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.


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 Kreapelins’ 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.

**Substance Abuse:**
A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by at least one of the following within a defined period in time:
- Failure to fulfil major role obligations
- Recurrent physically hazardous use
- Recurrent substance related legal problems
- Continued use despite use causing social or interpersonal problems

Criteria for dependence for the actual class of substance must never have been met.

**Substance Intoxication:**
Development of a reversible substance-specific syndrome due to recent exposure to the substance

Clinically significant maladaptive behavioural or psychological changes because of effects on the CNS, that develops shortly after use

Symptoms are not due to a general medical condition and are not better accounted for by another mental disorder

**Substance Dependence:**
A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by at least three of the following within a defined period of time:
- 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

**Substance Induced Psychotic Disorder:**
Evidence of prominent hallucinations or delusions developed within a month of substance intoxication or withdrawal

Not better accounted for by a Psychotic disorder that is not substance induced or occurring exclusively during the course of a delirium

**Tolerance:**
- Need for markedly increased amounts of the substance to achieve intoxication or desired effect
- Markedly diminished effect with continued use of the same amount of the substance

**Withdrawal:**
Characteristically significant symptoms develop due to reduction in substance use that has been heavy and prolonged

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. Amphetamines 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 5HT2A 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,
and may locally have considerable popularity among young adults (Hermle et al. 2008). Other substances include methylenedioxyamphetamine (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 Ca^{2+} - channels (Davies, 2003). Persistent abuse of alcohol may lead to neurologic/psychiatric conditions where psychotic symptoms are part of the clinical presentation (Thirthalli 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 Wernicke encephalopathy/Korsakoff’s 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 deals 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 increase 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; Margolese 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 Ulleval 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 ‘Ulleval 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.**

<table>
<thead>
<tr>
<th>Date</th>
<th>TOP database samples</th>
<th>Selection (exclusion criteria)</th>
<th>Papers</th>
<th>Substudy samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov 2006</td>
<td>N=329</td>
<td>• No data on lifetime use • Not UUH</td>
<td>I</td>
<td>N=148</td>
</tr>
<tr>
<td>Feb 2007</td>
<td>N=413</td>
<td>• Not strict schizophrenia spectrum or bipolar disorder.</td>
<td>II</td>
<td>N=336</td>
</tr>
<tr>
<td>Apr 2007</td>
<td>N=482</td>
<td>• Subjects with intake of opiates past 6 months • Not strict schizophrenia spectrum or bipolar disorder.</td>
<td>III</td>
<td>N=423</td>
</tr>
<tr>
<td>Jun 2008</td>
<td>N=547</td>
<td>• Use of other substances of abuse than cannabis past 6 months • Not attended elementary school in Norway. • Not neurocognitively assessed • Not strict schizophrenia spectrum or bipolar disorder.</td>
<td>IV</td>
<td>N=273</td>
</tr>
</tbody>
</table>

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 Ulleval 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 whished, 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 (Khantzian, 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


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: *(p<0.001), *(p=0.001), *(p<0.001).
Figure A2 (paper III). Level of illicit substance use; symptom levels by diagnostic group.

**a) Schizophrenia, N=252**

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 ≤ 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.

**b) Bipolar disorder, N=171**

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. *p ≤ 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 gruprene 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.