 – 7.8) were the strongest predictors of stimulant disorders. Unlike cannabis disorders, stimulant disorders were not associated with social disadvantage, lower income, fewer years of education or rural location.

People with lifetime stimulant disorders had rates of other lifetime mental health disorders which were 3 to 4 times greater than those of the general population: 42% had anxiety disorders and 29% affective disorders. One third (32%) reported suicidal ideation and nearly half of these (14%) reported a suicide attempt. Rates of imprisonment or homelessness were more than ten times those of the broader population.

Together these findings indicate that while the population prevalence of stimulant abuse and dependence is low, the impact of stimulant disorders may be significant because of the characteristics of the persons who are affected. Stimulant disorders are rarely isolated conditions. They may be an important additive risk in people who also have a family history of mental health disorders, prior features of affective or anxiety disorders and earlier and more frequent use of cannabis, alcohol and other drugs. These findings also underline the methodological challenge in separating the possible role of stimulants from those of cannabis and many other confounding factors. In addressing these challenges epidemiological approaches are needed to complement those of clinical studies.

Are stimulant use disorders more common in people with other risk factors for psychosis?

Chapter 1 briefly summarised arguments that vulnerability to psychosis occurs on a spectrum. Up to 10-20% of the population may have a broad vulnerability to psychosis (van Os and Kapur, 2009), and this vulnerability is not specific to psychosis but is shared with other mental health conditions (Mitchell and Porteous, 2011; Jacka and Berk, 2014).

The studies in Chapter 3 and Chapter 4 found that stimulant disorders were most common in people with other risk factors for psychosis. Younger males were the group most at risk for the onset of psychosis, and 8.4% of Australian males aged 16-29 had a lifetime stimulant use disorder. In addition, one in five (20%) people with a lifetime stimulant

disorder had a family history of psychosis or bipolar disorder, which was double the rate in the broader population. People with lifetime stimulant disorders were also twice as likely to have a family history of depression or anxiety.

Brief or subclinical psychotic symptoms are one marker of vulnerability to psychosis. Thirteen percent of people with lifetime stimulant disorders reported one or more psychotic experiences, a rate almost five times that in the broader population.

There is increasing evidence that cannabis use in early adolescence is a risk factor for the development of psychosis (Hall and Degenhardt, 2006; Murray et al., 2012). People with lifetime stimulant disorders have a much higher rate of adolescent cannabis use: 86% of people with lifetime stimulant disorders have used cannabis, and 50% of those first used cannabis by the age of 15.

Is greater stimulant availability in the community associated with more frequent admission for psychosis?

Variations in police arrests for drug possession can be used as an indirect measure of variations in drug availability in the community. Chapter 5 used police data on arrests for stimulant possession to assess whether variations in stimulant availability predicted variations in stimulant-related admissions to mental health units in NSW between 2000 and 2009.

Stimulant-related seizures and arrests increased steadily from 2000, peaked in 2007-2008 and then declined. There were substantial quarterly variations against this long term trend. Admissions to mental health units for stimulant-related disorders appeared to mirror this trend, although analysis was complicated by an increase in the number of mental health beds between 2000 and 2006.

After controlling for changes in mental health bed numbers, changes in stimulant availability predicted 34% of the variance in admissions to mental health units with a diagnosis of stimulant abuse or dependence, and 50% of the variance in stimulant-related (drug-induced) psychoses. There was no significant relationship between changes in stimulant availability and admissions for schizophrenia or other non-drug-induced psychoses.

There are arguments about the validity of using police seizure or arrest data as a measure of drug availability. These are discussed further below. Within these limitations, these

findings suggest that stimulant use may have a significant impact on the burden of psychosis at a population level and on health services. They also suggest that this impact is particularly felt through the precipitation of brief and drug-induced psychosis rather than through an effect on long term psychoses such as schizophrenia.

What is the prevalence of stimulant use disorders in people with first admission psychosis?

Chapter 6 examined 9,919 New South Wales residents aged 15-29 with a first psychosis admission. Half of the group had a comorbid substance use disorder, most commonly a cannabis use disorder (30%). Sixteen percent (16%) of first psychosis admissions had a diagnosis of a stimulant use disorder, including stimulant abuse, stimulant dependence or a specific stimulant-induced psychosis. This rate was slightly higher than the rate of comorbid alcohol diagnoses (14%).

The estimated prevalence of stimulant use disorders is likely to be an underestimate, for two reasons. First, 11% of the sample had a diagnosis of polydrug abuse or dependence, without further specification of the type of drug involved. In an unknown proportion of these cases stimulants will be one of the drugs involved. Second, the study used routine clinical diagnoses to identify substance comorbidity, and these are an insensitive measure. Therefore it is reasonable to conclude that *at least* one in six young people with a first psychosis admission in New South Wales had a stimulant use disorder.

The meta-analysis reported in Chapter 2 included 25 studies reporting on rates of stimulant use disorders in people with a first episode of psychosis, calculating a pooled estimate of 7.8% (95% CI 5.7% - 10.6%). This is half of the rate of stimulant disorders identified in people with a first admission psychosis in New South Wales. This difference is consistent with epidemiological evidence of a high rate of stimulant use disorders in Australia: the pooled estimate for early psychosis included several large cohorts from Western Europe and Scandinavia where rates of stimulant use disorder appear to be lower than in the USA and Australia.

People with a first admission psychosis in New South Wales were more than ten times as likely (OR 11.9, 95% CI 11.2 - 12.5) to have a stimulant use disorder than the age-matched Australian population. Their risk of alcohol-related disorders was only slightly greater than the age-matched population (OR 1.5, 95% CI 1.4 - 1.6), suggesting that the higher rate of stimulant disorders is not due to a non-specific increase in the risk of any

substance disorder. However the rate of cannabis-related disorders was even more substantially increased (OR 16.8, 95% CI 16.0 - 17.5). This suggests that while stimulants are particularly associated with diagnoses of brief and drug-induced psychoses, cannabis may be a more significant risk factor than stimulants when considered across the spectrum of psychosis diagnoses.

What are the correlates of stimulant use disorders in people with first admission psychosis?

Chapter 6 also examined the correlates of stimulant and other substance use disorders. In multivariate analysis, comorbid diagnosis of any substance disorder was associated with being male (OR 2.0, 95% CI 1.8 - 2.2), being born in Australia (OR 1.9, 95% CI 1.7 - 2.2) and living in non-metropolitan locations (OR 1.3, 95% CI 1.1 - 1.4). However, the associations of stimulant disorders differed significantly from those of cannabis disorders. The odds of comorbid cannabis use disorders declined with age, while stimulant use disorders were more common through to the late 20s. The odds of cannabis use disorder were greatest in rural locations, while stimulant use disorders were more common in urban locations (OR 1.2, 95% CI 1.1 - 1.4) and in less disadvantaged areas (OR 1.2, 95% CI 1.1 - 1.4). Cannabis and stimulants showed a similar distribution across diagnostic subtypes of psychosis but stimulant use disorders were more common in those with diagnoses of Brief Psychosis and Drug Induced Psychosis.

The findings of a particular association between stimulant diagnoses and brief and drug-induced psychoses are consistent with the findings from Chapter 5 that variations in stimulant availability were only associated with variations in admission for brief and drug-induced psychoses.

When compared to people with no comorbid substance diagnoses, cannabis use disorders were associated with a younger average age at first psychosis admission (22.7 years, compared to 23.5 years for people with no substance use disorder). By contrast, stimulant use disorders were associated with a significantly older average age at first psychosis admission (24.2 years). Older age at psychosis onset is usually associated with a more positive prognosis.

Are stimulant use disorders associated with readmission in the first two years of psychosis?

Chapter 7 examined 7,269 young people with a first psychosis admission and at least two years of follow-up with New South Wales mental health services. Readmission to hospital was used as an indirect measure of recurrence of psychosis, and predictors of time to readmission were examined using Cox proportional hazards regression. A diagnosis of stimulant or cannabis use disorder at first psychosis admission was not related to the risk of readmission over two years.

The findings of this study suggest that the long term pattern of drug use is more important in influencing outcome in psychosis than the cross-sectional presence of a comorbid drug diagnosis. The study examined a subset of people (n=4,993) for whom it was possible to derive a measure of ongoing drug use after their index episode. People who had drug use disorders at baseline but who ceased problem drug use had the lowest readmission rate over two years (40%) and people whose problem drug use continued had the highest readmission rate (66%). The lack of any difference an association between baseline substance use and later readmission may therefore reflect the effects of averaging of risk in these two groups.

The measure of ongoing drug use did not allow stimulants and cannabis to be examined separately. However the study found that a higher rate of readmission following a first psychosis episode occurred in people with longer or more severe stimulant use, as indicated by the presence of hospital admissions with a stimulant use disorder prior to the first psychosis admission (Hazard Ratio 1.4, 95% CI 1.1-1.7). The same was not true of cannabis use disorders. Previous chapters have suggested that stimulant use disorders are associated with brief and transient psychoses, which typically have a more positive outcome. The findings of this study suggest that more severe or prolonged stimulant misuse is a risk factor for recurrent psychosis.

Are stimulant use disorders associated with increased risk of progression to schizophrenia over five years?

Chapter 8 identified 24,306 individuals admitted to hospital with an ICD-10 psychosis diagnosis between 2000 and 2011. It examined the agreement between initial and final diagnosis over 5 years, and identified predictors of diagnostic change towards and away

from a final diagnosis of schizophrenia. The study examined persisting rather than baseline substance diagnoses.

Ongoing comorbid substance use disorders contributed both “signal” and “noise” to the diagnoses of people with psychosis. Nearly half (46%) of people with initial diagnoses of brief, atypical or drug-induced psychosis were later diagnosed with schizophrenia. Comorbid substance use diagnoses were also associated with diagnostic instability, reduced agreement between initial and final diagnoses, and greater likelihood of an initial schizophrenia diagnosis being revised to other disorders.

Stimulant use disorders differed significantly from cannabis use disorders in their associations with diagnostic instability and progression to schizophrenia. Stimulant use disorders were associated with greater diagnostic instability, less likelihood of diagnostic transition to schizophrenia (OR 0.81, 95% CI 0.67 – 0.97) and the highest likelihood that an initial schizophrenia diagnosis would be revised to other diagnoses (OR 2.21, 95% CI 1.67-2.93). By contrast, ongoing cannabis use disorders were associated with increased risk of transition to schizophrenia (OR 1.12, 95% CI 1.01 – 1.24) and more modest likelihood of revision away from an initial schizophrenia diagnosis (OR 1.30, 95% CI 1.13-1.49).

These findings underline the importance of examining stimulants and cannabis separately because they suggest that these two drug classes have distinct and specific effects on the development of psychosis. If the effects of these drugs were simply additive, people who used both cannabis and stimulants would be expected to have the highest rates of diagnostic instability and transition to schizophrenia. Instead, people with both cannabis and stimulant use disorder diagnoses had effects that were intermediate between those with cannabis use disorders alone and those with stimulant use disorders alone.

These findings also add to those of Chapters 5 and 6 in suggesting that while stimulant use disorders are common in psychosis they are associated with briefer psychoses and better outcomes. When compared to cannabis use disorders, stimulant use disorders – even if ongoing – may be associated with recurrent psychoses but appear to be associated with a lower risk of progression to a diagnosis of schizophrenia.

What is the prevalence of stimulant use disorders in people with schizophrenia?

Chapter 9 examined 13,624 people aged 18-50 with a diagnosis of schizophrenia who had ongoing contact with New South Wales mental health services. More than half (52%) had

at least one primary or comorbid substance use disorder diagnosis during the five-year study period. The most common specific substance diagnoses were cannabis (29%), alcohol (26%) and stimulant use disorders (14%). A further 12% of persons had unspecified or mixed (e.g. polydrug) substance use disorder. An unknown proportion of this group was likely to have had stimulant use disorders.

