

SUBSTANCE USE IN PSYCHOTIC DISORDER

USE PATTERNS AND RELATION TO CLINICAL AND
COGNITIVE CHARACTERISTICS IN SCHIZOPHRENIA AND
BIPOLAR DISORDER

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List of papers

The present thesis is based on the papers listed below, referred to in the text by their Roman numbers in brackets.

- I. Ringen PA, Melle I, Birkenæs AB, Engh JA, Færden A, Jónsdóttir H, Nesvåg R, Vaskinn A, Friis S, Larsen F, Opjordsmoen S, Sundet K, Andreassen OA. Illicit drug use in patients with psychotic disorders compared to the general population: A cross sectional study. *Acta Psychiatrica Scandinavica* 2008; 117:133-138.
- II. Ringen PA, Lagerberg TV, Birkenæs AB, Engh JA, Færden A, Jónsdóttir H, Nesvåg R, Friis S, Opjordsmoen S, Larsen F, Melle I, Andreassen OA. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. *Psychological Medicine* 2008; 38:1241-1249.
- III. Ringen PA, Melle I, Birkenæs AB, Engh JA, Færden A, Vaskinn A, Friis S, Opjordsmoen S, Andreassen OA. The level of illicit drug use is related to symptoms and pre morbid functioning in severe mental illness. *Acta Psychiatrica Scandinavica* 2008; 118:297-304.
- IV. Ringen PA, Vaskinn A, Sundet K, Jónsdóttir H, Simonsen C, Friis S, Opjordsmoen S, Melle I, Andreassen OA. Opposite relationships between cannabis use and neurocognitive functioning in schizophrenia and bipolar disorder. Submitted.

1. Introduction

1.1 . *Perspectives and definitions*

Severe Mental Illness and Psychotic Disorder

The schizophrenia spectrum and bipolar disorders constitute what is often called ‘severe mental illness’ (SMI) or ‘psychotic disorder’. The terms are general and require further clarification. The popularity of these rather inaccurate terms reflects the existing challenges in the categorisation of psychiatric conditions. The adjective ‘severe’ refers to the intensity of symptoms, the loss of daily functioning and the persistence over time that may be associated with the conditions. The propensity to experience psychotic episodes is a common feature for both spectra of disorders, and an alternative term is thus ‘psychotic disorder’.

‘Psychotic disorder’ is probably a more precise term than ‘SMI’ because SMI sometimes is used for a number of other psychiatric conditions as severe personality disorder or severe obsessive compulsive disorder, which do not have the same association with psychosis. For this thesis ‘psychotic disorder’ will be used as a common term for conditions in the broad schizophrenia and bipolar disorder range of disorders. The use of ‘psychotic disorder’ is however not without problems because psychosis also may evolve secondary to environmental (stress, intoxication) or clear organic causes (neurologic, infectious, electrolytic disturbance etc.), and contrary to schizophrenia, a diagnosis of bipolar disorder does not require psychotic symptoms.

The earliest known descriptions of psychotic symptoms date from the second millennium before Christ. In the Eber papyrus of Pharaonic Egypt the understanding of the disturbing mental states seem to involve physical explanations (Okasha and Okasha, 2000). Later, the humoral theory of classical Greece implied a similar physical way of conceptualising. After antiquity mental illness was in Europe increasingly viewed as something belonging to the realm of the soul, irrelevant to the physical world or the natural sciences. Mental deviation could be regarded as a divine punishment or as a result of diabolic influence. With the enlightenment a strict dualist position was formulated by Decartes, and later reductionist materialism emerged. Sigmund Freud wrote that his new psychological concepts were mere artificial and transient hypotheses waiting to be replaced by future advances of neuroscience (Freud, 1920). Today, after the post-modernist acknowledgment of the relativist perspective and decades with an exploding growth in biological knowledge we are still much reliant on concepts inspired by Freud, but the overwhelming majority of

contemporary theories of psychopathology postulate a physical substrate (Meyer-Lindenberg and Weinberger, 2006; Kendler, 2008).

Psychosis

Psychosis has at its core element a loss of testing of reality, and is characterised by typical symptoms of distorted perception (hallucinations), thought (paranoia, delusions, and various formal thought disorders), emotions, speech and/or physical behaviour.

The term 'psychosis' dates from 1845 (von Feuchtersleben, 1845), and the concept of the disorders we use today was first acknowledged by Emil Kraepelin who divided the psychotic disorders into dementia praecox and manic-depressive psychosis (Kraepelin, 1899). Today's diagnostic terms of schizophrenia and bipolar disorder conveys, one hundred years later, essentially the same as Kraepelin's model. Substantial efforts have been made in the search for etiological and pathoplastic factors; but still the underlying pathological mechanisms of psychosis are not deschiffered. The prevailing framework of conceptualising the disease mechanism is one of an inherited polygenetic vulnerability/diathesis interacting with exogenous/environmental stressors or protectors (van Os *et al.* 2008). Still, no genes or set of genes have to date been unequivocally linked to the disorders and no stressors are found to fully predict the evolvement of the psychotic conditions. A debate is going on whether the psychotic disorders are really fundamentally different categorical entities or whether they rather are variations across a continuum of psychotic states or propensities (Crow, 2008a).

Substance use

Chemical substances with a potential to alter the state of mind are used in most human cultures, including isolated indigenous tribal communities, and use of such substances traces back to the earliest human cultures (Dudley, 2002). Often their effect was said to bridge between the earthly and the spiritual world. Many psychoactive drugs involves substances naturally existing in the environment, such as plants or plant parts (cannabis, opium, coca, khat, kava, peyote), or mushrooms. Alcohol also exists naturally in the environment (Dudley, 2002); its production was an early invention and is known in most cultures. Use of psychoactive substances can be argued to have been an integrated part of human history and culture, with important roles in medicine, religion and social life. But as both acute and repetitive substance consumption often will cause unwanted behavioural changes, these perhaps more purposeful modes of substance use have also been problematic. The misfortunes associated with abuse are described in several texts throughout history from antiquity. Use of psychoactive substances (alcohol, illicit drugs and tobacco) has developed into present major

public health problems worldwide, and accounted for 9 % of all disability adjusted life years (DALYs) in year 2000 (WHO, 2008b).

Some substances have reached a considerable level of consumption in the general population, like cannabis, amphetamines and cocaine (EMCDDA, 2006). Several of these are known to have the ability to precipitate psychosis-like symptoms as hallucinations and/or delusions after ingestion (Thirthalli and Benegal, 2006). Although sociological theories have prevailed in the explanations of mechanisms for substance abuse for the last decades, biological models are gaining terrain.

Background for the current thesis

Growing use of recreational psychoactive substances is also seen in people with psychotic disorder, and it seems that drug use is even more common in this patient group than in the general population (Regier *et al.* 1990). This use is associated with increasing problems with the health care management of the psychiatric conditions, and psychoactive substances are regarded to be among the most important stressors in the development of acute psychosis. Furthermore, substances of abuse (ketamine, PCP, amphetamine) have been used as neurobiological model drugs for psychotic disorders. Thus, it has been speculated that the mechanisms involved in substance use behaviour can help elucidate the underlying pathological mechanisms of psychotic disorders (Coyle, 2006; Krystal *et al.* 2005)

However, the focus on the clinical relationship between use of psychoactive substances and severe mental disorders is quite new; research efforts have been scarce until recently and treatment of “double diagnosis” is still to a small degree evidence based. Differences in drug use patterns and their associations with symptoms and functioning have to a small extent been used to enlighten the important discussion of diagnostic delineation among different psychotic disorders. In this context, the current PhD thesis was planned.

1.2. Psychotic disorder

1.2.1. Schizophrenia

Definition

Schizophrenia, as defined in the DSM-IV diagnostic system (First and Tasman, 2004), is a disorder that lasts at least 6 months and have a presence of a minimum set of characteristic psychotic symptoms (criterion A symptoms) for at least a month (active phase). There must also be an advent of marked social dysfunction. If the active phase(s) occur together with

affective episode(s), and there has been at least 2 weeks with delusions or hallucinations in the absence of prominent mood symptoms, a schizoaffective disorder seems probable. In schizophreniform disorder, symptoms have shorter duration than 6 months and there is no requirement of a decline in functioning. These diagnostic entities may be called “schizophrenia spectrum disorders”, the common denominator being that there must be psychotic episodes occurring over some time and independently of eventual affective episodes.

Prevalence, course and implications

The prevalence of schizophrenia is more geographically varied than previously assumed, but is widely estimated at about 0.5 - 1.0 %, gender, urbanicity, latitude and migration is shown to influence incidence rates (McGrath *et al.* 2008).

Age at onset is normally in adolescence and young adulthood, but a significant proportion of patients (about 25 %) will have their debut after the age of 40 (Castle and Murray, 1993). A model of the natural course of the illness describes three phases: an early phase marked by deterioration in functioning; a middle phase with little change (stabilisation phase); and the last period called the improving phase (Breier *et al.* 1991). A long delay between onset of first psychotic symptoms and start of treatment (Duration of untreated psychosis – ‘DUP’) and a poor premorbid functioning have been shown to predict more negative symptoms and poor global functioning (Larsen *et al.* 2000). Negative symptoms and cognitive deficits are the main reasons for work disability (Green, 1996) which for some can be lifelong. Other main problems are ensuing social isolation and neglect of personal care; there is a higher risk for comorbidity as depression and suicidality as well as cardiovascular disease and physical injuries in accidents. The mortality rate is estimated to be twice that of the general population (First and Tasman, 2004). Schizophrenia is estimated to be responsible for between 1.5 and 3 % of the direct health care costs in a survey of several western countries, in addition there are considerable costs related to lost productivity and impact on the family (Knapp *et al.* 2004).

Standard treatment regimens include medication with effects on the dopamine transmitter system (‘antipsychotics’), psychosocial treatment/rehabilitation as well as psychotherapy directed towards the psychotic symptoms.

1.2.2. Bipolar disorder

Definition

The DSM-IV criteria (First and Tasman, 2004) for bipolar I disorder (BD I) demands the presence of a manic episode in the person's history. In bipolar II disorder (BD II) there must have been at least one major depressive episode and one episode of hypomania. Cyclothymic disorder reflects the presence of numerous periods with hypomanic symptoms and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode. Both mania and major depression may involve psychotic symptoms with delusions or hallucinations. In these bipolar spectrum disorders, the common denominator is that eventual psychotic episodes are always linked with episodes of affective dysregulation (depressive or manic episodes).

Mania and hypomania are defined by a distinct period of abnormally and persistently elevated, expansive or irritable mood accompanied by a set of related signs or symptoms. Mania is more severe than hypomania, distinguishable by the presence of psychosis, hospitalisation or marked impairment in social functioning. A major depression is characterised by a distinct period of persistent depressed mood or anhedonia, accompanied by a set of related signs or symptoms. Presence of psychosis implies higher severity.

Prevalence, course and implications

The prevalence numbers for bipolar disorder also varies across studies, but for bipolar I disorder the prevalence is thought to be about the same as for schizophrenia; around 1 % (Goodwin and Jamison, 2007). Bipolar II disorder has probably slightly higher prevalence rates.

Onset is as in schizophrenia usually in adolescence and young adulthood. The majority of patients will experience four or more episodes during life, duration of episodes ranging typically from 4 to 13 months; depressive episodes are usually longer than episodes of elevated mood (Goodwin and Jamison, 2007). The loss of functioning associated with illness episodes have consequences for the persisting level of psychosocial functioning, and the main cause for morbidity/mortality is considered to be depression and the related substantially increased risk for suicide (First and Tasman, 2004). Cognition is found to be compromised also in euthymic phase (Robinson *et al.* 2006), and there is a psychosocial impairment persisting for years in all areas of functioning even in patients without recurrence of episodes (Coryell *et al.* 1993). The rate of psychiatric hospitalisation is exceeded only by that for

schizophrenia (First and Tasman, 2004), associated healthcare costs are consequently considerable.

Standard prophylactic treatment include medication with a mood stabiliser (Lithium, antiepileptic or a novel antipsychotic), several kinds of psychotherapy are used adjuvantly.

1.3. Substances of abuse

A variety of chemical substances are known to precipitate hallucinations and/or delusions/paranoia in otherwise apparently healthy individuals after ingestion. Such substances thus constitute an important type of environmental stressors. The discoveries of some of the mechanisms of action of these substances in the brain have given unique possibilities to model the neurobiological underpinnings of such psychiatric symptoms (Abi-Saab *et al.* 1998; Seeman *et al.* 2006; Featherstone *et al.* 2007; Nabeshima *et al.* 2006; Corlett *et al.* 2007; Muller-Vahl and Emrich, 2008; Chambers and Taylor, 2004). The substances include drugs with a considerable level of consumption in the general population, like cannabis, amphetamines and cocaine.

Studies of the general population clearly indicate a growing and more varied use of illicit substances over the last decades (EMCDDA, 2006; Rehm *et al.* 2006; SAMHSA, 2006; SIRUS, 2006).

Substances of abuse are here defined as chemical substances which may be used in maladaptive patterns with negative functional consequences, potentially leading to fulfilment of diagnostic criteria for a substance use disorder (SUD). These are also substances that have the ability to induce psychiatric symptoms by direct effects on the central nervous system and represent specific substance-induced disorders. This delineation is in accordance with the description of substance-related conditions in the DSM-IV.

In the present thesis, the focus will especially be on substances which are known to have a high ability to induce psychotic-like symptoms and have shown a considerable prevalence of use in patient populations with psychotic disorder. These substances have their use or possession prohibited by law in most countries, and are thus often labelled illicit. These substances are cannabis, amphetamines and cocaine.

However, there are also other important substances. Because of their highly prevalent use, alcohol and tobacco will be described and have some focus in the present work. The clinical and theoretical picture will not be complete without a description of hallucinogens

which have limited general use, but, as the name implies, have strong psychosis-inducing properties.

The chemical compounds discussed under the current heading are in this thesis referred to as *substances of abuse* or just *substances*. Practice varies greatly in this field and alternate expressions could have been used conveying a similar content of meaning (e.g. “drug”). Practice varies also in the current papers and in paper I and III the term ‘drug’ is used. For reasons of clarity a choice has been made for this thesis, and the term used in the DSM system is applied. Use of substances without fulfilling criteria for a DSM diagnosis of abuse or dependency will be referred to as *use*, and the term *abuse* will be restricted to a defined disorder only. For an outline of the terms used in the diagnostic system DSM-IV, see figure 1.

Figure 1. Definitions of central diagnoses and concepts related to substance use according to the DSM-IV (condensed). The criteria are applied for substances individually.

<p>Substance Abuse: A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by at least <i>one</i> of the following within a defined period in time:</p> <ul style="list-style-type: none"> • Failure to fulfil major role obligations • Recurrent physically hazardous use • Recurrent substance related legal problems • Continued use despite use causing social or interpersonal problems <p><i>Criteria for dependence for the actual class of substance must never have been met.</i></p>	<p>Substance Intoxication: Development of a reversible substance-specific syndrome due to recent exposure to the substance <i>and</i> Clinically significant maladaptive behavioural or psychological changes because of effects on the CNS, that develops shortly after use <i>and</i> Symptoms are not due to a general medical condition and are not better accounted for by another mental disorder</p>
<p>Substance Dependence: A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by at least <i>three</i> of the following within a defined period of time:</p> <ul style="list-style-type: none"> • Tolerance • Withdrawal • More use than intended • Desire or unsuccessful effort to cut down on use • Use related behaviour is time consuming • Other important activities reduced • Cannot stop use despite knowledge of the use causing problems 	<p>Substance Induced Psychotic Disorder: Evidence of prominent hallucinations or delusions developed within a month of substance intoxication or withdrawal <i>and</i> Not better accounted for by a Psychotic disorder that is not substance induced or occurring exclusively during the course of a delirium</p>
<p>Tolerance: • Need for markedly increased amounts of the substance to achieve intoxication or desired effect <i>or</i> • Markedly diminished effect with continued use of the same amount of the substance</p>	<p>Withdrawal: Characteristic clinically significant symptoms develops due to reduction in substance use that has been heavy and prolonged</p>

For comprehensive description of criteria: see First and Tasman (2004).

1.3.1. Cannabis

Cannabis is a common denominator for preparations derived from the plant *Cannabis Sativa*, and cannabis seems to be the illegal drug with the highest prevalence of use in the western world (Green *et al.* 2005; SAMHSA, 2006; SIRUS, 2006). The preparations are made of different parts of the plant and have different levels of the primary psychoactive compound Δ -9-tetrahydrocannabinol (THC). The most common preparation is marijuana (herbal cannabis), followed by hashish (resin). THC is after ingestion distributed in fat tissue, and may thereafter be detected in urine for several weeks. Cannabis also has several other biochemical active constituents, of which less is known. One of these is cannabidiol (CBD), which seems to have antipsychotic effects (Morgan and Curran, 2008). New cultivation techniques have increased the potency of marijuana, according to level of THC, these preparations also contains the lowest concentrations of CBD (Potter *et al.* 2008).

At least two cannabis receptors have been identified, and a third is suspected; the CB 1 and CB 2 receptors are located both in the CNS and in peripheral tissues and are cloned (Muller-Vahl and Emrich, 2008). Several endocannabinoids have been identified, and are believed to act as neuromodulators by retrograde signalling in the CNS (Wilson and Nicoll, 2002). CB1 receptors are abundant in the brain reward circuitry, exerting an overall modulatory effect on the reward system. They also seem to participate in the rewarding and addictive properties of all substances of abuse, not only in the actions of endo- or exogenous cannabinoids (Maldonado *et al.* 2006; Lopez-Moreno *et al.* 2008).

THC injected intravenously in healthy subjects caused transient higher scores on a rating scale for delusional thoughts, elevated levels of the stress hormone cortisol, and impairment of memory function (D'Souza *et al.* 2004).

1.3.2. Amphetamines and cocaine

Amphetamine, methamphetamine and related compounds are laboratory engineered substances with a highly similar chemical makeup. Amphetamines are water soluble, often with a rapid renal excretion without any hepatic metabolism. Cocaine is found in the leaves of the South American plant *Coca*. It comes in either a hydrochloride salt formulation, or as a free base called "crack". Cocaine has gained availability and popularity in subcultures in Europe including Scandinavia over the last few years.

Both cocaine and amphetamine enhance monoaminergic neurotransmission by inhibition of the reuptake of monoamines. Amphetamines also act by releasing monoamines from brain neuronal boutons; this increases the postsynaptic action of noradrenaline (NA),

dopamine (DA) and serotonin (5-HT) (Johanson and Fischman, 1989; Seiden *et al.* 1993; Johanson and Fischman, 1989). Amphetamine has the highest affinity for DA and NA transporters, but a relatively low affinity for the 5-HT transporter. Cocaine, by contrast, has the highest affinity for the 5-HT transporter and much lower affinity for the DA and NA transporters (White and Kalivas, 1998).

The psychoactive effects of amphetamine and cocaine are similar and include locomotor stimulation, stereotyped behaviour, anorexia, euphoria and excitement. After ingestion, humans become confident, hyperactive and more talkative. Both physical and mental fatigue is reduced, and amphetamines have been used to improve performance of e.g. military pilots who need to remain alert under fatiguing conditions. Amphetamines are not thought to enhance performance in well-rested subjects (Eliyahu *et al.* 2007). The beneficiary effects of amphetamines and related compounds on patients suffering from attention deficit and hyperactivity disorders is thought to be mediated through DA-related enhancement of will-directed attentional control (Staller and Faraone, 2007).

Psychotic symptoms may occur, especially after repeated ingestion, and may evolve into a stimulant psychosis which includes auditory and visual hallucinations, paranoid ideation and aggressivity, and have resemblance with the symptoms of acute paranoid schizophrenia (Curran *et al.* 2004; Harris and Batki, 2000). Antipsychotic medication, acting on dopaminergic transmission, is effective in controlling symptoms. Amphetamine seem to have a stronger association to psychotic symptoms than cocaine (Mahoney *et al.* 2008). Level of substance use is shown to be associated with level of psychotic symptoms (Batki and Harris, 2004). Cocaine is reported to have especially strong psychological addictive properties (Bolla *et al.* 1998).

The actions of amphetamine have been the basis of the amphetamine model of schizophrenia (Featherstone *et al.* 2007; Krystal *et al.* 2005; Peleg-Raibstein *et al.* 2008; Snyder, 1973).

1.3.3. Hallucinogens

“Hallucinogen” is a term that describes substances known for their ability to elicit hallucinations and refers to a varied range of pharmacological substances. A strict definition of hallucinogens involves the agonists on the 5HT_{2A} receptor, namely lysergic acid diethylamide (LSD), mescaline and psilocybin (Fantegrossi *et al.* 2008). This has given rise to a serotonin hypothesis of psychosis (Aghajanian and Marek, 2000; Geyer and Vollenweider, 2008). Psilocybin is found in several plants and mushrooms (Carod Artal,

2003), and may locally have considerable popularity among young adults (Hermle *et al.* 2008). Other substances include methylenedioxymethylamphetamine (MDMA, “Ecstasy”), which enhance monoamine release (de la Torre *et al.* 2004), and phencyclidine (PCP, “Angel dust”) which is a NMDA receptor antagonist (Javitt and Zukin, 1991). The actions of PCP and related compounds were the basis of the Glutamate/NMDA model of psychosis (Abi-Saab *et al.* 1998). Glutamate and amphetamine are thought to contribute differentially to psychosis (Krystal *et al.* 2005), and an integration of the different models is called for. Traditionally, Cannabis/THC is sometimes classified as a hallucinogen, but is here discussed elsewhere.

Hallucinogens may often alter perception of all sensory modalities, and may induce lively visual and/or tactile hallucinations, something that is rare in “endogenous” psychosis. Use of LSD may lead to persisting perception disorder (Lerner *et al.* 2002).

Use of hallucinogens is widespread, but most often as part of a poly-abuse pattern, and seems to rarely be used on a regular basis (Wu *et al.* 2008).

1.3.4. Alcohol

The most prevalent substance of abuse in the western world is alcohol (ethanol); use of alcohol is common and integrated in mainstream culture. About 85-90 % of the adult population in northern and central Europe drink alcohol (Rehm *et al.* 2005). Dependence numbers varies; in the EU male and female 12 month dependence prevalence was 6.1 % and 1.1 % correspondingly (Rehm *et al.* 2005), and the overall 12 month dependence prevalence was 3.7 % in the U.S. in 2000 (SAMHSA, 2006). Ethanol is regarded as a central nervous system depressant, but has potent rewarding effects. The biochemical effects are complicated, and it seems like most of the brains’ transmitter systems are involved. Both acute and chronic administration of alcohol appears to have effect on all the major neurotransmitter systems.

Ethanol binds with and alters the function of several membrane-bound ligand-gated ion channels, most importantly the GABA_A receptor (Mihic, 1999), and the voltage-dependent Ca²⁺- channels (Davies, 2003). Persistent abuse of alcohol may lead to neurologic/psychiatric conditions where psychotic symptoms are part of the clinical presentation (Thirithalli and Benegal, 2006). “Pure” alcohol induced psychosis is rare; prevalence was recently found to be only 0.4 % in alcohol dependent patients treated in a university hospital (Soyka *et al.* 2007). Most of these conditions seem to be related to direct or indirect toxic effects of use over some time, as delirium or Wernickes encephalopathy/Korsakoffs psychosis.

1.3.5. Other substances

Khat is the most common name for the plant *Catha Edulis* which grows in eastern Africa and in the Arab peninsula. Recreational consumption is widespread amongst natives of this area. It contains the psychoactive substances cathinone and cathine which are chemically related to the catecholamines and amphetamines. Use is associated with psychotic episodes (Cox and Rampes, 2003).

Nicotine is the second most used substance as 20-40 % of the population of the western world smoke tobacco on a regular basis (SAMHSA, 2006; WHO, 2008a). Its use has been steadily declining in Europe and North America during the last decades (WHO, 2008a). Nicotine has no direct potentially psychosis inducing effects, although tobacco smoking can affect the metabolism of antipsychotics and thereby reduce their clinical effects (de Leon, 2004). Stimulating subtypes of nicotinic receptors have been shown to normalise some specific symptoms common in schizophrenia (Simosky *et al.* 2002). Schizophrenia patients have reported a stronger motivation to smoke than healthy controls. The main reasons for smoking: experienced pleasure and need for psychomotor stimulation were both related to antipsychotic medication (Barr *et al.* 2008).

Caffeine is a constituent of several products common in an average household, but can cause intoxication, anxiety and sleep disturbances. Caffeine use is not considered to be potentially abusive or addictive in the DSM-IV, but the issue is disputed (Satel, 2006). Caffeine has shown no potential to induce psychosis and enhances the effect of several antipsychotics by reducing their metabolisation.

The *opiate receptor agonists* (e.g. codeine, morphine and heroin), are amongst the most addictive substances known, as physical (and psychological) dependency evolves quickly. In medicine they are used as potent pain relievers. Unauthorised use is associated with severe psychosomatosocial debilitation, and is almost universally banned. Use among patients with psychotic disorder is limited (Margolese *et al.* 2004), and evidence actually point to a possible psychosis-protecting effect (Brizer *et al.* 1985).

The *benzodiazepine receptor agonists* used as anxiolytics or hypnotics have considerable addictive potential and have their use restricted to medical prescription in most countries. Their use is not associated with psychotic symptoms, but they are used as adjuvant medication in acute psychosis. Withdrawal symptoms may act as stressors.

1.4. Substance use in psychotic disorder; “dual diagnosis”

In the past years several longitudinal studies have concentrated on elucidating the strong associations found between substance use and psychotic disorder (Henquet *et al.* 2005; Henquet *et al.* 2006; Strakowski *et al.* 2007; Van Os *et al.* 2002). Accumulating evidence points to use of cannabis as a risk factor for later development of psychosis (Arseneault *et al.* 2004; Ferdinand *et al.* 2005; Henquet *et al.* 2005), and a recent comprehensive review estimates the increased risk of any psychotic outcome in individuals who had ever used cannabis to be 40 % (Moore *et al.* 2007).

There is also evidence that cannabis is a risk factor for mania (Henquet *et al.* 2006; Strakowski *et al.* 2007). Still, little is known about possible differentiated substance-vulnerability between schizophrenia and bipolar disorder. Traditionally the self-medication hypothesis (Khantzian, 1985), which predicts that patients use specific substances to relieve unpleasant symptoms by negative reinforcement, has been the predominant explanation for the increased prevalence of substance use among people with psychoses. The position of this theory is being challenged as biological evidence accumulates (Chambers *et al.* 2001), and has also been modified into a more general model partly because of lack of evidence for a selective use of substances (Mueser *et al.* 1998).

The etiological theories behind dual diagnosis can be classified according to the following models (Mueser *et al.* 1998):

- Common factor models
- Secondary substance use disorder models
- Secondary psychiatric illness models
- Bidirectional models

Common factors include shared genetic factors for both disorders, but there are a number of other factors that may independently increase vulnerability to both psychotic disorder and SUD, as socioeconomic status, personality/conduct disorder and cognitive dysfunctioning. Secondary substance use disorder may arise because of need for alleviation of symptoms or because of an increased vulnerability in patients with psychosis to experience negative effects of substances. Bidirectional models may be relevant if substance use trigger psychosis in a biologically vulnerable person, and if factors related to having a psychotic disorder maintains substance use behaviour.

1.4.1. Neurobiology of psychosis and substance use

The neurobiological abnormalities of SUD and psychotic disorder have overlapping features, since both seems to involve alterations especially in the dopaminergic signalling system in the striatum and medial forebrain, and both are associated with prefrontal hypofunction. Research on the neurobiology of psychotic disorders including subjects with comorbid SUDs has been called for in the ongoing work for the improvement of psychiatric nosology (Rounsaville, 2007).

Psychosis

Replicated findings from hundreds of structural, functional and neurochemical brain imaging studies of schizophrenia patients include reduction in wholebrain and hippocampal volumes, reduced N-acetyl aspartate (NAA) concentrations in the prefrontal cortex and hippocampus, dopamine D2 receptor upregulation in the striatum, and alteration in the relation between frontal and temporal activation. These findings are not attributable to medication effects (Gur *et al.* 2007). Specifically, cortical thinning has been found in prefrontal and temporal areas in schizophrenia (Nesvåg *et al.* 2008). Fewer studies have been conducted in bipolar disorder, and the findings are less consistent. Associations between neurocognition and brain structure have been found in schizophrenia (Antonova *et al.* 2004; Crespo-Facorro *et al.* 2007), and recently suggested also in bipolar disorder (Varga *et al.* 2008).

Genetic studies show increasing evidence for an overlap in genetic susceptibility in affective and non-affective psychoses; thereby challenging the traditional binary classification (Owen *et al.* 2007). Search for specific susceptibility genes for the disorders has been extensive, but yielded few concrete results. Recently, rare genetic variants (large recurrent microdeletions) were shown to account for a larger fraction of the overall genetic risk for schizophrenia than previously assumed (Stefansson *et al.* 2008).

The role of dopamine in psychosis is firmly established, supported by the fact that blockade of the dopamine D2 receptor is required for the antipsychotic effects of antipsychotic medication (Creese *et al.* 1976; Kapur *et al.* 2005).

Substance use

It seems that all substances of abuse involve activation of dopaminergic mesolimbic-cortical pathways which includes striatal structures in the ventromedial forebrain; most importantly the nucleus accumbens. This area is regarded as the most crucial processor of assigning motivational qualities to perceptions. These qualities can be described as related to salience- or reward aspects of internal or external stimuli. Use of substances can by this mechanism

strongly influence the human motivation for behaviour (Koob and Le Moal, 2001; Heimer, 2003; Kalivas and Volkow, 2005). As substance use also involves dysregulatory effects on the orbitofrontal cortex and anterior cingulate, a weakening of the prefrontal cortex' regulatory role on behaviour is the result, further enhancing the drugs' effect on behaviour (Volkow and Fowler, 2000). Prolonged use is associated with brain volumetric changes for different substances (Agartz *et al.* 2003; Berman *et al.* 2008; Chang *et al.* 2007; Schlaepfer *et al.* 2006) and long term heavy cannabis use specifically is recently shown to be related to bilateral reduction of hippocampal and amygdala volumes (Yucel *et al.* 2008).

'Dual diagnosis'

Psychosis is postulated to be generated by an 'aberrant assignment of novelty and salience to objects and associations' (Kapur *et al.* 2005), in which dopamine plays a pivotal role. As described over, all substances of abuse exerts their actions on the brain system dealing with such tasks. As the neuropathology of schizophrenia involves alterations in the neural substrate for positive reinforcement for behaviour, incentive motivation, behavioural inhibition and thus addictive behaviour, and, in addition, experimental interventions in research animals that model schizophrenia enhances motivational effects of reward-related stimuli, it has been postulated a neurobiological basis for substance abuse in schizophrenia (Chambers *et al.* 2001). Continuous administration of stimulants may lower the threshold for response through behavioural sensitisation or kindling; this has been shown in animal studies and is suggested as mechanisms by which substance use may precipitate schizophrenia or bipolar disorder (Goodwin and Jamison, 2007; Peleg-Raibstein *et al.* 2008).

1.4.2. Prevalence, use patterns and demographics

Drug use is regularly reported to be over-represented in patients with psychotic disorders (Green *et al.* 2005; Kavanagh *et al.* 2004). There is a considerable degree of uncertainty linked to prevalence estimates of persons with comorbid drug abuse and psychosis. Epidemiologic studies show large variations in lifetime drug abuse, with estimates of 22-70% in schizophrenia (Cantor-Graae *et al.* 2001; Green *et al.* 2005) and 14-61 % for bipolar disorder (Cassidy *et al.* 2001; Chengappa *et al.* 2000; Kilbourne *et al.* 2004; Sherwood Brown *et al.* 2001). For all psychotic disorders the lifetime prevalence for illicit *drug abuse* was 27.5 % in the USA -ECA study (Regier *et al.* 1990), and an Australian study found lifetime *repeated use* of illicit drugs in 45 % of patients (Kavanagh *et al.* 2004).

This large variation in prevalence rates may be caused by several factors. Different studies recruit subjects from different populations from different geographical areas, with

substantial variation in factors such as cultural propensity to drug use and availability of drugs both in general and specifically. Different studies also deal with different time periods while the patterns of drug use are changing in the respective areas (Green *et al.* 2005; Hambrecht and Hafner, 2000; Mueser *et al.* 1990). Since general drug use patterns change over time and geographical areas, it is difficult to compare prevalence rates across studies from different populations and different time periods.

As heavy drug-use increases the risk of psychotic episodes we may expect higher rates in acute samples including first episode patients. Different studies also report prevalence rates for time periods ranging from the here-and-now to life-time, and it is generally thought that recent use is under-reported.

