ADHERENCE TO PHARMACOLOGICAL TREATMENT IN PATIENTS WITH SEVERE MENTAL DISORDERS

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1. Acknowledgements

The studies of this thesis were carried out in the period from 2003 to 2007 at the section for Psychosis research, Division of Mental Health and Addiction, Oslo University Hospital, Ulleval and Institute of Clinical Medicine, Faculty of Medicine, University of Oslo. The studies were part of the Thematically Organized Psychosis (TOP) study.

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2. List of papers

Paper I

Jónsdóttir H, Engh JA, Friis S, Birkenæs A, Ringen PA, Vaskinn A, Sundet K, Opjordsmoen S, Andreassen OA. Measurement of insight in patients with bipolar disorder. Are self-rated scales developed for patients with schizophrenia applicable? J Nerv Ment Dis 2008 Apr;196 (4):333-5.

Paper II

Jónsdóttir H, Friis S, Horne R, Pettersen KI, Reikvam Å, Andreassen OA. Beliefs about medications: Measurement and relationship to adherence in patient with severe mental disorders. Acta Psychiatr Scand. 2009 Jan;119(1):78-84.

Paper III

Jónsdóttir H, Opjordsmoen S, Birkenaes AB, Engh JA, Ringen PA, Vaskinn A, Aamo TO, Friis S, Andreassen OA. Medication adherence in outpatients with severe mental disorders: relation between self-reports and serum level. J Clin Psychopharmacol. 2010 Apr;30(2):169-75.

Paper IV

Jónsdóttir H, Opjordsmoen S, Birkenaes AB, Engh JA, Ringen PA, Simonsen C Vaskinn A, Friis S, Sundet K, Andreassen OA. Predictors of medication adherence in patients with schizophrenia and bipolar disorder. Submitted.

3. Summary of study

Medication is a vital component in the treatment of patients with severe mental disorders, but it can be a challenge for clinicians to motivate patients to stay on medication. Nonadherence estimates vary between studies and this variation seems to reflect inconsistency in study design and methods. This makes it difficult to compare results and limits the generalizability of findings. However, some of the variation could also reflect true differences in adherence due to characteristics of the samples or the health care systems. Thus, it is of importance to measure adherence in large well described samples from different health care systems. It seems reasonable that being able to motivate patients to better adhere to their medication would improve adherence and thereby reduce suffering and save money. Therefore, it is important to understand better why patients do not follow medical advice. Previous studies have attempted to indentify predictors of adherence to medication. There are some consistencies between the different studies with regards to the different predictors of nonadherence, but some inconsistencies as well, and it is still unclear which clinical predictors are most important in schizophrenia and bipolar disorder. The measurement of adherence is a long standing methodological problem. There are several available methods. Direct measures include observing patients swallowing tablets and the measurement of level of medicine or metabolites in the blood. Indirect measures cover self reports and electronic medication monitors.

The main object of this thesis was to determine adherence rates in a Norwegian catchment area population of patients with severe mental disorders and to identify predictors for nonadherence in this population. To be able to do this, several methodological issues needed to be solved. This applied to the method of adherence measure, as well as the measure of some of the proposed predictors. The Birchwood Insight Scale (IS) used to measure insight and the Beliefs about Medicines Questionnaire (BMQ) used to measure beliefs about medication, needed to be validated for the patient sample in the current study. The first part of this thesis focuses on methodological issues regarding these questionnaires.

This report is based upon naturalistic data from the cross-sectional part of the Thematically Organized Psychosis (TOP) Study, carried out in joint collaboration between the University and University Hospitals of Oslo. Inclusion criteria for the TOP Study are broad, consisting of 1) being registered in the psychiatric services of any of the 4 University Hospitals in Oslo; 2) aged 18 to 65 years; 3) meeting the DSM-IV criteria for any major

psychotic or bipolar disorder; 4) understanding and speaking a Scandinavian language; 5) having no history of severe head trauma or neurological disease; and 6) having an Intelligence Coefficient (IQ) score over 70. From May 2003 through October 2006 a total of 385 patients were evaluated. Two hundred and eighty met with criteria for the studies of this thesis.

Acceptable psychometric properties were found for the IS when applied to patients with schizophrenia and bipolar I disorder. However, for patients with bipolar II disorder the scale seemed to work poorly. The BMQ had satisfactory psychometric properties for use in patients with severe mental disorders.