In Chapter 6 the rate of stimulant use disorder in New South Wales residents with first episode psychosis was estimated to be 16%, which is higher than the estimate in New South Wales residents with a schizophrenia diagnosis. However, the first admission group included a younger age range (16-29 years), and stimulant use disorders were more common in younger adults. Of people with schizophrenia aged 18 to 29 years, 21% had at least one stimulant use disorder diagnosis. This suggests that the rate of stimulant disorder in people with established diagnoses of schizophrenia is at least as high as the rate in first episode psychosis.

Consistent with findings in early psychosis, this rate of stimulant use disorder was higher than the meta-analytically derived pooled estimate for stimulant use disorders in people with established psychosis (Chapter 2). In that analysis the rate of stimulant use disorder in people with schizophrenia was 10.4% (95% CI 8.1%-13.4%). The rate of stimulant use disorder appears to be higher in the USA and Australia than in some other developed countries, and this increase is seen across the spectrum from the broader population, through early psychosis to ongoing psychoses such as schizophrenia.

What are the correlates of stimulant use disorders in people with schizophrenia?

The correlates of stimulant use disorders in schizophrenia were examined in Chapter 9. As in people with earlier stages of psychosis, stimulant use disorders had very substantial overlap with cannabis use disorders in people with schizophrenia: 80% of people with stimulant use disorders also had cannabis use disorders. Both cannabis and stimulant use disorders were more common in males, but there was less gender imbalance for stimulant than for cannabis use disorders. Stimulant use disorders peaked in people aged between 21 and 30 years, while cannabis use disorders were most common in teenagers and declined steadily with age. Stimulant use disorders were common in metropolitan locations (OR for rural locations 0.7, 95% CI 0.5 – 0.9) while cannabis use disorders were more common in rural locations (OR 1.5, 95% CI 1.4 – 1.7).

These differences in association between stimulant and cannabis use disorders in people with schizophrenia diagnoses were broadly consistent with the associations found in the Australian population (Chapters 3 and 4) and in people with a first psychosis admission (Chapter 6). In all groups, stimulant use disorders had a smaller gender imbalance than cannabis use disorders, occurred later, tended to be more common in urban rather than rural settings, were uncommon in migrants and were not associated with social disadvantage.

In people with schizophrenia, are stimulant use disorders associated with frequent service use, physical health problems or housing instability?

In people with early psychosis, stimulant use disorders were associated with more positive outcomes as reflected in shorter periods of specialist mental health service contact, diagnoses of brief, atypical or drug induced psychosis at first admission (Chapter 6 and 7) and a lower likelihood of making a diagnostic transition to schizophrenia (Chapter 8). These effects were largely in the opposite direction to those of cannabis. In people with both cannabis and stimulant use disorders most these associations were intermediate between those of cannabis use disorders alone and those of stimulant use disorders alone.

Chapter 9 found a different pattern of associations in people with established diagnoses of schizophrenia. It found that stimulant use disorders were associated with much greater levels of harm and more negative outcomes. Their effects appeared additive with those of cannabis, so that people with both cannabis and stimulant use disorders had worse outcomes than those with either cannabis or stimulant diagnoses alone.

People with schizophrenia who had both cannabis and stimulant diagnoses were nearly nine times more likely than peers with no substance use disorders (OR 8.9, 95% CI 7.9 – 10.1) to have frequent mental health admissions: 59% had more than five admissions over a five year follow-up period. They were also much more likely to have frequent Emergency Department contacts (OR 5.9, 95% CI 5.2 – 6.7) and admissions for physical health problems (OR 4.0, 95% CI 3.5 – 4.5). Nearly half (44%) had a hospital admission for self-harm or injury, 61% lived in more than three local areas during the follow-up period, 42% were living in a more disadvantaged area at the end of follow-up than at first admission and 18% had at least one period of homelessness.

The small group of people with schizophrenia who had stimulant use disorders but no cannabis use disorders had lower service use and fewer markers of physical or social harm than those with both cannabis and stimulant use disorders. However when compared to people with cannabis use disorders alone, they had higher rates of general hospital admission, self-harm or injury diagnoses, infectious disease diagnoses and homelessness.

SUMMARY FINDINGS

Taken together, the findings of these studies support several broad conclusions.

First, *stimulant abuse and dependence have a significant impact on overall burden of psychosis and on the Australian health system*. Stimulant use disorders are less common than cannabis or alcohol disorders in the population but they affect more than 97,000 Australians annually, or more than 30,000 people each year in New South Wales. They occur most often in younger people who also have other risk factors for the development of psychotic disorders, including male gender, a history of early cannabis use, a family history of psychosis, sub-clinical psychotic experiences and prior symptoms of depression and anxiety. At least one in six people with psychotic disorders (16% in first admission psychosis, 21% in people aged under 29 with established psychosis) had a diagnosis of stimulant abuse or dependence, a rate at least ten times greater than other young Australians.

In New South Wales mental health units, there were more than 400 admissions per year with diagnoses of stimulant-induced psychosis, and more than 1,100 admissions per year with a diagnosis of stimulant abuse or dependence. These comprised around 5% of total mental health admissions in the study period, and included more than 220 young people per year experiencing their first hospital admission. The rate of admission appeared to be influenced by stimulant drug supply, since hospital admissions with stimulant-related psychoses were significantly more common when stimulants were more available in the New South Wales community.

The meta-analysis presented in Chapter 2 suggests that the rate of stimulant use disorder in people with psychosis is higher in the USA and Australia than in other developed countries. This is consistent with findings that stimulant dependence is more prevalent in

the general population in the USA and Australasia (Degenhardt et al., 2014). Together these findings suggest that the impacts of stimulant misuse on people with psychosis may be greater in Australia and the USA than in other comparable countries. These impacts are likely to be felt by the individuals, their families and the health system.

Second, *comorbid stimulant use disorders are more strongly associated with acute psychoses than with progression to schizophrenia.* People with comorbid stimulant use disorders were more likely than those without substance use disorders to have initial diagnoses of brief, atypical, drug induced and affective psychosis and they were less likely to remain in contact with specialist mental health services after their first psychosis admission. Of those who remained in contact with services over 2-5 years, people with ongoing stimulant use disorders had a 20% lower likelihood of making a transition to a diagnosis of schizophrenia, and more than double the chance that an initial schizophrenia diagnosis would be revised to other conditions when compared to people with no drug use disorders. By contrast, cannabis use disorders were associated with an increased risk of transition to a diagnosis of schizophrenia.

Three published studies have directly assessed whether people who abuse cannabis and stimulants differ in their risk of acute or persistent psychosis. The findings in this thesis are consistent with findings that in the general population, stimulant abuse is associated with a greater risk of precipitating drug induced psychosis than is cannabis abuse (Degenhardt et al., 2007d). They are also consistent with findings that people with stimulant-induced psychoses have lower rates of transition to schizophrenia than people with cannabis-induced psychoses (Niemi-Pynttari et al., 2013).

The results reported here are less consistent with a recent large study (Callaghan et al., 2012) which found that people admitted to Californian hospitals for methamphetamine abuse and dependence had the same risk of progression to schizophrenia as people with cannabis-related admissions. Both groups had a higher rate of progression to schizophrenia than people with cocaine-related admissions, other substance admissions or a matched control group of people hospitalised for appendicitis. The differences between these studies may reflect differences in the populations examined: the studies presented in this thesis, like the study of Niemi-Pynttari and colleagues (Niemi-Pynttari et al., 2013) examined the risk of progression to schizophrenia in people who have already had a first psychosis admission and hence were at a higher risk of progression to schizophrenia than people hospitalised for drug-related but non-psychotic conditions. It is

also possible that different personal and social factors (such as age, gender or disadvantage) influence whether individuals use methamphetamine rather than cocaine in California and New South Wales, and that these factors may be associated with different risks of developing schizophrenia.

Third, while stimulant use disorders were associated with a lower risk of transition to schizophrenia, *among people with schizophrenia, the continued use of stimulants was associated with very significant harms*. As has been summarised above, people with diagnoses of schizophrenia who had ongoing stimulant use disorders had the highest rates of mental health admission, general hospital admission, Emergency Department contact, self-harm, injury, homelessness, housing instability and social decline. Most of these harms occurred more often among people who also had cannabis disorders. However, people with stimulant use disorders alone had higher rates of general hospital admission, self-harm, injury, infectious disease diagnoses and homelessness than those with cannabis use disorders alone.

These impacts are consistent with evidence from experimental challenges that small amounts of stimulants can worsen acute psychotic symptoms in people with schizophrenia (Curran et al., 2004). These effects may become stronger with continued stimulant exposure due to a process of sensitisation (O'Daly et al., 2011; Wang et al., 2010; Peleg-Raibstein et al., 2009; Featherstone et al., 2007; Ujike and Sato, 2004; Curran et al., 2004; Ujike, 2002; Hermens et al., 2009). However a simple dopamine sensitisation model is inconsistent with the finding (Chapter 8) that ongoing stimulant use is associated with a reduced risk of transition to schizophrenia following an index psychosis admission. Also, the harms seen in people with schizophrenia and stimulant use disorders are broader than a worsening of positive psychotic symptoms. They include social harms and instability as well as harms associated with dependent or intravenous drug use such as increased rates of physical health admissions, infectious disease and cardiovascular disease. In this seriously affected subgroup of people with schizophrenia, it is likely that continued stimulant misuse interacts with many other factors such as continuing cannabis use, greater vulnerability to positive psychotic symptoms and vulnerability to other cognitive, affective or interpersonal dimensions of psychosis.

The studies in this thesis suggest that rates of stimulant use disorder in people with psychosis have not increased over time, and that stimulants are associated with reduced likelihood of transition to a diagnosis of schizophrenia. These findings contrast with

concerns expressed over the last decade by Australian clinicians that stimulant abuse has increased demand for acute mental health services (Australian Senate Select Committee on Mental Health, 2006). The very poor outcomes for people with schizophrenia who continue stimulant misuse are likely to have influenced this concern. Around 11% of all people with schizophrenia had ongoing stimulant use disorders, but of those with frequent hospital admissions, one-third had a stimulant use disorder. Nearly 60% of people with both schizophrenia and a stimulant use disorder were frequent users of inpatient mental health services. Clinician concerns about the impact of stimulants at a population level may therefore partly reflect a "clinician's illusion" (Cohen and Cohen, 1984). However, the very serious impacts on individuals with schizophrenia who continue stimulant use are certainly not illusory.

Fourth, *the associations and impacts of stimulant use disorders in people with psychosis are distinct from those of cannabis.* The very substantial overlap between cannabis and stimulant use disorders was one reason for using epidemiological approaches in this research. This overlap was present in all groups examined; the proportion of people with a stimulant use disorder who also had a cannabis use disorder was 73% in the Australian population (lifetime disorders), 56% in first admission psychosis, 58% in people with mixed psychotic disorders and 80% in people with a diagnosis of schizophrenia.

Despite these overlaps, there were consistent differences in the associations of stimulant use disorders and cannabis use disorders. In all groups, cannabis use disorders were most common in people in their late teens and early twenties and were strongly associated with male gender and rural location. By contrast, stimulant use disorders were more common in people aged 25 to 30 years, had a less unequal gender balance, and were associated with less disadvantaged location (in first admission psychosis) and urban location (no rural excess in the general population or first admission psychosis, urban excess in established psychosis). Cannabis use disorders were associated with younger age at first drug use, younger age at first psychosis admission, greater likelihood of remaining in contact with specialist mental health services and greater likelihood of transition to a diagnosis of schizophrenia. Stimulant use disorders were associated with older age at first drug use and first psychosis admission, diagnoses of brief and drug induced psychosis, less ongoing service contact and reduced likelihood of diagnostic transition to schizophrenia. These differences remained in multivariate analyses which controlled for age, sex, social disadvantage and other potential confounders.