Cannabis use is of special interest, not only because of its popularity, but also because its use is more popular in the lower age groups, coinciding with the time of debut of the psychotic illness and at a point in time where there is important neurodevelopment in brain regions involved in addiction (Chambers *et al.* 2003). Cannabis (if not alcohol) will often be the introductory drug to other substances of abuse.

The prevalence numbers of substance use in psychotic disorder are thus linked with a high degree of uncertainty. New knowledge about the actual differences between patients with psychotic disorders and the general population regarding prevalence of illicit drug use, drug use patterns and demographic characteristics associated with drug use is therefore of considerable interest. It will aid the understanding of mechanisms associated with increased drug use in psychotic patients and help to improve planning of treatment and treatment services, it may also improve the understanding of the psychotic disorders themselves.

This issue can however only be solved by comparing representative patient samples to representative samples of the general population from the same area and time period; since drug availability and drug preference may vary. The most comprehensive study, comparing prevalence rates in the USA to the general population, is now two decades old (Regier *et al.* 1990). Recently several British studies have made use of comparisons with different general population estimates. The Scottish Comorbidity Study Group compared problematic substance use in a schizophrenia sample with a general population control sample from the same area, and found the risk for problematic substance use in schizophrenia to be over four times higher (McCreadie, 2002). Prevalence of substance use in first episode psychosis was found to be twice that of the general population in a sample from East of England (Barnett *et al.* 2007), a doubled prevalence rate in first episode was also found in a German study (Hambrecht and Hafner, 2000).

As prevalence to a high degree is population specific, there is a need for studies from different areas, and there are no larger studies from Scandinavia. Few studies on comorbidity monitor illicit substance use based on both reports and urine tests, very few have studied a representative sample of stable outpatients, and according to available information none have compared different kinds of general substance use in a well characterized *clinical* sample with a sample from the general population from the same time period and geographical area.

It is possible that less severe abuse, such as short duration and less amounts of substance use can be of importance for understanding the relationship between drug use and psychotic disorder. A smaller amount of use was shown to interact with COMT giving increasing risk for schizophreniform disorder (Caspi *et al.* 2005). There are few studies directly comparing frequency of substance use in patients with schizophrenia and bipolar disorder, and to the best of knowledge none of these have investigated patterns of use beyond type of substance abused (Mueser *et al.* 1992; Verdoux *et al.* 1996).

1.4.3. Clinical and functional outcome

Use of centrally stimulating agents and cannabis among individuals with psychosis has been related to deterioration seen in many outcome measures, as worsening of positive symptoms and depression, higher rate of hospital readmissions and increased suicide rates (Barak *et al.* 2008; Dixon *et al.* 1992; Grech *et al.* 2005; Hunt *et al.* 2002; Linszen *et al.* 1994; Margoiese *et al.* 2004; Miles *et al.* 2003; Mueser *et al.* 2001; Salyers and Mueser, 2001; Strakowski *et al.* 2000; Lambert *et al.* 2005). Substance use has been shown to be a considerable obstacle to treatment adherence, and often makes it necessary to increase the dose of antipsychotics to maintain symptom control, with increased risk of side-effects (Dixon *et al.* 1992; Hunt *et al.* 2002; Kavanagh *et al.* 2004; Owen *et al.* 2007; Zaretsky *et al.* 1993). Social functioning is negatively influenced, with higher incidence of aggression and violence, housing problems and imprisonment (Mullen *et al.* 2000; Scott *et al.* 1998; Wallace *et al.* 2004), and lower educational attainment (Kavanagh *et al.* 2004; Wallace *et al.* 2004). Furthermore, dual diagnosis patients have been found to have an earlier age at onset of psychosis compared to subjects with no history of drug use (Addington and Addington, 1998; Veen *et al.* 2004). There is also evidence that problems related to patients with co-morbid drug abuse contribute to a considerable rise in healthcare costs (Dickey and Azeni, 1996).

However, several findings question this apparent relation between co-morbid drug abuse and a poorer outcome in psychotic disorders. Cantwell (Cantwell, 2003) showed little or no change in symptoms, use of health care services or social function in patients with a co-

morbid drug abuse. Some studies even suggest a less severe form of illness with fewer negative symptoms in patients with a dual diagnosis (Addington and Addington, 1998; Dixon *et al.* 1991; Joyal *et al.* 2003; Salyers and Mueser, 2001). For schizophrenia patients with cannabis use, evidence seems to point at an association with less negative symptoms (Addington and Addington, 1998; Dubertret *et al.* 2006; Potvin *et al.* 2006; Swartz *et al.* 2006). In addition, former abusers had a better level of social function than those that never abused drugs. Larsen and colleagues (Larsen *et al.* 2006), in a sample of first-episode psychosis, found better premorbid social functioning and worse premorbid academic functioning in patients using substances than in non users.

1.4.4. Neurocognitive function in psychotic disorder and substance use

Cognitive deficit is a key feature of schizophrenia (Keefe *et al.* 2006). Early onset of the disorder and poor premorbid functioning is associated with greater deficits in attention and executive functioning (Silverstein *et al.* 2002). Neurocognitive dysfunction is also present in bipolar disorder (Martinez-Aran *et al.* 2007; Simonsen *et al.* 2008) albeit to a lesser degree than in schizophrenia (Daban *et al.* 2006; Cahill *et al.* 2006). Neurocognition is an important predictor of functional outcome in schizophrenia (Green *et al.* 2004) and the same relationship seems to exist for bipolar disorder (Green, 2006; Martinez-Aran *et al.* 2007).

Cannabis is the by far most commonly used non-alcoholic substance in psychotic disorder (Kavanagh *et al.* 2004; Green *et al.* 2005; Murray *et al.* 2007). Recent evidence suggests that cannabis impair cognition in healthy individuals, especially attention and memory functions like encoding, consolidation and retrieval (Ilan *et al.* 2004; Ranganathan and D'Souza, 2006). Neurocognitive deficits associated with cannabis use have traditionally been considered reversible and related to recent intake (Harrison, Jr. *et al.* 2002; Gonzalez *et al.* 2002; Iversen, 2003). However, recent evidence indicate that increasing years of cannabis use is associated with poorer performance in memory and attention (Solowij *et al.* 2002; Grant *et al.* 2003; Nordstrom and Hart, 2006). Early onset of cannabis use also seems to predict poorer cognitive performance than late-onset use (Pope, Jr. *et al.* 2003). Use of cocaine or amphetamine is linked with deficits in a range of neurocognitive domains, of which many does not seem to be transient (Rogers and Robbins, 2001).

Substance use in general seems to be associated with cognitive dysfunction in patients with psychotic disorder. However, the data is predominantly based on patients with schizophrenia spectrum disorders, and the results vary between studies. While Wobrock and colleagues (Wobrock *et al.* 2007), reported that substance use disorder was associated with

poor memory function in schizophrenia, substance abuse has also been found to be associated with improved neurocognition in first episode psychosis (McCleery *et al.* 2006). The presence of addiction has been associated with less impairment of memory (Potvin *et al.* 2005) and better executive functioning in schizophrenia (Joyal *et al.* 2003; Herman, 2004; Thoma *et al.* 2007; Potvin *et al.* 2007b). A fMRI study of social cognition in a mixed alcohol/cannabis abuse sample with schizophrenia showed higher degree of activation in brain regions associated with social skills (Potvin *et al.* 2007d).

The evidence supporting an association between specific cannabis use and altered neurocognition in schizophrenia is also inconclusive. A recent review reported three studies that found worse neurocognitive performance in cannabis users compared to non-users, while four studies found the opposite pattern (Coulston *et al.* 2007b). A recent meta-analysis showed that preferential use of cannabis was associated with better problem-solving, reasoning and visual memory in schizophrenia (Potvin *et al.* 2007a). Coulston and colleagues (Coulston *et al.* 2007a) found that better attention/processing speed and executive functioning was related to recency and frequency of cannabis use, but not to a DSM diagnosis of abuse/dependency in schizophrenia patients. However, schizophrenia patients seem more vulnerable to the acute effects of cannabis on memory function than healthy individuals (D'Souza *et al.* 2005). Persistent cannabis use prior to debut of schizophrenia is associated with improved cognition, while cannabis use at a similar age in healthy controls is associated with deteriorated cognition (Jockers-Scherubl *et al.* 2007). Thus, the longitudinal relationship is a key factor in these studies. Substance users with schizophrenia have been associated with higher levels of premorbid functioning than non-users (Arndt *et al.* 1992; Joyal *et al.* 2003).

There are few studies of substance abuse and neurocognition in bipolar disorder; apparently no studies have been conducted on cannabis use and neurocognitive functioning focusing specifically on bipolar disorder. One review has pointed to the similarity of cognitive deficits in bipolar disorder patients and in healthy controls with cannabis use (Cahill *et al.* 2006), and called for further investigation. In a mixed sample of schizophrenia and bipolar disorder, Liraud and Verdoux (Liraud and Verdoux, 2002) found that cannabis use was associated with poorer performance on an inhibition test. Carey *et al.* (Carey *et al.* 2003) found that drug abusing patients with schizophrenia or bipolar disorder performed better in nonverbal cognitive tests than non-abusers.

The findings of better premorbid social functioning, but worse premorbid academic functioning in drug-users with psychotic disorders (Larsen *et al.* 2006), are of interest since

psychosocial problems in childhood and adolescence are associated with later drug use (Siebenbruner *et al.* 2006), as well as with psychotic disorder in adults (Larsen *et al.* 2004; Owens and Johnstone, 2006). Dysfunction presenting before onset of illness may express traits which would be more closely related to genetic or early environmental factors. Thus, it is important to control for premorbid functioning when differences in functional traits between users and non-users are studied. However, it seems that no studies of substance use and neurocognitive function have controlled for premorbid factors.

1.4.5. Continuum hypothesis of psychosis

The traditional kraepelinian dichotomy between schizophrenia and bipolar disorder has been challenged over some time (Crow, 1986), recently with more force as more biological similarities have been revealed (Craddock *et al.* 2006; Craddock and Owen, 2007; Crow, 2008b; Ivleva *et al.* 2008; O'Donovan *et al.* 2008; Snyder, 1973). For instance are original candidate risk genes for schizophrenia now also found in affective disorders (Ivleva *et al.* 2008), and a recently identified schizophrenia susceptibility locus was also associated with an increased risk for bipolar disorder (O'Donovan *et al.* 2008). The continuum hypothesis of psychosis focuses on the similarities between schizophrenia and mood disorders, and the disorders are suggested as being at opposite extremes on a continuous spectrum of conditions with psychotic episodes (Craddock *et al.* 2007).

Studies focusing on the symptom dimensions across the functional psychosis continuum are called for (Ivleva *et al.* 2008). Drug use patterns and the relationships between drug use and outcome measures does not appear to have been investigated in a study of both disorders and interactions of substance use do not seem to have been used to inform this ontological question of psychiatry.

1.4.6. Introductory conclusion; unresolved issues and rationale for the thesis

So far current knowledge in the field has been outlined, the amount of findings is impressive and make the task of getting an overview challenging. However, as guidance for the rationale for this thesis, it becomes evident that there are several unresolved issues:

- *Prevalence of use compared with the general population.* Updated substance use rates from representative and well described patient groups are needed, and rates from the corresponding general population should be used for comparison. There are no such studies from Scandinavia.

- *Pattern of use.* More thorough descriptions of the substance use behaviour in patients with psychotic disorders are needed. Such descriptions could be informative in the search for the mechanisms involved and for improved clinical practice.
- *Drug use' relationship with symptoms.* There is a need for more studies on the association with outcome measures, and especially by level of substance use.
- *Drug use' relationship with neurocognition.* The findings are contradictory for psychotic disorders. There is particularly a need for studies in bipolar disorder.
- *Differences between BD and SCZ.* Classification of psychosis is complicated and heavily debated. More comparative studies of schizophrenia and bipolar disorder are needed, for future improvement of diagnostic systems

2. Aims of the thesis

The primary main aim of this study was to estimate level and investigate pattern of substance use in patients with psychotic disorders. The secondary main aim was to investigate associations between substance use and symptoms and functioning in patients with these disorders. The tertiary main aim was to investigate possible differences in these areas between schizophrenia and bipolar disorder.

Paper one

The aim of the first paper was to examine the level of illicit substance use, substance use patterns and its relationship to sociodemographic characteristics in a sample of patients with psychotic disorder compared with a representative sample from the general population in the same geographical area and time period.

Paper two

The aims of the second paper were to compare prevalence and type of alcohol and non-alcoholic drug use in highly representative samples of schizophrenia spectrum disorder and bipolar disorder, and to investigate possible differences in substance use patterns between the two different disorders.

Paper three

The aims of the third paper were: 1) to examine the association between levels of drug use and levels of positive, negative and general symptoms; 2) to examine the association between premorbid functioning in substance users and non-users; 3) to investigate the relationship between schizophrenia and bipolar disorder regarding the association between drug use, premorbid functioning and symptom levels.

Paper four

The aim of the fourth paper was to investigate if there were differences in neurocognitive functioning between cannabis users and non-users in schizophrenia and in bipolar disorder, and if these relationships were the same or different in the two diagnostic groups.

3. Material and method

3.1. Design

The study was part of the TOP (Thematic Organized Psychosis research) Study. The TOP study is a large translational research study at the University of Oslo, aiming at gaining more knowledge of the pathophysiological mechanisms of psychosis. The TOP study is approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. The TOP study now involves three of four hospitals with psychiatric units in Oslo, and with the Norwegian catchment area patient admittance system, this allows for a high degree of patient representativity. The population of Oslo County is approximately 550 000, and the greater metropolitan area includes approximately one million inhabitants. The main diagnostic groups included in the TOP study are schizophrenia and bipolar disorder. Patient inclusion started October 2002 and will go on for several years to come.

The current study is a naturalistic, cross sectional study involving group comparisons. For some of the papers, comparison groups from outside the TOP study have been used. In the first paper, a comparison group of the general population was established through cooperation with the Norwegian Institute for Alcohol and Drug Research, SIRUS. In addition, a larger sample of patients was assessed more briefly by their clinicians in order to have a comparison group to check for representativity of the primary patient sample.

3.2. Material

The TOP study aimed at recruiting all patients with psychotic disorders in treatment at the cooperating hospitals. When the inclusion started late in 2002 only Ullevål University Hospital (UUH) participated, and the first paper refers to a study sample from this catchment area only. Later also Lovisenberg-Diakonhjemmet and Aker University Hospital joined in, and the TOP total catchment area involved almost all city districts of Oslo in addition to some neighbouring municipalities in the county of Akershus.

To be eligible to the TOP study the patients had to be aged 18 - 65 years, have a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, psychotic disorder NOS, bipolar I disorder, bipolar II disorder or bipolar disorder NOS. Irregularly there was also inclusion of some patients with delusional disorder or major depressive disorder (MDD). Exclusion criteria were presence of a diagnosis of developmental disorder or serious brain damage and not speaking a Scandinavian language. Each patient was referred to the project by their treating clinician after an evaluation of their

eligibility and ability to give informed consent. Emphasis was put on recruiting all patients regardless of level of involvement in their respective treatment programs. The assessments were conducted by trained clinicians working as research fellows (MDs or psychologists) before signing the informed consent, and the interview started. The recruitment teams were based in outpatient clinics, where the patients were transferred after acute illness phases. This procedure restricted inclusion to symptomatically stable patients.

The study sample sizes differ from paper to paper, partly because of incrementing numbers of the main TOP study sample (and thus possibilities for improved statistical power), and partly because of different design needs in the different substudies.

In paper I, the primary study patient sample consisted of 148 patients recruited until July 2006, limited to patients from Ullevål University Hospital (UUH) and with information of any drug use during lifetime. The UUH has its catchment area in several different regions of the city of Oslo, and represent fairly well the city's variation in sociodemographic characteristics. Ten patients with MDD were included in a broader bipolar spectrum group, and two patients with delusional disorder were included in a broader schizophrenia group. A general population comparison sample was established through SIRUS' yearly surveys of the general population's consumption of illicit substances. This was done by phone-interviews with matched random subjects (Horverak and Bye, 2007). In this study SIRUS data from Oslo from 2004 was used. For matching purposes, participants aged 18-65 were selected, with a representative sample size of 327 people. A patient reference group was established by making use of a survey through the 'Ullevål 600' (U600) health care study of all patients from all clinical units of the Department of Psychiatry, UUH. The survey was undertaken in the same time period as the clinical study and comprised of a total of 1002 patients with ICD-10 F20-F39 diagnoses (psychoses and affective disorders). The patients were diagnosed according to ICD-10 criteria, and illicit drug use past 6 months was evaluated by the clinical staff, using the Clinician Drug Use Scale (Drake *et al.* 1989). Patients also included in the TOP study were removed from this U600 sample, leaving 849 patients to the reference group. The representativity of the TOP sample was evaluated by comparing TOP patients in the U600 reference group with the non-TOP patients in that group.

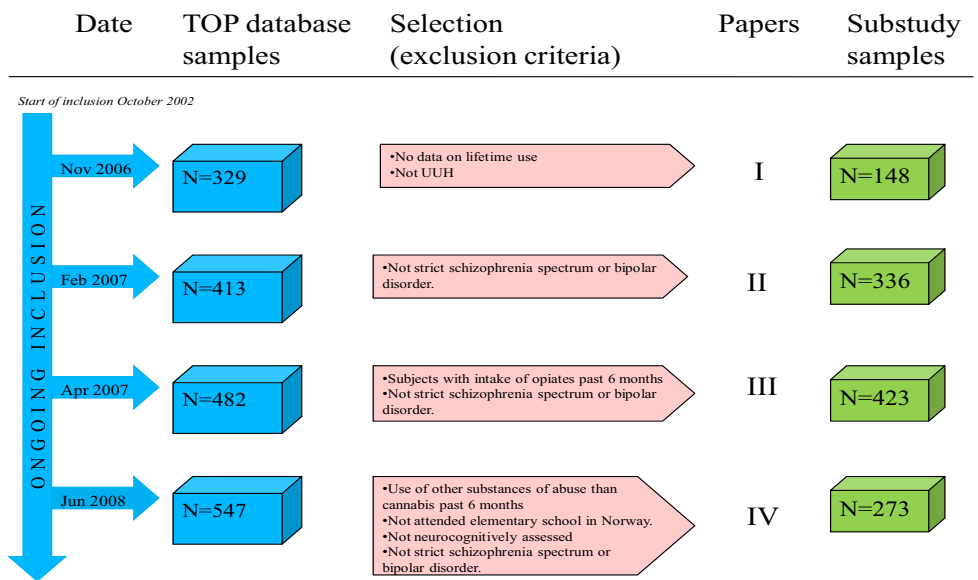
For the remaining papers patients with MDD, delusional disorder or brief psychotic disorder were excluded in order to make comparisons between stricter schizophrenia and bipolar disorder groups.

In paper two, the study sample consisted of 336 patients recruited until October 2006.

In paper three, the study sample was 423, recruited until October 2007. As this paper dealt with associations between psychosis-related symptoms and substance use, it focused on substances known to induce psychosis. As opiates may have a psychosis-protecting effect (Brizer *et al.* 1985), subjects with reported consumption of an opiate agonist during the past 6 months prior to inclusion were excluded.

In paper four, the study sample consisted of 273 patients, recruited until October 2007. As this study focused on neurocognitive function, the study sample was restricted to subjects who had been neurocognitively assessed and that had attended elementary school in Norway. Subjects with use of other substances of abuse than cannabis during the past 6 months were excluded in order to explore associations with cannabis use specifically.

Figure 2. Sampling procedure for the four individual substudies of the current thesis.



Dates in arrows indicate time of generating working file from TOP Main Clean File.

3.3. Methods

Assessments of diagnosis

Diagnosis was established using the Structural Clinical Instrument of Diagnosis for DSM-IV axis I disorders (SCID – I), modules A-E. All interviewers participated in regularly diagnostic consensus meetings led by a clinically well experienced professor of psychiatry. In addition, all raters finished a training course in SCID assessment based on the training program at the UCLA (Ventura *et al.* 1998). Mean overall Kappa for SCID diagnoses assessed by the UCLA procedure was 0.77. To assess reliability for actual study interviews a stratified random sample was drawn, consisting of cases from every assessment staff member. Anonymous vignettes describing symptoms and development of the illness were then rated by two experts blind to the study ratings. For the 28 vignettes the overall agreement for the nine DSM-IV diagnostic categories was 82 % and the overall Kappa again 0.77 (95 % CI: 0.60-0.94).

Assessment of sociodemography, functioning, symptoms and treatment

Symptoms were assessed by the Inventory of Depressive Symptomatology (IDS) (Rush *et al.* 1996) and the Positive and Negative Symptoms Scale (PANSS) (Kay *et al.* 1987). Global symptoms and psychosocial functioning were measured by the Global Assessment of Functioning Scale (GAF), and the scores were split into scales of symptoms (GAF-S) and functioning (GAF-F) to improve psychometric properties (Pedersen *et al.* 2007). Premorbid functioning was assessed by the Premorbid Adjustment Scale (PAS) (Cannon-Spoor *et al.* 1982). PAS scores were divided into Academic and Social domains according to premorbid age intervals (Larsen *et al.* 2004). Increasing scores on PAS signify poorer functioning and higher GAF scores signify fewer symptoms. For the rest of the symptom scores, high scores signify more symptoms. The intraclass coefficient (ICC) (Shrout and Fleiss, 1979) was 0.82 (95% CI: 0.66-0.94), 0.76 (95% CI: 0.58-0.92) and 0.73 (95% CI: 0.54-0.90) for PANSS positive, negative and general subscales respectively. The ICC for GAF-S was 0.86 (95% CI: 0.77-0.92), and for GAF-F 0.85 (95% CI: 0.76-0.92).

Data were collected about smoking habits, ethnicity, education, occupation, housing, marital/civil status and current psychopharmacological medication.

Neurocognitive assessment (paper four)

A comprehensive neuropsychological test battery was administered to all participants by psychologists or test technicians trained by a specialist in clinical neuropsychology. Tests from domains found to be sensitive to dysfunction in groups with cannabis use, bipolar disorder or schizophrenia were included. These were tests of psychomotor speed, attention,

working memory, executive functioning, verbal learning and tests of intellectual capacity. The tests are described in detail in the Methods section of paper IV.

Substance use assessment

Subjects were asked about type of drug ingested and total incidents of drug use during the last 14 days, 6 months and 24 months. They were also asked about their first time experience with drugs. In addition substance use disorders were diagnosed through the SCID-E module. All participants were screened for the presence of recreational drugs in the urine one hour prior to neurocognitive assessment.

Records were made of daily tobacco use and coffee drinking. For each of the substudies drug-positive urine samples were tested against self reported use, and reliability of self-report was deemed to be high for all of the sub-study samples.

3.4. Statistical analyses

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) versions 14.0 and 16.0 was used. Analyses included descriptive analysis (means and SD) and calculation of proportions. All tests were 2-tailed. Limits for significance were set at the 0.05 level or the 0.01 level (two-sided) depending on number of comparisons. For continuous data group differences were evaluated with independent two-sided *t*-tests in normally distributed data, and Mann-Whitney tests in skewed data. Group differences in categorical variables were explored with Chi-square or Fisher exact tests. Differences between multiple groups in normally distributed continuous variables were analyzed with factorial One-Way Analyses of Variance (one-way ANOVA) and post hoc Bonferroni tests were applied to control for multiple testing when considered appropriate. Correlations between variables were explored through Pearson or Spearman rank correlations according to type of data. Logistic regression analyses was used to control for potential confounders for categorical variables, and hierarchical multiple linear regression analysis was used to control for possible confounders for continuous variables.

Statistical analyses particular to each substudy have been thoroughly described in the four papers, and the reader is referred to them for further details.

3.5. Ethical aspects

Ethical challenges

The current research involved clinical interviews and cognitive testing, as well as somatic screening including urine analyses, all including highly sensitive personal information. Informed consent and confidentiality were thus central ethical issues. Despite rather comprehensive and time consuming assessments, the burden for each participant was similar to a thorough clinical diagnostic interview, and no interventions were performed. Thus the burden for each participant was considered acceptable. The project was performed with the approval of the Regional Ethics Committee (ref # 493-03-01179).

Data collection and handling

It was important that the participants knew how the collected information would be used and stored, and that measures to ensure confidentiality were secure. The following procedure is considered to have ensured this: Each participant had the study explained by a MD or a psychologist and received a written explanation covering the following: purpose of study; extent of investigations and interviews; personal information to be stored; how confidentiality would be maintained; time of project finish. Patients were explicitly informed; both orally and in writing, that participation in the study was voluntary, and that refusal to participate would not have any consequences for their future treatment. They were also informed of their right to see all data, and their right to have all data deleted at any occasion. Written informed consent was obtained prior to study participation. The collecting and handling of data were approved by the Norwegian Data Protection Agency (ref # 2003/2052) to preserve the personal privacy of the participants.

The TOP database was inspected and approved by the Clinical Monitor at Ullevål University Hospital (Audit Certificate 12.03.07). All personal information was treated with the same confidentiality as required within the EU countries medical system, and the only persons with access to personal information will be health care professionals with a duty of confidentiality. All personal identifiers were removed, and only a numerical code was used as identifier. This code was stored at a similar security level as the ordinary patient data elsewhere in the hospital system.

Participant perspective

The total evaluation time was several hours, something that sometimes was experienced as tiresome. In the case that the participants so wished, or in case the research fellow thought that the participant was not able to cooperate optimally, the assessments were divided over

several days. Pauses were frequent and encouraged by the professionals. The project covered expenses related to transport by taxi.

If the patient agreed to it, the clinician in charge of the treatment would receive a report on clinical findings, diagnostic evaluations and neuropsychological test results. The impression was that the evaluations provided by the TOP team were experienced as highly useful by both patients and clinicians.

Patients with these disorders are usually clearly capable of informed consent. However, as cognitive abilities may be affected, the written information was supplemented by thorough verbal information.

The experience was that most patients agreed to participation. The motivation for participating was, in addition to the contribution with new knowledge, that participants had the opportunity to have a more comprehensive evaluation of something the patients themselves experienced as a disturbing condition.

4. Results/Summary of papers

(Figures in appendix)

Paper I: Illicit drug use in patients with psychotic disorders compared with that in the general population: a cross-sectional study

Background: Prevalence estimates of illicit drug use in patients with psychotic disorders vary between studies, and only a few studies have compared prevalence estimates with those in the general population.

Method: Cross-sectional study comparing 148 stable-phase patients with schizophrenia or bipolar disorder with 329 representative general citizens of Oslo. A total of 849 patients from the same hospital department in the same time period constituted a patient reference group.

Results: Lifetime illicit drug use was 44% higher ($P < 0.001$) in study patients than in the general population sample; while lifetime use of amphetamine/cocaine was 160% higher ($P < 0.001$). No differences were found between substance users in the patient group or the general population for sociodemographic characteristics.

Conclusion: Patients with psychotic disorders in stable phase had a markedly higher lifetime use of any illicit substance, especially amphetamine/cocaine, than the general population. They also seemed to use drugs more periodically. The same sociodemographic characteristics were associated with increased illicit drug use in both patients and the general population.

Paper II: Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder

Background: Schizophrenia and bipolar disorder have partly overlapping clinical profiles, which include an overrepresentation of substance-use behaviour. There are few previous studies directly comparing substance-use patterns in the two disorders. The objective of the present study was to compare the prevalence of substance use in schizophrenia and bipolar disorder, and investigate possible differences in pattern and frequency of use.

Method: A total of 336 patients with schizophrenia or bipolar spectrum disorder from a catchment area-based hospital service were included in a cross-sectional study. In addition to

thorough clinical assessments, patients were interviewed about drug-use history, habits and patterns of use. The prevalence and drug-use patterns were compared between groups.

Results: Patients with bipolar disorder had higher rates of alcohol consumption, while schizophrenia patients more often used centrally stimulating substances, had more frequent use of non-alcoholic drugs and more often used more than one non-alcoholic drug. Single use of cannabis was more frequent in bipolar disorder.

Conclusion: The present study showed diagnosis-specific patterns of substance use in severe mental disorder. This suggests a need for more disease-specific treatment strategies, and indicates that substance use may be an important factor in studies of overlapping disease mechanisms.

Paper III: The level of illicit drug use is related to symptoms and premorbid functioning in severe mental illness

Background: There is conflicting data on drug abuse and outcome in severe mental illness. This study aimed to investigate if the current amount of illicit psychoactive drug use is related to symptom load or premorbid functioning across diagnosis in patients with severe mental illness.

Method: Symptom load, sociodemographic status, premorbid functioning and the level of use of illicit psychoactive drugs (amphetamine, cocaine, cannabis and ecstasy) was assessed in 423 subjects with schizophrenia or bipolar disorder in a cross sectional study.

Results: In schizophrenia there was a significant positive association between current amount of drug use and severity of psychiatric symptoms which was not found in bipolar disorder. For general symptoms there was a significant interaction effect between use groups and diagnostic groups, indicating an increase in general symptoms for the schizophrenia group with increasing use, but a decrease in the bipolar disorder group. High amount of illicit drug use was associated with poorer premorbid academic functioning in the whole sample. The association between symptom load and drug use was reduced but still significant after controlling for premorbid functioning.

Conclusion: The results indicate that the quantity of current drug use is related to more severe symptom load in schizophrenia, suggesting a direct association to drug use. However, high

amount of use was related to worse premorbid functioning in both disorders, indicating that predisposing factors also explain some of the symptom load.

Paper IV: Opposite relationships between cannabis use and neurocognitive functioning in schizophrenia and bipolar disorder

Background: Cannabis use is reported to be associated with altered neurocognitive functioning in severe mental disorders, but data is still inconclusive.

The study aimed to investigate the association between cannabis use and neurocognition in schizophrenia and bipolar disorder.

Method: 273 patients with schizophrenia or bipolar disorder underwent neuropsychological assessments and clinical characterisation including measures of substance use. Relationships between cannabis use and neurocognitive function was explored in the two diagnostic groups.

Results: In schizophrenia subjects, cannabis use was associated with poorer neurocognitive function, but the opposite was the case for the bipolar disorder subjects. These differences in neurocognitive function could not be explained by putative confounders.

Conclusion: The interaction effect of cannabis use with diagnosis suggests that cannabis use is differently related to neurocognition in bipolar disorder and schizophrenia.

5. General discussion

5.1 Methodology

5.1.1 Sample representativity

Selection bias may have occurred at various levels:

Source population for sample recruitment bias

As the Norwegian health care system is catchment area based and publicly funded, hospital affiliation is not biased for the actual geographic catchment area region or socioeconomic class. The study sample represented unselected cohorts; recruitments were distributed in time within a time interval of approximately four years. This distribution made the variables investigated less susceptible of measuring rapid transient variations in the society. The source population would only be biased if the population of the geographic catchment areas were not representative of the general population, but in the present case the source population is nearly identical to the total population of Oslo and some surrounding communities.

Health care receiving population bias

There were the following sources of bias in the psychiatric health care receiving population (inpatients and outpatients receiving treatment at the cooperating hospitals):

1. Chronicity issues:

In a sample of patients receiving specialized treatment there would be a probable over-representation of patients with a chronic course of their illness. However, some patients with persistent illness are living with stable functioning in their own homes or other institutions and receiving any necessary care from the primary health care system; this could lead to de-selection of stable patients with chronic-course or partial remission. In addition, some patients have only a marginal level of functioning, but have chosen not to receive recommended health care and are normally not fulfilling criteria for compulsory treatment; this would imply de-selection of the described patient category (but this group is however probably very small). The existence of patients with chronic psychosis that are not treated in the hospital system modifies the likely bias towards chronic course.

2. Drop-outs:

A number of patients admitted to the emergency ward for psychosis or severe depression are referred to further treatment at the outpatient clinics, but drop out. As most of the

inclusion took place in the outpatient clinics, this could bias the sample towards subjects with more factors promoting treatment adherence, as for instance social stability/network. Such factors have close correlation with risk factors for substance abuse; the result would be an under-representation of substance use in the hospital population.

Outpatient recruitment procedure bias

Subjects had to be deemed capable of cooperating in the interviews and giving informed consent; this prevented some patients in an exacerbation phase and a lesser number of patients with permanent severe impairments to be included at a given point in time. Likely conditions to predict failure to participate are strong paranoid delusions/ideation, massive negative symptoms or severe cognitive deficits. However, as the inclusion period ran over several years, most possible subjects should eventually be targeted for inclusion after remission of an acute episode.