Multiple adherence measures were used to establish adherence level in the study sample. The result was that outpatients with severe mental disorders showed relatively good adherence to prescribed medication. In addition, the use of self-report in adherence studies was addressed, with the conclusion that simple self report questionnaires seem to be a valid method for measuring adherence.

Regarding the proposed predictors for nonadherence; in schizophrenia, use of illegal substances, alcohol, beliefs about medication and poor insight were related to worse adherence. Schizophrenia patients with no adherence did better on tests of executive functioning, verbal learning and memory and had higher IQ than patients with better adherence. In bipolar disorder the use of illegal substances and alcohol and beliefs about medication were related to worse adherence. There was a significant association between poor adherence and some autonomic side effects; diarrhea, nausea and orthostatism in schizophrenia patients and with orthostatism and urine retention in bipolar disorder patients. Otherwise there was no significant relationship between side effects and adherence. Fully adherent schizophrenia patients had significantly higher BMI than partially adherent patients. In the bipolar patients there was no statistically significant difference of mean BMI between the different adherent groups.

Taken together, the present thesis suggests that insight can be measured with the IS in patients with schizophrenia and bipolar disorder, and that beliefs about medicines can be measured using the BMQ in patients with severe mental disorders. Further, outpatients with severe mental disorders showed relatively good adherence to prescribed medication. In this sample substance and alcohol use and beliefs about medication were important risk factors for nonadherence in patients with schizophrenia and bipolar disorder. Poor insight was also a risk factor, especially in schizophrenia. The results suggest that cognitive dysfunction is not a risk factor for nonadherence in these diagnostic groups.

4. Abbreviations

ANOVA	one way analysis of variance
BMI	Body mass index (weight in kg divided by the square of the height in m)
BMQ	Beliefs about Medicines Questionnaire
CVLT-II	California Verbal Learning Test
D-KEFS	Delis-Kaplan Executive Function System
DAI	Drug Attitude Inventory
DSM-IV	Diagnostic and Statistic Manual of Mental Disorders, 4th edition
FGA	First generation antipsychotic
IDS	Inventory of Depressive Symptoms
IQ	Intelligence Coefficient
IS	Birchwood Insight Scale
MARS	Medication Adherence Rating Scale
MEMS	Medication Event Monitoring System
MPR	Medication Possession Ratio
NART	National Adult Reading Test
PANSS	Positive and Negative Symptoms Scale
PTA	Primary Therapeutic Agent
RCT	Randomized Controlled Trial
SAI-E	Schedule of Assessment of Insight
SCID-I	Structured Interview for the DSM-IV Axis I Disorders
SGA	Second generation antipsychotic
SMI	Severe mental illness
SPSS	Statistical Package for the Social Sciences

SUMD	Scale to Assess Unawareness of Mental Disorders
TOP	Thematically Organized Psychosis Study
UKU	Udvalg for Kliniske Undersøkelser
WAIS-III	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WHO	World Health Organization
WMS-III	Wechsler Memory Scale

5. Introduction

5.1. Perspectives and definitions

Schizophrenia and bipolar disorder are two very disabling disorders and both are on the World Health Organization´s (WHO) top ten global list for disorders causing disability ("WHO-The global burden of disease 2004 update," 2008). These disorders are responsible for more disability than all forms of cancer or major neurologic conditions such as epilepsy and dementia of Alzheimer´s type. The reason is primarily because of the early onset and chronicity of these disorders across the life span. According to WHO estimates there are 26.3 million people worldwide that suffer from schizophrenia and the disorder is number 5 for men on the list for leading disabilities (years lost to disability) and number 6 for women. Schizophrenia is listed in disability class VII which is the highest class with severe disability. Twenty nine point five million people globally suffer from bipolar disorder according to WHO´s estimates and the disorder is number 7 for men and 8 for women on the WHO list for leading cause of disability. This disorder is listed in disability class V with moderate to severe disability. The schizophrenia spectrum and bipolar disorders constitute what is often called 'severe mental illness' (SMI) or 'psychotic disorder'. 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.

5.1.1. Schizophrenia

This is a disorder known in all settings and cultures. The prevalence of schizophrenia is more geographically varied than previously assumed, but it is estimated that 7 individuals per 1000 will be affected, but gender, urbanicity, latitude and migration have been shown to influence incidence rates (McGrath *et al*, 2008).