In the general population and in people with first admission psychosis, people with both cannabis and stimulant use disorders showed patterns of associations and clinical impacts that were intermediate between those with cannabis or stimulant disorders alone. This suggests that these substances had diverse impacts and actions. Only in people with diagnoses of schizophrenia did the impacts of cannabis and stimulant use disorders appear additive: those with both diagnoses experienced greater harms than those with either diagnosis alone.

LIMITATIONS

Each chapter has included a section addressing limitations of the specific study which it presents. This section briefly discusses some additional limitations of individual studies, and brings together some limitations shared by several of the studies presented in this thesis.

Before discussing the implications of these findings, this section briefly addresses some of the limitations of the studies presented in this thesis. Each chapter has described its individual limitations, but there are number of shared limitations which affect several of these studies.

All studies presented here combined disorders of individual stimulant drug use (methamphetamine, amphetamine, ecstasy, cocaine) into a single “stimulant use disorder” category. The rationale for this has been described in Chapter 1. These drugs share some common mechanisms but also differ from each other in some important respects. Therefore the associations and impacts of stimulant use disorders are likely to involve a mix of shared and specific effects. Combining these drugs into a single category may help to highlight shared effects but obscure important differences between drugs which may be relevant to any association between stimulants and psychosis.

First, there may be differences in *who* uses which drugs: within the population studied there may be differences in age, gender or socio-cultural background between users of methamphetamine, ecstasy and cocaine. Second, there may be differences in *how* individual stimulant drugs are used. In Australia, amphetamine users report more frequent use than users of other stimulants: 24% of amphetamine users report using monthly or more frequently, compared with 15% of ecstasy users and 13% of cocaine users

(Australian Institute of Health and Welfare, 2011). Amphetamine is much more likely to be injected than cocaine: 25% of injecting drug users in NSW report that methamphetamine was the most frequent drug injected, compared to 1% for cocaine (Stafford and Burns, 2014). Third, there may be differences in the *mechanisms* by which stimulant drugs affect neurological function. Some of the mechanisms through which stimulants are hypothesised to contribute to psychosis, such as neurotoxity (Barr et al., 2006; Hanson et al., 2004) and dopaminergic sensitisation (Hermens et al., 2009; Curran et al., 2004), appear to be more marked for methamphetamine than for cocaine, perhaps due to methamphetamine's effects on intracellular dopamine function as well as intrasynaptic dopamine levels (Seger, 2010). Fourth, there may be differences in the *impacts and associations* of individual stimulant drugs within the population being studied. For example, Australian methamphetamine users report higher rates of self-reported mental health disorder (25%) and high or very high psychological distress (21%) when compared to users of ecstasy (mental disorder 16%, psychological distress 15%) or cocaine (mental disorder 17%, psychological distress 18%) (Australian Institute of Health and Welfare, 2011).

In summary, it follows that in combining different stimulant drugs into a single category, there is a risk of reducing sensitivity and producing Type II error when examining for associations and impacts. However, it is difficult to find a sample with sufficient diagnostic precision to examine individual drugs meaningfully as well as sufficient scale and power to examine associations and impacts while controlling for other confounders and cannabis use. As discussed in Chapter 1, the main reason for using a single stimulant disorder category has been that the data sources used in this research cannot reliably distinguish individual stimulant drug disorders.

The studies use data from a cross-sectional household survey and from longitudinal health databases. Observational epidemiology is a powerful tool for identifying disease risk factors and generating hypotheses, but it is less effective in testing causal hypotheses (McGrath, 2007; McGrath, 2008). The results of several studies are consistent with stimulants playing a causal role in precipitating or worsening some episodes of psychosis but they fall short of demonstrating a causal link. The studies have attempted to measure and control for relevant confounders but it is possible that other unmeasured factors may explain the associations reported.

Chapters 3 and 4 used data from a national household survey, the Australian National Survey of Mental Health and Wellbeing (NSMHWB). Household surveys are likely to underestimate the prevalence of illicit drug use (McKetin et al., 2005). They sample conventional households, and so they may not include groups with high rates of drug use such as people in transient or temporary accommodation or people who are homeless. They are unlikely to detect small geographical "hotspots" of drug use. They require people to disclose drug use to an interviewer not known to them, and so may be sensitive to the effects of stigma. These effects may differ for different subgroups and for different types of illicit drugs.

The NSMHWB was designed to study high prevalence mental health and substance use disorders (Slade et al., 2009). There is uncertainty in the survey's estimates of stimulant use disorder prevalence, especially when examining 12-month rates or subgroups by age or sex. The response rate for the 2007 survey was 60% (Slade et al., 2009) creating the potential for selection or sampling bias.

Because drug markets are illegal and unregulated, there is no simple and reliable measure of drug supply within a population. Three indirect measures of drug supply have typically been used: drug price (Cunningham et al., 2013a; Hyatt and Rhodes, 1995; Cook et al., 2002; Caulkins, 2007; Johnson and Golub, 2007), drug purity (Cunningham et al., 2009; Hyatt and Rhodes, 1995; Caulkins, 2007) and drug-related arrests or seizures (Cunningham and Liu, 2005; Rosenfeld and Decker, 1999) . Chapter 5 used data on police arrests for drug possession as an indirect measure of variations in drug availability in the community. Some have argued that arrest data of this type is not a valid measure of drug supply because changes in political focus or policing activity may also lead to an increase in arrests independent of changes in drug availability (Caulkins, 2007; Rosenfeld and Decker, 1999). However, there are also limitations to other potential indicators. In particular price data may be a less sensitive measure of availability, because in variations in supply drug suppliers will typically modify drug purity (e.g. "cutting" drugs with other substances) in order to maintain standardised sale amounts and prices (Caulkins, 2007). Drug purity data was not available for the current research. Rosenfeld (Rosenfeld and Decker, 1999) argued that, despite real limitations, police arrests data were a valid indicator of drug supply. The concurrent and construct validity of the measure has also been demonstrated in a series of studies examining the effectiveness of drug precursor controls in the USA, Canada and Mexico. Cunningham and colleagues have used arrests data from the US Drug Enforcement Agency's "System to Retrieve Information from Drug

Evidence" (STRIDE) and other state data systems (Cunningham and Liu, 2005; Cunningham et al., 2012; Cunningham et al., 2013b; Cunningham et al., 2013a) and found that precursor controls were followed by specific reductions in arrests. These were consistent with changes in other indicators including reductions in purity (Cunningham et al., 2013a; Cunningham et al., 2009) reductions in admissions for drug-related problems (Cunningham et al., 2010; Cunningham and Liu, 2008 ; Cunningham and Liu, 2003) and increases in drug price Cunningham, 2013 #2157}.

There are several other possible limitations of the use of arrest data. In NSW in the period studied there was a degree of public concern about amphetamine use, including concern that reductions in heroin availability in Australia in the early 2000s may have resulted in substitution of amphetamine use for heroin use (Snowball et al., 2008). Amphetamines were a focus of police activity during this period (NSW Police Force, 2007). Therefore it is possible that some of the increase in arrests during this period reflected an increase in police focus or activity as well as, and related to, an increase in amphetamine availability. A program of accelerated commissioning of mental health beds was undertaken in NSW from 2002-03, although this occurred in response to broader concerns about bed access and occupancy and was not linked to specific concerns about or resources for any individual drug[1] . However, chapter 5 did not examine for change in arrests or drug availability after a certain time point, as is typically done in studies examining the effectiveness of precursor controls. It examined quarterly fluctuations in arrests and hospital admissions, finding a significant correlation between these over a decade. The political or police focus on amphetamines is unlikely to have fluctuated on a quarterly basis over this extended period.

An additional limitation to consider regarding the use of arrests data in Chapter 5 is that police arrests and hospital admissions are not entirely independent, because some individuals may be present in both datasets. Some people arrested for substance-related offences will be found to have features of psychosis and be referred by police for hospital admission. This may be one factor explaining a relationship between arrests and hospital admissions. However this is unlikely to account for the findings of Chapter 5: it is likely that only a small minority of police arrests for possession would be found to be unwell in this

[1] *http://www.parliament.nsw.gov.au/prod/parlment/hansart.nsf/V3Key/LA20060907014*

way, and only a minority of NSW hospital admissions for psychosis occur on referral from Police (unpublished NSW Health data). In addition, NSW Police encountering a person who is so unwell as to require immediate referral to hospital would usually divert that person out of the criminal justice system using the provisions of the NSW Mental Health Act, and many such individuals would not be charged or appear in crime statistics.

A final limitation to consider regarding Chapter 5 is that it used an Ordinary Least Squares Regression approach to examine time-based data. This approach was used because the study examined quarterly fluctuations over an extended period rather than seeking to examine for a sustained change following a specific time-based event such as a change in regulations. This approach was undertaken after testing indicated that there was no systematic seasonal variation in the data being examined. However, the use of time-series approaches may have been more robust and should be considered in extending this study to examine more recent time period.

Chapters 5 to 9 used clinical data collected by New South Wales health services, including data from hospital admissions, community mental health service contacts and Emergency Department (ED) visits. Using routine health service data is one strategy for obtaining a large, representative population sample. Registers or datasets based on routine health service data may be particularly valuable for studying psychotic disorders, because people with these disorders have very high rates of service contact (Morgan and Jablensky, 2010; Byrne et al., 2005). However using these datasets involves a trade-off between statistical power and precision. There are at least four key areas of limitation that affect these data, namely, the accuracy of psychosis diagnoses, the accuracy of substance use diagnoses, the bluntness of available measures and the completeness of data gathered from “public” (state-operated) mental health services.

First, Chapters 5 to 9 used clinical diagnoses to define study inclusion, identify subgroups of psychosis, and examine diagnostic progression and change. These purposes all require reliable diagnostic data. An individual may have many diagnoses made by different clinicians at different times, without use of structured interviews or standardised diagnostic instruments. These diagnoses are accordingly less reliable than research diagnoses. To maximise diagnostic accuracy, most of the studies in this thesis have prioritised diagnostic data from inpatient settings. In New South Wales health services, inpatient diagnostic data is extracted and coded by professional medical records coders using all available information in the clinical record, and the rate of incomplete diagnosis is low when

compared to community mental health data. The studies have also used diagnostic algorithms which were tested against a reference dataset of people with psychosis who had been diagnosed using a research diagnostic interview: this testing process is described in Appendix A (Sara et al., 2014d). This testing found acceptable agreement between algorithm-based and research diagnoses.

Second, the studies in Chapters 5 to 9 used clinical diagnoses of substance use disorders as indirect measures of problem drug use. Substance comorbidities are often under-recorded in routine clinical practice because of lack of disclosure of substance use, lack of questioning about substance use or failure to record a substance diagnosis even when substance use is recognised by the clinician. Therefore diagnoses of substance use disorders are likely to be a specific but insensitive measure of problem substance use (Large et al., 2012). Compounding this problem, around 10% of people in the first admission psychosis and schizophrenia clinical samples had diagnoses of polydrug or unspecified substance disorder. It was not possible in these cases to identify the specific substances used. It is reassuring that the prevalence estimates for cannabis and stimulant use disorders in these studies were comparable with estimates from studies which had used clinical or research methods to identify substance use disorders. The use of diagnoses extracted by clinical coders may have reduced some of the under-enumeration of substance comorbidity. In addition, in the five years preceding these studies, New South Wales mental health services also maintained an active process of clinical benchmarking. This provided service managers with regular feedback on the quantity and quality of diagnostic data entered by their services, and aimed to encourage improved data collection.

Third, the use of routine data collections has also required the use of “blunt” and indirect measures. Direct measures of the severity of psychotic symptoms, level of function or degree of recovery were not available for this research. Substance use diagnoses have been used as measures of both initial (Chapter 6) and continuing drug use (Chapters 7, 8 and 9); these do not measure the duration or severity of substance use disorders. Hospital readmission was used to measure relapse following a first psychosis episode (Chapter 7), and hospital readmission, service contacts and changes in address were used as measures of clinical and social outcomes in people with schizophrenia (Chapter 9). Hospital readmission is a widely used indicator of relapse in psychosis (Gleeson et al., 2010), however lack of readmission does not equate with symptomatic or functional

recovery, and many significant relapses in persons with psychoses may be managed without hospital readmission.