Personal factors in the cooperating outpatient clinic professionals (physicians, psychologists, nurses or specialised social workers) could affect their judgement or inclination to attract or motivate candidates. A less skilled professional could be more uncertain in his/hers evaluations and thus have higher thresholds for recruiting. Such a factor would bias the sample towards better functioning. Some professionals might also have antipathic convictions against research or for some unprofessional reason be overly protective on behalf of “their” patients. Possible bias from this would be harder to predict, but it is likely that poorer functioning would become under-represented. Effort was put on integrating the project in all parts of the hospital organization, and local leaders cooperated with the research fellows located at the outpatient clinics to inform, educate and motivate the clinicians; thus aiming at obtaining maximal recruiting rates, and minimal personal bias. Research fellows also participated regularly in forums which enabled them to get an overview of circulating patients and thereby recognize possible research subjects. The number of recognized recruitable patients of the UUH that declined to participate, or were not included for other reasons, was by autumn 2008 57 of a total of 430 (13 %). Due to the Norwegian person data security act, further information on the non-recruited patients was inaccessible.

Using the U600 study involving all patients (n=1002) from the UUH, TOP patients in that sample were compared with non-included patients on reported drug use and the rates of reported use were highly similar between groups (Paper I). There were no significant statistical differences between the TOP study sample and the patient reference group (U600) in mean age or gender distribution. This indicates that the patients participating in the TOP study are highly representative for the total patient population in their levels of substance use.

The prevalence of substance use found in the U600 study was somewhat lower than the prevalence numbers found in the TOP study sample of paper I (15.2 % vs. 23.0 % respectively). A higher degree of substance use reported in the TOP study could be explained by the more thorough examination in the TOP study than in the U600 study, with consequently greater likeliness to detect substance use. The prevalence number of substance use of the TOP study sample of paper I is slightly lower than the prevalence number obtained in the most recent main TOP study sample (N=547) from June 2008 used in paper IV (25.6 %); there are thus no indications of a positive selection bias of substance use in the sample used in that paper relative to the largest main TOP sample.

Implications of bias for interpretation of the results

The recruitment procedure did not seem to de-select substance abusers to the TOP sample according to the comparison with the U600 study. The psychiatric health care receiving population might have some bias towards lower rates of substance use relative to the total population with psychotic disorder which would affect the present prevalence estimations.

5.1.2 Validity and reliability of assessments

All instruments used in the current thesis are widely used and have their validity well documented (see Methods). The PANSS is developed for schizophrenia, and in this thesis the instrument has been applied to bipolar disorder as well. However there are several studies using the PANSS in bipolar disorder, and serious validity problems have not been encountered (Daneluzzo *et al.* 2002; Nitsche and Kallert, 2007).

Reliability of self report of drug use (and thus the validity of the main drug use measure) was controlled with urine tests in different samples and was shown to be high. In paper I, one of ten positive urine tests on illicit substance had a false negative report. Several key measures are based on self-report and thus imply some uncertainty even if both self-reports of substance use (Weiss *et al.* 1998), and PAS data (Brill *et al.* 2007) previously have been shown to have a high degree of validity. SIRUS used phone interviews, which has been shown to have a high degree of agreement compared to face to face interviews (Wells *et al.* 1988).

In order to optimise reliability, all interviewers in the TOP study participated in standardised training in all parts of the protocol. Tests for inter-rater reliability were conducted for the SCID diagnoses, PANSS and GAF scores and showed very good to excellent results; with a kappa for concordance of diagnosis of 0.77, ICC for PANSS general of 0.73 and ICC for GAF-S of 0.86 (for details see Methods).

Apart for a possible 10 % underestimation of substance use by self report, there is thus no specifically suspected uncertainty of the current findings due to methodological problems with the assessments.

5.1.3 Limitations of the design

The cross-sectional design does not enable conclusions about cause and effect. However, the use of a measure of premorbid function, which is clearly preceding current drug use, allows for some causative assumptions. The problem with causality arises with most studies of the pathological mechanisms of substance use in humans. There are serious ethical issues related to randomization, which makes such studies impossible. Furthermore, longitudinal studies are also limited by a naturalistic design, so there is a limited possibility to study causality. One of the very few interventional studies done in the field is referred to (D'Souza *et al.* 2005), but as a laboratory study it has other limitations.

The primary and secondary main aims of the thesis involve study of 'psychotic disorders'. The participation of patients without a history of psychosis in the bipolar disorder group may thus confound the interpretation of the results according to the role of psychosis. If psychotic experiences are core clinical factors in explaining phenotypic variation in severe mental illness, delineation between psychosis and non-psychosis would be appropriate inside the bipolar disorder group. A widely defined bipolar disorder group could therefore bias the results towards greater phenotypic differences between schizophrenia and bipolar disorder in the current study than had been the case if only BD I and BD II with psychosis had been selected. However, as clarified in the introduction, 'psychotic disorder' is here defined as conditions associated with a high propensity to evolve psychotic states; patients with BD II and MDD (participating in paper I) have a significantly elevated risk for evolving psychotic episodes compared to patients with psychiatric illness in general.

Although the main sample size is large compared to other studies, the sample was not large enough for doing elaborate analyses of all subgroups of interest.

The assessments are limited to registration of reported use; information about subjective preferences or experiences is thus not recorded. Such information would have added more to the patient perspective, and information on motivation for use would have improved the understanding of mechanisms leading to substance use in this patient group.

There is no information on the content of THC and other active substances in the reported consumed cannabis, which is of relevance when considering pharmacological effects. Unknown active substances could affect the results, and give greater variation in the

data with less probability for finding significant associations. Furthermore, a possible uneven distribution between groups could cause bias. Specifically, could a possible antipsychotic effect of e.g. cannabidiol or other compounds complicate interpretation of the results.

The clustering of different substances in several of the analyses is not unproblematic as substances have different effects on the CNS which can lead to confounding. However, in paper III the selection of substances was based on a common psychosis-inducing ability. In paper II a delineation was made between alcohol and other substances as alcohol use is much more prevalent than other substance use and there are several studies indicating that alcohol use patterns, motivators or consequences may be different from those for cannabis or centrally stimulating drugs within diagnostic groups or between diagnostic groups (Gregg *et al.* 2007; Potvin *et al.* 2007c; Strakowski *et al.* 2007).

Possible systematic differences in drug use between schizophrenia and bipolar disorder patients from time periods before our assessment window are not accounted for, and represent potential confounders.

The groups of drug use levels were created by a median-split design, and the threshold for “high-use” was set at a level of 9 incidents of substance use and above the past 6 months, something that not necessarily corresponds to a clinically or pharmacologically meaningful threshold. This level would by many not be regarded as “high use”, and a low threshold for high use could reduce the probability of finding significant associations between levels of use and symptoms. In addition, some aspects related to very high level of substance use could be missed. However, the purpose was not to study pharmacological effects.

Paper IV included many neuropsychological tests. There is a continuous debate about the specificity of the cognitive measures. It can be argued that the neuropsychological tests are different measures for broader domains, and that their selection into the study is hypothesis-driven. In the verbal memory/learning domain, there were associations with cannabis use on logical memory; the findings are strengthened by similar findings in closely related CVLT subtests. Adjustment for multiple tests was thus not considered to be a self-evident part of this paper, but the risk for type I error should be considered. The unequal sample sizes in paper IV between cannabis users and non-users and a possible greater variation the cannabis using group may lead to problems with interpreting the ANOVA analyses, over-reporting of significant differences may result.

5.2 Discussion of main results

The main findings of the present study can be summarised in the following points:

1. Patients in a combined sample of schizophrenia and bipolar disorder had higher levels of non-alcoholic substance use than the general population. This was especially pronounced for use of amphetamine or cocaine.
2. There was a significant positive association between current amount of non-alcoholic substance use and severity of psychiatric symptoms in the schizophrenia group.
3. High amount of non-alcoholic substance use was associated with poorer premorbid academic functioning in both disorders.
4. Comparisons of substance use behaviour in schizophrenia and bipolar disorder yielded different results:
 - a. Schizophrenia patients more often used centrally stimulating substances, had more frequent use of non-alcoholic drugs and more often used more than one non-alcoholic drug.
 - b. Patients with bipolar disorder had higher rates of alcohol consumption and had more frequently single use of cannabis.
5. Cannabis use showed an interaction effect with diagnosis on neurocognitive functioning; in schizophrenia cannabis use was associated with poorer neurocognitive functioning whilst in bipolar disorder cannabis use was associated with better neurocognitive functioning.

Higher prevalence of non-alcoholic substance use in psychotic disorder

In the comparisons with the general population, our findings of over 40 % higher lifetime prevalence of any illicit substance use are similar to other studies' findings. The over 150 % higher prevalence for amphetamine/cocaine use in our mixed schizophrenia and bipolar disorder sample is however previously unreported. The estimated prevalence of recent and medium term illicit drug use in the patient sample is in the lower range of estimates from other studies of psychotic disorder populations (Green *et al.* 2005; Cantor-Graae *et al.* 2001; Kavanagh *et al.* 2004). One explanation for this difference could be that most studies of illicit drug use in psychotic patients are done in samples from acute care settings or first-episode samples. Such acute samples may – due to the effect of drug abuse in precipitating

psychotic episodes – have an overrepresentation of drug using patients relative to the total patient population with psychotic disorder.

The study found similar relationships between drug use and being single and having lower educational levels for both patients and controls. While there were clear differences in life-time use of non-alcoholic substances, the differences in medium term use were small and did not reach statistical significance. For recent use no differences were seen at all. The ratio of illicit drug use in patients versus controls thus seemed to increase with increased observational time, suggesting differences in patterns of use in patients versus healthy controls. Reports from periods with short observational windows make it more difficult to detect use in individuals with mainly periodic use. The current data thus suggest that patients with psychotic disorders may have a more periodic pattern of illicit drug use than what is the case for the general population. This may be in line with a supersensitivity model where patients with psychosis are less likely to sustain moderate substance use over time without negative consequences (Mueser *et al.* 1998).

Positive association between amount of non-alcoholic substance use and severity of psychiatric symptoms in schizophrenia

The association between more severe current psychopathology and use of psychoactive illicit substances in schizophrenia seems to be true only for a certain amount of use.

Higher levels of amphetamines in urine in substance induced psychosis has been related to higher PANSS positive, general and total psychopathology scores (Batki and Harris, 2004), but a relationship between level of reported recent drug use and current symptom load has not been shown earlier in a sample of mainly stable outpatients. There are few studies investigating quantity of use, but the current results are in contrast to earlier findings in schizophrenia showing no association between symptom load and level of cannabis use (Hamera *et al.* 1995). The results may be in line with previous suggestions of substance use secondary to psychosis in order to alleviate symptoms (Khantjian, 1985) and that patients may use more drugs because of higher symptom levels (Mueser *et al.* 1998). The findings can however be interpreted in line with experimental studies showing increase in positive, negative and general symptoms after drug administration in schizophrenia (D'Souza *et al.* 2005), and the association may suggest that the negative effect of psychoactive drugs is directly related to current use. Premorbid functioning was not found to be a confounder, indicating an association between symptoms and drug use independent of predisposing

factors. The present findings indicate that drug use has important clinical implications, even in patients who do not meet the criteria for a DSM diagnosis of abuse or dependence, and that quantity of use may be a relevant factor independently of eventual aversive effects leading to a diagnosis of abuse or addiction.

Poor premorbid functioning was associated with level of drug use in psychotic disorder

The observed relationship between current drug use and premorbid functioning indicates that poorer premorbid functioning might be a risk factor for later development of drug use behaviour in patients with severe mental illness. Poor academic functioning may be an early susceptibility trait for later problematic drug use in both schizophrenia and bipolar disorder patients.

This is in line with earlier reports of increased likelihood of drug abuse disorders related to poor premorbid academic functioning (Larsen *et al.* 2006). Environmental factors in the childhood and adolescence could influence both premorbid functioning and susceptibility to later drug use. Another possible explanation is a common biological susceptibility for developing both drug abuse and severe mental illness (Chambers *et al.* 2001).

Different substance use patterns in schizophrenia and bipolar disorder

Clear differences in the substance use patterns of schizophrenia and bipolar disorder patients were found. Patients with bipolar disorder had higher rates of alcohol consumption, while schizophrenia patients more often used centrally stimulating substances, had more frequent use of non-alcoholic drugs in general and more often used more than one non-alcoholic drug. These characteristics would not have been revealed through a diagnosis of abuse or dependence only, which shows the importance of evaluating substance use beyond the abuse or addiction diagnosis when the relationship to severe mental disorders is studied.

About twice as many schizophrenia patients as bipolar patients were abstaining from alcohol and twice as many bipolar patients could be defined as having harmful use of alcohol than schizophrenia patients. High rates of alcohol abuse in bipolar patients have been reported in numerous studies (Sherwood Brown *et al.* 2001). Alcohol use may induce affective, and most often depressive, episodes (Strakowski *et al.* 2000) and one could speculate about the existence of mechanisms linking alcohol-use to bipolar disorder specifically.

Studies concerning alcohol consumption in patients with schizophrenia have been more diverging. In line with the current results several studies report lower rates of alcohol consumption in schizophrenia patients than in the general population (Etter and Etter, 2004; Picchioni and Murray, 2000). This could be due to possible mechanisms linked with schizophrenia that limit alcohol use, such as lower income or less social interactions. A higher prevalence of abstaining in the schizophrenia group could represent previous problematic use, although no association between a lifetime diagnosis of alcohol abuse/dependence and current abstaining was found. Many studies, however, show higher rates of alcohol use disorders among schizophrenia patients as compared to healthy controls (Farrell *et al.* 1998; Green *et al.* 2007) and schizophrenia patients have been found to show increased euphoric and stimulatory responses to alcohol (D'Souza *et al.* 2006).

Our findings regarding prevalence of use of centrally stimulating substances in schizophrenia and bipolar patients per se are more or less in line with other studies (Winokur *et al.* 1998; Mueser *et al.* 2001; Chengappa *et al.* 2000; Kilbourne *et al.* 2004). The higher proportion of stimulant use in the schizophrenia group compared to the bipolar group is however different from earlier comparisons between the two diagnostic groups, which found the prevalences to be more similar (Mueser *et al.* 1992; Verdoux *et al.* 1996), or with higher prevalence in the bipolar disorder group (Regier *et al.* 1990). Overall cannabis use did not differ between diagnostic groups after controlling for age and gender.

When individuals with schizophrenia used non-alcoholic drugs they tended to have more polysubstance use and a higher frequency of use. Non-alcoholic drug users with bipolar disorder on the other hand, more often used only cannabis. Bipolar disorder patients generally showed a stronger tendency for mono-use than the schizophrenia group. Preference for limited use of one type of substance could possibly reflect better functioning in the bipolar disorder group, as one would expect a higher level of discriminative ability in order to maintain a more selective use pattern. The fact that bipolar disorder patients are indeed reported to have less cognitive deficits than schizophrenia patients (Daban *et al.* 2006) could support this interpretation.

The findings from our investigation of the different substance groups could be related to self-medication of symptoms, as indeed studies showing that patients with particular diagnoses select specific substances have been considered to be able to add to such evidence (Mueser *et al.* 1998). Depressive symptoms in bipolar patients have been reported to motivate for and be alleviated by substance use (Weiss *et al.* 2004). The finding that negative symptoms are in some studies reported to be milder in schizophrenia patients with substance

use disorder (Joyal *et al.* 2003; Potvin *et al.* 2006; Talamo *et al.* 2006), may also fit into this view.

Associations between cannabis use and neurocognitive functioning in schizophrenia and bipolar disorder

We found opposite associations between cannabis use and measures of verbal memory and executive functioning in schizophrenia and bipolar disorder. The interaction effects remained significant also after controlling for potential confounders.

In the schizophrenia group, the neuropsychological test performance was poorer in the cannabis users compared to the abstainers on all measures; reaching statistical significance for attention, executive functioning and verbal memory.

In the bipolar disorder group, the neuropsychological test performance was numerically better in most of the measured areas for cannabis users, but reached statistical significance only for executive functioning. Our findings of an interaction effect may explain why the only previous study investigating a mixed diagnostic sample (Liraud and Verdoux, 2002) did not find any association between cannabis use and neurocognition as this study did not examine the diagnostic groups separately.

It is of interest that cannabis use was not related to differences in general cognitive functioning, but rather associated with differences in specific domains of cognition. The finding of a negative association with verbal memory in schizophrenia patients was as expected from earlier studies (D'Souza *et al.* 2005), but the positive associations in bipolar disorder were unexpected. There are several psychoactive components of cannabis, with potentially different neurochemical effects (Morgan and Curran, 2008). Drugs modulating brain signalling can hamper cognition, while others may also enhance certain types of cognitive performance (Turner *et al.* 2004). The putative effect might however be indirect, and related to other factors. For instance, the anxiolytic effect of cannabis could improve cognition in patients with high level of co-morbid anxiety (Simon *et al.* 2004), as anxiety may interfere with attentional control and thus cognitive performance (Eysenck *et al.* 2007). In our sample, anxiety ratings were equal for the two diagnostic categories. However, bipolar disorder patients with cannabis use had significantly lower anxiety ratings on the PANSS G2 item than non-users; which was not the case in the schizophrenia group. In this cross-sectional study one cannot discern whether cannabis use has different effects in the two disorders, or whether there are different subgroups of patients that are at risk for cannabis use in the two

diagnostic groups. A possible preference for the best functioning bipolar disorder patients and the poorest functioning schizophrenia patients to use cannabis could be an alternative explanation for the results, but this seems less likely as controlling for premorbid functioning did not affect the interaction of diagnosis and cannabis use on neurocognitive functioning.

The present study is apparently also the first to report of an association between cannabis use and altered neurocognitive functioning in bipolar disorder. The findings may indicate that improved cognition is related to current cannabis use in these patients. However, the statistical association was weak, and would not remain significant after a correction for multiple comparisons.

The findings in the schizophrenia subjects of an association with cannabis use and worse performance on the Interference tests supports the findings of Liraud & Verdoux (Liraud and Verdoux, 2002). The findings of poorer verbal learning/memory and attention are in line with the findings of acute cannabis effects by D'Souza and colleagues (D'Souza et al. 2005). However, there are still unsolved questions, as improved cognition in the areas of attention and executive function has been indicated to be related to relatively current cannabis use in subjects with schizophrenia (Sevy *et al.* 2007; Coulston *et al.* 2007a).

Comparison Schizophrenia – Bipolar disorder; continuum theory of psychosis

The following differences between the two diagnostic categories are reported in the current study:

- Clear differences in drug use patterns. Schizophrenia patients had more stimulant and polysubstance use; bipolar disorder patients had more alcohol use.
- An interaction effect of level of drug use with diagnosis on general symptom level. With higher levels of drug use the trend was for symptoms to be higher in schizophrenia and lower in bipolar disorder.
- An interaction effect of cannabis use with diagnosis on neurocognitive functioning. Cannabis use was associated with poorer neurocognitive performance in schizophrenia but better neurocognitive performance in bipolar disorder.

The differences suggest there are different mechanisms underlying substance use behaviour, symptom formation and neurocognitive functioning in bipolar disorder and schizophrenia. Pharmacological actions of ingested substances could be different and thereby affecting the

pathophysiological mechanisms differently in the two disorders. On the other hand, characteristics of patients pertaining to a diagnostic category could influence substance use behaviour differently in the two disorders. Different substance preferences between diagnostic groups could reflect a possible role of self-medication through differences in the substances' effect on symptoms; i.e. that bipolar patients tend to use substances that are “relaxing” such as alcohol and cannabis while schizophrenia patients use more centrally stimulating agents. However, some symptomatic and cognitive domains were not affected in different directions and the association between drug use and premorbid functioning did not differ between diagnoses.

The current findings may have implications for the conceptual understanding of the disorders. The differences found between the diagnostic categories seem to be in opposition to a theory of a continuous psychotic-disorder spectrum (Craddock and Owen, 2007; Crow, 1986), and strengthen the validity of a categorical approach. However, the findings do not necessarily contradict the continuum theory as drug use patterns show considerable overlap, and could also be operating along a continuum. The pattern of substance use behaviour found in the schizoaffective disorder group could support a possible “in-between” position, but due to the low number, the results are difficult to interpret.

Discussion of underlying mechanisms

If replicated, the current findings raise important questions about causality which the papers of this thesis cannot answer. However, the current results may form the basis of some speculation about underlying mechanisms. The central question is thus: do psychotic symptoms or level of neurocognitive functioning cause substance use behaviour or does substance use behaviour cause psychotic symptoms or influence level of neurocognitive functioning?

Secondary psychiatric illness models

As mentioned earlier, acute substance use can cause transient increase in symptoms and decline in neurocognitive functioning (D'Souza *et al.* 2004). Further evidence indicates persisting effects with early onset and prolonged substance use of some magnitude (Lambert *et al.* 2005; Moore *et al.* 2007). The literature thus indicates that some “pharmacological” effects of substances seem probable. How could this hypothesis fit with the current data? The current study was not designed for the study of pharmacological effects, but in papers III and

IV, associations with substance use and outcome measures were found. As the current study did not focus on ongoing use, only a smaller proportion of subjects labelled “substance users” had positive urine tests of illicit substances. Acute direct effect of substances does thus seem a less probable explanation of the current findings. However, effects of long-term chronic substance use cannot be ruled out. Another explanation could be that the group of long-term chronic substance use also used drugs in the critical period before illness onset, thus triggering illness development, and current symptom profile is secondary to the illness. Findings from longitudinal studies (Caspi *et al.* 2005), where low grade substance use in adolescence was shown to increase risk for later psychotic experiences in genetically vulnerable individuals, may make such speculations relevant. Long-term follow up studies or careful assessment of premorbid substance use could help to answer this question.

Secondary substance use disorder models

Symptoms may lead to substance use behaviour if unpleasant symptoms are experienced to be relieved by drug intake. Cross sectional data are hard to interpret in this context as both a high and a low level of symptoms associated with substance use could be taken as signs of self medication effects. It is nevertheless considered plausible that such effects are at play and could lead to some of the current results. Records of personal experiences could have helped clarifying this.

Common factor models

The more probable causative factors include common factors which individually increase risk for both psychosis and substance use. Both conditions are associated with impairment in frontal lobe functioning, something which may predispose to impairment in judgement (Bechara *et al.* 1994; Damasio *et al.* 1994). Psychosis can be regarded as a loss of ability to discriminate between internal or external stimuli, and abnormal assignment of salience to stimuli has been proposed as a possible basis for development of psychotic experiences (Jensen *et al.* 2007). The crucial role of substances of abuse in affecting the mesolimbic dopaminergic system thought to be responsible for regulating salience is widely accepted. On this basis an intriguing hypothesis is the existence of common biological vulnerability or shared genetic factors for both substance use behaviour and psychosis, as proposed by Chambers and colleagues (Chambers *et al.* 2001). Impairment in neurocognitive functioning could be related to both genetic and environmental factors and could increase risk for both psychotic disorder and substance use. If neurocognitive impairment was related to psychotic

experiences, the association between substance use and neurocognitive impairment would be stronger in the schizophrenia group than in the bipolar disorder group and could thereby possibly account for some of the current findings. Sociodemographic factors may also independently increase risk for symptoms, neurocognition and substance use. As bipolar disorder patients have better socioeconomic functioning than schizophrenia patients such interactions could also affect the current results.

This brief discussion of possible etiological associations is based on limited knowledge, but it seems probable that the cause-effect interactions are highly complex and multidirectional.

Clinical implications

Assessment of substance use should be an important part of the standard psychiatric interview. The current findings show that variations in substance use have clinical significance, and give reason to adopt a fairly comprehensive approach to the exploration of substance use habits. It is important to notice that even sub-diagnostic substance use may have clinical implications. Furthermore, diagnosis of drug abuse or dependence is not the same as a precise description of drug use habits. A closer description of the substance use behaviour will convey information of a different type and beyond the information given in the diagnosis of drug abuse. The finding that 3-4 times more schizophrenia patients have had any use of amphetamines or cocaine than bipolar patients can be taken as a strong indication that either schizophrenia implies a stronger inclination to use this kind of drugs, that this kind of drug use gives a higher risk for schizophrenia, or that we have to look for a common confounder. This kind of information was lost when only the fulfilment of the DSM criteria of abuse was considered

The findings indicate that use of cannabis should be evaluated when assessing neurocognition in both schizophrenia and bipolar disorder. Eventual evidence of positive effects of cannabis on neurocognition in any disorder must be weighed against evidence for poor outcome in other areas of functioning. The evidence linking drug use/abuse with poor outcome in severe mental disorder (Cerullo and Strakowski, 2007; Henquet et al. 2006; Moore et al. 2007) must still be decisive for clinical advice.

The study shows an over-exposure of amphetamine and/or cocaine in the schizophrenia patient group. This should call for clinical concern, taking established knowledge of the detrimental effects on prognosis of these drugs into account.

Recent advances in treatment regimens for severe mental disorders with co-morbid drug abuse (Mueser *et al.* 2003) are based on general principles which stress the importance of individually tailored and integrated approaches. If the two main severe mental disorders differ in drug-use susceptibility and drug-use habits on group levels, then the planning of the health care services for these patient groups should be adjusted accordingly. This suggests a need for disease specific treatment strategies.

Future research

The current findings suggest that important information is lost when only considering fulfilment of the criteria for the DSM diagnoses of abuse or dependence. Future studies on substance use in severe mental disorder should include more comprehensive descriptions of substance use habits; as assessments of current and historic use patterns, including dose and type of preferred drug.

Future studies should focus on drug use patterns' possible association with other clinical measures as motivation for use and preferably also longitudinal aspects, as well as more biological parameters such as genetics and brain imaging.

The findings of different relationships with substance use in bipolar disorder and schizophrenia suggest that future studies should focus on clearly defined diagnostic or phenomenological categories; as different mechanisms might be at play in broad and heterogeneous diagnostic clusters.

The findings of opposite associations between cannabis use and outcome measures in schizophrenia and bipolar disorder indicate different underlying mechanisms, but should be replicated in independent samples. The interaction may suggest different psychopathological mechanisms underlying these symptom domains in bipolar disorder and schizophrenia, and more similarities in negative and positive domains. This is, however, speculative, and should be investigated with new studies targeting specific hypotheses.

6. General conclusions

- Patients with psychotic disorders seem to have a significantly higher lifetime prevalence of any illicit substance use compared to the general population.
- There seems to be over-exposure of amphetamine and cocaine in patients with psychotic disorders relative to the general population.
- The association between more severe current psychopathology and use of psychoactive illicit substances seems to be true only for a certain amount, and only in schizophrenia.
- There seems to be diagnosis-specific patterns of substance use in schizophrenia and bipolar disorder.
- The present findings of an interaction effect of cannabis use with diagnosis on neurocognition suggest that cannabis use is differently related to neurocognition in bipolar disorder and schizophrenia.

7. References

- Abi-Saab,W.M., D'Souza,D.C., Moghaddam,B. & Krystal,J.H. (1998). The NMDA antagonist model for schizophrenia: promise and pitfalls. *Pharmacopsychiatry* **31** Suppl 2:104-109.
- Addington,J. & Addington,D. (1998). Effect of substance misuse in early psychosis. *Br J Psychiat Suppl* **172**(33):134-136.
- Agartz,I., Brag,S., Franck,J., Hammarberg,A., Okugawa,G., Svinhufvud,K. & Bergman,H. (2003). MR volumetry during acute alcohol withdrawal and abstinence: a descriptive study. *Alcohol* **38**(1):71-78.
- Aghajanian,G.K. & Marek,G.J. (2000). Serotonin model of schizophrenia: emerging role of glutamate mechanisms. *Brain Res Rev* **31**(2-3):302-312.
- Antonova,E., Sharma,T., Morris,R. & Kumari,V. (2004). The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res* **70**(2-3):117-145.
- Arndt,S., Tyrrell,G., Flaum,M. & Andreasen,N.C. (1992). Comorbidity of substance abuse and schizophrenia: the role of pre-morbid adjustment. *Psychol Med* **22**(2):379-388.
- Arseneault,L., Cannon,M., Witton,J. & Murray,R.M. (2004). Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiat* **184**(2):110-117.
- Barak,Y., Baruch,Y., Achiron,A. & Aizenberg,D. (2008). Suicide attempts of schizophrenia patients: A case-controlled study in tertiary care. *J Psychiat Res* **42**(10):822-826.
- Barnett,JH., Werners,U., Secher,SM., Hill,KE., Brazil,R., Masson,K., Pernet,DE., Kirkbride,JB., Murray,GK., Bullmore,ET. & Jones,PB. (2007). Substance use in a population-based clinic sample of people with first-episode psychosis. *Br J Psychiat* **190**(6):515-520.
- Barr,A.M., Procyshyn,R.M., Hui,P., Johnson,J.L. & Honer,W.G. (2008). Self-reported motivation to smoke in schizophrenia is related to antipsychotic drug treatment. *Schizophr Res* **100**(1-3):252-560.
- Batki,S.L. & Harris,D.S. (2004). Quantitative drug levels in stimulant psychosis: relationship to symptom severity, catecholamines and hyperkinesia. *Am J Addict* **13**(5):461-470.
- Bechara,A., Damasio,A.R., Damasio,H. & Anderson,S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50**(1-3):7-15.
- Berman,S., O'Neill,J., Fears,S., Bartzokis,G. & London,E.D. (2008). Abuse of amphetamines and structural abnormalities in the brain. *Ann N Y Acad Sci* **1141**:195-220.
- Bolla,K.I., Cadet,J.L. & London,E.D. (1998). The neuropsychiatry of chronic cocaine abuse. *JNeuropsychiat Clin Neurosci* **10**(3):280-289.
- Breier,A., Schreiber,J.L., Dyer,J. & Pickar,D. (1991). National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Arch Gen Psychiat* **48**(3):239-246.

- Brill,N., Reichenberg,A., Rabinowitz,J., Harary,E., Lubin,G., Davidson,M. & Weiser,M. (2007). Accuracy of self-reported premorbid functioning in schizophrenia. *Schizophr Res* **97**(1-3):103-108.
- Brizer,D.A., Hartman,N., Sweeney,J. & Millman,R.B. (1985). Effect of methadone plus neuroleptics on treatment-resistant chronic paranoid schizophrenia. *Am J Psychiat* **142**(9):1106-1107.
- Cahill,C.M., Malhi,G.S., Ivanovski,B., Lagopoulos,J. & Cohen,M. (2006). Cognitive compromise in bipolar disorder with chronic cannabis use: cause or consequence? *Expert Rev Neurother* **6**(4):591-598.
- Cannon-Spoor,H.E., Potkin,S.G. & Wyatt,R.J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull* **8**(3):470-484.
- Cantor-Graae,E., Nordstrom,L.G. & McNeil,T.F. (2001). Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden. *Schizophr Res* **48**(1):69-82.
- Cantwell,R. (2003). Substance use and schizophrenia: effects on symptoms, social functioning and service use. *Br J Psychiat* **182**:324-329.
- Carey,K.B., Carey,M.P. & Simons,J.S. (2003). Correlates of substance use disorder among psychiatric outpatients: focus on cognition, social role functioning, and psychiatric status. *J Nerv Ment Dis* **191**(5):300-308.
- Carod Artal,F.J. (2003). [Neurological syndromes associated with the ingestion of plants and fungi with a toxic component (II). Hallucinogenic fungi and plants, mycotoxins and medicinal herbs]. *Rev Neurol* **36**(10):951-960.
- Caspi,A., Moffitt,T.E., Cannon,M., McClay,J., Murray,R., Harrington,H., Taylor,A., Arseneault,L., Williams,B. & Braithwaite,A. (2005). Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction. *Biol Psychiat* **57**(10):1117-1127.
- Cassidy,F., Ahearn,E.P. & Carroll,B.J. (2001). Substance abuse in bipolar disorder. *Bipolar Disord* **3**(4):181-188.
- Castle,D.J. & Murray,R.M. (1993). The epidemiology of late-onset schizophrenia. *Schizophr Bull* **19**(4):691-700.
- Cerullo,M.A. & Strakowski,S.M. (2007). The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Subst Abuse Treat Prev Policy* **2**:29.
- Chambers,R.A., Krystal,J.H. & Self,D.W. (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiat* **50**(2):71-83.
- Chambers,R.A., Taylor,J.R. & Potenza,M.N. (2003). Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiat* **160**(6):1041-1052.
- Chambers,R.A. & Taylor,J.R. (2004). Animal modeling dual diagnosis schizophrenia: Sensitization to cocaine in rats with neonatal ventral hippocampal lesions. *Biol Psychiat* **56**(5):308-316.

- Chang,L., Alicata,D., Ernst,T. & Volkow,N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction* **102** Suppl 1:16-32.
- Chengappa,K.N., Levine,J., Gershon,S. & Kupfer,D.J. (2000). Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. *Bipolar Disord* **2**(3 Pt 1):191-195.
- Corlett,P.R., Honey,G.D. & Fletcher,P.C. (2007). From prediction error to psychosis: ketamine as a pharmacological model of delusions. *J Psychopharmacol* **21**(3):238-252.
- Coryell,W., Scheftner,W., Keller,M., Endicott,J., Maser,J. & Klerman,G.L. (1993). The enduring psychosocial consequences of mania and depression. *Am J Psychiat* **150**(5):720-727.
- Coulston,C.M., Perdices,M. & Tennant,C.C. (2007b). The Neuropsychology of cannabis and other substance use in schizophrenia: review of the literature and critical evaluation of methodological issues. *Aust N Z J Psychiatry* **41**(11):869-884.
- Coulston,C.M., Perdices,M. & Tennant,C.C. (2007a). The neuropsychological correlates of cannabis use in schizophrenia: lifetime abuse/dependence, frequency of use, and recency of use. *Schizophr Res* **96**(1-3):169-184.
- Coyle,J.T. (2006). Substance use disorders and Schizophrenia: a question of shared glutamatergic mechanisms. *Neurotox Res* **10**(3-4):221-233.
- Cox,G. & Rapses,H. (2003). Adverse effects of Khat: a review. *Adv Psychiat Treat* **9**: 456-463.
- Craddock,N., O'Donovan,M.C. & Owen,M.J. (2006). Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophr Bull* **32**(1):9-16.
- Craddock,N., O'Donovan,M.C. & Owen,M.J. (2007). Phenotypic and genetic complexity of psychosis. Invited commentary on ... Schizophrenia: a common disease caused by multiple rare alleles. *Br J Psychiat* **190**:200-203.
- Craddock,N. & Owen,M.J. (2007). Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry* **6**(2):84-91.
- Creese,I., Burt,D.R. & Snyder,S.H. (1976). Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science* **192**(4238):481-483.
- Crespo-Facorro,B., Barbadillo,L., Pelayo-Ter+ín,J.M. & Rodr+iguez-S+ánchez,J.M. (2007). Neuropsychological functioning and brain structure in schizophrenia. *Int Rev Psychiat* **19**(4):325-336.
- Crow,T.J. (1986). The continuum of psychosis and its implication for the structure of the gene. *Br J Psychiatry* **149**(4):419-429.
- Crow,T.J. (2008a). Craddock & Owen vs Kraepelin: 85 years late, mesmerised by "polygenes". *Schizophr Res* **103**(1-3):156-160.
- Crow,T.J. (2008b). The 'big bang' theory of the origin of psychosis and the faculty of language. *Schizophr Res* **102**(1-3):31-52.

- Curran,C., Byrappa,N. & McBride,A. (2004). Stimulant psychosis: systematic review. *Br J Psychiat* **185**(3):196-204.
- D'Souza,D.C., bi-Saab,W.M., Madonick,S., Forselius-Bielen,K., Doersch,A., Braley,G., Gueorguieva,R., Cooper,T.B. & Krystal,J.H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiat* **57**(6):594-608.
- D'Souza,D.C., Gil,R.B., Madonick,S., Perry,E.B., Forselius-Bielen,K., Braley,G., Donahue,L., Tellioglu,T., Zimolo,Z., Gueorguieva,R. & Krystal,J.H. (2006). Enhanced sensitivity to the euphoric effects of alcohol in schizophrenia. *Neuropsychopharmacology* **31**(12):2767-2775.
- D'Souza,D.C., Perry,E., Macdougall,L., Ammerman,Y., Cooper,T., Wu,Y.T., Braley,G., Gueorguieva,R. & Krystal,J.H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* **29**(8):1558-1572.
- Daban,C., Martinez-Aran,A., Torrent,C., Tabares-Seisdedos,R., Balanza-Martinez,V., Salazar-Fraile,J., Selva-Vera,G. & Vieta,E. (2006). Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychother Psychosom* **75**(2):72-84.
- Damasio,H., Grabowski,T., Frank,R., Galaburda,A.M. & Damasio,A.R. (1994). The Return of Phineas Gage: Clues About the Brain from The Skull of a Famous Patient. *Science* **264**(5162):1102-1105.
- Daneluzzo,E., Arduini,L., Rinaldi,O., Di Domenico,M., Petrucci,C., Kalyvoka,A. & Rossi,A. (2002). PANSS factors and scores in schizophrenic and bipolar disorders during an index acute episode: a further analysis of the cognitive component. *Schizophr Res* **56**(1-2):129-136.
- Davies,M. (2003). The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. *J Psychiat Neurosci* **28**(4):263-274.
- de la Torre,R., Farre,M., Roset,P.N., Pizarro,N., Abanades,S., Segura,M., Segura,J. & Cami,J. (2004). Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. *Ther Drug Monit* **26**(2):137-144.
- de Leon,J. (2004). Psychopharmacology: Atypical Antipsychotic Dosing: The Effect of Smoking and Caffeine. *Psychiat Serv* **55**(5):491-493.
- Dickey,B. & Azeni,H. (1996). Persons with dual diagnoses of substance abuse and major mental illness: their excess costs of psychiatric care. *Am J Public Health* **86**(7):973-977.
- Dixon,L., Haas,G., Weiden,P.J., Sweeney,J. & Frances,A.J. (1991). Drug abuse in schizophrenic patients: clinical correlates and reasons for use. *Am J Psychiat* **148**(2):224-230.
- Dixon,L., Weiden,P.J., Haas,G., Sweeney,J. & Frances,A.J. (1992). Increased tardive dyskinesia in alcohol-abusing schizophrenic patients. *Compr Psychiat* **33**(2):121-122.
- Drake,R.E., Osher,F.C. & Wallach,M.A. (1989). Alcohol use and abuse in schizophrenia. A prospective community study. *J Nerv Ment Dis* **177**(7):408-414.

- Dubertret,C., Bidard,I., Ades,J. & Gorwood,P. (2006). Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. *Schizophr Res* **86**(1-3):284-290.
- Dudley,R. (2002). Fermenting fruit and the historical ecology of ethanol ingestion: is alcoholism in modern humans an evolutionary hangover? *Addiction* **97**(4):381-388.
- Eliyahu,U., Berlin,S., Hadad,E., Heled,Y. & Moran,D.S. (2007). Psychostimulants and military operations. *Mil Med* **172**(4):383-387.
- EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). Annual report 2006. (<http://ar2006.emcdda.europa.eu/en/home-en.html>) Accessed: 12 December 2006.
- Etter,M. & Etter,J.F. (2004). Alcohol consumption and the CAGE test in outpatients with schizophrenia or schizoaffective disorder and in the general population. *Schizophr Bull* **30**(4):947-956.
- Eysenck,M.W., Derakshan,N., Santos,R. & Calvo,M.G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion* **7**(2):336-353.
- Fantegrossi,W.E., Murnane,K.S. & Reissig,C.J. (2008). The behavioral pharmacology of hallucinogens. *Biochem Pharmacol* **75**(1):17-33.
- Farrell,M., Howes,S., Taylor,C., Lewis,G., Jenkins,R., Bebbington,P., Jarvis,M., Brugha,T., Gill,B. & Meltzer,H. (1998). Substance misuse and psychiatric comorbidity: an overview of the OPCS National Psychiatric Morbidity Survey. *Addict Behav* **23**(6):909-918.
- Featherstone,R.E., Kapur,S. & Fletcher,P.J. (2007). The amphetamine-induced sensitized state as a model of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiat* **31**(8):1556-1571.
- Ferdinand,R.F., Sondeijker,F., van der Ende,J., Selten,J.P., Huizink,A. & Verhulst,F.C. (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction* **100**(5):612-618.
- First,M.B. & Tasman,A. (2004). *DSM-IV-TR Mental Disorders. Diagnosis, etiology and treatment*. Wiley: Chichester.
- Freud,S. (1920). Beyond the pleasure principle. In *Collected works vol XVIII*, (Anonymous), Hogarth Press: London.
- Geyer,M.A. & Vollenweider,F.X. (2008). Serotonin research: contributions to understanding psychoses. *Trends Pharmacol Sci* **29**(9):445-453.
- Gonzalez,R., Carey,C. & Grant,I. (2002). Nonacute (residual) neuropsychological effects of cannabis use: a qualitative analysis and systematic review. *J Clin Pharmacol*.**42**(11 Suppl):48S-57S.
- Goodwin,F.K. & Jamison,K.R. (2007). *Manic-Depressive Illness*. 2 edn. New York.
- Grant,I., Gonzalez,R., Carey,C.L., Natarajan,L. & Wolfson,T. (2003). Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc* **9**(5):679-689.

- Grech,A., Van,O.J., Jones,P.B., Lewis,S.W. & Murray,R.M. (2005). Cannabis use and outcome of recent onset psychosis. *Eur Psychiatry* **20**(4):349-353.
- Green,A.I., Drake,R.E., Brunette,M.F. & Noordsy,D.L. (2007). Schizophrenia and co-occurring substance use disorder. *Am J Psychiat* **164**(3):402-408.
- Green,B., Young,R. & Kavanagh,D. (2005). Cannabis use and misuse prevalence among people with psychosis. *Br J Psychiat* **187**:306-313.
- Green,M.F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiat* **153**(3):321-330.
- Green,M.F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiat* **67 Suppl 9**:3-8.
- Green,M.F., Kern,R.S. & Heaton,R.K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res* **72**(1):41-51.
- Gregg,L., Barrowclough,C. & Haddock,G. (2007). Reasons for increased substance use in psychosis. *Clin Psychol Rev* **27**(4):494-510.
- Gur,R.E., Keshavan,M.S. & Lawrie,S.M. (2007). Deconstructing psychosis with human brain imaging. *Schizophr Bull* **33**(4):921-931.
- Hambrecht,M. & Hafner,H. (2000). Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. *Aust N Z J Psychiat* **34**(3):468-475.
- Hamera,E., Schneider,J.K. & Deviney,S. (1995). Alcohol, cannabis, nicotine, and caffeine use and symptom distress in schizophrenia. *J Nerv Ment Dis* **183**(9):559-565.
- Harris,D. & Batki,S.L. (2000). Stimulant Psychosis: Symptom Profile and Acute Clinical Course. *Am J Addict* **9**(1):28-37.
- Harrison,G.P., Jr., Gruber,A.J., Hudson,J.I., Huestis,M.A. & Yurgelun-Todd,D. (2002). Cognitive measures in long-term cannabis users. *J Clin Pharmacol* **42**(11 Suppl):41S-47S.
- Heimer,L. (2003). A new anatomical framework for neuropsychiatric disorders and drug abuse. *Am J Psychiat* **160**(10):1726-1739.
- Henquet,C., Krabbendam,L., De,G.R., ten,H.M. & Van,O.J. (2006). Cannabis use and expression of mania in the general population. *J Affect Disord* **95**(1-3):103-110.
- Henquet,C., Krabbendam,L., Spauwen,J., Kaplan,C., Lieb,R., Wittchen,H.U. & Van,O.J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* **330**(7481):11.
- Herman,M. (2004). Neurocognitive functioning and quality of life among dually diagnosed and non-substance abusing schizophrenia inpatients. *Int J Ment Health Nurs* **13**(4):282-291.
- Hermle,L., Kovar,K.A., Hewer,W. & Ruchow,M. (2008). [Hallucinogen-induced psychological disorders]. *Fortschr Neurol Psychiatr* **76**(6):334-342.

- Horverak,Ø. & Bye,E. Det norske drikkemønsteret : en studie basert på intervjudata fra 1973-2004 (<http://www.sirus.no/internett/alkohol/publication/348.html>). Accessed 1 January 2008.
- Hunt,G.E., Bergen,J. & Bashir,M. (2002). Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophr Res* **54**(3):253-264.
- Ilan,A.B., Smith,M.E. & Gevins,A. (2004). Effects of marijuana on neurophysiological signals of working and episodic memory. *Psychopharmacology (Berl)* **176**(2):214-222.
- Iversen,L. (2003). Cannabis and the brain. *Brain* **126**(Pt 6):1252-1270.
- Ivleva,E., Thaker,G. & Tamminga,C.A. (2008). Comparing Genes and Phenomenology in the Major Psychoses: Schizophrenia and Bipolar 1 Disorder. *Schizophr Bull* **34**(4):734-742.
- Javitt,D.C. & Zukin,S.R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiat* **148**(10):1301-1308.
- Jensen,J., Willeit,M., Zipursky,R.B., Savina,I., Smith,A.J., Menon,M., Crawley,A.P. & Kapur,S. (2007). The Formation of Abnormal Associations in Schizophrenia: Neural and Behavioral Evidence. *Neuropsychopharmacology* **33**(3):473-479.
- Jockers-Scherubl,M.C., Wolf,T., Radzei,N., Schlattmann,P., Rentzsch,J., Gomez-Carrillo de,C.A. & Kuhl,K.P. (2007). Cannabis induces different cognitive changes in schizophrenic patients and in healthy controls. *Prog Neuropsychopharmacol Biol Psychiat* **31**(5):1054-1063.
- Johanson,C.E. & Fischman,M.W. (1989). The pharmacology of cocaine related to its abuse. *Pharmacol Rev* **41**(1):3-52.
- Joyal,C.C., Halle,P., Lapierre,D. & Hodgins,S. (2003a). Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophr Res* **63**(3):297-299.
- Kalivas,P.W. & Volkow,N.D. (2005). The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* **162**(8):1403-1413.
- Kapur,S., Mizrahi,R. & Li,M. (2005). From dopamine to salience to psychosis--linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res* **79**(1):59-68.
- Kavanagh,D.J., Waghorn,G., Jenner,L., Chant,D.C., Carr,V., Evans,M., Hemnan,H., Jablensky,A. & McGrath,J.J. (2004). Demographic and clinical correlates of comorbid substance use disorders in psychosis: multivariate analyses from an epidemiological sample. *Schizophr Res* **66**(2-3):115-124.
- Kay,S.R., Fiszbein,A. & Opler,L.A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* **13**(2):261-276.
- Keefe,R.S., Bilder,R.M., Harvey,P.D., Davis,S.M., Palmer,B.W., Gold,J.M., Meltzer,H.Y., Green,M.F., Miller,d.D., Canive,J.M., Adler,L.W., Manschreck,T.C., Swartz,M., Rosenheck,R., Perkins,D.O., Walker,T.M., Stroup,T.S., McEvoy,J.P. & Lieberman,J.A.

- (2006). Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology* **31**(9):2033-2046.
- Kendler,K.S. (2008). Explanatory Models for Psychiatric Illness. *Am J Psychiat* **165**(6):695-702.
- Khantjian,E.J. (1985). The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiat* **142**(11):1259-1264.
- Kilbourne,A.M., Cornelius,J.R., Han,X., Pincus,H.A., Shad,M., Salloum,I., Conigliaro,J. & Haas,G.L. (2004). Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord* **6**(5):368-373.
- Knapp,M., Mangalore,R. & Simon,J. (2004). The Global Costs of Schizophrenia. *Schizophr Bull* **30**(2):279-293.
- Koob,G.F. & Le Moal,M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* **24**(2):97-129.
- Kraepelin,E. (1899). *Psychiatrie: ein Lehrbuch für Studierende und Ärzte. Klinische Psychiatrie. II.* 6 edn. Johann Ambrosius Barth: Leipzig.
- Krystal,J.H., Perry,E.B., Jr., Gueorguieva,R., Belger,A., Madonick,S.H., bi-Dargham,A., Cooper,T.B., Macdougall,L., bi-Saab,W. & D'Souza,D.C. (2005). Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Arch Gen Psychiat* **62**(9):985-994.
- Lambert,M., Conus,P., Lubman,D.I., Wade,D., Yuen,H., Moritz,S., Naber,D., McGorry,P.D. & Schimmelmann,B.G. (2005). The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. *Acta Psychiat Scand* **112**(2):141-148.
- Larsen,T.K., Friis,S., Haahr,U., Johannessen,J.O., Melle,I., Opjordsmoen,S., Rund,B.R., Simonsen,E., Vaglum,P.V. & McGlashan,T.H. (2004). Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. *Br J Psychiat* **185**:108-115.
- Larsen,T.K., Melle,I., Auestad,B., Friis,S., Haahr,U., Johannessen,J.O., Opjordsmoen,S., Rund,B.R., Simonsen,E., Vaglum,P. & McGlashan,T.H. (2006). Substance abuse in first-episode non-affective psychosis. *Schizophr Res* **88**(1-3):55-62.
- Larsen,T.K., Moe,L.C., Vibe-Hansen,L. & Johannessen,J.O. (2000). Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. *Schizophr Res* **45**(1-2):1-9.
- Lerner,A.G., Gekkopf,M., Skladman,I., Oyffe,I., Finkel,B., Sigal,M. & Weizman,A. (2002). Flashback and Hallucinogen Persisting Perception Disorder: clinical aspects and pharmacological treatment approach. *Isr J Psychiat Relat Sci* **39**(2):92-99.
- Linszen,D.H., Dingemans,P.M. & Lenior,M.E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiat* **51**(4):273-279.

- Liraud,F. & Verdoux,H. (2002). [Effect of comorbid substance use on neuropsychological performance in subjects with psychotic or mood disorders]. *Encephale* **28**(2):160-168.
- Lopez-Moreno,J.A., Gonzalez-Cuevas,G., Moreno,G. & Navarro,M. (2008). The pharmacology of the endocannabinoid system: functional and structural interactions with other neurotransmitter systems and their repercussions in behavioral addiction. *Addict Biol* **13**(2):160-187.
- Mahoney,J.J., Kalechstein,A.D., De La Garza,R. & Newton,T.F. (2008). Presence and Persistence of Psychotic Symptoms in Cocaine- versus Methamphetamine-Dependent Participants. *Am J Addict* **17**(2):83-98.
- Maldonado,R., Valverde,O. & Berrendero,F. (2006). Involvement of the endocannabinoid system in drug addiction. *Trends Neurosci* **29**(4):225-232.
- Margolese,H.C., Malchy,L., Negrete,J.C., Tempier,R. & Gill,K. (2004). Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. *Schizophr Res* **67**(2-3):157-166.
- Martinez-Aran,A., Vieta,E., Torrent,C., Sanchez-Moreno,J., Goikolea,J.M., Salamero,M., Malhi,G.S., Gonzalez-Pinto,A., Daban,C., varez-Grandi,S., Fountoulakis,K., Kaprinis,G., Tabares-Seisdedos,R. & yuso-Mateos,J.L. (2007). Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord* **9**(1-2):103-113.
- McCleery,A., Addington,J. & Addington,D. (2006). Substance misuse and cognitive functioning in early psychosis: a 2 year follow-up. *Schizophr Res* **88**(1-3):187-191.
- McCreadie,RG. (2002). Use of drugs, alcohol and tobacco by people with schizophrenia: case--control study. *Br J Psychiat* **181**(4):321-325.
- McGrath,J., Saha,S., Chant,D. & Welham,J. (2008). Schizophrenia: A Concise Overview of Incidence, Prevalence, and Mortality. *Epidemiol Rev* **30**:67-76.
- Meyer-Lindenberg,A. & Weinberger,D.R. (2006). Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci* **7**(10):818-827.
- Mihic,S.J. (1999). Acute effects of ethanol on GABAA and glycine receptor function. *Neurochem Int* **35**(2):115-123.
- Miles,H., Johnson,S., mponsah-Afuwape,S., Finch,E., Leese,M. & Thornicroft,G. (2003). Characteristics of subgroups of individuals with psychotic illness and a comorbid substance use disorder. *Psychiat Serv* **54**(4):554-561.
- Moore,T.H., Zammit,S., Lingford-Hughes,A., Barnes,T.R., Jones,P.B., Burke,M. & Lewis,G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**(9584):319-328.
- Morgan,C.J. & Curran,H.V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiat* **192**(4):306-307.
- Mueser,K.T., Drake,R.E. & Wallach,M.A. (1998). Dual diagnosis: a review of etiological theories. *Addict Behav* **23**(6):717-734.

- Mueser, K.T., Essock, S.M., Drake, R.E., Wolfe, R.S. & Frisman, L. (2001). Rural and urban differences in patients with a dual diagnosis. *Schizophr Res* **48**(1):93-107.
- Mueser, K.T., Noordsy, D.L., Drake, R.E. & Fox, L. (2003). *Integrated treatment for dual disorders: A Guide to Effective Practice*. The Guilford Press: New York.
- Mueser, K.T., Yarnold, P.R. & Bellack, A.S. (1992). Diagnostic and demographic correlates of substance abuse in schizophrenia and major affective disorder. *Acta Psychiatr Scand* **85**(1):48-55.
- Mueser, K.T., Yarnold, P.R., Levinson, D.F., Singh, H., Bellack, A.S., Kee, K., Morrison, R.L. & Yadam, K.G. (1990). Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. *Schizophr Bull* **16**(1):31-56.
- Mullen, P.E., Burgess, P., Wallace, C., Palmer, S. & Ruschena, D. (2000). Community care and criminal offending in schizophrenia. *Lancet* **355**(9204):614-617.
- Muller-Vahl, K.R. & Emrich, H.M. (2008). Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. *Expert Rev Neurother* **8**(7):1037-1048.
- Murray, R.M., Morrison, P.D., Henquet, C. & Di, F.M. (2007). Cannabis, the mind and society: the hash realities. *Nat Rev Neurosci* **8**(11):885-895.
- Nabeshima, T., Mouri, A., Murai, R. & Noda, Y. (2006). Animal model of schizophrenia: dysfunction of NMDA receptor-signaling in mice following withdrawal from repeated administration of phencyclidine. *Ann N Y Acad Sci* **1086**:160-168.
- Nesvåg, R., Lawyer, G., Varnäs, K., Fjell, A.M., Walhovd, K.B., Frigessi, A., Jönsson, E.G. & Agartz, I. (2008). Regional thinning of the cerebral cortex in schizophrenia: Effects of diagnosis, age and antipsychotic medication. *Schizophr Res* **98**(1-3):16-28.
- Nitsche, I. & Kallert, T.W. (2007). Standardized Assessment of Psychopathology by Relatives of Mentally Disordered Patients. *Psychopathology* **40**(4):242-253.
- Nordstrom, B.R. & Hart, C.L. (2006). Assessing cognitive functioning in cannabis users: cannabis use history an important consideration. *Neuropsychopharmacology* **31**(12):2798-2799.
- O'Donovan, M.C., Craddock, N., Norton, N., Williams, H., Peirce, T., Moskva, V., Nikolov, I., Hamshere, M., Carroll, L., Georgieva, L., Dwyer, S., Holmans, P., Marchini, J.L., Spencer, C.C.A., Howie, B., Leung, H.T., Hartmann, A.M., Moller, H.J., Morris, D.W., Shi, Y., Feng, G., Hoffmann, P., Propping, P., Vasilescu, C., Maier, W., Rietschel, M., Zammit, S., Schumacher, J., Quinn, E.M., Schulze, T.G., Williams, N.M., Giegling, I., Iwata, N., Ikeda, M., Darvasi, A., Shifman, S., He, L., Duan, J., Sanders, A.R., Levinson, D.F., Gejman, P.V., Cichon, S., Nothen, M.M., Gill, M., Corvin, A., Rujescu, D., Kirov, G. & Owen, M.J. (2008). Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet* **40**(9):1053-1055.
- Okasha, A. & Okasha, T. (2000). Notes on mental disorders in Pharaonic Egypt. *Hist Psychiat* **11**(44):413-424.

- Owen,M.J., Craddock,N. & Jablensky,A. (2007). The genetic deconstruction of psychosis. *Schizophr Bull* **33**(4):905-911.
- Owens,D.G. & Johnstone,E.C. (2006). Precursors and prodromata of schizophrenia: findings from the Edinburgh High Risk Study and their literature context. *Psychol Med* **36**(11):1501-1514.
- Pedersen,G., Hagtvet,K.A. & Karterud,S. (2007). Generalizability studies of the Global Assessment of Functioning-Split version. *Compr Psychiat* **48**(1):88-94.
- Peleg-Raibstein,D., Knuesel,I. & Feldon,J. (2008). Amphetamine sensitization in rats as an animal model of schizophrenia. *Behav Brain Res* **191**(2):190-201.
- Picchioni,M.M. & Murray,R.M. (2000). Overvalued ideas about alcoholism and schizophrenia. *Addiction* **95**(12):1860-1863.
- Pope,H.G., Jr., Gruber,A.J., Hudson,J.I., Cohane,G., Huestis,M.A. & Yurgelun-Todd,D. (2003). Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend* **69**(3):303-310.
- Potter,D.J., Clark,P. & Brown,M.B. (2008). Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *J Forensic Sci* **53**(1):90-94.
- Potvin,S., Briand,C., Prouteau,A., Bouchard,R.H., Lipp,O., Lalonde,P., Nicole,L., Lesage,A. & Stip,E. (2005). CANTAB explicit memory is less impaired in addicted schizophrenia patients. *Brain Cogn* **59**(1):38-42.
- Potvin,S., Joyal,C.C., Pelletier,J. & Stip,E. (2007b). Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis. *Schizophr Res* **100** (1-3):242-251.
- Potvin,S., Sepehry,A.A. & Stip,E. (2007c). Meta-analysis of depressive symptoms in dual-diagnosis schizophrenia. *Aust N Z J Psychiat* **41**(10):792-799.
- Potvin,S., Sepehry,A.A. & Stip,E. (2006). A meta-analysis of negative symptoms in dual diagnosis schizophrenia. *Psychol Med* **36**(4):431-440.
- Potvin,S., Mancini-Marie,A., Fahim,C., Mensour,B. & Stip,E. (2007d). Processing of social emotion in patients with schizophrenia and substance use disorder: An fMRI study. *Soc Neurosci* **2**(2):106-116.
- Ranganathan,M. & D'Souza,D.C. (2006). The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology (Berl)* **188**(4):425-444.
- Regier,D.A., Farmer,M.E., Rae,D.S., Locke,B.Z., Keith,S.J., Judd,L.L. & Goodwin,F.K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* **264**(19):2511-2518.
- Rehm,J., Room,R., van den,B.W. & Jacobi,F. (2005). Alcohol use disorders in EU countries and Norway: an overview of the epidemiology. *Eur Neuropsychopharmacol* **15**(4):377-388.

- Rehm, J., Taylor, B. & Room, R. (2006). Global burden of disease from alcohol, illicit drugs and tobacco. *Drug Alcohol Rev* **25**(6):503-513.
- Robinson, L.J., Thompson, J.M., Gallagher, P., Goswami, U., Young, A.H., Ferrier, I.N. & Moore, P.B. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord* **93**(1-3):105-115.
- Rogers, R.D. & Robbins, T.W. (2001). Investigating the neurocognitive deficits associated with chronic drug misuse. *Curr Opin Neurobiol* **11**(2):250-257.
- Rounsaville, B.J. (2007). DSM-V Research Agenda: Substance Abuse/Psychosis Comorbidity. *Schizophr Bull* **33**(4):947-952.
- Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B. & Trivedi, M.H. (1996). The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med* **26**(3):477-486.
- Salyers, M.P. & Mueser, K.T. (2001). Social functioning, psychopathology, and medication side effects in relation to substance use and abuse in schizophrenia. *Schizophr Res* **48**(1):109-123.
- SAMHSA (Substance Abuse and Mental Health Administration). Reports on specific drugs (<http://www.oas.samhsa.gov/drugs.cfm>). Accessed: 12 December 2006.
- Satel, S. (2006). Is Caffeine Addictive? - A Review of the Literature. *Am J Drug Alcohol Ab* **32**(4):493-502.
- Schlaepfer, T.E., Lancaster, E., Heidebreder, R., Strain, E.C., Kosel, M., Fisch, H.U. & Pearlson, G.D. (2006). Decreased frontal white-matter volume in chronic substance abuse. *Int J Neuropsychopharmacol* **9**(2):147-153.
- Scott, H., Johnson, S., Menezes, P., Thornicroft, G., Marshall, J., Bindman, J., Bebbington, P. & Kuipers, E. (1998). Substance misuse and risk of aggression and offending among the severely mentally ill. *Br J Psychiat* **172**:345-350.
- Seeman, P., Schwarz, J., Chen, J.F., Szechtman, H., Perreault, M., McKnight, G.S., Roder, J.C., Quirion, R., Boksa, P., Srivastava, L.K., Yanai, K., Weinshenker, D. & Sumiyoshi, T. (2006). Psychosis pathways converge via D2high dopamine receptors. *Synapse* **60**(4):319-346.
- Seiden, L.S., Sabol, K.E. & Ricaurte, G.A. (1993). Amphetamine: effects on catecholamine systems and behavior. *Annu Rev Pharmacol Toxicol* **33**:639-677.
- Sevy, S., Burdick, K.E., Visweswarajah, H., Abdelmessih, S., Lukin, M., Yechiam, E. & Bechara, A. (2007). Iowa gambling task in schizophrenia: a review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophr Res* **92**(1-3):74-84.
- Sherwood Brown, E., Suppes, T., Adinoff, B. & Rajan Thomas, N. (2001). Drug abuse and bipolar disorder: comorbidity or misdiagnosis? *J Affect Disord* **65**(2):105-115.
- Shrout, P.E. & Fleiss, J.L. (1979). Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* **86**(2):420-428.

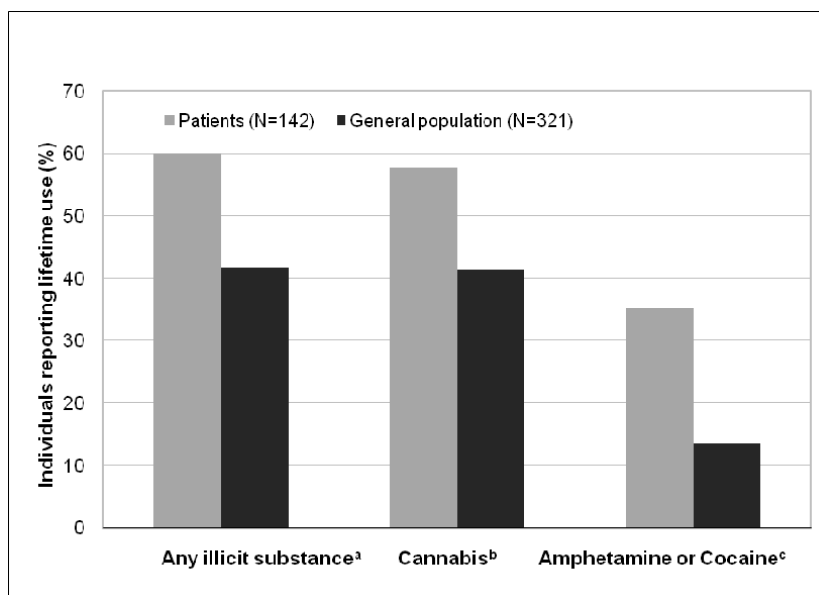
- Siebenbruner, J., Englund, M.M., Egeland, B. & Hudson, K. (2006). Developmental antecedents of late adolescence substance use patterns. *Dev Psychopathol* **18**(2):551-571.
- Silverstein, M.L., Mavrolefteros, G. & Close, D. (2002). Premorbid adjustment and neuropsychological performance in schizophrenia. *Schizophr Bull* **28**(1):157-165.
- Simon, N.M., Otto, M.W., Wisniewski, S.R., Fossey, M., Sagduyu, K., Frank, E., Sachs, G.S., Nierenberg, A.A., Thase, M.E. & Pollack, M.H. (2004). Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiat* **161**(12):2222-2229.
- Simonsen, C., Sundet, K., Vaskinn, A., Birkenaes, A.B., Engh, J.A., Hansen, C.F., Jonsdottir, H., Ringen, P.A., Opjordsmoen, S., Friis, S. & Andreassen, O.A. (2008). Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. *Bipolar Disord* **10**(2):245-255.
- Simosky, J.K., Stevens, K.E. & Freedman, R. (2002). Nicotinic agonists and psychosis. *Curr Drug Targets CNS Neurol Disord* **1**(2):149-162.
- SIRUS (Norwegian Institute for Alcohol and Drug Research). The drug situation in Norway 2006 (<http://www.sirus.no/internet/narkotika/publication/329.html>). Accessed: 1 December 2006.
- Snyder, S.H. (1973). Amphetamine Psychosis: A "Model" Schizophrenia Mediated by Catecholamines. *Am J Psychiat* **130**(1):61-67.
- Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B. & Vendetti, J. (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* **287**(9):1123-1131.
- Soyka, M., Taschner, B. & Clausius, N. (2007). Neuroleptic treatment of alcohol hallucinosis: case series. *Pharmacopsychiatry* **40**(6):291-292.
- Staller, J.A. & Faraone, S.V. (2007). Targeting the dopamine system in the treatment of attention-deficit/hyperactivity disorder. *Exp Rev Neurotherapeut* **7**(4):351-362.
- Stefansson, H., Rujescu, D., Cichon, S., Pietilainen, O.P.H., Ingason, A., Steinberg, S., Fossdal, R., Sigurdsson, E., Sigmundsson, T., Buizer-Voskamp, J.E., Hansen, T., Jakobsen, K.D., Muglia, P., Francks, C., Matthews, P.M., Gylfason, A., Halldorsson, B.V., Gudbjartsson, D., Thorgeirsson, T.E., Sigurdsson, A., Jonasdottir, A., Jonasdottir, A., Bjornsson, A., Mattiasdottir, S., Blondal, T., Haraldsson, M., Magnusdottir, B.B., Giegling, I., Moller, H.J., Hartmann, A., Shianna, K.V., Ge, D., Need, A.C., Crombie, C., Fraser, G., Walker, N., Lonnqvist, J., Suvisaari, J., Tuulio-Henriksson, A., Paunio, T., Touloupoulou, T., Bramon, E., Di Forti, M., Murray, R., Ruggeri, M., Vassos, E., Tosato, S., Walshe, M., Li, T., Vasilescu, C., Muhleisen, T.W., Wang, A.G., Ullum, H., Djurovic, S., Melle, I., Olesen, J., Kiemenev, L.A., Franke, B., Sabatti, C., Freimer, N.B., Gulcher, J.R., Thorsteinsdottir, U., Kong, A., Andreassen, O.A., Ophoff, R.A., Georgi, A., Rietschel, M., Werge, T., Petursson, H., Goldstein, D.B., Nothen, M.M., Peltonen, L., Collier, D.A., St Clair, D. & Stefansson, K. (2008). Large recurrent microdeletions associated with schizophrenia. *Nature* **455**(7210):232-236.