Fourth, these studies only included people with psychosis who had contact with NSW state-operated ("public") mental health services. People with psychosis who were only in contact with "private" health services (primary care, specialist outpatient psychiatry, private hospitals) or who were not in contact with any health service were not included. However, in the Australian health system, the care of people with psychoses is primarily the responsibility of state-operated mental health services. In New South Wales, private hospitals do not provide involuntary psychiatric care, and less than 5% of admissions of young people with psychosis occur in private hospitals (see Chapter 6). Most Australians with schizophrenia and other enduring psychoses have contact with public specialist mental health services (Morgan et al., 2011). People with psychosis who only had contact with community services and no hospital admissions over the periods studied (varying from 5 to 11 years) would not have been included in the studies in Chapters 6 through 9. Their diagnoses, substance comorbidities and outcomes are likely to have differed systematically from people who had at least one admission in the period. They are likely to have had less severe psychotic disorders and a lower rate of comorbid drug use disorders.

In examining diagnostic change or the course of illness over time (Chapters 7, 8 and 9), information was only available on people who had continued contact with specialist mental health services. Following a first psychosis admission, 31% of people had no further contact with New South Wales inpatient or community mental health services during the follow-up period (Chapter 7). In people with persisting psychosis 40% had service contact for less than two years after an index admission, and so were excluded from analysis of diagnostic stability and outcomes (Chapter 8). Having brief contact with services was associated with being younger and having diagnoses of brief, atypical or drug-induced psychosis. It was not consistently associated with substance comorbidity. For some people, loss of contact with specialised services may be a sign of symptom resolution and recovery (Warner, 2009; Emsley et al., 2011). By focusing on people remaining in contact with services, the results of these studies may therefore be biased towards people with more severe illnesses and more negative outcomes. However, some people losing contact with specialised services have equivalent rates of positive symptoms and substance use to those remaining in care (Stowkowy et al., 2012). The focus of the current research has been on people accessing public mental health services. The findings of these studies

may therefore not generalise to the smaller group of people with psychoses who are in contact only with private services or who have no service contact.

STRENGTHS

These limitations are partly balanced by some strengths of the current research. Evidence about the impacts of stimulants on psychotic disorders has been limited because of the methodological challenge of separating stimulants from other confounders, and particularly from cannabis disorders. The use of an epidemiological approach has allowed the development of large, representative, multi-diagnostic datasets which have had the statistical power to separate any effects of stimulant and cannabis abuse. These studies showed that stimulant and cannabis abuse appeared to have distinct and at times opposing effects on the course and outcome of psychosis. They join only a handful of other studies that have examined this question (Degenhardt et al., 2007d; Callaghan et al., 2012; Niemi-Pynttari et al., 2013). All of these studies have used epidemiological approaches, demonstrating the potential for such approaches to complement clinical studies. Indeed, they may be one of the few ways of untangling a highly confounded issue such as stimulant comorbidity.

A second strength was that the current research combined data from a national household survey of the Australian population with data collected over a comparable period in a large state health system serving around one third of the Australian population. Together these datasets allow comparison of the rate and correlates of stimulant use disorders on a spectrum from the general population, through early psychosis, to established psychoses such as schizophrenia. Few studies of psychosis have taken such an approach. This approach has shown that many of the correlates of stimulant use disorders in people with psychosis are shared by people with stimulant use disorders in the broader population. The consistency of associations within these different data sources allows greater confidence in the reliability of these findings. New South Wales has similar population characteristics, patterns of drug use and health system organisation to other Australian states and territories, meaning that findings from this research can be generalised within Australia. This strength is of course also a limitation, in that some findings from this research may not apply to other countries if their population characteristics, patterns of drug use, health systems or pathways to care differ substantially from those in Australia.

The component studies have individual strengths, and contribute to the limited evidence base on this issue in several additional ways. Chapter 2 provides the first meta-analysis of the rates of stimulant use disorder in people with psychosis. Chapter 3 provides the first study since the Epidemiological Catchment Area (ECA) Survey (Regier et al., 1990) to report rates of stimulant abuse or dependence diagnosed according to standardised criteria in a representative population sample. In Chapters 6 and 7, data are presented on 9,919 people with a first admission for psychosis: this one of the largest cohorts of first episode psychosis described and one of the few to specifically examine stimulant use disorders. Chapters 8 and 9 examine diagnostic stability, course and outcome in established psychosis. They add to the few studies of this issue by examining a broad, multi-diagnostic clinical sample of the type usually encountered in “real world” mental health service delivery.

IMPLICATIONS

The final section of this discussion first considers the implications of these findings in the context of current models of psychotic disorder and current views of substance comorbidity in psychosis. It then considers possible implications of these studies for prevention, for health service planning and for individual clinical care.

Models of psychosis

Chapter 1 briefly summarised evidence that psychotic disorders are heterogeneous conditions which involve a broad spectrum of vulnerability within the population. For a minority of vulnerable individuals, genetic, developmental, personal and environmental factors may interact in complex ways to cause progression from psychotic symptoms to enduring psychotic syndromes such as schizophrenia. Dimensional and developmental models of psychosis provide the theoretical background to this thesis, and offer a way of interpreting the findings of the studies presented here.

Dopamine abnormalities have been seen as central to the pathophysiology of schizophrenia (Laruelle and Abi-Dargham, 1999; Keshavan et al., 2011; Seeman, 2011). Because stimulants are potent dopamine agonists whose effects increase with repeated use through a process of sensitisation, stimulant-induced psychoses have often been used as model psychoses in studying schizophrenia (Hermens et al., 2009; Machiyama, 1992; Sato et al., 1992; Snyder, 1973). A dopamine sensitisation model of stimulant psychosis would predict that repeated stimulant use should increase the risk of developing

schizophrenia. Instead, the studies in this thesis have found that while stimulant use was associated with acute psychosis, ongoing stimulant use was associated with a *reduced* risk of receiving a later diagnosis of schizophrenia, when compared to people with no continuing drug use or with cannabis use disorders.

There are a number of possible explanations for these findings. They may reflect limits in our diagnostic measures for substance use or psychosis, therefore reflecting the "noise" of substance-related diagnostic uncertainty rather than the "signal" of true reduction in risk. However, the findings are consistent with other research (Niemi-Pynttari et al., 2013) which has found that stimulant-induced psychoses are associated with a lower risk of progression to schizophrenia than cannabis-induced psychoses. Alternatively, the findings may be due to confounding, since stimulant use disorders were associated with other positive prognostic factors, including older age at first psychosis admission, more acute onset of psychosis and a lesser gender imbalance. In first admission psychosis, stimulant disorders were associated with higher socio-economic status and urban location, which may predict better access to services and supports. However differences between cannabis and stimulants remained after controlling for these confounding factors in multivariate analyses.

Dimensional models of psychosis offer another explanation for these findings. These models emphasise that positive psychotic symptoms such as hallucinations and delusions are only one dimension of psychosis, and that the full syndrome of schizophrenia typically involves abnormal function in other dimensions such as cognition, affect or interpersonal function (van Os and Kapur, 2009; Heckers et al., 2013; Barch et al., 2013). Abnormalities in dopamine function appear to be particularly associated with positive psychotic symptoms (Insel, 2010; Paparelli et al., 2011). Other dimensions of psychosis may instead be associated with abnormalities in other neurotransmitter systems and pathways; for example glutamate abnormalities have been implicated in negative symptoms (Paparelli et al., 2011) and GABA abnormalities may play a role in motivational and affective processes (D'Souza et al., 2009; Thoma and Daum, 2013; Wong, 2013). Therefore stimulants may act on dopamine pathways to precipitate acute psychotic symptoms, but their effects may be insufficient to produce a syndrome of schizophrenia unless they occur in people with broader vulnerabilities and/or other stressors (such as continued cannabis use) which also act on cognition, motivation or other clinical dimensions. Consistent with this, a recent study found that people with acute amphetamine-related psychoses had the

same levels of hallucinations and delusions as people with schizophrenia, but much lower levels of negative, cognitive and affective symptoms (Panenka et al., 2013).

Dimensional and staged models of psychosis may also explain why cannabis is associated with a greater risk of developing schizophrenia when it is less directly associated with increased positive psychotic symptoms. Amphetamines and cocaine are more potent dopamine agonists than cannabis (Paparelli et al., 2011; McKetin et al., 2013), and therefore it is possible that stimulants precipitate positive psychotic symptoms in people with lower personal vulnerability to psychosis. There is growing evidence that people with substance-related psychosis who cease substance use may have better outcomes than people with psychosis who have never used substances (Mullin et al., 2012; Lambert et al., 2005). These “former substance users” have fewer neurological soft signs and fewer negative symptoms than those without substance abuse (Yucel et al., 2012; Loberg and Hugdahl, 2009), probably reflecting lower developmental vulnerability to psychosis. However these studies have not examined whether former cannabis users and former stimulant users differ systematically in other ways that may affect vulnerability to psychoses.

A further explanatory factor may be that people use cannabis at a younger age than they use stimulants. This means that people are exposed to cannabis at a time of greater developmental vulnerability. In addition, most people with stimulant disorders have had prior cannabis use or disorder. Therefore, most people with a first episode stimulant-induced psychosis have already cleared a lower “first hurdle” of cannabis exposure without having had a psychotic episode. Therefore people with a first episode of stimulant-induced psychosis are most probably drawn from a *lower* risk sub-population from which individuals with the greatest vulnerability to schizophrenia have been selected out at an earlier age due to cannabis exposure.

There are several ways in which these hypotheses could be tested in future research. To assess whether stimulants are more “psychotogenic” than cannabis, it would be possible to compare the nature and severity of transient psychotic symptoms in recreational users of cannabis, stimulants or other drugs. One recent study has found that the odds of psychotic symptoms were increased more than ten-fold during periods of regular amphetamine use, compared to a doubling of psychotic symptoms during periods of cannabis use (McKetin et al., 2013). To assess whether different drugs precipitate psychosis in people with different levels of vulnerability it would be possible to compare

people with cannabis or stimulant related psychoses for differences in neurological soft signs, neurocognitive function, prior academic achievement or family history of psychosis. Population-level case registers could be used to examine outcomes for the small group of people with psychoses precipitated by hallucinogens such as LSD, by assessing whether they also have positive outcomes and a lower rate of transition to schizophrenia than persons with cannabis use disorders.

Substance comorbidity in psychosis

Debate continues about the nature of the relationship between substance use and psychosis. Does the association reflect causation (drugs causing psychosis), self-medication (psychosis leading to drug use) or confounding (shared vulnerabilities underlying both drug use and psychosis)? All three factors are likely to contribute, however there is growing consensus that causal explanations account for at least part of the relationship.

There are several strands of evidence that substance misuse plays a causal role in psychosis. Cannabis, stimulants and other drugs have been shown to produce psychotic symptoms in experimental challenges in healthy volunteers and people with psychoses (Murray et al., 2012; D'Souza et al., 2004; Angrist et al., 1974), and psychosis-like behaviours in animal models (Gururajan et al., 2012). Meta-analytic evidence suggests that drug use is associated with earlier onset of psychosis (Large et al., 2011). Observational studies find a dose-relationship between greater drug use and more severe psychotic symptoms (McKetin et al., 2006b; Wade et al., 2007; Foti et al., 2010; McKetin et al., 2013). Longitudinal studies show that drug use typically precedes psychosis (Hall and Degenhardt, 2000; van Dijk et al., 2012) and that continued drug use affects course and outcome (Wade et al., 2007).