- Strakowski,S.M., Delbello,M.P., Fleck,D.E. & Arndt,S. (2000). The impact of substance abuse on the course of bipolar disorder. *Biol.Psychiat* **48**(6):477-485.
- Strakowski,S.M., DelBello,M.P., Fleck,D.E., Adler,C.M., Anthenelli,R.M., Keck,P.E.J., Arnold,L.M. & Amicone,J. (2007). Effects of Co-occurring Cannabis Use Disorders on the Course of Bipolar Disorder After a First Hospitalization for Mania. *Arch Gen Psychiat* **64**(1):57-64.
- Swartz,M.S., Wagner,H.R., Swanson,J.W., Stroup,T.S., McEvoy,J.P., McGee,M., Miller,d.D., Reimherr,F., Khan,A., Canive,J.M. & Lieberman,J.A. (2006). Substance use and psychosocial functioning in schizophrenia among new enrollees in the NIMH CATIE study. *Psychiatr Serv* **57**(8):1110-1116.
- Talamo,A., Centorrino,F., Tondo,L., Dimitri,A., Hennen,J. & Baldessarini,R.J. (2006). Comorbid substance-use in schizophrenia: relation to positive and negative symptoms. *Schizophr Res* **86**(1-3):251-255.
- Thirthalli,J. & Benegal,V. (2006). Psychosis among substance users. *Curr Opin Psychiatr* **19**(3):239-245.
- Thoma,P., Wiebel,B. & Daum,I. (2007). Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. *Schizophr Res* **92**(1-3):168-180.
- Turner,D.C., Clark,L., Pomarol-Clotet,E., McKenna,P., Robbins,T.W. & Sahakian,B.J. (2004). Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. *Neuropsychopharmacol* **29**(7):1363-1373.
- Van Os,J., Bak,M., Hanssen,M., Bijl,R.V., de Graaf,R. & Verdoux,H. (2002). Cannabis Use and Psychosis: A Longitudinal Population-based Study. *Am J Epidemiol* **156**(4):319-327.
- van Os,J., Rutten,B.P. & Poulton,R. (2008). Gene-Environment Interactions in Schizophrenia: Review of Epidemiological Findings and Future Directions. *Schizophr Bull* **34**(6):1066-1082.
- Varga,M., Babovic,A., Flekkoy,K., Ronneberg,U., Landro,N., David,A. & Opjordsmoen,S. (2008) Reduced insight in bipolar I disorder: neurofunctional and neurostructural correlates. A preliminary study. *J Affective Dis*. Published online: 5 December 2008. doi:10.1016/j.jad.2008.11.005
- Veen,N.D., Seltin,J.P., van,d.T., I, Feller,W.G., Hoek,H.W. & Kahn,R.S. (2004). Cannabis use and age at onset of schizophrenia. *Am J Psychiat* **161**(3):501-506.
- Ventura,J., Liberman,R.P., Green,M.F., Shaner,A. & Mintz,J. (1998). Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). *Psychiat Res* **79**(2):163-173.
- Verdoux,H., Mury,M., Besancon,G. & Bourgeois,M. (1996). [Comparative study of substance dependence comorbidity in bipolar, schizophrenic and schizoaffective disorders]. *Encephale* **22**(2):95-101.
- Volkow,N.D. & Fowler,J.S. (2000). Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex* **10**(3):318-325.

- von Feuchtersleben,E. (1845). *Lehrbuch der ärztlichen Seelenkunde*. Gerold: Vienna, Austria.
- Wallace,C., Mullen,P.E. & Burgess,P. (2004). Criminal offending in schizophrenia over a 25-year period marked by deinstitutionalization and increasing prevalence of comorbid substance use disorders. *Am J Psychiat* **161**(4):716-727.
- Weiss,R.D., Kolodziej,M., Griffin,M.L., Najavits,L.M., Jacobson,L.M. & Greenfield,S.F. (2004). Substance use and perceived symptom improvement among patients with bipolar disorder and substance dependence. *J Affect Disord* **79**(1-3):279-283.
- Weiss,R.D., Najavits,L.M., Greenfield,S.F., Soto,J.A., Shaw,S.R. & Wyner,D. (1998). Validity of substance use self-reports in dually diagnosed outpatients. *Am J Psychiat* **155**(1):127-128.
- Wells,K.B., Burnam,M.A., Leake,B. & Robins,L.N. (1988). Agreement between face-to-face and telephone-administered versions of the depression section of the NIMH diagnostic interview schedule. *J Psychiat Res* **22**(3):207-220.
- White,F.J. & Kalivas,P.W. (1998). Neuroadaptations involved in amphetamine and cocaine addiction. *Drug Alcohol Depen* **51**(1-2):141-153.
- WHO (World Health Organization). Prevalence of current tobacco use among adults aged < 15 years (<http://www.who.int/whosis/en/>). Accessed: 1 October 2008a.
- WHO (World Health Organization). The global burden of substance abuse, WHO Global burden of disease (http://www.who.int/substance_abuse/facts/global_burden/en/). Accessed: 1 December 2008b.
- Wilson,R.I. & Nicoll,R.A. (2002). Endocannabinoid signalling in the brain. *Science* **296**(5568):678-682.
- Winokur,G., Turvey,C., Akiskal,H., Coryell,W., Solomon,D., Leon,A., Mueller,T., Endicott,J., Maser,J. & Keller,M. (1998). Alcoholism and drug abuse in three groups--bipolar I, unipolars and their acquaintances. *J Affect Disord* **50**(2-3):81-89.
- Wobrock,T., Sittinger,H., Behrendt,B., D'Amelio,R., Falkai,P. & Caspari,D. (2007). Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. *Eur Arch Psych Clin N* **257**(4):203-210.
- Wu,L.T., Ringwalt,C.L., Mannelli,P. & Patkar,A.A. (2008). Hallucinogen Use Disorders Among Adult Users of MDMA and Other Hallucinogens. *Am J Addiction* **17**(5):354-363.
- Yucel,M., Solowij,N., Respondek,C., Whittle,S., Fornito,A., Pantelis,C. & Lubman,D.I. (2008). Regional Brain Abnormalities Associated With Long-term Heavy Cannabis Use. *Arch Gen Psychiat* **65**(6):694-701.
- Zaretsky,A., Rector,N.A., Seeman,M.V. & Fornazzari,X. (1993). Current cannabis use and tardive dyskinesia. *Schizophr Res* **11**(1):3-8.

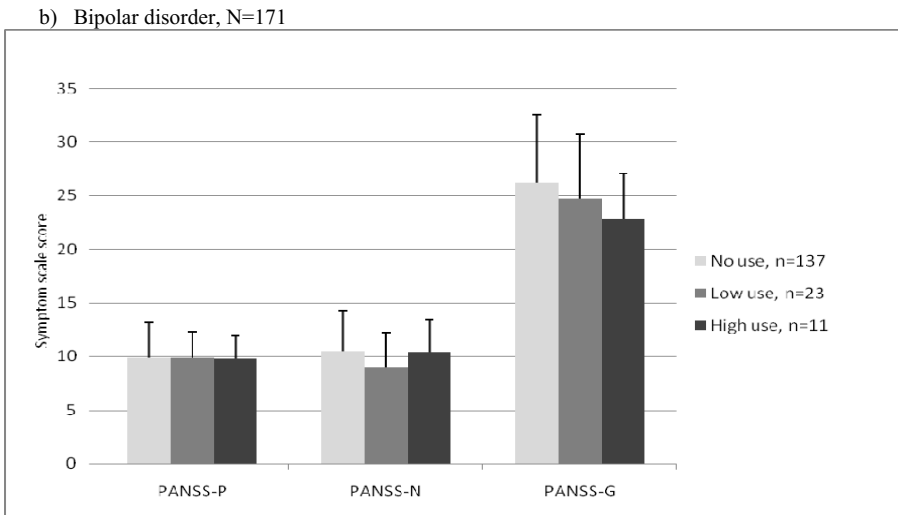
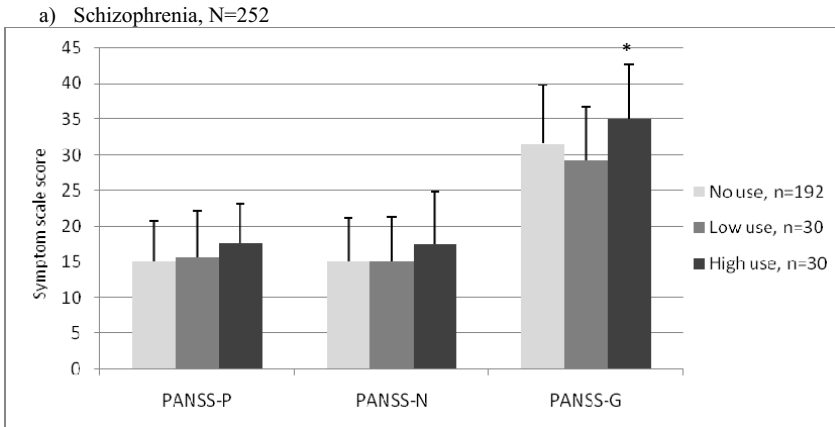
Appendix with figures

Figure A1 (paper I). Reported lifetime use of illicit substances in patients with psychotic disorder and comparison subjects of the general population.



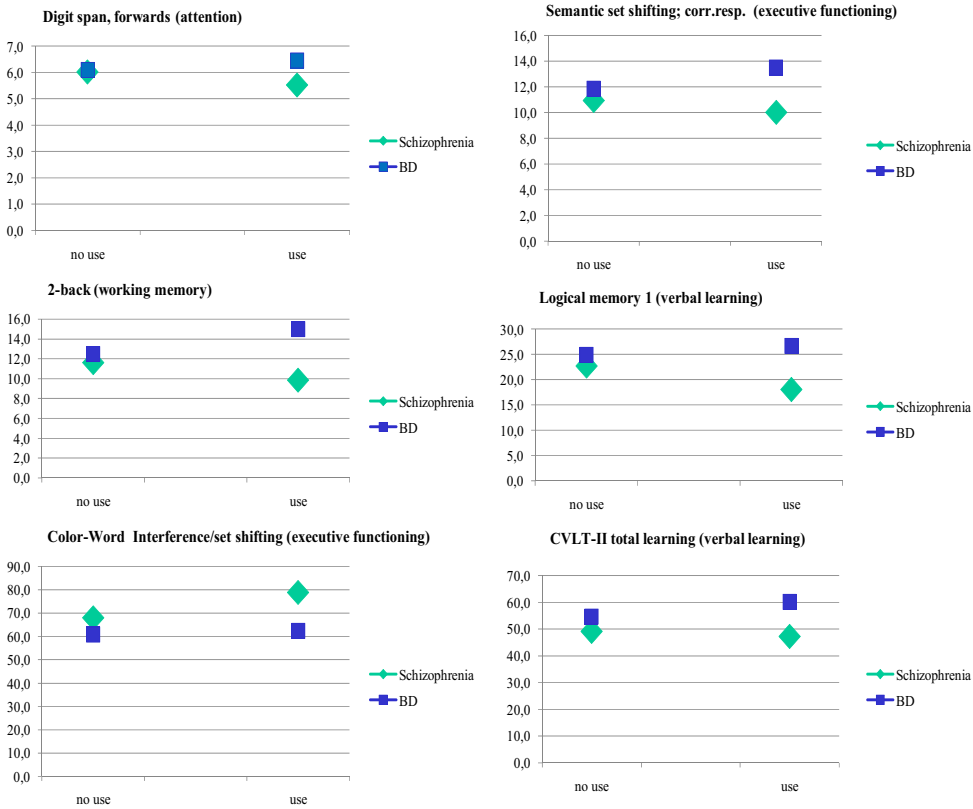
Significant difference between groups: ^a($p < 0.001$), ^b($p = 0.001$), ^c($p < 0.001$).

Figure A2 (paper III). Level of illicit substance use; symptom levels by diagnostic group.



No use: no incidents past 6 months. Low use: 1-8 incidents past 6 months. High use: 9 incidents and more past 6 months. Columns represent mean scores. Bars represent one standard deviation. *: compared to Low use group; $p \leq 0.05$. Univariate ANOVA tests with post-hoc Bonferroni tests; pairs of use level groups with significant differences between them are indicated. PANSS; Positive and Negative Syndrome Scale, P; positive, N; negative, G; general.

Figure A3 (paper IV). Neuropsychological test performance according to diagnosis with and without cannabis use past 6 months. Schizophrenia (with cannabis use): n=140 (n=23); Bipolar disorder (with cannabis use): n=133 (N=18)



ERRATA

1. Figur A2: Figurnøkkelen er rettet; stjerne indikerer nå forskjell mellom gruppene med 'høy' og 'lav' bruk. 'Symptoms' i forklaringen av forkortelsen PANSS er rettet til 'Syndrome'. Uaktuelle beskrivelser er slettet.
2. Formattering av referanser: flere journalnavn var ikke forkortet ihht ISI WOK, dette er nå rettet.

Illicit drug use in patients with psychotic disorders compared with that in the general population: a cross-sectional study

Ringen PA, Melle I, Birkenæs AB, Engh JA, Færden A, Jónsdóttir H, Nesvåg R, Vaskinn A, Friis S, Larsen F, Opjordsmoen S, Sundet K, Andreassen OA. Illicit drug use in patients with psychotic disorders compared with that in the general population: a cross-sectional study.

Objective: Prevalence estimates of illicit drug use in psychotic disorders vary between studies, and only a few studies compared prevalence estimates with those in the general population.

Method: Cross-sectional study comparing 148 stable-phase patients with schizophrenia or bipolar disorder with 329 representative general citizens of Oslo. A total of 849 patients from the same hospital department in the same time period constituted a patient reference group.

Results: Lifetime illicit drug use was 44% higher ($P < 0.001$) in study patients than in the general population sample; while lifetime use of amphetamine/cocaine was 160% higher ($P < 0.001$). No differences were found between user groups for sociodemographic characteristics.

Conclusion: Patients with psychotic disorders in stable phase had a markedly higher lifetime use of any illicit substance, especially amphetamine/cocaine, than the general population. They also seemed to use drugs more periodically. The same sociodemographic characteristics were associated with increased illicit drug use in both groups.

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Key words: psychotic disorders; cannabis; psychostimulants

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Significant outcomes

- A clearly significantly higher prevalence of use of any illicit substance, and a 160% higher prevalence of stimulant use, in severe mental disorders compared with that in the corresponding general population.
- The same sociodemographic characteristics were associated with increased illicit drug use in both groups.
- There seemed to be differences in drug-use patterns between patients and the general population.

Limitations

- Some substance-use report periods were constructed differently in the patient and control groups, leading to a possible underestimation of the level of illicit drug use in patients in those periods.
- The study relied on self-report for historical data on substance use. Recent use was, however, controlled for by urine samples.
- The cross-sectional design of this study does not allow for assumptions of causality.

Introduction

The prevalence of use and misuse of illicit drugs is assumed to be higher in patients with psychotic

disorders than in the general population. The standard reference – the Epidemiologic Catchment Area study (1) – is now two decades old and from a period where especially the use of cannabis was less

prevalent than now. The number of recent studies, which made comparison with the normal population, is few and limited to epidemiological studies with limited clinical data (2, 3). Additionally, the reported levels vary widely across studies (from 15% to 70%); a variation that has been attributed to both differences in measurements, diagnostic composition, populations of origin and time periods (1–11).

Knowledge about the actual differences between psychotic patients and the general population regarding prevalence of illicit drug use, drug-use patterns and demographic characteristics associated with drug use is of considerable interest. It will aid in the understanding of mechanisms associated with increased drug use in psychotic patients and also help to improve planning of treatment and treatment services. This issue can, however, only be solved by comparing representative patient samples to representative samples of the general population from the same area and time period; as drug availability and drug preference may vary. To our knowledge, there are no such studies based on recent patient samples.

The present report originates from the study of a large sample of patients with psychotic disorder from a catchment area-based treatment organization. Efforts were made to keep the sample highly representative through a comparison with a simpler measure of drug use in a very large – close to total – sample of all patients with psychotic disorders treated in the treatment organization in the same time period. The accuracy of drug-use measurements in the clinical sample was ensured by using both self-reports and urine tests.

Aims of the study

The aim of this study was to examine the rate of illicit drug use, drug-use patterns and its relationship to sociodemographic characteristics in the study sample compared with a representative sample from the general population in the same geographical area and time period.

Material and methods

This cross-sectional study included a primary, well-characterized study patient sample and a comparison sample from the general population. In addition, a larger sample of patients was assessed more briefly (patient reference sample – U600 group) by their clinicians to constitute a comparison group to assess the representativeness of the primary patient study sample.

Patient study sample (TOP group)

The study was a part of the Thematic Organized Psychosis Research (TOP) study. Patients were recruited from the Department of Psychiatry at the Ullevål University Hospital (UUH); a catchment area-based service covering 190 000 inhabitants in Oslo, Norway (the total population of Oslo is approximately 550 000, the greater metropolitan area includes approximately one million inhabitants). The catchment area's five city districts are located in different parts of the city and are representative of the city's variation in sociodemographic characteristics.

The recruitment teams were based in the outpatient clinics, where patients were transferred after acute illness phase. This procedure restricted inclusion of people in the most acute phase. We did not have specific inclusion criteria on the basis of symptom load, but recruitment was on the basis of a clinical evaluation of the patient being able to participate in the clinical interviews and other assessments related to the protocol. Furthermore, eligible patients were between 18 and 65 years old and met the DSM-IV criteria for a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, psychotic disorder NOS, bipolar I disorder, bipolar II disorder and bipolar disorder NOS. Patients with a developmental disorder (IQ < 70) or brain damage were excluded. Recruitment was conducted by motivating the local clinicians to encourage eligible patients to join the study. As recruitment was conducted by the clinician, we did not know the exact number of eligible patients who were not referred. However, there were eight clearly eligible patients who refused to participate.

Emphasis was placed on recruiting all patients regardless of level of involvement in their respective treatment programs. A total of 148 patients consecutively admitted to the study comprised the TOP group.

The patients were interviewed by MDs or psychologists. Diagnoses were established using the Structural Clinical Instrument of Diagnosis for DSM-IV axis I disorders (SCID-I), modules A–E (12). All interviewers were trained in the SCID, participated in regular diagnostic consensus meetings led by a well-experienced clinical researcher in the field of diagnostics in psychotic disorders and finished a training course in SCID assessment based on the training program at UCLA (13). Mean overall kappa for SCID diagnoses assessed by the UCLA was 0.77. To assess reliability for actual study interviews, a stratified random sample was drawn, comprising cases from every

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assessment staff member. Anonymous vignettes describing symptoms and development of the illness were then rated by two experts blind to the study ratings. For the 28 vignettes, the overall agreement for the nine DSM-IV diagnostic categories was 82% and the overall kappa again 0.77 (95% CI 0.60–0.94). Patients were interviewed about their first-time experience with illicit drugs and their use of drugs during the past 14 days, past 6 months, past 24 months as well as lifetime exposure. In addition, urine samples were screened for the most common drugs of abuse. Symptom load was assessed by the Inventory of Depressive Symptoms (IDS), the Positive and Negative Syndrome Scale (PANSS), the Young Mania Rating Scale (YMRS) and the Global Assessment of Functioning (GAF) scale – split version.

Patient reference sample (U600 group)

All patients from all clinical units of the Department of Psychiatry, UUH, were surveyed through the Ullevål 600 health care study in the same time period as the clinical study, comprising a total of 1002 with ICD-10 F20–F39 diagnoses (psychoses and affective disorders). The TOP group sample was removed from the reference sample, leaving 849 patients to the reference group. The patients were diagnosed according to ICD-10 criteria, and illicit drug use past 6 months was evaluated by the clinical staff, using the Clinician Drug Use Scale (14).

General population comparison sample (SIRUS group)

This group was established through cooperation with the Norwegian Institute for Alcohol and Drug Research (SIRUS). The SIRUS conducts yearly surveys of the consumption of illicit substances in the general population by personal interviews with standardized questionnaires. Subjects are randomly selected according to a detailed selection protocol and weighted to gender, age and address (15). For the purpose of this study, we used SIRUS data from the city of Oslo from 2004, with participants aged 18–65 years, giving a representative control group of 327 people. Data collected from the SIRUS survey included: age, gender, smoking, educational level, occupational and marital status, as well as reported illicit drug use for the past month, past 12 months and lifetime exposure. After a complete description of the study to the subjects, written informed consent was obtained.

The periods of reported illicit drug use in the TOP study thus differed somewhat from the SIRUS sample. The following drug-use periods

were used across samples: 'Recent' (TOP: 14 days, SIRUS: 1 month), 'Medium term' (TOP: 6 months, SIRUS: 12 months), 'Long term' (24 months, TOP only) and lifetime (TOP and SIRUS). The groups were deliberately defined with a shorter reporting period for TOP subjects to have a conservative estimate of the patient group as the hypothesis was that patients would show higher rates of illicit drug use.

There were no statistically significant differences among the three samples in mean age or gender distribution (Table 1). Mean age for TOP patients was 35.5 years (SD 11.3). The SIRUS group's mean age was 36.0 years (SD 12.0). Of the TOP patients, 46% had a schizophrenia spectrum disorder, 43% bipolar spectrum disorder and 11% other psychotic disorders. Fourteen per cent had a secondary diagnosis of illicit substance abuse or dependence, and 13% had a secondary diagnosis of alcohol abuse or dependence. Mean symptom scores indicated that they were in a stable phase of illness, and were as follows: IDS: 19.2 (SD 14.4), YMRS: 5.1 (SD 4.9), PANSS: 56.8 (SD 16.9), GAF-S: 47.3 (SD 12.6) and GAF-F: 48.3 (SD 12.9). The patient reference group (U600) had a mean age of 39.7 years (SD 13.1), 53% were males. As expected, TOP patients had significantly poorer social functioning assessed with demographic variables than the general population. Tobacco smoking was twice as common in the TOP group as in the SIRUS group (Table 1).

Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences (spss, Chicago, IL, USA) version 14.0. Group differences in categorical data were evaluated with chi-squared tests and normally distributed interval data were evaluated with Student's *t*-tests. All tests were two sided. Age-adjusted odds ratios were calculated using separate binary logistic regression analyses with 'Drug use in time period' as the dependent variable.

Table 1. Sociodemographic variables

	TOP (N = 148)		SIRUS (N = 327)		P-value
	n	%	n	%	
Male	68	45.9	159	48.6	0.621
Always single*	91	61.5	119	36.6	<0.001
No higher education†	100	68.0	110	33.8	<0.001
No occupation	79	53.4	48	15.1	<0.001
Daily smoking	84	57.1	81	24.8	<0.001

Chi-squared (Fisher's exact test).

*Never married or cohabitating.

†Max. 12 years of education.

Results

The prevalence rates of reported total illicit drug use (past 6 months) for the study and reference patient populations (TOP and U600 group) were almost identical, 15.5% and 15.2% respectively. This demonstrates that the rate of recent drug use in the study group is similar to that in the total population receiving treatment in the catchment area.

Of 10 TOP patients with positive urine tests of any illicit substance, only one denied current use, implying that a deliberate under-reporting of current use did not seem to be prominent.

The rates of reported illicit drug use in the TOP and SIRUS groups are shown in Table 2. Cannabis was, by far, the most commonly used drug both in the patient study sample and in the general population sample. In both the TOP and SIRUS groups, there were an increased number of illicit drug users with increasing drug-use reporting

period. There were no significant differences in recent use between the two groups. For medium-term use, patients used more illicit drugs overall and especially more amphetamine/cocaine, but these differences did not reach statistical significance. The lifetime rates were significantly higher among patients, with a 44% higher total use, and a 160% higher prevalence for amphetamine/cocaine use.

There was a clear association with age, in both the TOP and SIRUS groups; lifetime users were 5.0 and 7.0 years younger than non-users respectively ($P = 0.033$ and $P < 0.001$).

Illicit drug use at all time points was associated with being single among both patients and in the general population in bivariate analyses (Table 3). However, the association was lower for patients than for the normal population sample. Except for medium-term use, there were no statistically significant differences in the age-adjusted odds ratios for being single between users and non-users in the

Table 2. Self-reported use of illicit drugs per time period. TOP $n = 148^*$, SIRUS $n = 321$

	Any illicit substance			Cannabis			Amphetamine and Cocaine		
	TOP	Sirus	<i>P</i> -value	TOP	Sirus	<i>P</i> -value	TOP	Sirus	<i>P</i> -value
Recent	16 (10.8)	27 (8.4)	0.395	13 (8.8)	24 (7.5)	0.713	4 (2.7)	5 (1.6)	0.475
Medium term	34 (23.0)	53 (16.5)	0.098	26 (17.6)	50 (15.6)	0.592	13 (8.8)	14 (4.4)	0.087
Long term	56 (37.8)			46 (31.1)			28 (18.9)		
Lifetime	85 (59.9)	134 (41.7)	<0.001	82 (57.7)	133 (41.4)	0.001	50 (35.2)	43 (13.5)	<0.001

Chi-square (Fishers' exact test). Recent: use past 14 days/past month, Medium term: use past 6 months/past 12 months, Long term: use past 24 months. Values are given as n (%).

*Missing reliable information on lifetime use in six patients.

Table 3. The relationship between sociodemographic characteristics and drug use in study patients and in the general population

	TOP ($N = 148$) [*]						SIRUS ($N = 321$)					
	Use		No use		<i>P</i> -value	Analysis	Use		No use		<i>P</i> -value	Analysis
	<i>n</i>	%†	<i>n</i>	%†			<i>n</i>	%†	<i>n</i>	%†		
Recent	16		132				27		294			
Male	11	68.8	57	43.2	0.065	2.9 (0.9–8.9)	15	55.6	142	48.3	0.548	1.5 (0.6–3.3)
Always single	14	87.5	77	58.3	0.024	3.7 (0.7–19.0)	21	77.8	96	32.9	<0.001	4.6 (1.7–12.7)
No higher education	14	87.5	86	65.6	0.093	3.0 (0.6–14.0)	13	48.1	93	31.8	0.092	2.2 (1.0–5.0)
No occupation	11	68.8	68	51.5	0.289	2.5 (0.8–7.6)	4	15.4	43	15.0	1.000	1.4 (0.4–4.6)
Medium term	34		114				53		268			
Male	22	64.7	46	40.4	0.018	2.8 (1.2–6.4)	26	49.1	131	48.9	1.000	0.8 (1.1–0.6)
Always single	30	88.2	61	53.5	<0.001	4.7 (1.4–15.4)	36	67.9	81	30.5	<0.001	1.9 (0.8–4.7)
No higher education	30	88.2	70	61.9	0.003	3.8 (1.2–11.8)	24	45.3	82	30.8	0.055	2.2 (1.2–4.3)
No occupation	20	58.8	59	51.8	0.558	1.6 (0.7–3.6)	9	17.3	38	14.6	0.671	1.9 (0.8–4.7)
Lifetime	85		57				133		188			
Male	42	49.4	24	42.1	0.493	1.3 (0.7–2.7)	65	48.5	92	49.2	0.910	1.0 (0.6–1.5)
Always single	59	69.4	28	49.1	0.022	1.9 (0.9–4.3)	68	50.7	49	26.5	<0.001	2.0 (1.2–3.3)
No higher education	62	72.9	35	62.5	0.200	1.5 (0.7–3.0)	45	33.8	61	32.8	0.904	1.2 (0.7–1.9)
No occupation	49	57.6	27	47.4	0.336	1.7 (0.8–3.4)	23	17.3	24	13.4	0.343	2.1 (1.1–4.3)

Chi-squared (Fishers' exact test). Recent: use past 14 days/past month. Medium term: use past 6 months/past 12 months. Always single: never married or cohabitating. No higher education: max 12 years of education. Age adj. OR: age-adjusted odds ratios.

*Missing reliable information on lifetime use in six patients.

†Percentages of individuals by sociodemographic characteristic, within drug-use groups.

patient group. Again, with the exception of medium-term use, where illicit drug users from both groups showed lower educational levels than non-users, there was no clear association with drug use and educational level or occupational status. The patterns were the same when investigating only cannabis users. The groups using other substances were too small to allow for subgroup analyses.

Discussion

This study presents, to our knowledge, unique data on the level of illicit drug use in a sample of patients with psychotic disorders in a stable phase of illness compared with a representative selection of the general population from the same geographical catchment area. The main finding of the study is a methodologically solid confirmation that patients with psychotic disorders have a significantly higher lifetime prevalence of any illicit substance use compared with the general population. The use of a comparison sample from the same area and time period makes it possible to indicate an especially marked increase in the lifetime use of amphetamine and cocaine. These results were obtained in a patient sample that did not differ from the total patient population in a catchment area-based hospital organization in respect of drug use, and the methods of drug-use detection had a high degree of reliability.

While there were clear differences in lifetime use, the differences in medium-term use were small and did not reach statistical significance. For recent use, no differences were seen at all. The ratio of illicit drug use in patients vs. controls thus seems to increase with increased observational time, suggesting differences in patterns of use in patients vs. healthy controls. Report periods with short observational windows make it more difficult to detect use in individuals with mainly periodic use. The current data thus suggest that patients with psychotic disorders may have a more periodic pattern of illicit drug use than what is the case for the general population. An alternative explanation is that our selection criteria of patients in stable illness phase could bias our sample towards patients with less degree of sustained use, as continuing use may destabilize the illness. However, the similarity between the study sample and the patient reference sample (U600) argues against this explanation.

The estimated prevalence of recent and medium-term illicit drug use in the patient sample is in the lower range of estimates from other studies of psychotic disorder populations (3, 16, 17). One explanation for this difference could be that most

studies of illicit drug use in psychotic patients are conducted in samples from acute care settings or first-episode samples. Such acute samples may – due to the effect of drug abuse in precipitating psychotic episodes – have an over-representation of drug-using patients relative to the general patient population. The close correspondence in rates of illicit drug use between the study group (TOP group) and the large reference patient population (U-600 group) from the same hospital and time period indicates that the findings are not a consequence of selection bias due to recruitment procedures for the research study patients and the close correspondence between self-reports and urine tests indicates that the patients did not under-report their illicit drug use.

The study found similar relationships between drug use and being single and having lower educational levels for both patients and controls, especially for persons with medium-term use. This might indicate that the relationship between social functioning and drug use or misuse is the same in both groups. However, the statistical power in these analyses was limited.

The study shows an over-exposure of centrally stimulating substances in this patient group. This should call for clinical concern, taking established knowledge of the detrimental effects of these drugs into account.

Future studies should focus on identifying possible differences in the pattern of use, probing both into patient characteristics and illicit drug-use patterns across timelines, dose and type of preferred drug.

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Declaration of interest

All authors declare that they have no competing interests to disclose.

References

1. REGIER DA, FARMER ME, RAE DS et al. Comorbidity of mental disorders and other drug abuse. Results from the epidemiologic catchment area (ECA) study. *JAMA* 1990;**264**:2511–2518.

Ringen et al.

2. McCREADIE RG. Use of drugs, alcohol and tobacco by people with schizophrenia: case-control study. *Br J Psychiatry* 2002;**181**:321–325.
3. GREEN B, YOUNG R, KAVANAGH D. Cannabis use and misuse prevalence among people with psychosis. *Br J Psychiatry* 2005;**187**:306–313.
4. MUESER KT, YARNOLD PR, LEVINSON DF et al. Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. *Schizophr Bull* 1990;**16**:31–56.
5. CASSIDY F, AHEARN EP, CARROLL BJ. Substance abuse in bipolar disorder. *Bipolar Disord* 2001;**3**:181–188.
6. KILBOURNE AM, CORNELIUS JR, HAN X et al. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord* 2004;**6**:368–373.
7. SWARTZ MS, WAGNER HR, SWANSON JW et al. Substance use in persons with schizophrenia. Baseline prevalence and correlates from the NIMH CATIE study. *J Nerv Ment Dis* 2006;**194**:164–172.
8. CANTWELL R, BREWIN J, GLAZEBROOK C et al. Prevalence of substance misuse in first-episode psychosis. *Br J Psychiatry* 1999;**174**:150–153.
9. LARSEN TK, MELLE I, AUESTAD B et al. Substance abuse in first-episode non-affective psychosis. *Schizophr Res* 2006;**88**:55–62.
10. WADE D, HARRIGAN S, EDWARDS J et al. Course of substance misuse and daily tobacco use in first-episode psychosis. *Schizophr Res* 2006;**31**:145–150.
11. ADDINGTON J, ADDINGTON D. Patterns, predictors and impact of substance use in early psychosis: a longitudinal study. *Acta Psychiatr Scand* 2007;**115**:304–309.
12. AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC: American Psychiatric Association, 1994.
13. VENTURA J, LIBERMAN RP, GREEN MF et al. Training and quality assurance with the Structured Clinical Interview for DSM-IV I/P (SCID). *Psychiatr Res* 1998;**79**:163–173.
14. DRAKE RE, OSHER FC, WALLACH MA. Alcohol use and abuse in schizophrenia: a prospective community study. *J Nerv Ment Dis* 1989;**177**:408–414.
15. STATENS INSTITUTT FOR RUSMIDDELFORSKNING/NORWEGIAN INSTITUTE FOR ALCOHOL AND DRUG RESEARCH (SIRUS). Oslo, Norway: Det norske drikkemønsteret. *SirusRapport nr. 2/2007*. Available at: <http://www.sirus.no/files/pub/348/sirusrap.2.07.pdf> [cited 1 October 2007].
16. CANTOR-GRAAE E, NORDSTRØM LG, McNEIL TF. Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden. *Schizophr Res* 2001;**48**:69–82.
17. KAVANAGH DJ, WAGHORN G, JENNER L et al. Demographic and clinical correlates of comorbid substance use disorders in psychosis: multivariate analyses from an epidemiological sample. *Schizophr Res* 2004;**66**: 115–124.

Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder

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Background. Schizophrenia and bipolar disorder have partly overlapping clinical profiles, which include an over-representation of substance-use behaviour. There are few previous studies directly comparing substance-use patterns in the two disorders. The objective of the present study was to compare the prevalence of substance use in schizophrenia and bipolar disorder, and investigate possible differences in pattern and frequency of use.

Method. A total of 336 patients with schizophrenia or bipolar spectrum disorder from a catchment area-based hospital service were included in a cross-sectional study. In addition to thorough clinical assessments, patients were interviewed about drug-use history, habits and patterns of use. The prevalence and drug-use patterns were compared between groups.

Results. Patients with bipolar disorder had higher rates of alcohol consumption, while schizophrenia patients more often used centrally stimulating substances, had more frequent use of non-alcoholic drugs and more often used more than one non-alcoholic drug. Single use of cannabis was more frequent in bipolar disorder.

Conclusions. The present study showed diagnosis-specific patterns of substance use in severe mental disorder. This suggests a need for more disease-specific treatment strategies, and indicates that substance use may be an important factor in studies of overlapping disease mechanisms.

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Introduction

The level of substance use in patients with severe mental illness is known to be high. This includes the diagnostic groups of both schizophrenia and bipolar disorder, but the prevalence of substance use in these groups varies considerably across studies (Regier *et al.* 1990; Mueser *et al.* 1992; Cassidy *et al.* 2001; Kilbourne *et al.* 2004; Green *et al.* 2005; Swartz *et al.* 2006). Studies of the general population indicate differences in the prevalence of non-alcoholic drug use across different countries, and a varied prevalence of individual drug use across studies (Rehm *et al.* 2005; European Monitoring Centre for Drugs and Drug Addiction, 2006; Norwegian Institute for Alcohol and Drug Research, 2006; Office of Applied Studies & Substance Abuse and Mental Health Services Administration, 2006).

Assuming the drug-use habits of patients with severe mental illness reflect those of the general population, this could partly explain the diverging prevalence data in patient populations. There are, however, few comparative studies between the general population and patient populations to support this hypothesis.

Substance use has been associated with a more severe course and outcome in both schizophrenia and bipolar disorder. Use of stimulants has been linked with criminality, violence and homelessness in severe mental disorders (Mueser *et al.* 2001; Miles *et al.* 2003), and high levels of cannabis use have been associated with increased psychopathology in both schizophrenia and bipolar disorder (Van Os *et al.* 2002; Strakowski *et al.* 2007). Alcohol use has been associated with depression in bipolar disorder (Strakowski *et al.* 2000). Use of several substances (poly-use) has been associated with substance-use disorder in schizophrenia (Swartz *et al.* 2006).

Several lines of evidence indicate overlapping clinical profiles in schizophrenia and bipolar disorder (Crow, 1998; Murray *et al.* 2004; Craddock *et al.* 2006),

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but substance-use behaviour is studied to a limited extent in this context. Samples of patients with bipolar disorder are regularly found to have high levels of alcohol use (Sherwood Brown *et al.* 2001), and in epidemiological studies a higher degree of drug use than schizophrenia patients (Regier *et al.* 1990). Several studies have reported high levels of cannabis use in schizophrenia patients (Kavanagh *et al.* 2002; Green *et al.* 2005; Swartz *et al.* 2006), and the association between early cannabis use and later increased risk for schizophrenia seems now well documented (Moore *et al.* 2007). About 80% of patients with severe mental illness are addicted to tobacco (de Leon *et al.* 2002; Ziedonis *et al.* 2003).

There are few data about patterns of substance use (amount of total substance use, mono- *versus* poly-substance use, and regular *versus* sporadic use) and amount of use in severe mental disorders. It is expected that increased knowledge about the substance-use profiles for the two disorders can improve the phenotypic descriptions and thereby shed light on the nature of the conditions. A thorough patient characterization along with detailed descriptions of substance use could also reveal new aspects of the conditions necessary to improve the treatment of these complicated clinical conditions. To our knowledge, there are few studies directly comparing frequency of substance use in patients with schizophrenia and bipolar disorder, and none of these have investigated patterns of use beyond type of substance abused (Drake *et al.* 1989; Mueser *et al.* 1992; Verdoux *et al.* 1996). Also, few studies have investigated potentially harmful use that is below the level needed to meet the diagnostic criteria for abuse or addiction. It is not necessarily the case that the threshold for negative effects of drug use directly corresponds to the criteria for a DSM-IV or International Classification of Diseases (ICD)-10 diagnosis of abuse. It is possible that drug use of shorter duration and smaller amount can have important implications for understanding the relationship between drug use and severe mental illness, as for instance illustrated by studies showing that any cannabis use in adolescence interacted with a catechol-*O*-methyltransferase genotype to increase the risk for schizophreniform disorder (Caspi *et al.* 2005). This is in line with studies of the impact of any level of drug use as important factors in relation to other diseases like cancer (Hashibe *et al.* 2005) or to neurotoxicity (Cadet *et al.* 2007).

The present data were collected on a catchment area sample of predominantly stable out-patients. In a previous report from this ongoing study we have shown that patients with severe mental illness use about 50% more non-alcoholic drugs, and especially more centrally stimulating substances, than the

general population (P. A. Ringen *et al.* unpublished observations).

The aims of the present study were to compare prevalence and type of alcohol and non-alcoholic drug use in representative samples of schizophrenia spectrum disorder and bipolar disorder, and to investigate possible differences in substance-use patterns between the two disorders.

Method

Sample

The present study was part of the Thematic Organized Psychosis Research (TOP) study, in which patients were recruited from the Departments of Psychiatry at Ullevål University Hospital, Aker University Hospital and Diakonhjemmet Hospital, all in Oslo (Norway). The three departments cover a geographical catchment area including 10 districts of Oslo and five suburbs. The catchment area corresponds to 485 000 inhabitants, Oslo's total population is about 550 000 (county), or 850 000 including the greater metropolitan area. The districts are located in different areas of the city and represent the city's variation in socio-demographic characteristics fairly well.

Inclusion criteria were as follows. To be eligible for the study the patients had to be aged 18–65 years, have a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar I disorder, bipolar II disorder or bipolar disorder not otherwise specified (NOS). The recruitment teams were based in the out-patient clinics, where patients were transferred after acute illness phases. This procedure restricted inclusion of people in the most acute phases. We did not have specific inclusion criteria based on symptom load, but on a clinical evaluation of being able to participate in the clinical interviews and other assessments related to the protocol. Exclusion criteria were presence of a diagnosis of developmental disorder or serious brain damage and not speaking a Scandinavian language.

The present study sample is comprised of patients who were consecutively referred to the study from the out-patient clinics. A total of 336 patients were included in a cross-sectional study from October 2002 through to October 2006. The patients were recruited by their clinician, and thus the exact number of eligible patients who were not referred to the study based on the clinicians' decisions is unknown. However, there were 48 clearly eligible patients who were referred but refused to participate. The patient records at Ullevål University Hospital showed that a total of 1002 patients with either schizophrenia or bipolar disorder received treatment in any psychiatric department

from May 2005 until the end of the patient inclusion of the present study. This constituted a reference group. The present study sample did not differ significantly from this reference group in proportion of subjects reporting non-alcoholic drug use in the previous 6 months (15.5% and 15.2% respectively). The patient reference sample had a mean age of 39.7 (s.d. = 13.1) years and 53% were males. There were no statistically significant differences between the two samples in mean age or gender distribution.

Emphasis was put on recruiting all patients regardless of their ability to adhere to their respective treatment programmes.

Patients were divided into a schizophrenia patient group (schizophrenia, schizophreniform disorder and schizoaffective disorder) and a bipolar disorder group (bipolar I, bipolar II or bipolar disorder NOS).

Instruments/assessments

The patients were interviewed by trained clinicians (doctors of medicine or psychologists). Diagnoses were established using the Structural Clinical Interview for the DSM-IV Axis I disorders (SCID-I), modules A-E (APA, 1994). The E module includes assessment and diagnostics of the substance-use disorders. All interviewers participated in regular diagnostic consensus meetings led by a well-experienced clinical researcher in the field of diagnostics in severe mental disorders and finished a training course in SCID assessment based on the training programme at the University of California, Los Angeles (UCLA) (Ventura *et al.* 1998). Mean overall kappa for SCID diagnoses assessed by the UCLA was 0.77. To assess reliability for actual study interviews a stratified random sample was drawn, consisting of cases from every assessment staff member. Anonymous vignettes describing symptoms and development of the illness were then rated by two experts blind to the study ratings. For the 28 vignettes the overall agreement for the nine DSM-IV diagnostic categories was 82% and the overall kappa again 0.77 (95% confidence interval 0.60–0.94).

When trying to investigate for possible relationships between schizophrenia and bipolar disorder and drug-use habits, we found that the most simple and natural first step would be describing all levels of drug use in the two groups. This was done by simply asking for any use at different time intervals. Patients were asked about accumulated incidents of substance use during the previous 14 days, 6 months and 24 months, where type of substance was specified. These questions were validated in two ways. (1) Urine samples: of 10 patients with positive urine tests of any illicit substance, only one denied current use, implying that the patients' self-reports were fairly sensitive for

current use of illicit substances. (2) Clinical information: the results of the research interviews were compared with data collected by the clinicians in the larger sample of $n=1002$ (the reference group), as shown in the previous section.

Reported mean amount of alcohol use in different intervals equivalent to at least two units or more of ethanol daily were considered 'harmful use'. Patients reporting more incidents of psychoactive substance use than the common median for the two diagnostic groups were labelled 'high users'.

Statistical analyses

All analyses were conducted by using the statistical package for the social sciences (SPSS) version 14.0 (SPSS Inc., Chicago, IL, USA). Group differences in independent samples of continuous variables were evaluated with independent t tests, and group differences in dichotomous data were evaluated with χ^2 /Fisher's exact tests. Differences between the groups in age and gender distribution were controlled for with logistic regression analyses, and in the Results section, we refer to these age- and gender-adjusted significance levels only. Group differences in incidents of use were analysed with non-parametric Mann-Whitney tests.

Results

The patient mean age was 35.2 (s.d. = 11.0) years and 170 (50.6%) of the patients were male. Of the patients, 156 (46.4%) had schizophrenia, 39 (11.6%) schizoaffective disorder and 15 (4.5%) schizophreniform disorder (schizophrenia patient group). A total of 68 (20.2%) had bipolar I disorder, 49 (14.6%) bipolar II disorder and nine (2.7%) bipolar NOS disorder (bipolar patient group).

Age and gender were unevenly distributed between the diagnostic groups. Mean age for the schizophrenia patient group was 33.3 (s.d. = 9.3) years, and for the bipolar disorder patient group 38.5 (s.d. = 12.0) years; the difference between schizophrenia and bipolar disorder was highly statistically significant ($p < 0.001$).

The schizophrenia group contained 56.7% males ($n=119$), significantly proportionally more than the 40.5% ($n=51$) males in the bipolar disorder group ($p=0.005$). The patient reference sample had a mean age of 39.7 (s.d. = 13.1) years; 531 (53%) were males.

Patients reporting alcohol use in the 6-month and 24-month time intervals were significantly younger than the abstaining patients ($p=0.005$ and $p=0.001$ respectively). Patients reporting non-alcoholic drug use were significantly younger in all time intervals.

Table 1. Reported use of substances, according to age and gender^a

	Previous 2 weeks			Previous 6 months			Previous 24 months		
	Yes	No	<i>p</i>	Yes	No	<i>p</i>	Yes	No	<i>p</i>
Non-alcoholic drug use									
Mean age, years (s.d.)	29.9 (8.1)	35.5 (11.0)	0.009	28.8 (7.5)	36.8 (11.0)	<0.001	29.2 (7.9)	37.6 (11.0)	<0.001
Male gender, <i>n</i> (%)	20 (74.1)	146 (48.8)	0.015	44 (62.9)	122 (47.7)	0.031	63 (62.4)	104 (45.8)	0.006
Alcohol use									
Mean age, years (s.d.)	34.5 (11.1)	35.4 (10.6)	0.421	34.0 (10.4)	38.0 (11.7)	0.005	34.0 (10.5)	39.3 (11.7)	0.001
Male gender, <i>n</i> (%)	93 (52.5)	71 (48.6)	0.504	130 (52.8)	33 (44.0)	0.190	138 (52.9)	25 (43.1)	0.193

s.d., Standard deviation.

^a Analysed using independent *t* tests and Fisher exact tests.**Table 2.** Reported use of non-alcoholic drugs^a

	Schizophrenia <i>n</i> (%)	Bipolar <i>n</i> (%)	OR	95% CI	<i>p</i> ^b
Any non-alcoholic drug					
Previous 14 days	21 (10.5)	6 (4.8)	1.5	0.6–4.1	0.388
Previous 6 months	53 (26.4)	17 (13.6)	1.5	0.8–2.9	0.213
Previous 24 months	69 (34.0)	32 (25.6)	0.9	0.9–1.5	0.669
Cannabis					
Previous 14 days	19 (9.4)	5 (4.0)	1.8	0.6–5.0	0.294
Previous 6 months	41 (20.3)	14 (11.2)	1.3	0.6–2.5	0.534
Previous 24 months	55 (27.2)	29 (23.2)	0.7	0.4–1.3	0.282
Amphetamine and/or cocaine					
Previous 14 days	7 (3.4)	1 (0.8)	2.5	0.3–21.2	0.415
Previous 6 months	25 (12.4)	3 (2.4)	4.4	1.3–15.4	0.019
Previous 24 months	39 (19.3)	7 (5.6)	2.8	1.2–6.8	0.019

OR, Odds ratio; CI, confidence interval.

^a Schizophrenia, *n* = 210; bipolar disorder, *n* = 126.^b *p* values of OR after adjusting for age and gender.

Male gender was significantly associated with non-alcoholic drug use at all time intervals, but gender was not associated with alcohol use (Table 1). Daily tobacco smoking was reported by 59.1% (*n* = 120) of the schizophrenia patients, and by 51.2% (*n* = 64) of the bipolar disorder patients; the difference was not statistically significant after adjusting for age and gender.

Schizophrenia patients had higher overall non-alcoholic drug-use prevalence for all time intervals than the bipolar patients, about four times higher rates of amphetamine and/or cocaine use, and about two times higher rates of cannabis use. However, when controlling for group differences in age and gender in the regression analyses, only the differences in the use of the centrally stimulating substances amphetamine and/or cocaine remained statistically significant (Table 2).

When assessing drug use over the previous 24 months, 66.0% of the schizophrenia patients and 74.4% of the bipolar disorder patients did not report any drug use (median number of incidents of drug use in the previous 24 months for both patient groups was 0). When assessing reported drug users in the previous 24 months only, median frequency of use was 48 (25th and 75th percentiles 6.0 and 284.5) in the schizophrenia group and 3 (25th and 75th percentiles: 1.0 and 26.8) in the bipolar disorder group (*p* < 0.001).

Of the patients reporting non-alcoholic drug use in the previous 24 months, patients with bipolar disorder were significantly more likely to use only one substance, even after adjusting for age and gender differences. Cannabis was the only non-alcoholic drug used significantly more often in the bipolar group. Single use of centrally stimulating substances was nominally

Table 3. Pattern of reported use of non-alcoholic drugs in the previous 24 months

	All patients ^a		Reported users only ^b		OR	95% CI	<i>p</i> ^c
	Schizophrenia <i>n</i> (%)	Bipolar <i>n</i> (%)	Schizophrenia <i>n</i> (%)	Bipolar <i>n</i> (%)			
Only one drug used	39 (19.2)	27 (21.6)	39 (51.5)	27 (84.4)	0.5	0.3–1.0	0.048
Only cannabis use	26 (12.8)	24 (19.7)	26 (37.7)	24 (75.0)	0.4	0.2–0.7	0.004
Only amphetamine or cocaine use	9 (4.4)	2 (1.6)	9 (13.0)	2 (6.3)	2.5	0.5–12.6	0.260
Two or more drugs used	30 (14.8)	5 (4.0)	30 (43.5)	5 (15.6)	2.9	1.0–7.9	0.044
High use ^d	41 (20.2)	8 (6.4)	41 (59.1)	8 (25.0)	4.3	1.6–11.3	0.004

OR, Odds ratio; CI, confidence interval.

^aSchizophrenia, *n* = 210; bipolar disorder, *n* = 126.

^bSchizophrenia, *n* = 69; bipolar disorder, *n* = 32.

^c*p* values of OR after adjusting for age and gender.

^dHigh use: 24 incidents of use or more in the previous 24 months.

Table 4. Reported use of alcohol^a

	Schizophrenia <i>n</i> (%)	Bipolar <i>n</i> (%)	OR	95% CI	<i>p</i> ^b
Any alcohol use					
Previous 14 days	90 (45.5)	87 (69.6)	0.3	0.2–0.5	<0.001
Previous 6 months	143 (71.7)	104 (84.6)	0.3	0.2–0.6	<0.001
Previous 24 months	153 (76.6)	110 (90.2)	0.2	0.1–0.4	<0.001
Mean use >2 units/day					
Previous 14 days	16 (7.9)	15 (12.0)	0.6	0.3–1.4	0.262
Previous 6 months	15 (7.4)	18 (14.4)	0.5	0.2–1.0	0.044
Previous 24 months	15 (7.4)	21 (16.8)	0.3	0.2–0.7	0.004

OR, Odds ratio; CI, confidence interval.

^aSchizophrenia, *n* = 210; bipolar disorder, *n* = 126.

^b*p* values of OR after adjusting for age and gender.

more prevalent in schizophrenia patients, but this difference did not reach statistical significance. Schizophrenia patients had, however, significantly more poly-substance use and a higher proportion of 'high-users', also after controlling for age and gender (Table 3). A total of 80 (65.5%) bipolar patients and 86 (43.4%) schizophrenia patients reported alcohol as the only substance used during the previous 24 months. Regression analysis controlling for age and gender showed this difference to be significant (*p* = 0.004). When assessing mono-use of any substance, including alcohol, the figures were 106 (86.2%) and 122 (61.6%) for bipolar and schizophrenia patients respectively. The difference was again highly significant after controlling for age and gender (*p* < 0.001).

Alcohol use was more frequent among patients with bipolar disorder than with patients with schizophrenia; this difference remained highly significant across all time intervals, also after controlling for age

and gender. More bipolar patients also had defined harmful use of alcohol in the previous 6 and 24 months after adjustment for age and gender (Table 4).

Relatively more patients with schizophrenia had a lifetime DSM-IV diagnosis of non-alcoholic drug abuse or dependence, but the difference compared with the bipolar group did not reach statistical significance. Overall rates of alcohol and substance abuse or dependence did not differ significantly between the diagnostic groups after adjustment for age and gender (Table 5).

When considering the schizoaffective disorder patients separately, we found that this group resembled the 'narrow-schizophrenia' group in alcohol use, and had statistically significantly more abstainers than the bipolar group (*p* = 0.019 at the 24-month interval after adjusting for age and gender). The schizoaffective group had also a significantly lower proportion using only cannabis (*p* = 0.042) compared

Table 5. DSM-IV diagnosis of abuse/dependence^a

	Schizophrenia <i>n</i> (%)	Bipolar <i>n</i> (%)	OR	95% CI	<i>p</i> ^b
Any non-alcoholic drug	25 (11.9)	9 (7.1)	1.4	0.6–3.2	0.442
Alcohol	26 (12.4)	17 (13.5)	0.9	0.4–1.7	0.711
Any substance	41 (19.5)	26 (20.6)	0.8	0.8–1.5	0.494

OR, odds ratio; CI, confidence interval.

^aSchizophrenia, *n* = 210; bipolar disorder, *n* = 126.

^b*p* values of OR after adjusting for age and gender.

with the bipolar group of individuals. There was a trend that the schizoaffective disorder patients resembled the bipolar group in having a lower proportion of psychoactive drug users compared with the 'narrow-schizophrenia' group, but this did not reach statistical significance. However, the schizoaffective group was small (*n* = 39), which limits the statistical power of the analysis and makes the findings hard to interpret. The mean age of the schizoaffective disorder patients was 37.9 (S.D. = 11.4) years, statistically significantly higher (*p* < 0.001) than the 'narrow-schizophrenia' group [mean age 32.2 (S.D. = 9.2) years]. Of the schizoaffective disorder patients, 41% (*n* = 16) were males, significantly less than in the 'narrow-schizophrenia' group [60.2% males (*n* = 103), *p* = 0.023]. There were no statistically significant differences in demographics between the schizoaffective disorder patients and the bipolar disorder patients.

Discussion

The main finding of the present study was clear differences in substance-use patterns in schizophrenia and bipolar disorder. Patients with bipolar disorder had higher rates of alcohol consumption, while schizophrenia patients more often used centrally stimulating substances, had more frequent use of non-alcoholic drugs in general and more often used more than one non-alcoholic drug. These characteristics would not have been revealed through a diagnosis of abuse or dependence only, which shows the importance of evaluating substance use beyond the abuse or addiction diagnosis when the relationship to severe mental disorders is studied.

About twice as many schizophrenia patients as bipolar patients were abstaining from alcohol and twice as many bipolar patients could be defined as having harmful use of alcohol than schizophrenia patients. High rates of alcohol abuse in bipolar patients have been reported in numerous studies (Sherwood Brown *et al.* 2001). Alcohol use may induce affective, and most often depressive, episodes (Strakowski *et al.* 2000) and one could speculate about the existence of

mechanisms linking alcohol use to bipolar disorder specifically.

Studies concerning alcohol consumption in patients with schizophrenia have been more diverging. In line with the current results several studies report lower rates of alcohol consumption in schizophrenia than in the general population (Etter & Etter, 2004; Picchioni & Murray, 2000). This could be due to possible mechanisms linked with schizophrenia that limit alcohol use, such as lower income or fewer social interactions. A higher prevalence of abstaining in the schizophrenia group could represent previous problematic use, although we found negative correlations between a lifetime diagnosis of alcohol abuse/dependence and current abstaining. Many studies, however, show higher rates of alcohol-use disorders among schizophrenia patients as compared with healthy controls (Farrell *et al.* 1998; Green *et al.* 2007) and schizophrenia patients have been found to show increased euphoric and stimulatory responses to alcohol (D'Souza *et al.* 2006). Our findings regarding prevalence of use of centrally stimulating substances in schizophrenia and bipolar patients *per se* are more or less in line with other studies (Winokur *et al.* 1998; Mueser *et al.* 2001; Chengappa *et al.* 2000; Kilbourne *et al.* 2004). The higher proportion of stimulant use in the schizophrenia group compared with the bipolar group is, however, different to earlier comparisons between the two diagnostic groups, which found the prevalences to be more similar (Mueser *et al.* 1992; Verdoux *et al.* 1996), or with higher prevalence in the bipolar disorder group (Regier *et al.* 1990). Overall cannabis use did not seem to differ between diagnostic groups after controlling for age and gender.

When individuals with schizophrenia used non-alcoholic drugs they tended to have more poly-substance use and a higher frequency of use. Non-alcoholic drug users with bipolar disorder, on the other hand, more often used only cannabis. Bipolar disorder patients generally showed a stronger tendency for mono-use than the schizophrenia group. Preference for limited use of one type of substance could possibly reflect better functioning in the bipolar

disorder group, as one would expect some level of discriminative ability in order to maintain a selective use pattern. The fact that bipolar disorder patients are indeed reported to have fewer cognitive deficits than schizophrenia patients (Daban *et al.* 2006) could support this interpretation.

The findings from our investigation of the different substance groups could be related to self-medication of symptoms (Khantzian, 1985). Depressive symptoms in bipolar patients have been reported to motivate for and be alleviated by substance use (Weiss *et al.* 2004). Negative symptoms are in some studies reported to be milder in schizophrenia patients with substance-use disorder (Joyal *et al.* 2003; Potvin *et al.* 2005; Talamo *et al.* 2006). Following this line of reasoning, it is plausible that different substance preferences between diagnostic groups could reflect differences in the substances' effect on symptoms; i.e. that bipolar patients tend to use substances that are 'relaxing' such as alcohol and cannabis while schizophrenia patients use more centrally stimulating agents. However, a longitudinal study would be needed to address this question as both present and absent symptoms in a substance-using patient population could be regarded as indications of self-medication.

In recent years several longitudinal studies have concentrated on elucidating the strong associations found between substance use and severe mental illness (Strakowski *et al.* 2000; Van Os *et al.* 2002; Henquet *et al.* 2005, 2006; Strakowski *et al.* 2007). Evidence is accumulating that cannabis is a risk factor for schizophrenia (Van Os *et al.* 2002; Henquet *et al.* 2005), and possibly also for mania (Henquet *et al.* 2006; Strakowski *et al.* 2007). These results suggest a genetically linked vulnerability for substance use and severe mental disorders, but still little is known about possible differentiated substance-vulnerability between schizophrenia and bipolar disorder. The present findings of clear differences in drug-use patterns could be related to different interactions between genetic susceptibility and substance use for the two disorders. Such differences seem to be in opposition to a theory of a continuous psychotic-disorder spectrum (Crow, 1998; Craddock *et al.* 2006), and could suggest that schizophrenia and bipolar disorder are separate entities. However, our findings do not necessarily contradict this theory, as drug-use patterns show considerable overlap, and could also be operating along a continuum. Our results from the schizoaffective disorder group could support a possible 'in-between' position, but due to the low number, the results are difficult to interpret.

Recent advances in treatment regimens for severe mental disorders with co-morbid drug abuse (Mueser *et al.* 2003) are based on general principles which stress

the importance of individually tailored and integrated approaches. If the two main severe mental disorders differ in drug-use susceptibility and drug-use habits on group levels, then the planning of the healthcare services for these patient groups should be adjusted accordingly.

The present findings were obtained in a sample from a catchment area-based healthcare system. This makes the data more representative for these patient populations than other studies, as for instance the CATIE study (Swartz *et al.* 2006). The inclusion of out-patients provides data from a stable patient population, avoiding the impact of drug use related to acute exacerbations seen in emergency ward studies. The study also has shortcomings, mainly that it is limited to cross-sectional registration of reported use, and thus cannot answer questions about causality or about subjective preferences or experiences. The patient selection criteria are not without some biasing effect; the study has excluded clinically unstable patients and there could be a possible over-representation of chronic cases in this sample of patients receiving specialized treatment. Possible systematic differences in drug use between schizophrenia and bipolar disorder patients from time periods before our assessment window are not accounted for, and represent potential confounders. The concrete availability of drugs of abuse on the illegal market in Oslo could affect the results, but prevalence of drug use in Oslo seems to be similar to reports from several other European countries (Rehm *et al.* 2005; European Monitoring Centre for Drugs and Drug Addiction, 2006).

The present study confirmed diagnosis-specific patterns of substance use in severe mental disorder. This suggests a need for disease-specific treatment strategies, and indicates separate underlying disease mechanisms. Future studies should focus on drug-use patterns' possible association with other clinical measures as motivation for use and preferably also longitudinal aspects, as well as more biological parameters such as genetics and brain imaging.

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Declaration of Interest

None.

References

- APA (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychological Association: Washington, DC.
- Cadet JL, Krasnova IN, Jayanthi S, Lyles J (2007). Neurotoxicity of substituted amphetamines: molecular and cellular mechanisms. *Neurotoxicity Research* **11**, 183–202.
- Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene \times environment interaction. *Biological Psychiatry* **57**, 1117–1127.
- Cassidy F, Ahearn EP, Carroll BJ (2001). Substance abuse in bipolar disorder. *Bipolar Disorders* **3**, 181–188.
- Chengappa KNR, Levine J, Gershon S, Kupfer DJ (2000). Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. *Bipolar Disorder* **2**, 191–195.
- Craddock N, O'Donovan MC, Owen MJ (2006). Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophrenia Bulletin* **32**, 9–16.
- Crow TJ (1998). From Kraepelin to Kretschmer leavened by Schneider. The transition from categories of psychosis to dimensions of variation intrinsic to *Homo sapiens*. *Archives of General Psychiatry* **55**, 502–504.
- Daban C, Martínez-Aran A, Torrent C, Tabarés-Seisdedos R, Balanzá-Martínez V, Salazar-Fraile J, Selva-Vera G, Vieta E (2006). Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychotherapy and Psychosomatics* **75**, 72–84.
- de Leon J, Diaz FJ, Rogers T, Browne D, Dinsmore L (2002). Initiation of daily smoking and nicotine dependence in schizophrenia and mood disorders. *Schizophrenia Research* **56**, 47–54.
- Drake RE, Osher FC, Wallach MA (1989). Alcohol use and abuse in schizophrenia: a prospective community study. *Journal of Nervous and Mental Disorder* **177**, 408–414.
- D'Souza DC, Gil RB, Madonick S, Perry EB, Forselius-Bielen K, Braley G, Donahue L, Tellioglu T, Zimolo Z, Guerguieva R, Krystal JH (2006). Enhanced sensitivity to the euphoric effects of alcohol in schizophrenia. *Neuropsychopharmacology* **31**, 2767–2775.
- Etter M, Etter J-F (2004). Alcohol consumption and the CAGE test in outpatients with schizophrenia or schizoaffective disorder and in the general population. *Schizophrenia Bulletin* **30**, 947–956.
- European Monitoring Centre for Drugs and Drug Addiction (2006). Annual Report 2006: The state of the drugs problem in Europe. EMCDDA: Lisbon, Portugal (<http://ar2006.emcdda.europa.eu/en/home-en.html>). Accessed 12 December 2006.
- Farrell M, Howes S, Taylor C, Lewis G, Jenkins R, Bebbington P, Jarvis M, Brugha T, Gill B, Meltzer H (1998). Substance misuse and psychiatric comorbidity: an overview of the OPCS National Psychiatric Morbidity Survey. *Addictive Behaviors* **23**, 909–918.
- Green AI, Drake RE, Brunette MF, Noordsy DL (2007). Schizophrenia and co-occurring substance use disorder. *American Journal of Psychiatry* **164**, 402–408.
- Green B, Young R, Kavanagh D (2005). Cannabis use and misuse prevalence among people with psychosis. *British Journal of Psychiatry* **187**, 306–313.
- Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF (2005). Epidemiologic review of marijuana use and cancer risk. *Alcohol* **35**, 265–275.
- Henquet C, Krabbendam L, de Graaf R, ten Have M, van Os J (2006). Cannabis use and expression of mania in the general population. *Journal of Affective Disorders* **95**, 103–110.
- Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen H-U, van Os J (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *British Medical Journal* **330**, 11–16.
- Joyal CC, Hallé P, Lapierre D, Hodgins S (2003). Substance abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophrenia Research* **63**, 297–299.
- Kavanagh DJ, McGrath J, Saunders JB, Dore G, Clark D (2002). Substance misuse in patients with schizophrenia: epidemiology and management. *Drugs* **62**, 743–755.
- Khantzian EJ (1985). The self medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *American Journal of Psychiatry* **142**, 1259–1264.
- Kilbourne AM, Cornelius JR, Han X, Pincus HA, Shad M, Salloum I, Conigliaro J, Haas GL (2004). Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disorders* **6**, 368–373.
- Miles H, Johnson S, Amponsah-Afuwape S, Finch E, Leese M, Thornicroft G (2003). Characteristics of subgroups of individuals with psychotic illness and a comorbid substance use disorder. *Psychiatric Services* **54**, 554–561.
- Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **28**, 319–328.
- Mueser KT, Essock SM, Drake RE, Wolfe RS, Frisman L (2001). Rural and urban differences in patients with a dual diagnosis. *Schizophrenia Research* **48**, 93–107.
- Mueser KT, Noordsy DL, Drake RE, Fox L (2003). *Integrated Treatment for Dual Disorders: A Guide to Effective Practice*. The Guilford Press: New York.
- Mueser KT, Yarnold PR, Bellack AS (1992). Diagnostic and demographic correlates of substance abuse in schizophrenia and major affective disorder. *Acta Psychiatrica Scandinavica* **85**, 48–55.
- Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C (2004). A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia Research* **71**, 405–416.