There are also plausible theoretical mechanisms linking drug use and psychotic symptoms. Cannabis, stimulants and other substances are likely to contribute to the development of psychosis through complex and interacting neurochemical, genetic, epigenetic and structural mechanisms (Remington et al., 2014; Wobrock et al., 2013; Thoma and Daum, 2013; Maziade and Paccalet, 2013; Di Forti et al., 2013; Yucel et al., 2012; Palaniyappan et al., 2012; Murray et al., 2012).

The research in this thesis has not aimed to explore or test these mechanisms. However the findings of this research highlight ways in which social and environmental factors may

contribute to the relationship between substance use and psychosis. While people with psychosis misused stimulants at a higher rate than the general population, the rate and type of stimulant drug misused in people with psychosis mirrored regional variations in the broader population. Stimulant use disorders in Australia were associated with age, gender, rural location, migrant status and disadvantage in a way that was broadly consistent in the general population, in early psychosis and in established psychosis. Factors such as the type and quantity of drugs available, social attitudes to drug use, exposure to drug use in peers, mental health literacy, social and educational opportunities, stressors, support and resilience are all likely to influence whether a young person initiates or continues to use stimulants or other substances. The shared associations of stimulant use disorders in people with psychosis and the broader population suggest that young people with psychosis who misuse stimulants may do so for the same reasons as other young people. The much higher rate of stimulant use disorders in young people with psychosis may suggest that they are more sensitive to these social and environmental factors.

One implication of these findings for future research is that studies comparing stimulants and other substances in psychosis should, where possible, measure and control for potential social confounders such as age, rural/urban location, migration status and social disadvantage. It may be possible to test whether people with a vulnerability to psychosis are more sensitive to social and environmental pressures towards drug use. Two interesting research strategies for studying cannabis comorbidity have been the use of structural equation modelling in longitudinal clinical data (Foti et al., 2010) and asking young people with psychosis about their reasons for drug use (Kolliakou et al., 2013; Kolliakou et al., 2011; Henquet et al., 2010). Both strategies could be applied specifically to examine the subjective experience and time-course of stimulant use in young people who are at risk of psychosis, such as people accessing primary care youth services.

Prevention

Effective prevention strategies for psychosis could have significant impacts on suffering, disability and cost (World Health Organisation, 2004). It may be feasible to reduce the incidence of psychosis by targeting well understood and potentially preventable risk factors. Substance abuse is prominent amongst these, along with factors such as perinatal complications, head injury and trauma.

Like many other countries, Australia has used criminal sanctions and seizures to limit drug supply and prevent drug-related harms. There is currently robust debate about the

effectiveness of this strategy (Magura and Magura, 2007; Hall and Lynskey, 2009; Roehr, 2011; Strang et al., 2012). Two findings of the current research are relevant to this issue. First, stimulant disorders were common in people with psychosis and had a significant impact on the overall burden of psychosis in the population through their association with acute psychosis and their impact in people with chronic psychosis. Second, during periods of increased availability of stimulants in the community, there were increases in admissions for stimulant-related psychoses. These findings suggest that strategies which reduced stimulant availability could reduce the prevalence of stimulant-related psychoses and the impact on individuals and health services. Conversely, strategies which increased stimulant availability would be likely to increase the prevalence of stimulant-related psychoses.

However, these findings do not provide a sufficient argument against decriminalisation of amphetamine or other substances. They do not demonstrate that criminal sanctions reduce drug availability, or that decriminalisation would lead to increased availability. One argument against current legal approaches is that they have failed to reduce drug supply: cannabis, stimulants and other substances are widely available despite their illegal status. Stimulant supply may be targeted by border controls, seizures and control of precursor chemicals required for domestically manufactured drugs such as methamphetamines. Evidence regarding the effectiveness of these strategies is mixed: some studies have shown that amphetamine precursor controls lead to a reduction in measures of amphetamine supply or use, however this may be offset by importation or the use of alternative manufacturing methods which may limit the effectiveness of these strategies in preventing drug-related harms (Callaghan et al., 2009; Nonnemaker et al., 2011; McKetin et al., 2011; Colfax et al., 2010). Measures restricting access to over the counter compound preparations may have a paradoxical effect of increasing amphetamine purity, because they target precursors used by smaller scale and lower quality producers (Colfax et al., 2010; Cunningham et al., 2009). A recent analysis of Australian national crime and health service data found that even large drug seizures had no measurable effect on stimulant or other drug-related presentations in Australia (Wan et al., 2014).

The types of prevention strategies used for other chronic health conditions provide an alternative to legal approaches. Dimensional and clinical staging models of psychosis are particularly compatible with broader mental health prevention frameworks (Mrazek and Hagerty, 1994). Universal mental health prevention measures may focus on many issues including mental health literacy and “first aid”, stigma, resilience, health behaviours such

as substance use and the treatment of common mental symptoms. All may be relevant in preventing substance-related psychoses.

The research in this thesis suggests several groups in the Australian population who may benefit from targeted prevention activities. First, rural youth, who have very high rates of cannabis use and dependence and in whom stimulant use may therefore be a significant additive risk factor for psychoses. Second, older, urban and less socially disadvantaged stimulant users, such as those accessing stimulants through music festivals and social events. This group may benefit from more specific messages about the risks of psychosis with stimulant use, the possible prognostic significance of brief and transient psychotic symptoms and the potential for stimulant-related harms to sensitise and increase with repeated use. Third, people with a history of psychosis or other serious mental health problem in a close relative such as a parent, grandparent or sibling. The evidence for genetic vulnerability in psychosis is very clear, and family history is one of the strongest predictors of individual risk (Tsuang et al., 2010). However, mental health prevention strategies rarely include messages about family history and the way in which this may interact with environmental stressors such as drugs. The inclusion of family history in preventative health messages has become more frequent in some areas of physical health, such as prevention strategies aimed at breast cancer or melanoma. However, there are also clear reasons for caution. A family history of mental illness substantially increases the relative risk of psychosis, but psychoses are still uncommon disorders and the absolute risk of developing psychosis remains low even in people with an affected first-degree relative. We need to avoid creating unnecessary anxiety or avoidance of help-seeking in either the person targeted or their affected relatives. However once a person has presented for the first time with a psychotic disorder, it should be a high priority to ensure that they understand their own genetic and developmental risk factors for recurrence or progression to a more severe disorder.

Further research is needed to develop, implement and evaluate targeted prevention strategies for cannabis and stimulant-related psychoses. Such research could include the development and assessment of strategies specifically targeting rural youth. It could also include further research on community knowledge about the importance of family risk factors in developing mental health conditions, and the effectiveness and acceptability of prevention messages which target this issue.

Health services planning

The findings from the current research have implications for health service planning in New South Wales and other Australian states and territories. They underline the importance of broadly focused and accessible mental health services for young people and adults, including those with stimulant-associated psychoses. This research found that many people with stimulant use disorders in the broader population had brief and transient psychotic symptoms, and often also had mood and anxiety disorders. At first contact with mental health services many had diagnoses of brief, atypical and drug-induced psychosis. These initial diagnoses were poor predictors of final diagnosis, and more than half went on to have a diagnosis of schizophrenia. Many had positive outcomes, but a subgroup experienced very significant problems, including physical health problems and social dislocation.

A service system responsive to these needs should have several attributes. It would have low barriers to entry, assessing people as early as possible. It would be multi-diagnostic, accepting people with a spectrum of symptoms, as well as established psychotic disorders. It would see the diagnosis and treatment of comorbid substance use disorders as part of its core business, and not a reason to exclude people from care. It would also be able to offer continuity of care as people's needs, clinical situation or living conditions change. These are not novel messages in Australian healthcare: many state and territory specialist mental health services have implemented reforms of this type (New South Wales Health Department, 2001; Petrakis et al., 2012; Preston et al., 2003), and model youth and early intervention services developed in the state of Victoria, Australia, have played an important leadership role (McGorry et al., 2009; McGorry et al., 2008; Yung and McGorry, 2007; Alvarez-Jimenez et al., 2011; Henry et al., 2010). More recently Australia has made a significant national investment in a youth-focused mental health service model ('headspace') providing easier entry to primary care mental health services (McGorry et al., 2007; Rickwood et al., 2014) . Debate continues about the cost-effectiveness of these service models and the opportunity costs of these investments (Nielssen et al., 2012; McGorry, 2012; Yung, 2012; Castle, 2012). The studies in this thesis do not address whether one service model is more effective than another, but underline some of the properties that any effective service model should have.

Services can only be effective if they deliver effective interventions. However, there is limited evidence for effective interventions in stimulant use disorders. A systematic review of psychosocial interventions in stimulant dependence (Knapp et al., 2007) found that overall response to treatment was modest and that no single psychosocial treatment was

more effective than any other. CBT, relapse prevention approaches and contingency management have all been found to have some effectiveness, especially when delivered more intensively (Colfax et al., 2010). The Methamphetamine Treatment Project (MTP) tested an integrated "Matrix model" of treatment, which combined CBT with 12-step program approaches, family therapy and psychoeducation in an intensive program requiring between 1 and 13 hours per week of attendance (Rawson et al., 2004): the program reported modest positive outcomes, with better retention in care and fewer positive urine drug screens in the active treatment group. A recent review suggests that contingency management may be more effective than CBT in cocaine dependence (Farronato et al., 2013).

Medication strategies have been described as a "frustrating therapeutic landscape" (Panenka et al., 2013) (p174). It has been proposed that prescribed stimulants, including dexamphetamine, methylphenidate or modafanil, could be used as a replacement treatment in amphetamine or cocaine dependence (Elkashef et al., 2008; Castells et al., 2010; Mariani and Levin, 2012). However a recent Cochrane review of 11 trials found no benefit of stimulant replacement therapy in amphetamine dependence (PerezMana et al., 2012). In addition, prescribed stimulants are typically contraindicated in people with psychosis due to the risk that they may worsen psychotic symptoms. Many other medications have also been trialled, including naltrexone, buproprion, antipsychotics and antidepressants. Some evidence supports the use of mirtazapine (an antidepressant which blocks both serotonin and noradrenaline reuptake) (Panenka et al., 2013), however most reviewers have concluded that "clinical trials have yielded no broadly effective pharmacotherapy" (Brensilver et al., 2013)(p.449).

For people who have stimulant use disorders and psychosis, intervention is even more complex and the evidence even more limited. A recent Cochrane review (Hunt et al., 2013) of psychosocial treatments in people with a dual diagnosis of psychosis and substance use disorder examined broad outcomes including retention in care and reductions in substance use. The interventions studied included long term integrated care, contingency management, motivational interviewing, cognitive behavioural therapy and skills training. The review found few differences between any specific intervention and treatment as usual, and no evidence favouring any one intervention over others.

A recent review of medication strategies for people with dual diagnoses (Murthy and Chand, 2012) focused on antipsychotic choice, arguing that more sedating antipsychotics

such as clozapine or quetiapine may offer some advantages. However, the clinical challenge for young people with psychosis and stimulant use is rarely one of medication choice: the greater challenges involve engagement, motivation, supporting changes in substance use and encouraging adherence to any form of psychosocial or medical treatment.

The research findings outlined in this thesis underline the scale of stimulant comorbidity and its potential impact in people with psychosis. The lack of specific and effective interventions for this problem has several implications for health service research and planning. First, services should prioritise clinical research to develop and test interventions for this group. Because evidence is so limited, there is an important role for clinical innovation and properly conducted pilot studies. Second, the mental health workforce needs support in delivering "treatment as usual" as effectively as possible. Rather than focusing on highly specialised interventions, mental health staff need a broad base of skills in engagement, education, and motivational interventions. The studies in this thesis found that people with early psychoses and stimulant use disorder had lower rates of progression to schizophrenia, but that once people had an established diagnosis of schizophrenia they had worse outcomes and much greater service use. This suggests that services have a window of opportunity in which to act assertively to prevent poor long term outcomes. This requires clinicians to see comorbid psychosis and stimulant use disorder as a marker of both high risk and high opportunity, and not as a reason for therapeutic pessimism. It also requires service structures and resources which support clinicians in responding assertively.