- Norwegian Institute for Alcohol and Drug Research (2006). Rusmidler i Norge 2006. SIRIUS: Oslo (<http://www.sirus.no>). Accessed 1 December 2006.
- Office of Applied Studies, Substance Abuse and Mental Health Services Administration (2006). Drugs (heroin, PCP, LSD, cocaine, club drugs, alcohol, tobacco, marijuana, etc.) on SAMHSA's Office of Applied Studies website. US Department of Health and Mental Services: Rockville, MD (<http://www.oas.samhsa.gov/drugs.cfm>). Accessed 12 December 2006.
- Picchioni MM, Murray RM (2000). Overvalued ideas about alcoholism and schizophrenia. *Addiction* 95, 1860–1863.
- Potvin S, Sèphery AA, Stip E (2005). A meta-analysis of negative symptoms in dual diagnosis schizophrenia. *Psychological Medicine* 36, 431–440.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK (1990). Comorbidity of mental disorders and other substance abuse. Results from the epidemiologic catchment area (ECA) study. *Journal of the American Medical Association* 264, 2511–2518.
- Rehm J, Room R, van den Brink W, Kraus L (2005). Problematic drug use disorders in EU countries and Norway: an overview of the epidemiology. *European Neuropsychopharmacology* 15, 389–397.
- Sherwood Brown E, Suppes T, Adinoff B, Rajan Thomas N (2001). Substance abuse and bipolar disorder: comorbidity or misdiagnosis? *Journal of Affective Disorders* 65, 105–115.
- Strakowski SM, DelBello MP, Fleck DE, Adler CM, Anthenelli R, Keck PE, Arnold LM, Amicone J (2007). Effects of co-occurring cannabis use disorders on the course of bipolar disorder after a first hospitalization of mania. *Archives of General Psychiatry* 64, 57–64.
- Strakowski SM, DelBello MP, Fleck DE, Arndt S (2000). The impact of substance abuse on the course of bipolar disorder. *Biological Psychiatry* 48, 477–485.
- Swartz MS, Wagner HR, Swanson JW, Scott Stroup T, McEvoy JP, Canive JM, Miller DD, Reimherr F, McGee M, Khan A, Van Dorn R, Rosenheck RA, Liebermann JA (2006). Substance use in persons with schizophrenia. Baseline prevalence and correlates from the NIMH CATIE study. *Journal of Nervous and Mental Disorders* 194, 164–172.
- Talamo A, Centorino F, Tondo L, Dimitri A, Hennen J, Baldessarini RJ (2006). Comorbid substance abuse in schizophrenia: relation to positive and negative symptoms. *Schizophrenia Research* 86, 251–255.
- Van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H (2002). Cannabis use and psychosis: a longitudinal population-based study. *American Journal of Epidemiology* 156, 319–327.
- Ventura J, Liberman RP, Green MF, Shaner A, Mintz J (1998). Training and quality assurance with the Structured Clinical Interview for DSM-IV I/P (SCID). *Psychiatry Research* 79, 163–173.
- Verdoux H, Mury M, Besancon G, Bourgeois M (1996). Comparative study of substance dependence comorbidity in bipolar, schizophrenic and schizoaffective disorders. *Encephale* 22, 95–101.
- Weiss RD, Kolodziej M, Griffin ML, Najavits LM, Jacobson LM, Greenfield SF (2004). Substance use and perceived symptom improvement among patients with bipolar disorder and substance dependence. *Journal of Affective Disorders* 79, 279–283.
- Winokur G, Turvey C, Akiskal H, Coryell W, Solomon S, Leon A, Mueller T, Endicott J, Maser J, Keller M (1998). Alcoholism and substance abuse in three groups – bipolar I, unipolars and their acquaintances. *Journal of Affective Disorders* 50, 81–89.
- Ziedonis D, Williams JM, Smelson D (2003). Serious mental illness and tobacco addiction: a model program to address this common but neglected issue. *American Journal of the Medical Sciences* 326, 223–230.

The level of illicit drug use is related to symptoms and premorbid functioning in severe mental illness

Ringen PA, Melle I, Birkenaes AB, Engh JA, Faerden A, Vaskinn A, Friis S, Opjordsmoen S, Andreassen OA. The level of illicit drug use is related to symptoms and premorbid functioning in severe mental illness.

Objective: There is conflicting data on drug abuse and outcome in severe mental illness. This study aims to investigate if the amount of illicit psychoactive drug use is related to symptom load or premorbid functioning across diagnosis in patients with severe mental illness.

Method: Symptom load, sociodemographic status, premorbid functioning and the level of use of illicit psychoactive drugs were assessed in 423 subjects with schizophrenia or bipolar disorder in a cross-sectional study.

Results: High amount of illicit drug use was associated with poorer premorbid academic functioning. In schizophrenia, there was a significant positive association between amount of drug use and severity of psychiatric symptoms. The association between symptom load and drug use was significant after controlling for premorbid functioning.

Conclusion: The results suggest a direct association between the quantity of current drug use and more severe symptoms in schizophrenia. Poor premorbid functioning was related to high amount of use, but did not explain the difference in symptom load.

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Key words: psychotic disorders; cannabis; psychostimulants

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Significant outcomes

- High level of drug use was associated with higher levels of positive, negative and general symptoms in schizophrenia, but not in bipolar disorder.
- High level of drug use was associated with poorer premorbid functioning in both disorders.
- The association between use level and symptoms in schizophrenia remained significant after controlling for premorbid functioning.

Limitations

- The cross-sectional design does not allow for assumptions of causality.
- Illicit drugs known to induce psychoses were pooled independently of possible differences in pharmacological properties.
- The number of patients with bipolar disorder and high level of drug use was small and implies a risk of type II error.

Introduction

The use of amphetamines, cocaine and cannabis is over-represented in patients with psychotic illness (1, 2), and can precipitate psychotic disorders or mania in vulnerable individuals (3, 4). Such abuse

has been associated with poorer course and outcome in both schizophrenia and bipolar disorder (5–7), lower social functioning in a mixed diagnostic sample (1) and more aggressive behaviour in a general psychotic illness sample (8). However, several findings in schizophrenia question this

apparently consistent relation (9), and even suggest a less severe form of illness in patients with a dual diagnosis (10, 11) including less negative symptoms (12). In a mixed schizophrenia and bipolar disorder sample, Carey et al. (13) found better cognition in substance abusers and better current social functioning in former abusers than in patients that never abused.

These conflicting data can only partly be explained by variations in methodology and patient samples (12) and other factors must be involved. A potential candidate to explain variations in illness severity is the quantity of drugs used, as there are indications that the severity of the drug-use disorder is associated with outcome (14). Laboratory studies have shown increase in positive, negative and general symptoms in patients with schizophrenia after intravenous administration of Δ^9 -tetrahydrocannabinol (THC), the main psychoactive component of cannabis (15). Increase in psychosis-like symptoms and anxiety has also been found in non-psychotic individuals after THC injection (16) and after cocaine administration (17). There are also indications of a dose-response association for amphetamine and psychotic symptoms (18). The effects of THC, cocaine or amphetamine on patients with bipolar disorder have not been examined directly.

Studies have reported that drug users have better premorbid social functioning but worse premorbid academic functioning than non-users (19). Poor premorbid functioning is related to more severe illness and symptom variants in schizophrenia (20). Variation in premorbid functioning may thus better explain the variation in illness severity than current drug use. This is also of interest because psychosocial problems in childhood and adolescence are associated with both drug use (21, 22) and severe mental illness in adults (23, 24). Thus, premorbid functioning may also be an important explanation of differences in symptom severity.

There seems to be important differences in clinical features and drug-use patterns between schizophrenia and bipolar disorders (25). Such relationships may be important in the understanding of these disorders and the currently debated continuum hypothesis of bipolar disorder and schizophrenia (26). In spite of this, the relationship among drug use, symptom severity and potential premorbid predictors has not been investigated in a study of both disorders.

This study is based on a large, unselected sample of consecutive patients with schizophrenia and bipolar disorder recruited from a catchment area-based psychiatric service. Previous reports based on a smaller subsample have shown that the study

patients use drugs to the same extent as patients who did not enter the study and that drug users were younger than non-users (27). Differences in drug-use patterns between patients with schizophrenia and bipolar disorder have also been reported (28).

Aims of the study

The aim of this study was to examine the following hypotheses: i) there is a relationship between higher levels of drug use and higher levels of positive, negative and general symptoms; ii) there are differences in premorbid functioning between users and non-users; iii) there are differences between schizophrenia and bipolar disorder regarding the association between drug use, premorbid functioning and symptom levels.

Material and methods

It has been chosen to focus on the use of cannabis, amphetamines, cocaine and hallucinogens despite differences in pharmacological effects as there is considerable clinical evidence that these drugs have psychosis-inducing properties. We excluded opiate agonists, where evidence actually point to a use of possible psychosis-protecting effect (29).

Participants

The study was part of the Thematic Organized Psychosis Research (TOP) study. Patients were recruited from the in-patient and out-patient psychiatric services at the departments of psychiatry at Ullevål University Hospital, Aker University Hospital and Diakonhjemmet Hospital in Oslo, Norway. At the moment of study entry, 84% were treated as out-patients. The three departments cover a catchment area of 485 000 inhabitants (88% of Oslo's total population), both inner city areas and suburbs, and representing fairly well the sociodemographic characteristics of the city.

Inclusion criteria were as follows: patients had to be between 18 and 65 years, clinically assessed to be able to participate in extensive interviews and have a DSM-IV diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar I disorder, bipolar II disorder or bipolar disorder not otherwise specified (NOS). Exclusion criteria were presence of a pronounced cognitive deficit (IQ below 70), severe brain damage or not speaking a Scandinavian language. For this particular substudy, subjects with reported consumption of an opiate agonist past 6 months were also excluded.

Illicit psychoactive drug use in patients with severe mental illness

Four hundred and twenty-three patients were included from October 2002 to October 2007; the inclusions were performed by research fellows in cooperation with the treating clinicians. This study sample comprised the first patients who were consecutively referred to the study. Emphasis was put on recruiting all patients regardless treatment adherence. The patients were recruited by their clinician and thus the exact number of eligible patients who were not referred to the study based on the clinicians' decisions is unknown. However, there were 57 clearly eligible patients who were referred but refused to participate.

Central demographic data are shown in Table 1. One hundred and eighty-seven patients (44.2%) had schizophrenia, 48 (11.3%) had schizoaffective disorder and 17 (4.0%) had schizophreniform disorder (forming the schizophrenia patient group). One hundred and four patients (24.6%) had bipolar I disorder, 60 (14.2%) had bipolar II disorder and seven (1.7%) had bipolar NOS disorder (forming the bipolar disorder patient group). The schizophrenia patients were younger than the bipolar disorder patients and more were male (Table 1). The mean age of debut of psychosis was 25.9 years (SD 9.4), mean number of psychotic episodes was 2.2 (SD 3.4), mean number of depressive episodes was 4.1 (SD 8.7), mean number of hospital admissions was 2.7 (SD 4.0) and mean total length of hospitalization was 3.2 years (SD 2.0). As primary medication, 70.9% used a second generation antipsychotic, 15.2% used lithium or an antiepileptic, 8.1% used an antidepressant and 4.9% used a first generation antipsychotic. Ninety-four (22.2%) subjects reported illicit drug use past 6 months, of

these 84.0% reported use of cannabis, 22.3% use of amphetamines, 14.9% use of cocaine, 3.2% use of ecstasy, 2.1% use of LSD or mescaline, 2.1% use of hallucinogenic mushrooms, 1.1% use of Khat and 1.1% reported use of γ -hydroxybutyric acid (GHB).

Procedure and measures

All patients consecutively referred to the study were interviewed by research fellows with previous clinical training (psychiatric residents/psychiatrists or clinical psychologists). The structural clinical interview for the DSM-IV axis I disorders (SCID-I), modules A-E (30) were used for diagnostic purposes. All interviewers participated in regular diagnostic consensus meetings led by a well-experienced clinical researcher in the field of diagnostics in severe mental illness (SO) and completed a training course in SCID assessment based on the training programme at University of California, Los Angeles (UCLA) (31). Mean overall kappa for SCID diagnoses assessed by the UCLA training programme was 0.77. To assess reliability for actual study interviews, a stratified random sample, consisting of cases from every assessing staff member was drawn. Anonymous vignettes describing symptoms and development of the illness were then rated by two experts blind to the study ratings. For the 28 vignettes, the overall agreement for the nine DSM-IV diagnostic categories was 82% and the overall kappa was 0.77 (95% CI: 0.60–0.94).

Symptoms were assessed by the Positive and Negative Symptoms Scale (PANSS) (32). Premorbid functioning was assessed by the Premorbid Adjustment Scale (PAS) (33). PAS scores were divided into academic and social domains according to premorbid age intervals (23).

The intraclass correlation coefficient (1.1) was 0.73, 0.73 and 0.71 for PANSS positive, negative and general subscales respectively.

Patients were interviewed semistructurally about non-alcoholic drug use during the past 6 months, where the different substances were asked for specifically and their use quantified by adding up number of episodes recalled. When episodes were too frequent for precise recall, effort was put to identify typical periods of mean weekly use and add up by number of weeks for that period. Data on incidents of use past 6 months were pooled for all non-alcoholic substances, and specific incidents for each drug were not recorded unless only one type of drug had been used.

Patients were then grouped into three groups based on this information. Three hundred and twenty-nine denied any use and constitute the 'no-use' group. To assess amount of use, the 94 patients

Table 1. Demographics, premorbid functioning and symptoms

	Total sample (<i>n</i> = 423)	Schizophrenia group (<i>n</i> = 252)	Bipolar disorder group (<i>n</i> = 171)
<i>n</i> (%)			
Male gender	215 (50.8)	147 (58.3)	68 (39.8)**
Always single	266 (62.9)	176 (69.8)	90 (52.6)**
No higher education	268 (63.7)	192 (76.8)	76 (44.4)**
No occupation	255 (60.4)	183 (72.9)	72 (42.1)**
Daily smoking	232 (55.0)	142 (56.6)	90 (52.6)
Alcohol abuse	60 (14.2)	34 (13.5)	26 (15.2)
Mean (SD)			
Age	34.3 (11.0)	33.0 (10.1)	36.3 (9, 11)**
PAS academic <11 years	1.6 (1.2)	1.7 (1.3)	1.4 (1.1)*
PAS social <11 years	1.2 (1.3)	1.3 (1.4)	1.1 (1.2)
PANSS-positive	13.2 (5.6)	15.5 (5.7)	9.9 (3.1)**
PANSS-negative	13.3 (5.9)	15.4 (6.2)	10.3 (3.7)**
PANSS-general	29.3 (8.0)	31.8 (8.2)	25.8 (6.2)**

* $P \leq 0.05$, ** $P \leq 0.001$ comparisons between schizophrenia and bipolar disorder. Chi-squared tests or Fisher exact tests for categorical data; *t*-test for continuous variables; higher scores indicate poorer functioning.

PAS, Premorbid Adjustment Scale; academic, academic functioning (PAS items 1 and 2); social, social functioning (PAS items 3 and 4).

reporting use during the last 6 months were divided in two groups based on the median frequency of drug intake across all diagnostic groups entering the larger TOP study (nine incidents past 6 months). Fifty-three subjects reported nine incidents or more and constitute the 'high-use' group while 41 reported less than nine incidents and constitute the 'low-use' group. Median incidents of use within the low-use and the high-use group were 2 (range: 1–8) and 26 (range 9–192) respectively.

We did not assess level of alcohol use in this study because its possible psychosis-inducing properties are not known, and total abstainers are in minority also among people with severe mental disorders (28).

Urine samples were drawn from 379 subjects and analyzed for illicit substances. Of the 17 subjects with positive samples for cannabis, only three denied recent use, indicating a high reliability of self-report.

Schizophrenia patients were significantly more often males and younger than bipolar disorder patients. Schizophrenia patients had significantly more symptoms, poorer current social functioning and poorer premorbid academic functioning than bipolar disorder patients. There were no significant differences between the diagnostic groups in smoking or alcohol abuse (Table 1).

As reported previously from a smaller subsample (27), there were statistically significant associations between drug use and age, gender, marital status, level of education, daily smoking and alcohol-abuse disorder. Mean age (SD) of the no-use group was 36.0 (11.2), the low-use group was 28.5 (8.3) and the high-use group was 28.5 (7.7). Drug users (both high users and low users) were significantly younger than non-users ($P = 0.001$, univariate analysis of variance, with correction for gender, diagnosis, marital status, education and alcohol abuse). Drug users were also significantly more often single ($P < 0.001$), daily smokers ($P < 0.001$), DSM-IV alcohol abusers ($P < 0.001$) and with shorter education ($P < 0.001$) than non-users. Except that the high-use group consisted of significantly more daily smokers than the low-use group, there were no statistical differences between the use groups. There were significantly more men (65.9%) in the high-use group ($P = 0.046$).

Statistical analyses

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 16.0 was used for all statistical analyses. Limits for significance were set at the 0.05 level (two-sided). Differences between diagnostic groups in continuous and

categorical variables were analyzed with two-sided independent *t*-tests and Fisher exact tests respectively. The variable describing drug use last 6 months was significantly skewed and could not be transformed to a normal distribution. Creation of the three use level groups enabled cross-diagnosis comparisons. Differences in premorbid functioning, positive, negative and general symptom between use level groups were first analyzed with one-way ANOVAS with *post hoc* Bonferroni tests. There was a significant interaction effect for diagnostic group and use level group for general symptoms, and for the subsequent analyses the sample was stratified according to diagnostic group (schizophrenia or bipolar disorder). Correlations between symptom levels, use levels and background variables that might mediate their relationships were explored through Spearman rank correlations (Table 3). Finally, the possibility of confounders of the relationship between each symptom area (positive, negative and general) and use level groups were explored through hierarchical multiple linear regression analysis. As both ANOVAS and the initial regression analyses (without the possible confounders) indicated that the main difference was between the 'high-use' group and the 'low-use' and 'no-use' groups, level of use were in these analyses represented by the dichotomous variable 'high-use' vs. 'no- or low-use', entered at the last step of the analysis.

The study is approved by the Data Inspectorate of Norway and the Regional Ethics Committee of the Eastern Norway Health Authority.

Results

Premorbid functioning

Childhood premorbid academic functioning was statistically significantly poorer in high users than in non-users or low users in the whole sample ($P < 0.001$, univariate ANOVA test, corrected for gender and diagnosis). The low-use group had a trend ($P = 0.061$) for better premorbid social functioning than non-users or high users (Fig. 1). There were statistically significant correlations between drug use level and symptoms for the independent variables age, gender, years of education and premorbid academic functioning (Table 2) in the whole sample.

Symptoms

There was a general trend in the whole sample that the high-use group had more symptoms compared with the other use groups. For the

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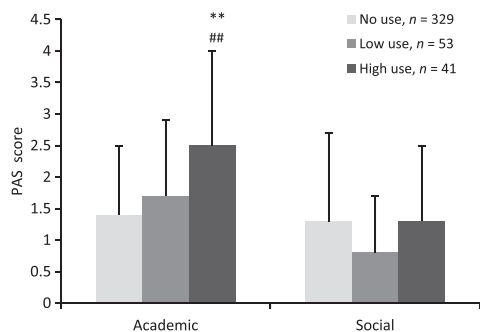


Fig. 1. Level of drug use and premorbid functioning (PAS). No use: no incidents past 6 months; low use: 1–8 incidents past 6 months; high use: nine incidents and more past 6 months; columns represent mean scores; bars represent one standard deviation; **compared with no-use group ($P \leq 0.01$); ## compared with low-use group ($P \leq 0.01$). Univariate ANOVA tests (corrected for gender and diagnosis) and *post hoc t*-test for continuous variables. Higher scores indicate poorer functioning. Academic, academic functioning (PAS items 1 and 2); Social, social functioning (PAS items 3 and 4).

Table 2. Bivariate relationships between drug-use level, symptoms and significant independent variables

	Drug-use level	PANSS (positive)	PANSS (general)	PANSS (negative)
Diagnosis	-0.056	-0.512**	0.438**	0.387**
Age	-0.291*	-0.060	-0.106*	-0.056
Gender	-0.109**	-0.118*	-0.233**	-0.071
Education, years	-0.218**	-0.282**	-0.281**	-0.242**
PAS social <11 years	-0.036	0.112*	0.141**	0.218**
PAS academic <11 years	0.209**	0.117*	0.115*	0.162**

Spearman's rho correlations.* $P < 0.05$; ** $P < 0.01$.

PAS, Premorbid Adjustment Scale; academic, academic functioning (PAS items 1 and 2); social, social functioning (PAS items 3 and 4).

PANSS-negative sumscore, this was significant compared with both the no-use and the low-use groups. For the PANSS-positive sumscore, the difference was significant compared with the no-use group, and for the PANSS general sumscore, the difference was significant compared with the low-use group (Table 3). For the positive and negative sumscores, there were no interaction effects between use group and diagnostic group. For the general sumscore, there was a significant interaction effect ($F = 3.249$, $df = 2$, $P = 0.040$), indicating an increase in general symptoms for the schizophrenia group with increasing use, but a decrease in the bipolar group. In the evaluation of possible confounders for the relationship between drug use and symptom levels, the diagnostic groups were analyzed separately.

Multiple linear regression analysis

Schizophrenia group: for positive symptoms, there was a significant effect of high use entered as last variable ($\beta = 0.160$, $P = 0.025$) after correction for gender, age and premorbid academic functioning. For negative symptoms, there was a significant effect of high use entered as last variable ($\beta = 0.156$, $P = 0.027$) after correction for gender, age and premorbid academic functioning. For general symptoms, there was a significant effect of high use entered as last variable ($\beta = 0.140$, $P = 0.050$) after correction for gender, age and premorbid academic functioning. Premorbid academic functioning did not contribute with a significant effect in the last step of the final models for any of the PANSS sumscores.

Table 3. Level of drug use and symptom levels

	No use (1)	Low use (2)	High use (3)	Significance	
				ANOVA	<i>post hoc</i>
Whole sample <i>n</i> = 423	<i>n</i> = 329	<i>n</i> = 53	<i>n</i> = 41		
PANSS-positive	13.0 (5.4)	13.2 (5.8)	15.6 (5.9)	$P = 0.015$	1 vs. 3
PANSS-negative	13.2 (5.6)	12.4 (6.0)	15.7 (7.2)	$P = 0.017$	1 vs. 3, 2 vs. 3
PANSS-general	29.4 (7.9)	27.3 (7.2)	31.7 (8.9)	$P = 0.029$	2 vs. 3
Schizophrenia <i>n</i> = 252	<i>n</i> = 192	<i>n</i> = 30	<i>n</i> = 30		
PANSS-positive	15.1 (5.6)	15.7 (6.5)	17.7 (5.4)	n.s.	
PANSS-negative	15.1 (6.0)	15.0 (6.3)	17.6 (7.3)	n.s.	
PANSS-general	31.6 (8.2)	29.3 (7.4)	35.0 (7.7)	$P = 0.024$	2 vs. 3
Bipolar disorder <i>n</i> = 171	<i>n</i> = 137	<i>n</i> = 23	<i>n</i> = 11		
PANSS-positive	9.9 (3.3)	9.9 (2.4)	9.8 (2.1)	n.s.	
PANSS-negative	10.5 (3.8)	9.0 (3.2)	10.4 (3.0)	n.s.	
PANSS-general	26.2 (6.3)	24.7 (6.0)	22.8 (4.3)	n.s.	

Values are expressed as mean (SD).

No use: no incidents past 6 months; low use: 1–8 incidents past 6 months; high use: nine incidents and more past 6 months. Univariate ANOVA tests with *post hoc* Bonferroni tests; pairs of use level groups with significant differences between them are indicated. PANSS, Positive and Negative Symptom Scale; n.s., not significant.

In the bipolar disorder group, there was no effect of level of drug use on symptoms neither in the bivariate analyses nor after correction for possible confounders in the regression analyses.

Discussion

The main finding of this study was a significant positive association between current amount of drug use and severity of psychiatric symptoms in schizophrenia, which was not found in bipolar disorder. The association between symptom load and drug use was reduced, but still significant after controlling for premorbid functioning.

A relationship between level of recent drug use and current symptom load in schizophrenia has to the best of our knowledge not been shown earlier. The association may suggest that the negative effect of psychoactive drugs is directly related to current use. This is in line with previous suggestions (34) and experimental studies showing increase in positive, negative and general symptoms after drug administration in schizophrenia (15). However, this study is cross-sectional, and we cannot rule out that patients use more drugs because of higher symptom levels, in line with the self-medication hypothesis (35). Several previous studies have investigated drug abuse in severe mental disorders, but the amount of drug use has received little attention. These findings indicate that drug use has important clinical implications, even without fulfilling the criteria for DSM diagnoses of abuse or dependence.

There were no clear associations between levels of symptoms and drug use in bipolar disorder patients. This discrepancy between schizophrenia and bipolar disorder may indicate a different association between drug use and symptoms, in line with reports of different patterns of drug use in these disorders (28). However, the lack of association in bipolar disorder could be a type II error, because of low number in the high-use group.

The observed relationship between current drug use and premorbid functioning indicates that poorer premorbid functioning might be a risk factor for later development of drug-use behaviour in patients with severe mental illness. This is in line with earlier reports of increased likelihood of drug-abuse disorders related to premorbid functioning (19). The bivariate correlation analyses showed that both current drug use and premorbid functioning was associated with symptom load; indicating that premorbid functioning could serve as a mediator for the apparent relationship between drug use and symptoms. But when both drug use and premorbid functioning

were entered in the regression analyses, only the level of drug use maintained its association with symptom load. This suggests a direct association between symptom load and level of current drug use that is not mediated through differences in premorbid functioning. Environmental factors in the childhood and adolescence could influence both premorbid functioning and susceptibility to later drug use. Another possible explanation is a common biological susceptibility for developing both drug abuse and severe mental illness (36). Our results were in line with previous findings of better psychosocial functioning in drug-using patients (37), although the results did not reach statistical significance.

There was, however, a significant interaction effect of diagnosis with regard to general symptoms, with increasing symptoms in schizophrenia and decreasing symptoms in bipolar disorder with increasing levels of drug use. General symptoms include more affective and anxiety measures, which are common symptoms in both disorders. The interaction may suggest different psychopathological mechanisms underlying these symptom domains in bipolar disorder and schizophrenia, and more similarities in negative and positive domains. This is, however, speculative and should be investigated with new, hypothesis-based investigations. The association between drug use and premorbid functioning did not seem to differ between diagnoses, which seem to suggest similar psychopathological mechanisms for these aspects.

This study has some limitations. The cross-sectional design does not enable causative conclusions, except for premorbid function, which is clearly preceding current drug use. The rating of drug use was based on self-reports and could therefore be inaccurate. The urine analysis, however, largely confirmed the patients' reports of current use. Our groups of drug-use levels were created by a median-split design, and the threshold for 'high-use' was set at a level that not necessarily corresponds to a clinically or pharmacologically meaningful threshold, something which may lead to confounding effects. However, the purpose was not to study pharmacological effects. The median split approach to separate the use groups makes the high-use group heterogeneous because there is a skewed distribution of data. It also makes the high-use group small in the bipolar disorder group.

To conclude, the association between more severe current psychopathology and use of psychoactive illicit substances seems to be true only for a certain amount and only in schizophrenia. Poor academic functioning may be an early

susceptibility trait for later problematic drug use, but did not explain the variation in symptoms. Further studies addressing the associations between drug use and severe mental illness should include information about level of use.

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Declaration of interest

None.

References

1. KAVANAGH DJ, WAGHORN G, JENNER L et al. Demographic and clinical correlates of comorbid drug use disorders in psychosis: multivariate analyses from an epidemiological sample. *Schizophr Res* 2004;**66**:115–124.
2. GREEN B, YOUNG R, KAVANAGH D. Cannabis use and misuse prevalence among people with psychosis. *Br J Psychiatry* 2005;**187**:306–313.
3. MOORE TH, ZAMMIT S, LINGFORD-HUGHES A et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007;**28**:319–328.
4. HENQUET C, KRABBENDAM L, DE GRAAF R, TEN HAVE M, VAN OS J. Cannabis use and expression of mania in the general population. *J Affect Disord* 2006;**95**:103–110.
5. STRAKOWSKI SM, DELBELLO MP, FLECK DE, ARNDT S. The impact of drug abuse on the course of bipolar disorder. *Biol Psychiatry* 2000;**48**:477–485.
6. MARGOLESE HC, MALCHY L, NEGRETE JC, TEMPIER R, GILL K. Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. *Schizophr Res* 2004;**67**:157–166.
7. GRECH A, VAN OS J, JONES PB, LEWIS SW, MURRAY RM. Cannabis use and outcome of recent psychosis. *Eur Psychiatry* 2005;**20**:349–353.
8. SCOTT H, JOHNSON S, MENEZES P et al. Drug misuse and risk of aggression and offending among the severely mentally ill. *Br J Psychiatry* 1998;**172**:345–350.
9. CANTWELL R, SCOTTISH COMORBIDITY STUDY GROUP. Drug abuse and schizophrenia: effects on symptoms, social functioning and service use. *Br J Psychiatry* 2003;**182**:324–329.
10. JOYAL CC, HALLÉ P, LAPIERRE D, HODGINS S. Drug abuse and/or dependence and better neuropsychological performance in patients with schizophrenia. *Schizophr Res* 2003;**63**:297–299.
11. DUBERTRET C, BIDARD I, ADÉS J, GORWOOD P. Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. *Schizophr Res* 2006;**86**:284–290.
12. POTVIN S, SEPIERY AA, STIP E. A meta-analysis of negative symptoms in dual diagnosis schizophrenia. *Psychol Med* 2006;**36**:431–440.
13. CAREY KB, CAREY MP, SIMONS JS. Correlates of drug use disorder among psychiatric outpatients: focus on cognition,

- social role functioning, and psychiatric status. *J Nerv Ment Dis* 2003;**191**:300–308.
14. WADE D, HARRIGAN S, MCGORRY PD, BURGESS PM, WHELAN G. Impact of severity of substance use disorder on symptomatic and functional outcome in young individuals with first-episode psychosis. *J Clin Psychiatry* 2007;**68**:767–774.
15. D'SOUZA DC, ABI-SAAB WM, MADONICK S et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 2005;**57**:594–608.
16. D'SOUZA DC, PERRY E, MACDOUGAL LL et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004;**8**:1558–1572.
17. MOONEY M, SOFIOGLU M, DUBISH-POULSON S, HATSUKAMI DK. Preliminary observations of paranoia in a human laboratory study of cocaine. *Addict Behav* 2006;**31**:1245–1250.
18. BATKI SL, HARRIS DS. Quantitative drug levels in stimulant psychosis: relationship to symptom severity, catecholamines and hyperkinesias. *Am J Addict* 2004;**13**:461–470.
19. LARSEN TK, MELLE I, AUESTAD B et al. Substance abuse in first episode non-affective psychosis. *Schizophr Res* 2006;**88**:55–62.
20. MACBETH A, GUMLEY A. Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. *Acta Psychiatr Scand* 2008; **117**: 85–99. doi: 10.1111/j.1600-0447.2007.01134.x.
21. KING SM, IACONO WG, MCGUE M. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction* 2004;**99**:1548–1559.
22. SIEBENBRUNER J, ENGLUND MM, EGELAND B, HUDSON K. Developmental antecedents of late adolescence substance use patterns. *Dev Psychopathol* 2006;**18**:551–571.
23. LARSEN TK, FRIIS S, HAAHR U et al. Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. *Br J Psychiatry* 2004;**185**:108–115.
24. OWENS DG, JOHNSTONE EC. Precursors and prodromata of schizophrenia: findings from the Edinburgh High Risk Study and their literature context. *Psychol Med* 2006;**36**:1501–1514.
25. SHERWOOD BROWN E, SUPPES T, ADINOFF B, RAJAN THOMAS N. Substance abuse and bipolar disorder: comorbidity or misdiagnosis? *J Affect Disord* 2001;**65**:105–115.
26. CRADDOCK N, O'DONOVAN MC, OWEN MJ. Phenotypic and genetic complexity of psychosis. Invited commentary on Schizophrenia: a common disease caused by multiple rare alleles. *Br J Psychiatry* 2007;**190**:200–203.
27. RINGEN PA, MELLE I, BIRKENAES AB et al. Illicit drug use in patients with psychotic disorders compared with that in the general population: a cross-sectional study. *Acta Psychiatr Scand* 2008;**2**:133–138.
28. RINGEN PA, LAGERBERG TV, BIRKENAES AB et al. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. *Psychol Med* 2007;**38**:1–9.
29. BRIZER DA, HARTMAN N, SWEENY J, MILLMAN RB. Effect of methadone plus neuroleptics on treatment-resistant chronic paranoid schizophrenia. *Am J Psychiatry* 1985;**142**:1106–1107.
30. AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and statistical manual of mental illness, 4th edn. Washington, DC: American Psychiatric Association, 1994.
31. VENTURA J, LIBERMAN RP, GREEN MF, SHANER A, MINTZ J. Training and quality assurance with the structured clinical interview for DSM-IV I/P (SCID). *Psychiatry Res* 1998;**79**:163–173.