Care for the individual

This thesis began by describing "Tim", a young man who had presented to hospital with an acute psychosis in the context of stimulant abuse. This discussion concludes by considering implications for an individual such as Tim. Considering the evidence regarding stimulant use disorders and psychosis, including the findings of the current research, what might good care look like for Tim and his family?

Ideally, Tim and his family would have been exposed to a range of prevention messages long before he first used any substances. School-based programs might have detected and responded to his shyness and social anxiety, perhaps equipping him with strategies for managing stress and anxiety, and building his resilience. They would have provided him with age-appropriate information about the potential health and mental health risks of

drug use, including the risks of psychosis. This should have included broad information about detecting and responding to common mental health symptoms and ways of accessing advice and health care. It might also have included messages about the importance of family history and genetic vulnerability as risk factors.

During Tim's education at technical college, there would have been opportunity for some of these messages to be reinforced more strongly. In his attendance at live music events, he might have been exposed to targeted campaigns about the importance of seeking help for transient psychotic symptoms and the risks of developing enduring psychoses. These messages could again emphasise the importance for Tim of understanding his own family history and other risk factors. Ideally, Tim and his family would have had awareness of and access to a range of health or counselling services.

At the time of Tim's first presentation with psychosis, services would have responded assertively. They would have conducted a detailed assessment that included urine drug screening to ensure accurate identification of any substances he was using, as well as a detailed developmental, family and drug-use history. While managing Tim's acute psychosis according to current treatment guidelines, they would also have ensured that Tim's substance use was a specific target of treatment. Clinical staff would have had a range of assessment and basic treatment skills that allowed them to focus on these conditions without requiring referral to an external service, and to be supported by appropriate supervision, consultation and professional development.

Tim and his family would have received good education and information, including information about drug and alcohol treatment and support services. Critically, clinicians would ensure that Tim and his family were aware that his choices about whether he continued substance use would have a major impact on his outcome, and that people who cease substance use after a first episode of psychosis have good outcomes, low rates of readmission and low rates of progression to schizophrenia. Mental health services would ensure that Tim was offered assertive follow-up and support even if his symptoms resolved quickly, and these efforts would include helping him to return to his studies.

If Tim did continue to use stimulants and other substances, or have ongoing psychotic symptoms, services would continue to work assertively with him, aiming to minimise any harms, ensuring that he had relevant information about safe drug use (such as injecting if he was using drugs intravenously) or safe sex. They would ensure detailed cognitive assessment, and tailor their messages and care to Tim's particular strengths and needs.

They would ensure ongoing support and education for Tim's family. If Tim did change address, they would work assertively to encourage him to remain in contact with services, continuing to see him or ensuring good communication and handover to a new treatment service.

The paragraphs above describe how an ideal health care system might respond to a person with a stimulant-related psychosis. A strong clinical and economic case has been made for the importance of early intervention in people with risk factors for psychosis (Fusar-Poli et al., 2013). For a young person like Tim, an episode of psychosis may have many possible trajectories and may end in positive outcomes. Good clinical care has the potential to influence Tim's trajectory, however even with ideal care Tim may develop an enduring psychosis. Once a person has developed an enduring psychosis such as schizophrenia, the personal and social costs are substantial: current treatments, even optimally delivered, can avert less than one quarter of the burden of schizophrenia (Andrews et al., 2004). The studies reported in this thesis suggest that addressing stimulant use should be one component of good care. Some strategies for providing this care would require service changes or investments, but many could be delivered by current services within existing resources. Further research is needed to identify the most effective and efficient interventions for stimulant use in psychosis.

Conclusion

Epidemiological approaches can help to distinguish the effects of stimulants from those of cannabis. The studies in this thesis have shown that stimulants make a significant contribution to the burden of psychosis in Australia. Stimulant use disorders are also most common in people with other vulnerabilities to psychosis. It follows that strategies aimed at preventing stimulant use or responding to the earliest symptoms of psychosis are essential. Once a psychotic episode has been precipitated, there is an important opportunity for effective intervention, because stimulant disorders are associated with brief psychoses and with a lower risk of transition to schizophrenia. Comorbid stimulant use is a positive prognostic sign in early psychosis, but only if stimulant use stops. People with schizophrenia who continue to use stimulants have very poor outcomes.

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APPENDICES

Appendix A: Testing of diagnostic algorithms

This appendix describes the development and testing of the method used for extraction of psychosis diagnoses from NSW Health datasets (method used in Chapters 5,6,7,8 & 9).

This chapter is based on the publication: **Sara, G., L. M. Luo, V. J. Carr, A. Raudino, M. J. Green, K. R. Laurens, K. Dean, M. Cohen, P. Burgess and V. Morgan (2014). Comparing algorithms for deriving psychosis diagnoses from longitudinal administrative clinical records. Social Psychiatry and Psychiatric Epidemiology. 49: 1729-1737.**

ABSTRACT

Purpose

Registers derived from administrative datasets are valuable tools in psychosis research, but diagnostic accuracy can be problematic. We sought to compare the relative performance of four methods for assigning a single diagnosis from longitudinal administrative clinical records when compared to reference diagnoses.

Methods

Diagnoses recorded in inpatient and community mental health records were compared to research diagnoses of psychotic disorders obtained from semi-structured clinical interviews for 289 persons. Diagnoses were derived from administrative datasets using four algorithms; ‘At least one’ diagnosis, ‘Last’ or most recent diagnosis, ‘Modal’ or most frequently occurring diagnosis, and ‘Hierarchy’ in which a diagnostic hierarchy was applied. Agreements between algorithm-based and reference diagnoses for overall presence/absence of psychosis and for specific diagnoses of schizophrenia, schizoaffective disorder, and affective psychosis were examined using estimated prevalence rates, overall agreement, ROC analysis and kappa statistics.

Results

For the presence/absence of psychosis, the most sensitive and least specific algorithm (‘At least one’ diagnosis) performed best. For schizophrenia, ‘Modal’ and ‘Last’ diagnoses had

greatest agreement with reference diagnosis. For affective psychosis, ‘Hierarchy’ diagnosis performed best. Agreement between clinical and reference diagnoses was no better than chance for diagnoses of schizoaffective disorder. Overall agreement between administrative and reference diagnoses was modest, but may have been limited by the use of participants who had been screened for likely psychosis prior to assessment.

Conclusions

The choice of algorithm for extracting a psychosis diagnosis from administrative datasets may have a substantial impact on the accuracy of the diagnoses derived. An ‘Any diagnosis’ algorithm provides a sensitive measure for the presence of any psychosis, while ‘Last diagnosis’ is more accurate for specific diagnosis of schizophrenia and a hierarchical diagnosis is more accurate for affective psychosis.

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INTRODUCTION

There is increasing scope to derive case register information from electronic health records and administrative databases (Perera et al., 2009). As most people living with psychotic illnesses have contact with health services (Jablensky et al., 2000; Morgan et al., 2011) such registers may be particularly helpful for research into psychotic disorders (Morgan and Jablensky, 2010; Byrne et al., 2005).

Diagnostic accuracy is essential for an effective case register. It forms the first of four dimensions proposed by Mortensen (Mortensen, 1995), who argued that an effective case register should (i) maximise the precision of the disease estimate, (ii) minimise selection bias, (iii) minimise information bias, and (iv) allow for control of relevant confounders. Byrne and colleagues (Byrne et al., 2005) reviewed studies of diagnostic accuracy in case registers, finding that there was no 'gold standard' on this issue. Morgan and Jablensky (Morgan and Jablensky, 2010) have recently called for further studies examining and benchmarking the quality of register data.

Diagnostic accuracy may be considered both cross-sectionally and longitudinally. Cross-sectional studies validate register diagnoses against research or clinical diagnoses for a single episode of illness, such as an individual hospital admission, or over a limited follow-up period (Crabbe et al., 1999; Fennig et al., 1994; Goodman et al., 1984; Kristjansson et al., 1987; Löffler et al., 1994; Øiesvold et al., 2012; Sytema et al., 1989; Taiminen et al., 2001; Keskimani, 1991; Robinson and Tataryn, 1997; Kessing, 1998). However, a longitudinal perspective is also important for enduring or recurring conditions such as schizophrenia and other psychotic disorders. An individual may have contact with services over many years, and their records may include several diagnoses made by different clinicians at different stages of care. For most research purposes it is necessary to allocate a single diagnosis for an individual. Therefore, an algorithm is required to derive a single diagnosis for an individual from diagnoses made during multiple episodes of care.

Four main methods have been used, each with possible advantages and disadvantages. First, the occurrence of at least one diagnosis of psychosis in a person's record may be seen as sufficient for defining the condition of interest (Jin et al., 2004; Kirkby et al., 1998; West et al., 2000). This approach ('At least one' psychosis diagnosis) is likely to be sensitive, but risks a high false positive rate. Second, diagnoses may be weighted by frequency of occurrence, focusing on the modal ('dominant') diagnosis for an individual (Kirkby et al., 1998; McConville and Walker, 2000), or defining a threshold such as two or

more occurrences of a diagnosis (Lichtenstein et al., 2006). This approach may be more specific, but its results may vary depending on the level of detail at which diagnoses are grouped, or the frequency threshold set. Third, the timing of diagnosis may be considered, using the first ('incident') diagnosis for an individual (Jin et al., 2004; McConville and Walker, 2000; Sigurdsson et al., 1999) or the most recent diagnosis (Valuri et al., 2001). Psychosis diagnoses can change over time, and may vary more for some subtypes of psychosis, so timing-based approaches may produce different results for different conditions. Finally, a diagnostic hierarchy may be applied so that when multiple diagnoses are present, one is seen as representing a 'higher order' diagnostic concept which can account for the others (McConville and Walker, 2000; Isohanni et al., 1997; Makikyro et al., 1998; Ruschena et al., 1998; Wallace et al., 1998). This approach is familiar to clinicians, however currently proposed hierarchies have a limited evidence base, and different diagnostic systems may apply different hierarchies.

To our knowledge, no study has compared the relative performance of these methods in a single clinical sample. These methods may produce estimates of psychosis prevalence that differ in sensitivity, specificity and accuracy. Understanding the properties of these methods may assist in method selection when designing studies using linked register data.

The aim of this study is to compare the relative performance of four different algorithms (at least one diagnosis, last diagnosis, modal diagnosis, and hierarchical diagnosis) for deriving a single person diagnosis from a large longitudinal administrative database. Diagnoses were extracted from hospital admissions and community mental health contacts over a ten-year period in the state of New South Wales (NSW), Australia. These were compared with a reference diagnosis obtained from a semi-structured clinical interview. Agreement between administrative and reference diagnoses was examined for broad categorisation (psychosis/no psychosis) and for individual psychosis diagnoses of schizophrenia, schizoaffective disorder and affective psychosis.

METHODS

Participants

Participants were drawn from the second Australian national survey of psychosis (Morgan et al., 2011), which sampled people aged 18 – 64 with severe mental disorders who were in contact with public specialised mental health services or non-government organisations from April 2009 to March 2010.

Participants in the national survey were recruited from seven regions, covering approximately 10% of the age-matched Australian population (Morgan et al., 2012) and were identified by a two phase screening process. First a psychosis screener (Jablensky et al., 2000) assessed for a lifetime history of hallucinations, delusions, antipsychotic medication or receiving a diagnosis of psychotic disorder from a doctor. The screener was designed to favour sensitivity, and testing showed acceptable screening properties: sensitivity 0.98 (95% CI 0.97−0.98), specificity 0.41 (95% CI 0.35−0.46), positive predictive value 0.90 (95% CI 0.89−0.91) and negative predictive value 0.76 (95% CI 0.69−0.83) (Morgan et al., 2012) . Second, a random sample (stratified by catchment site and age) of those who screened positive underwent a semi-structured clinical interview.

Enumeration and clinical characteristics of national survey participants have been detailed elsewhere (Morgan et al., 2012). Of 7,995 people screened and randomised, 1,825 (23%) were interviewed. Reasons for non-interview included refusal (30%), being uncontactable (15%), being too unwell for interview (12%), having other exclusion criteria (6%), or not being required at the completion of planned interviews (14%). Sixty percent of participants were male, 58% were aged over 35, and most had diagnoses of schizophrenia (47%), bipolar disorder (18%) or schizoaffective disorder (16%). Average duration of illness was 15 years (median 12 years), 51% had multiple episodes with good or partial recovery between episodes and 31% had a continuous chronic illness.

Participants in the current study were all 319 individuals from the two NSW sites of the national survey.

Reference diagnoses

Diagnoses made by the national survey were used as reference diagnoses. These were obtained using the Diagnostic Interview for Psychosis (DIP), which is designed for use by clinical interviewers in large epidemiological surveys (Castle et al., 2006). The DIP has

good inter-rater (kappa 0.74) and test-retest (kappa 0.65) reliability for broad ICD-10 diagnostic categories, and good diagnostic validity compared with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Castle et al., 2006). Interviews were conducted by mental health professionals who worked in public mental health services and were trained in administration of the DIP. Inter-rater reliability between interviewers was good (averaged pairwise agreement = 0.94) (Morgan et al., 2012) . The OPCRIT algorithm (McGuffin et al., 1991) within the DIP software provided lifetime diagnoses according to ICD-10 and DSM-IV criteria, reducing subjective bias in the interpretation of symptoms and signs.

Administrative diagnoses

Data on hospital admissions and community mental health contacts were obtained from the NSW Health Information Exchange (HIE) from the beginning of available register data (July 2000) to the time of national survey assessment (March 2010). Only admissions staying at least one night in a designated mental health unit were included. Inpatient diagnoses were recorded at discharge from hospital by trained medical record coders, based on the diagnoses recorded by the treating psychiatrist or other medical officer. Community diagnoses were recorded by treating mental health clinicians at each community contact. Data for both settings included principal (primary reason for hospitalisation or contact) and secondary diagnoses, coded using the Australian Modification of ICD-10 (National Centre for Classification in Health, 2010).

Diagnostic algorithms

Three-month statistical episodes of care were constructed for community contacts. This was required because NSW community mental health data records diagnoses at each individual contact. Inpatient and community episodes of care for an individual were then combined to derive a single person diagnosis.

Four diagnostic algorithms were applied. ‘At least one’ diagnosis was present if the individual had at least one primary diagnosis of a particular psychosis diagnosis. ‘Last’ diagnosis was coded using the most recent mental health diagnosis; if multiple diagnoses were made at the last episode, the primary diagnosis was used. ‘Modal’ diagnosis was the most frequent primary mental health diagnosis, summarised to the three-digit level (e.g. ‘F20’). ‘Hierarchy’ psychosis diagnosis applied the following sequence: organic psychoses, schizophrenia, schizoaffective disorder, affective psychosis, brief/drug induced/atypical

psychosis, and then all other diagnoses. Personality disorder and intellectual disability diagnoses were excluded from calculation in all algorithms, since the presence of these disorders does not exclude concurrent diagnosis of psychosis. For statistical episodes of community care, each diagnostic algorithm was first applied to derive a single diagnosis per community episode, and then applied to combine all inpatient and community episodes for that person.

Diagnoses were grouped at two levels. First, a binary psychosis/no psychosis variable was examined. Psychoses included all diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, depression with psychosis specified, acute and transient psychoses, delusional disorders, induced delusional disorders, drug-induced psychosis, other psychoses and psychoses not otherwise specified. Schizotypal disorder and organic psychoses were excluded. Second, diagnostic agreement was examined for three mutually exclusive psychosis groups: Schizophrenia (F20), Schizoaffective Disorder (F25) and Affective Psychoses, which included bipolar disorder (F30, F31) and depressive episodes where psychosis was specified (F32.3, F32.30, F32.31, F33.3).

Preliminary analyses tested different options for construction of ‘modal’ and ‘last’ diagnoses, giving different weightings to primary or additional diagnoses, and to Axis I or Axis II conditions. Preliminary analyses also found no systematic differences in diagnostic agreement between inpatient and community settings. Hence, inpatient and community diagnoses were combined for a final person diagnosis, with the same algorithm being applied across both settings. Details of these analyses are available from the corresponding author on request.

Data Linkage

All survey participants consented to linkage of their research data with state administrative databases. Ethics approval for linkage was obtained from the Human Research Ethics Committee of the Hunter New England Area Health Service. Participants’ survey records were linked to their NSW HIE records using name, date of birth, sex and local health service identifier where this was present.

Statistical analysis

DIP diagnoses were used as the ‘gold standard’ against which the derived clinical diagnoses were compared. Differences between included and excluded subjects were examined using Pearson’s Chi-square for categorical variables and independent sample t-

tests for continuous variables. Agreement between administrative and reference diagnoses was evaluated using prevalence estimates, percentage agreement, positive predictive value, negative predictive value, sensitivity and specificity. ROC analysis was undertaken, calculating area under the curve (AUC). Cohen's Kappa, and prevalence and bias adjusted kappa (PABAK) (Sim and Wright, 2005; Chen et al., 2009) were calculated. PABAK takes into account the prevalence of the disorder within the sample as well as the discrepancy between the proportion of diagnoses assigned by different raters. PABAK and 95% confidence intervals for kappa were calculated using DAG_stat (Mackinnon, 2000). Other analyses were conducted in SPSS Version 21 (IBM Corp. 2012. IBM SPSS for Windows, Version 21. Armonk, NY. IBM Corp.).

RESULTS

Eighteen participants were excluded because their research and clinical records could not be linked. A further 12 participants had no recorded diagnosis in the HIE. Thus, the final sample for the present study consisted of 289 participants, 91% of the available sample. The 30 participants excluded did not differ significantly from study participants on age or gender but were more likely to have had a reference diagnosis of a non-psychotic condition (19% of excluded participants, 12% of included participants. Chi-square = 4.9, df=1, $p < 0.05$). All 12 subjects with no administrative diagnosis had only brief community mental health contact.

The average age of participants was 40 (range 19 – 65) and 60% were male (Table A.1). Half had reference diagnoses of schizophrenia. Most (91%) had both inpatient and community mental health care prior to assessment; two had only received inpatient care. Participants had an average of 10.6 admissions to mental health units prior to their assessment (SD 16.9, range 0-188 admissions).

Table A.1. Characteristics of participants with administrative and reference diagnoses (n = 289).

Male n (%)	174 (60%)
Age	
Mean (SD)	39.9 (10.6)
Range	19 - 65
ICD-10 Reference diagnosis n (%)	
Schizophrenia	144 (50%)
Schizoaffective Disorder	35 (12%)
Affective Psychosis	53 (18%)
Other psychosis	22 (8%)
Depression (without psychosis)	28 (10%)
Did not meet full criteria for psychosis	7 (2%)
Type of contact n (%)	
Inpatient and Community Care	263 (91%)
Community care only	24 (8%)
Inpatient care only	2 (0.6%)
Hospital admissions	
Mean (SD)	10.6 (16.9)
Range	1 - 188

The ‘At least one’ psychosis algorithm produced higher rates for all diagnoses examined (Figure A.1) and a prevalence estimate closest to the reference diagnoses for the binary psychosis/no psychosis distinction. However, for all individual diagnoses, the ‘At least one’ algorithm produced higher prevalence estimates, including more than two-fold increases in estimated rates of schizoaffective disorder and affective psychoses. ‘Hierarchy’ diagnoses varied according to the priority given within the hierarchy, producing substantially higher estimates of schizophrenia prevalence than the reference diagnoses, but substantially lower estimates of affective psychosis. Using a ‘Hierarchy’ approach estimates of schizoaffective disorder were almost zero, because nearly all individuals with a schizoaffective disorder diagnosis also had other diagnoses of schizophrenia or affective psychosis. ‘Modal’ and ‘Last’ algorithms produced similar estimates for all diagnoses examined, and most closely matched the rates estimated using reference diagnoses.

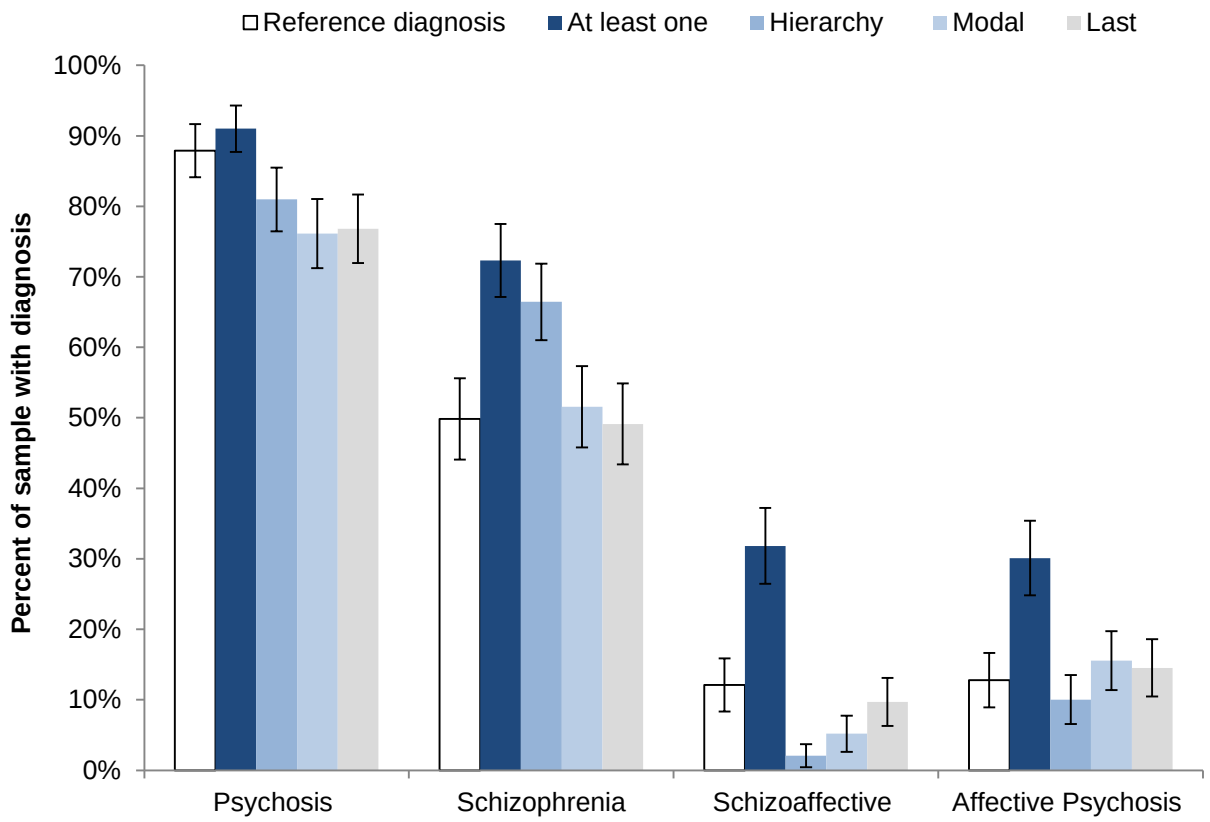

Figure A.1. Comparison of diagnostic algorithms. Estimated prevalence of any psychosis and of specific psychosis diagnoses: reference diagnoses from research interview compared with four algorithms for deriving diagnoses from longitudinal administrative data.