Ringen et al.

32. KAY SR, FISZBEIN A, OPLER LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;**13**:261–276.
33. CANNON-SPOOR HE, POTKIN SG, WYATT RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull* 1982;**8**:470–484.
34. VAN OS J, BAK M, HANSEN M, BIL RV, DE GRAAF R, VERDOUX H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol* 2002;**156**:319–327.
35. KHANTZIAN EJ. The self medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry* 1985;**142**:1259–1264.
36. CHAMBERS RA, KRYSAL JH, SELF DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry* 2001;**50**:71–83.
37. SWARTZ MS, WAGNER HR, SWANSON JW et al. Substance use and psychosocial functioning in schizophrenia among new enrollees in the NIMH CATIE study. *Psychiatr Serv* 2006;**57**:1110–1116.

Opposite relationships between cannabis use and neurocognitive functioning in schizophrenia and bipolar disorder.

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Abstract

Background: Cannabis use is associated with altered neurocognitive functioning in severe mental disorders, but data is still inconclusive.

Aims: To investigate the association between cannabis use and neurocognition in schizophrenia and bipolar disorder.

Method: 273 patients with schizophrenia or bipolar disorder underwent neuropsychological assessments and clinical characterisation including measures of substance use. Relationships between cannabis use and neurocognitive function was explored in the two diagnostic groups.

Results: In schizophrenia subjects, cannabis use was associated with poorer neurocognitive function, but the opposite was the case for the bipolar disorder subjects. These differences in neurocognitive function could not be explained by putative confounders.

Conclusions: The interaction effect of cannabis use with diagnosis suggests that cannabis use is differently related to neurocognition in bipolar disorder and schizophrenia.

Declaration of interest: None.

Introduction

Cognitive deficit is a key feature of schizophrenia and neurocognitive dysfunction is also present in bipolar disorder, albeit to a lesser degree (1-4). Substance use, especially cannabis, is highly prevalent in both schizophrenia and bipolar disorder patients (5-7). Cannabis use is here associated with poorer symptomatic and functional outcome (8;9), but the association between cannabis use and neurocognition is unclear. In the only existing intervention study, the administration of Δ^9 -tetrahydrocannabinol (THC) to patients with schizophrenia was followed by a temporary reduction in verbal learning and memory (10). The few existing clinical studies, however, have mainly shown equal or better cognitive functioning in cannabis users with schizophrenia compared to abstainers (11-13). Even less is known about the effects of cannabis use on neurocognition in bipolar disorder. The only existing study of a combined sample including both patients with schizophrenia and bipolar disorder (14), found no clear associations between cannabis use and neurocognition.

Both neuropsychological test performance and individual effects of substance use can be regarded as endophenotypes; mediating factors between the neurobiological substrate and the expressed phenotype (15). Information on the relationship between cannabis use and neurocognition in these two disorders may thus provide new knowledge about underlying disease mechanisms. This can help in discerning whether there is a continuum of traits between the diagnostic groups rather than distinct categories as proposed in the mood-psychosis spectrum continuum model (16;17).

The aim of the present study is to investigate if there are differences in neurocognitive functioning between cannabis users and non-users in schizophrenia and in bipolar disorder, and if these relationships are the same or different in the two diagnostic groups. The study is

based on a large and comprehensively characterised patient population, with the possibility to control for a range of putative confounders of the relationships.

Method

Setting

The study is part of the Thematic Organized Psychosis Research (TOP) study. Patients were recruited from the Departments of Psychiatry at Ullevål University Hospital (UUH), Aker University Hospital (AUH) and Diakonhjemmet Hospital (DH) in Oslo. The three departments cover a geographical catchment area including 10 districts of Oslo and five suburbs. The catchment areas covers 485 000 inhabitants (88% of Oslo's total population), are located in different areas of the city and are representative of the city's variation in sociodemographic characteristics.

Clinical assessments

Diagnoses were established using the Structural Clinical Interview for the DSM-IV axis I disorders (SCID – I), modules A-E(18). All interviewers participated in regular diagnostic consensus meetings led by an experienced clinical researcher in the field of diagnostics in severe mental disorder. In addition, all raters finished a course in SCID assessment based on the training program at the UCLA (19). Mean overall Kappa for SCID diagnoses assessed by the UCLA procedure was 0.77. To assess reliability for actual study interviews a stratified random sample was drawn, consisting of cases from every assessment staff member.

Anonymous vignettes describing symptoms and development of the illness were then rated by

two experts blind to the study ratings. For the 28 vignettes the overall agreement for the nine DSM-IV diagnostic categories was 82 % and the overall Kappa again 0.77 (95 % CI: 0.60-0.94).

Psychotic symptoms were assessed by the Positive and Negative Symptoms Scale (PANSS) (20). Global symptoms and psychosocial functioning were measured by the Global Assessment of Functioning Scale (GAF), and the scores were split into scales of symptoms (GAF-S) and functioning (GAF-F) to improve psychometric properties (21). Premorbid functioning was assessed by the Premorbid Adjustment Scale (PAS) (22). PAS scores were divided into Academic and Social domains according to premorbid age intervals (23). Increasing scores on PAS signify poorer functioning and higher GAF scores signify fewer symptoms. For the rest of the symptom scores, high scores signify more symptoms.

Substance use assessments

Substance use disorders were diagnosed through the SCID-E module. Patients were additionally interviewed about their use of substances in predefined previous time-periods, with structured questions about the specific substances they had used and the amount of use of each substance. Records were also made of daily nicotine and caffeine use. Current medication, including the use of psychopharmacological substances at the day of testing, was also recorded. All participants were screened for the presence of THC or other recreational drugs in the urine one hour prior to the neurocognitive assessment. Nine subjects had THC in their urine, of these only one denied recent use, implying a high reliability of self-report. One subject had amphetamine in the urine.

Neurocognitive assessment

A comprehensive neuropsychological test battery was administered to all participants by psychologists or test technicians trained by a specialist in clinical neuropsychology.

Tests from domains previously found to be sensitive to dysfunction in groups with cannabis use, bipolar disorder and/or schizophrenia were included.

General cognitive functioning: The number of errors on the Norwegian research version of the *National Adult Reading Test* (NART)(24) was used as a measure of premorbid IQ.

Current IQ was assessed with the *Wechsler Abbreviated Scale of Intelligence* (WASI)(25). All subjects showed adequate neuropsychological test effort as indicated by scoring less than two errors on the forced recognition trial of the California Verbal Learning Task (CVLT-II)(26).

Psychomotor speed: The Digit Symbol test from Wechsler Adult Intelligence Scale (WAIS-III)(27) was used as a measure of psychomotor speed.

Verbal learning and memory: From the Logical Memory test, part of the Wechsler Memory Scale (WMS-III)(28), the total number of items immediately recalled from two short stories that were read once each was used as a measure of verbal learning, while the total number of items freely recalled after 30 min was used to measure delayed verbal recall. From the California Verbal Learning Task (CVLT-II)(26) the total number of words repeated immediately after five reading trials of a list of 16 words was used as an additional measure of verbal learning. The number of words freely recalled after 30 min, was used to measure delayed verbal recall.

Attention and working memory: With the Digit Span Test (forward version), from the Wechsler Adult Intelligence Scale (WAIS-III)(27), the maximum number of digits repeated in the same order as presented was used as a measure of focused attention and the maximum number of digits repeated in a backward order of presentation (backward version) was used as a measure of working memory. The Working Memory–Mental Arithmetic Test (WM–MA)(29) is a computer-based test requiring that a button be pressed every time the two numbers displayed on the screen are the same as the numbers displayed two screen pictures back ('2-back'). Number of correct responses minus the number of false positives (commissions) was used as a measure of working memory.

Executive functioning: From the Verbal Fluency Test, part of the Delis Kaplan Executive Functioning System (D-KEFS)(30) the number of words beginning with the letters 'F', 'A', and 'S' generated separately within 60 seconds was used as a measure of phonetic fluency. The number of animals' and boys' names generated separately within 60 seconds was used as a measure of semantic fluency. Finally, the number of fruit and furniture generated while alternating between the two categories was used as a measure of semantic set shift. From the third trial in the Color–Word Interference Test, part of the Delis Kaplan Executive Functioning System (D-KEFS)(30), the time taken to name the colour of the ink on a list of written names of colours that are incongruent with the colour of the ink was used to measure interference control. From the fourth trial, the time taken to complete the alternation between naming the colour of the ink and naming the written word was included as a measure of interference set shift.

Higher scores on the neuropsychological tests signify better performance on all tests except for the NART and the D-KEFS interference tests where higher scores signify poorer performance.

Subjects

The two hundred and seventy three patients that consecutively gave consent to enter the study from May 2003 through September 2007 are included in the present part of the study. Each patient was referred to the project by their treating clinician after an evaluation of their eligibility and ability to give informed consent. Emphasis was put on recruiting all patients regardless of level of involvement in their respective treatment programs. The assessments were conducted by trained clinicians working as research fellows (MDs or psychologists) before signing the informed consent, and the interview started. The recruitment teams were based in out-patient clinics, which patients were transferred to after acute illness phases. This procedure restricted inclusion to symptomatically stable patients.

Further inclusion criteria were: Age 18 to 65 years and meeting the DSM-IV criteria for a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, bipolar I disorder, bipolar II disorder or bipolar disorder NOS. Subjects had to be fluent in a Scandinavian language. Exclusion criteria were presence of a diagnosis of developmental disorder (IQ<70) or acquired brain damage (head injury with hospitalisation). For the present part of the study patients had to have Norwegian as their first language or have received their compulsory schooling in Norway (to ensure validity of the neuropsychological tests) and not use any other substances than cannabis during the last 6 months.

Mean age was 35.4 years (SD 11.3). 48.7 % (N=133) were male. 40.3 % (N=110) had schizophrenia, 3.3 % (N=9) schizophreniform disorder, 7.7 % (N=21) schizoaffective disorder (schizophrenia group), 28.9 % (N=79) bipolar I disorder, 17.9 % (N=49) bipolar II disorder and 1.8 % (N=5) had bipolar NOS disorder (bipolar disorder group). Schizophrenia patients were younger (mean age 33.3 years, SD 10.1) than bipolar patients (mean age 37.6 years, SD 12.1), more often male (55.0 % vs. 42.1 %) and had a poorer premorbid academic functioning (PAS academic). As expected we found poorer neurocognitive functioning in schizophrenia versus bipolar disorder patient groups. These differences were highly statistically significant ($p < 0.001$) in all areas except NART errors ($p = 0.01$), Digit Span forwards ($p = 0.11$) and WM-MA ($p = 0.06$) (MannWhitney U-test). Among subjects reporting cannabis use past 6 months, the median number of incidents of cannabis use was 4.5, and the median number of daily cigarettes was 10. As reported earlier (31;32), subjects with cannabis use were younger ($p < 0.001$), more often daily tobacco users ($p < 0.001$), had less education ($p = 0.010$) and poorer premorbid functioning measured by NART ($p = 0.051$) than non-users. Cannabis use was associated with more positive symptoms ($p = 0.041$) (Table 1). There was a trend level for a poorer premorbid IQ, indicated by more NART errors, in the cannabis use group compared to the non-users ($p = 0.05$).

Statistical procedures

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0 was used. All tests were 2-tailed with a predefined level of significance of 0.05. Group differences in categorical data were evaluated with chi-square tests. For continuous data group differences were evaluated with independent *t*-tests for normally distributed data, and Mann-

Whitney tests for skewed data. The bivariate relationships between cannabis use, diagnosis, neuropsychological test performance and significant demographic and clinical independent variables were analyzed using Spearman rank correlations. Differences in the measures of neurocognitive functioning for cannabis users and non-users and for the two diagnostic categories (including interaction effects) were analyzed with factorial ANOVAs. We did not correct for multiple testing, since the current neuropsychological tests can be considered to be different measures for broader domains which were selected based on specific hypotheses derived from previous findings (10;13). Finally, the possibility of confounders of the relationship between each neuropsychological test and cannabis use groups were explored through hierarchical multiple linear regression analysis. Background variables that were unequally distributed between the cannabis use groups and/or diagnostic groups, while at the same time being associated with the neuropsychological test results (diagnosis, age, gender, years of education, premorbid academic functioning and daily tobacco use) were entered hierarchically in the analyses; with the interaction term of diagnosis X cannabis use entered last.

Results

There only main effect of belonging to the cannabis use group versus the no use group in the analyses of the total patient group (both diagnostic groups combined) was a statistically significant poorer result for the Inhibition-set shifting subtest of the Color–Word Interference test ($p=0.01$) (Table 2). In the schizophrenia group cannabis users performed significantly poorer than the non-using group on the Digit Span Forwards test, on the Color–Word Interference set shifting subtest (with a trend for the same test without the set-shifting

condition) and on the Logical Memory test. In addition there was a trend for poorer functioning on the CVLT-II total learning (Table 2). In the bipolar disorder group cannabis users however performed significantly *better* on the Semantic fluency and Semantic set shifting subtest of the Verbal fluency test (D-KEFS) (Table 2). There were statistically significant interaction effects (poorer functioning in cannabis using patients with schizophrenia compared to non-users; better functioning in cannabis using patients with bipolar disorder compared to non-users) for Digit span forwards, Semantic fluency, Semantic set shifting (correct responses and shifts) and Logical memory, with trend levels for Semantic fluency and CVLT-II total learning.

Multiple linear regression analyses controlling for effects of possible predictors unevenly distributed between the groups did not indicate that the interaction effects were caused by the presence of confounding variables.

Discussion

Our main finding was the presence of opposite associations between cannabis use and measures of verbal memory and executive functioning in schizophrenia and bipolar disorder. The interaction effects remained significant also after controlling for potential confounders.

To the best of our knowledge this is the first study addressing the relationship between cannabis and neurocognitive function for the two diagnostic categories in this way. In the schizophrenia group, the neuropsychological test performance was poorer in the cannabis users compared to the abstainers on all measures; reaching statistical significance for attention, executive functioning and verbal memory. In the bipolar disorder group, the neuropsychological test performance was numerically better in most of the measured areas for

cannabis users, but reached statistical significance only for executive functioning. Our findings of an interaction effect may explain why the only previous study investigating a mixed diagnostic sample (14) did not find any association between cannabis use and neurocognition as this study did not examine the diagnostic groups separately.

The current findings may have implications for the conceptual understanding of the disorders. The traditional Kraepelinian dichotomy between schizophrenia and bipolar disorder has recently been challenged as biological similarities have been revealed, and the disorders are suggested as opposite extremes on a continuous spectrum of conditions with psychotic episodes (33). The opposite directions for the associations between cannabis use and neurocognition in schizophrenia and bipolar disorder, suggests that different mechanisms are related to the effect of cannabis on neurocognition in the two disorders. However, some cognitive domains were not affected in different directions, and it is not known whether there is a linear relationship between the actual amount of cannabis used and the impact on neurocognitive functioning. Thus, while our overall findings do not support the continuum model, dimensional explanations cannot be ruled out.

It is of interest that cannabis use was not related to differences in general cognitive functioning, but rather associated with differences in specific domains of cognition. The finding of a negative association with verbal memory in schizophrenia patients was as expected from earlier experiments (10), but the positive associations in bipolar disorder were unexpected. There are several psychoactive components of cannabis, with potentially different neurochemical effects (34). Drugs modulating brain signalling can hamper cognition, while others may also enhance certain types of cognitive performance (35). The putative effect might however be indirect, and related to other factors. For instance, the anxiolytic effect of cannabis

could improve cognition in patients with high level of co-morbid anxiety (36), as anxiety may interfere with attentional control (37). In our sample, anxiety ratings were equal between the two diagnostic categories. However, bipolar disorder patients with cannabis use had significantly lower anxiety ratings on the PANSS G2 item than non-users; which was not the case in the schizophrenia group. In this cross-sectional study we cannot discern whether cannabis use has different effects in the two disorders, or whether there are different subgroups of patients that are at risk for cannabis use in the two diagnostic groups. A possible preference for the best functioning bipolar disorder patients and the poorest functioning schizophrenia patients to use cannabis could be an alternative explanation for the results, but this seems less likely as controlling for premorbid functioning did not affect the interaction of diagnosis and cannabis use on neurocognitive functioning.

As far as we are aware of, the present study is also the first report of an association between cannabis use and altered neurocognitive functioning in bipolar disorder. The findings may indicate that improved cognition is related to current cannabis use in these patients. However, the statistical association was weak, and would not remain significant after a correction for multiple comparisons. Findings should be replicated in independent samples. The findings in the schizophrenia subjects of an association with cannabis use and worse performance on the Interference tests supports the findings of Liraud & Verdoux (14). The findings of poorer verbal learning/memory and attention are in line with the findings of acute cannabis effects by D'Souza and colleagues (10). However, there are still unsolved questions, as improved cognition in the areas of on attention and executive function has been indicated to be related to relatively current cannabis use in subjects with schizophrenia (13;38).

Our findings indicate that use of cannabis should be evaluated when assessing neurocognition in both schizophrenia and bipolar disorder. Further studies should focus on clearly defined diagnostic or phenomenological categories; as different mechanisms might be at play in broad and heterogeneous diagnostic clusters. Eventual evidence of positive effects of cannabis on neurocognition in any disorder must be weighed against evidence for poor outcome in other areas of functioning. The evidence linking drug use/abuse with poor outcome in severe mental disorder (39-41) must still be decisive for clinical advice.

The current study has some limitations. It is cross-sectional and cannot answer questions about causations. There is no precise information on the content of THC and other active substances in the cannabis, which is of relevance when considering pharmacological effects. Unknown active substances could affect the results. Several key measures are based on self-report and thus imply some uncertainty even if both self-reports of substance use (42), and PAS data (43) previously have been shown to have a high degree of validity. Thus, clinical longitudinal studies are required for the investigation of the neuropsychopharmacological properties of cannabinoids in schizophrenia and bipolar disorder. Intervention studies should aim at discerning the role of the different cannabinoid compounds.

To conclude, the present findings of an interaction effect of cannabis use with diagnosis suggests that cannabis use is differently related to neurocognition in bipolar disorder and schizophrenia. These findings of opposite effects indicated different underlying mechanisms, but should be replicated in independent samples.

Declarations of interest

All authors declare that they have no competing interests to disclose.

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References:

- (1) Daban C, Martinez-Aran A, Torrent C, Tabares-Seisdedos R, Balanza-Martinez V, Salazar-Fraile J, et al. Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychother Psychosom* 2006;75(2):72-84.
- (2) Keefe RS, Bilder RM, Harvey PD, Davis SM, Palmer BW, Gold JM, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology* 2006;31:2033-46.
- (3) Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord* 2007;9:103-13.
- (4) Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Hansen CF, et al. Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. *Bipolar Disord* 2008;10:245-55.
- (5) Kavanagh DJ, Waghorn G, Jenner L, Chant DC, Carr V, Evans M, et al. Demographic and clinical correlates of comorbid substance use disorders in psychosis: multivariate analyses from an epidemiological sample. *Schizophr Res* 2004;66:115-24.
- (6) Green B, Young R, Kavanagh D. Cannabis use and misuse prevalence among people with psychosis. *Br J Psychiatry* 2005;187:306-13.
- (7) Murray RM, Morrison PD, Henquet C, Di FM. Cannabis, the mind and society: the hash realities. *Nat Rev Neurosci* 2007;8:885-95.
- (8) Grech A, Van OJ, Jones PB, Lewis SW, Murray RM. Cannabis use and outcome of recent onset psychosis. *Eur Psychiatry* 2005;20:349-53.
- (9) Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* 2005;330:11.
- (10) D'Souza DC, bi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, et al. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry* 2005;57:594-608.
- (11) Coulston CM, Perdices M, Tennant CC. The Neuropsychology of cannabis and other substance use in schizophrenia: review of the literature and critical evaluation of methodological issues. *Aust N Z J Psychiatry* 2007;41:869-84.
- (12) Potvin S, Joyal CC, Pelletier J, Stip E. Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis. *Schizophr Res* 2008;100:242-51.

- (13) Coulston CM, Perdices M, Tennant CC. The neuropsychological correlates of cannabis use in schizophrenia: lifetime abuse/dependence, frequency of use, and recency of use. *Schizophr Res* 2007;96:169-84.
- (14) Liraud F, Verdoux H. [Effect of comorbid substance use on neuropsychological performance in subjects with psychotic or mood disorders]. *Encephale* 2002;28:160-8.
- (15) Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636-45.
- (16) Craddock N, O'Donovan MC, Owen MJ. Phenotypic and genetic complexity of psychosis. Invited commentary on ... Schizophrenia: a common disease caused by multiple rare alleles. *Br J Psychiatry* 2007;190:200-3.
- (17) Van OJ, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med* 2008;8:1-17.
- (18) American Psychiatric Association. Diagnostic and Statistical Manual of Mental illness. Fourth edition ed. Washington DC: American Psychiatric Association; 1994.
- (19) Ventura J, Liberman RP, Green MF, Shaner A, Mintz J. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). *Psychiatry Res* 1998;79:163-73.
- (20) Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-76.
- (21) Pedersen G, Hagtvet KA, Karterud S. Generalizability studies of the Global Assessment of Functioning-Split version. *Compr Psychiatry* 2007;48:88-94.
- (22) Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull* 1982;8:470-84.
- (23) Larsen TK, Friis S, Haahr U, Johannessen JO, Melle I, Opjordsmoen S, et al. Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. *Br J Psychiatry* 2004;185:108-15.
- (24) Vaskinn A, Sundet K. Estimating pre-morbid IQ: a Norwegian version of National Adult Reading Test. *J Norw Psychol Assoc* 2001;38:1133-40.
- (25) Wechsler D. Wechsler Abbreviated Scale of Intelligence (WASI), Norwegian manual supplement. Stockholm: 2007.
- (26) Delis D, Kramer JH, Kaplan E, Ober, BA. California Verbal Learning Test, second edition (CVLT-II). Norwegian manual supplement. 2004. Stockholm, Pearson Assessment.

- (27) Wechsler D. Wechsler Adult Intelligence Scale, third edition (WAIS-III). Norwegian manual supplement. 2003. Stockholm, Pearson Assessment.
- (28) Wechsler D. Wechsler Memory Scala, third edition (WMS-III). Norwegian manual supplement. 2008. Stockholm, Pearson Assessment.
- (29) Hugdahl K, Rund BR, Lund A, Asbjornsen A, Egeland J, Ersland L, et al. Brain activation measured with fMRI during a mental arithmetic task in schizophrenia and major depression. *Am J Psychiatry* 2004;161:286-93.
- (30) Delis D, Kaplan E, Kramer JK. The Delis-Kaplan Executive Function System (D-KEFS). Norwegian manual supplement. 2005. Stockholm, Pearson Assessment.
- (31) Ringen PA, Melle I, Birkenaes AB, Engh JA, Faerden A, Jonsdottir H, et al. Illicit drug use in patients with psychotic disorders compared with that in the general population: a cross-sectional study. *Acta Psychiatr Scand* 2008;117:133-8.
- (32) Ringen PA, Melle I, Birkenaes AB, Engh JA, Faerden A, Vaskinn A, et al. The level of illicit drug use is related to symptoms and premorbid functioning in severe mental illness. *Acta Psychiatr Scand* 2008; In Press.
- (33) Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophr Bull* 2006;32:9-16.
- (34) Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry* 2008;192:306-7.
- (35) Turner DC, Clark L, Pomarol-Clotet E, McKenna P, Robbins TW, Sahakian BJ. Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. *Neuropsychopharmacology* 2004;29:1363-73.
- (36) Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry* 2004;161:2222-9.
- (37) Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. *Emotion* 2007;7:336-53.
- (38) Sevy S, Burdick KE, Visweswaraiiah H, Abdelmessih S, Lukin M, Yechiam E, et al. Iowa gambling task in schizophrenia: a review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophr Res* 2007;92:74-84.
- (39) Cerullo MA, Strakowski SM. The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Subst Abuse Treat Prev Policy* 2007;2:29.
- (40) Henquet C, Krabbendam L, De GR, ten HM, Van OJ. Cannabis use and expression of mania in the general population. *J Affect Disord* 2006;95:103-10.

- (41) Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007;370:319-28.
- (42) Weiss RD, Najavits LM, Greenfield SF, Soto JA, Shaw SR, Wyner D. Validity of substance use self-reports in dually diagnosed outpatients. *Am J Psychiatry* 1998;155:127-8.
- (43) Brill N, Reichenberg A, Rabinowitz J, Harary E, Lubin G, Davidson M, et al. Accuracy of self-reported premorbid functioning in schizophrenia. *Schizophr Res* 2007;97:103-8.

Tables

Table 1. Sample characteristics.

Cannabis use past 6 months N (%)	No cannabis use		Cannabis use	
	232 (85.0)		41 (15.0)	
	n	%	n	%
Male gender	108	46.6	25	61
Schizophrenia ¹	88	37.9	22	53.7
Schizophreniform Disorder ¹	8	3.4	1	2.4
Schizoaffective Disorder ¹	21	9.1	0	0.0 *
Bipolar Disorder I ¹	67	28.9	12	29.3 **
Bipolar Disorder II ¹	44	19.0	5	12.2
Bipolar Disorder NOS ¹	4	1.7	1	2.4
Cannabis abuse/dependency ¹	17	7.3	16	39.0 **
Cocaine abuse/dependency ¹	0	0.0	1	2.4
Amphetamine abuse/dependency	4	1.7	1	2.4
Alcohol abuse/dependency ¹	28	12.1	7	17.1
Daily use of tobacco	105	45.5	33	80.5 **
Daily use of caffeine	201	86.6	35	85.4
Use of antipsychotics ²	154	66.4	30	73.2
Use of anticholinergic ²	1	0.4	0	0.0
Use of antidepressant ²	87	37.5	12	29.3
Use of antiepileptic ²	62	26.7	15	36.6
Use of lithium ²	22	9.5	3	7.3
Cannabis in urine	2	0.9	7	18.9 **
	Mean	S.D.	Mean	S.D.
Age	36.7	11.3	28.4	8.8 **
GAF symptoms	51.0	13.6	49.9	15.8
GAF function	50.9	12.6	48.2	15.0
PANSS positive symptoms	12.1	4.8	13.8	5.8 *
PANSS negative symptoms	12.7	5.4	13.1	6.3
WASI IQ	107	13.0	104.9	13.8
NART error score	16.2	8.3	19.0	8.2 *
PAS premorbid academic functioning	2.9	2.1	3.6	2.7
Years of education	14.0	2.8	12.8	2.6 **

¹DSM-IV diagnoses. ²Regular use by prescription. T-tests for parametric data, Mann-Whitney tests for nonparametric data, * p≤0.05, ** p≤0.01. Fisher exact tests for categorical data. GAF: Global Assessment of Functioning; PANSS: Positive and Negative Symptom Scale; IDS: Inventory of depressive symptoms; YMRS: Young Mania Rating Scale; WASI: Wechsler Abbreviated Scale of Intelligence; NART: National Adult Reading Test; PAS: Premorbid Adjustment Scale.

Table 2. Neurocognitive performance with and without cannabis use.

	All			Schizophrenia			Bipolar disorder			Diagnosis X Cannabis use						
	No use (n=232)		Use (n=41)	No use (n=117)		Use (n=23)	No use (n=115)		Use (n=18)							
	Mean	S.D.	P	Mean	S.D.	P	Mean	S.D.	P							
<i>Psychomotor speed</i>																
Digit Symbol (WAIS-III)	60.5	16.6	60.9	18.1	0.915	56.4	15.6	53.8	18.6	0.483	64.8	16.7	69.8	13.1	0.220	0.166
<i>Attention/working memory</i>																
Digit Span, forwards (WAIS-III)	6.1	1.0	5.9	1.2	0.471	6.0	1.0	5.5	0.9	0.024	6.1	1.1	6.4	1.2	0.227	0.019
Digit Span, backwards (WAIS-III)	4.5	1.1	4.3	1.0	0.371	4.3	1.0	4.1	1.1	0.441	4.6	1.3	4.5	0.7	0.699	0.874
2-Back (WM-MA)	12.0	7.4	12.4	7.0	0.774	11.6	7.0	9.8	8.1	0.331	12.5	7.7	15.0	4.8	0.178	0.100
<i>Executive functioning</i>																
Phonetic fluency; VFT	39.3	12.2	40.5	13.2	0.562	37.3	12.3	36.6	13.8	0.804	41.3	11.8	45.4	10.8	0.158	0.236
Semantic fluency; VFT	40.9	10.3	42.5	11.3	0.361	39.3	10.2	38.1	10.3	0.622	42.4	10.1	47.8	10.5	0.038	0.062
Semantic set shifting; correct responses; VFT	11.4	3.3	11.6	3.4	0.637	10.9	2.9	10.0	3.1	0.178	11.9	3.7	13.5	2.9	0.071	0.009
Semantic set shifting; correct shifts; VFT	12.6	2.9	12.9	2.8	0.749	12.1	2.6	11.2	2.4	0.150	13.1	3.2	14.8	2.0	0.032	0.023
Color-Word Interference Test, time to complete	60.2	19.5	64.6	22.4	0.193	63.0	19.3	72.0	25.8	0.054	57.3	19.4	55.1	12.1	0.632	0.090
Interference/set shifting; time to complete	64.4	16.6	71.7	20.6	0.014	68.0	17.8	78.9	22.5	0.011	60.8	14.6	62.4	13.4	0.657	0.103
<i>Verbal Learning</i>																
Logical memory 1 (WMS-III)	23.8	7.0	22.1	6.7	0.174	22.7	6.9	18.1	5.6	0.005	24.9	6.9	26.7	4.6	0.295	0.007
Logical memory 2 (WMS-III)	20.2	7.5	18.3	8.0	0.152	18.9	7.1	13.6	7.2	0.003	21.6	7.7	23.6	4.9	0.278	0.004
CVLT-II total learning	51.9	11.5	52.9	12.1	0.606	49.1	10.9	47.2	12.1	0.458	54.7	11.3	60.2	7.5	0.051	0.052
CVLT-II delayed recall	11.9	3.3	12.0	3.4	0.792	11.2	3.2	10.7	3.5	0.582	12.6	3.1	13.6	2.6	0.179	0.179

Independent t-tests and factorial ANOVA tests. S.D.: Standard Deviation; WASI: Wechsler Abbreviated Scale of Intelligence; NART: National Adult Reading Test; WAIS: Wechsler Adult Intelligence Scale; WM-MA: Working Memory – Mental Arithmetics; VFT: Verbal Fluency Test; WMS: Wechsler Memory Scale; CVLT: California Verbal Learning Test.