Absolute agreement between administrative and reference diagnoses was only in the 'fair' range (Landis and Koch, 1977), with kappa ranging from 0.23 to 0.36 (Table A.2). The exception was schizoaffective disorder, where kappa ranged from 0.01 to 0.09. For the broader 'any psychosis' group, the 'At least one' diagnosis algorithm had the highest overall agreement, but had lower specificity than 'Modal' and 'Last' algorithms. For schizophrenia, 'Modal' and 'Last' algorithms performed best on most measures and appeared indistinguishable from each other. For affective psychoses, the 'Hierarchy' algorithm achieved the best overall agreement with reference diagnoses. PABAK corrects for either high or low prevalence within the sample and therefore produced increased estimates of agreement in disorders whose prevalence in our sample was closer to 0% or 100% (any psychosis kappa 0.27 – 0.36, PABAK 0.60 – 0.76. Schizoaffective disorder, kappa 0.01 – 0.09, PABAK 0.33 – 0.73), but no change in estimated agreement for schizophrenia, whose prevalence in our sample was close to 50%. The Area Under the Curve (AUC) obtained from ROC analysis was highest for 'Modal' and 'Last' diagnoses in the 'any psychosis' group and in schizophrenia, and highest for the 'At least one' algorithm

in affective psychosis. However the confidence intervals for most AUC estimates overlapped, suggesting modest differences in performance of these algorithms.

Of 142 persons with a ‘Last’ administrative diagnosis of schizophrenia, 44 (31%) were reassigned to other reference diagnoses, particularly schizoaffective disorder (15 participants), affective psychoses (14), and other psychoses (12). Conversely, of 28 persons with a ‘Last’ administrative diagnosis of schizoaffective disorder, only six had a reference diagnosis of the same disorder and a third (10) were reassigned to a reference diagnosis of schizophrenia (Table A.3).

Table A.2. Concordance between administrative and reference diagnoses, comparing four different algorithms for assignation of diagnosis from administrative data.

Diagnosis and algorithm	Diagnostic agreement (%)	Sensitivity (%)	Specificity (%)	AUC (95% CI)	PPV (%)	NPV (%)	Cohen's kappa (95% CI)	PABAK (95% CI)
Psychosis								
At least one	88	95	37	0.66 (0.55 - 0.77)	92	50	0.36 (0.19 - 0.53)	0.76 (0.68 - 0.83)
Hierarchy	81	85	49	0.67 (0.56 - 0.77)	92	31	0.27 (0.13 - 0.41)	0.61 (0.52 - 0.70)
Modal	80	82	66	0.74 (0.64 - 0.84)	95	33	0.34 (0.21 - 0.46)	0.60 (0.51 - 0.69)
Last	81	83	66	0.74 (0.65 - 0.84)	95	34	0.35 (0.22 - 0.48)	0.61 (0.52 - 0.70)
Schizophrenia								
At least one	64	86	41	0.64 (0.57 - 0.70)	59	75	0.27 (0.17 - 0.37)	0.27 (0.16 - 0.38)
Hierarchy	61	78	45	0.61 (0.55 - 0.68)	58	67	0.23 (0.12 - 0.33)	0.22 (0.11 - 0.34)
Modal	66	68	65	0.66 (0.60 - 0.73)	66	67	0.33 (0.22 - 0.44)	0.33 (0.22 - 0.44)
Last	68	67	68	0.67 (0.61 - 0.74)	68	67	0.35 (0.24 - 0.46)	0.35 (0.24 - 0.46)
Schizoaffective								
At least one	66	43	70	0.56 (0.46 - 0.67)	16	90	0.07 (-0.03 - 0.18)	0.33 (0.22 - 0.44)
Hierarchy	87	3	98	0.50 (0.40 - 0.61)	17	88	0.01 (-0.08 - 0.10)	0.73 (0.65 - 0.81)
Modal	85	9	95	0.52 (0.41 - 0.62)	20	88	0.05 (-0.08 - 0.18)	0.70 (0.61 - 0.78)
Last	82	17	91	0.54 (0.44 - 0.65)	21	89	0.09 (-0.05 - 0.23)	0.65 (0.56 - 0.73)
Affective Psychosis								
At least one	74	65	75	0.70 (0.60 - 0.79)	28	94	0.25 (0.14 - 0.37)	0.47 (0.37 - 0.58)
Hierarchy	87	38	94	0.66 (0.55 - 0.77)	48	91	0.35 (0.19 - 0.51)	0.74 (0.66 - 0.81)
Modal	82	41	88	0.64 (0.54 - 0.75)	33	91	0.26 (0.12 - 0.41)	0.64 (0.55 - 0.73)
Last	82	38	89	0.63 (0.53 - 0.74)	33	91	0.25 (0.10 - 0.40)	0.65 (0.56 - 0.73)

Note: *AUC* Area under curve, *PPV* Positive Predictive Value, *NPV* Negative Predictive Value, *PABAK* Prevalence and Bias Adjusted Kappa.

Table A.3. Comparison between administrative and reference diagnoses, using the 'Last' diagnosis algorithm

	Reference diagnosis						
Clinical diagnosis ("Last" algorithm)	**Schizophrenia**	**Schizoaffective disorder**	**Affective psychosis [a]**	**Other psychoses**	**Affective disorder**	**No psychosis [b]**	**TOTAL**
Schizophrenia	96	15	14	12	5		142
Schizoaffective	10	6	6	2	3	1	28
Affective psychosis	14	5	19	2	1	1	42
Other Psychosis	7	0	1	1	1		10
Affective disorder	8	5	8	2	7	3	33
Non-psychotic disorder	9	4	5	3	11	2	34
TOTAL	144	35	53	22	28	7	289

Note: (a) Reference diagnoses of 'Affective disorder' exclude Affective psychosis. (b) Did not meet full criteria for an ICD-10 diagnosis of a psychotic disorder.

DISCUSSION

We compared longitudinal diagnoses obtained from routinely-collected administrative health data with reference diagnoses obtained from the Diagnostic Interview for Psychosis in 289 people who screened positive for psychotic illness. We found significant differences in performance between the four algorithms. Our findings are consistent with the few studies that have compared the relative performance of different diagnostic methods. Kirkby (Kirkby et al., 1998) found that diagnostic reliability for schizophrenia was low in individuals for whom schizophrenia diagnosis constituted a minority of their total diagnoses, and that a 'Modal' diagnosis was therefore more accurate than an 'At least one' diagnosis. McConville and Walker (McConville and Walker, 2000) found that modal diagnosis performed better than first (incident) diagnosis for schizophrenia and related psychotic disorders. Valuri (Valuri et al., 2001) found that for psychotic disorders the diagnosis at most recent discharge had higher agreement with research (OPCRIT) (McGuffin et al., 1991) diagnoses than did modal diagnosis.

Variation in diagnoses over time may reflect inter-rater and information variability, as well as true variation due to change in the individual's condition. The mix of these factors may influence the performance of these algorithms differently for different disorders. Many people with later diagnoses of schizophrenia are initially diagnosed with brief, atypical, drug-induced or affective psychoses, However, a diagnosis of schizophrenia, once made, is relatively stable over time (Bromet et al., 2011; Schwartz et al., 2000). Variation in specific diagnosis over time should have little impact on the binary psychosis/no psychosis distinction, since all are psychotic conditions. The most sensitive and least specific algorithm ('At least one') appeared to perform best for this broad distinction. By contrast, the finding that the 'Last' diagnosis was most accurate for schizophrenia is consistent with the progression to this diagnosis over time, as well as the greater diagnostic certainty that may follow a longer period of assessment. The similarity between 'Modal' and 'Last' diagnoses for schizophrenia is consistent with the stability of the diagnosis of schizophrenia once made. Although 'Modal' and 'Last' algorithms performed identically for schizophrenia, a 'Last' diagnosis approach may be preferable for identifying schizophrenia, as it may be less sensitive to variations in the period of time included in calculation, and is computationally simpler.

For affective psychosis (including bipolar disorder) 'Hierarchy' diagnosis performed relatively well on measures of agreement. This implies that administrative diagnoses for

people with these conditions may not converge on a stable diagnosis over time as seen in schizophrenia. People with reference diagnoses of bipolar disorder continued to have episodes of care with other diagnoses, including non-psychotic depressive episodes, anxiety disorders, and substance disorders; this may reflect true clinical variation and comorbidity as well as diagnostic error. Using a diagnostic hierarchy may have filtered out these effects.

Overall agreement between clinical and reference diagnoses was no better than chance for schizoaffective disorder. This may reflect the smaller size of this group; however it also highlights the imprecision of this diagnosis in routine clinical practice. Many people with clinical diagnoses of schizophrenia or bipolar disorder had at least one diagnosis of schizoaffective disorder, and therefore an 'At least one' diagnosis algorithm greatly over-estimated its prevalence. Conversely, nearly all people with a clinical diagnosis of schizoaffective disorder also had clinical diagnoses of schizophrenia, and so a hierarchical approach produced a very low estimate for the rate of schizoaffective disorder.

Limitations

The absolute level of agreement between administrative diagnoses and reference diagnoses was in the lower part of the range for published studies. We found overall rates of diagnostic agreement from 61% to 88% depending on algorithm and diagnosis, with kappa up to 0.36. Studies validating clinical diagnoses of schizophrenia against research diagnoses have reported overall rates of diagnostic agreement from 71% (Arajärvi et al., 2005) to 98% (Keskimani, 1991), and kappa from 0.31 (Erdman et al., 1987) to 0.69 (McConville and Walker, 2000).

Several limitations of this study may have contributed to the modest overall agreement between administrative and reference diagnoses. First, administrative systems record diagnoses made by many clinicians over a long period, and are unlikely to align completely with a cross-sectional research diagnosis. Second, the reference diagnoses in this study may itself also be imprecise, being based on a two stage assessment using a psychosis screener then a research interview (the DIP) conducted by a clinician without long prior contact with the participant. A recent study of long term diagnostic stability in psychosis suggests that clinician diagnoses may at times be more sensitive than research diagnoses in anticipating later diagnostic changes (Bromet et al., 2011). Third, the administrative register used in this study commenced approximately ten years prior to the study, limiting the timespan of diagnostic data available for each individual.

The method of selection of participants for this study is also likely to have had a significant impact on absolute levels of diagnostic agreement. Participants were not a random sample of service users, and underwent diagnostic interview only after screening positive for probable psychosis. As a result, only 12% of the study group had a reference diagnosis of a non-psychotic disorder, compared with at least 50% of NSW public mental health service users whose primary diagnoses are of non-psychotic conditions. Administrative and reference diagnoses are likely to have agreed on the absence of psychosis for many of these people. The screening process therefore excluded many true negative diagnostic agreements from our study group, reducing agreement for measures dependent on the true negative rate (percent agreement, specificity, negative predictive value and kappa). The national survey from which our participants were drawn interviewed a random sample of 164 screen-negative participants, finding a false negative rate of 24%. We have modelled the potential impact of these missing cases on diagnostic agreement, assuming (i) the screener false negative rate for the two sites in our study was the same as the national rate, (ii) 50% of service users at our sites had a non-psychotic disorder and (iii) disagreement between administrative and reference diagnoses for non-psychotic disorders was equal to that for psychotic disorders. For agreement on the binary 'psychosis/no psychosis' distinction and using the 'At least one' algorithm, inclusion of these screened cases increased specificity from 37% to 90% and kappa from 0.36 to 0.65. Our study focuses on the relative performance of algorithms rather than on the absolute level of agreement: it is unlikely that the effect of screening would differentially affect the performance of any of the algorithms tested, since the threshold used in screening was substantially lower than that set by any of the algorithms, and the items included in screening (e.g. lifetime presence of psychotic symptoms) are independent of the items included in those algorithms.

Conclusions

The choice of algorithm for extracting a psychosis diagnosis from clinical datasets may have a substantial impact on the accuracy of the diagnoses constructed. There may be no single ideal algorithm for all diagnoses. The 'At least one' algorithm had highest agreement for identifying the presence of a psychotic disorder generally. 'Modal' and 'Last' diagnosis performed best for schizophrenia, while 'Hierarchy' diagnoses performed best for affective psychoses. Overall agreement between clinical and reference diagnosis was very poor for schizoaffective disorder. Larger samples including a balance of psychotic and non-psychotic conditions would be of value for future studies.