Schizophrenia, as defined in the DSM-IV-TR diagnostic system (*Diagnostic and statistical manual of mental disorders : DSM-IV-TR*, 2000) is a disorder that lasts at least 6 months and has a presence of a minimum set of characteristic signs and symptoms (both positive and negative) for at least a month (active phase). These signs and symptoms are associated with marked social or occupational dysfunction. The modal age of onset is between 18 and 25 years in men, and for women between 25 and the mid-30s (*Diagnostic and statistical manual of mental disorders : DSM-IV-TR*, 2000). The symptoms of schizophrenia

are commonly divided into positive and negative, but it is now generally accepted that cognitive deficits are also a core aspect of the disorder (Fioravanti *et al*, 2005; Kelly *et al* , 2000). The positive symptoms constitute the active psychotic symptoms, the delusions and hallucinations, whereas the negative symptoms comprise the affective flattening, poverty of speech, lack of motivations and social withdrawal. The negative symptoms account for a substantial degree of morbidity associated with the disorder and the positive and negative symptoms seem to follow independent courses over time (Eaton *et al*, 1995). According to the definition (DSM-IV) schizophrenia involves dysfunction in one or more major areas of functioning. Hence, in patients the functioning is clearly below that which had been achieved before the onset of symptoms.

People with schizophrenia have a higher risk for comorbidity like substance abuse and depression and for suicidality, as well as chronic somatic diseases such as cardiovascular disease and diabetes. The mortality rate is estimated to be two – three times that of the general population (McGrath *et al* 2008). 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). According to the WHO website (http://www.who.int/mental_ health/management /schizophrenia/en/), more than 50% of people with schizophrenia are not receiving appropriate care and 90% of those are in developing countries.

Schizophrenia remains a major concern within health care because of its severe consequence on the life of the patients and their families, and because of its long duration. The WHO predicts that schizophrenia will remain among the top ten causes of disability well into the twenty-first century.

5.1.2. Bipolar disorder

Even though the prevalence numbers for bipolar disorder vary across studies, the prevalence of bipolar I disorder has been thought to be around 1% (Goodwin & Jamison, 2007). Recent data from the World Mental Health Survey Initiative, a project of the WHO, show somewhat lower numbers. In a cross-sectional household survey of 61 392 adults in 111 countries across America, Europe and Asia, the total lifetime prevalences were 0.6% for bipolar I disorder, 0.4% for bipolar II disorder and 1.4% for subthreshold bipolar disorder (Merikangas *et al*, 2011). In this survey there was some cross-site variation in the prevalence rates, but the

severity, impact and patterns of comorbidity were remarkably similar internationally. In the same survey approximately half of those with bipolar I disorder reported age of onset before the age of 25 years and those with bipolar II disorder reported a slightly later age of onset. A recent Norwegian study found that the mean age of onset defined as the start of the first affective episode was 23 years (Larsson *et al*, 2010).

The DSM-IV-TR definition (*Diagnostic and statistical manual of mental disorders : DSM-IV-TR*, 2000) of bipolar spectrum disorders, is based on the identification of mood episodes occurring over time. Diagnosis of bipolar I disorder demands the presence of a manic episode in the person's history. In bipolar II disorder there must have been at least one major depressive episode and one episode of hypomania. Cyclothymic disorder is a chronic, fluctuating mood disturbance involving numerous periods of 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. 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 functioning. 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.

Bipolar disorder is associated with higher risk of psychiatric comorbidity like substance abuse and anxiety disorders and data suggests that 65% of patients with bipolar disorder have a comorbid condition (McElroy *et al*, 2001). In addition patients with bipolar disorder have increased risk for general medical conditions like cardiovascular disease, pulmonary conditions and diabetes (Perron *et al*, 2009). There are few comprehensive cost-of-illness studies that focus primarily on bipolar disorders (Kleinman *et al*, 2003), but even so it is clear that direct medical costs associated with inpatient and outpatient management are significant. These costs were estimated to be $7.6 billion in the United States in 1991 (Wyatt & Henter, 1995) and in addition there are considerable costs related to the loss of productivity.

Bipolar disorder is like schizophrenia a major concern within health care and is predicted to remain on WHOS´s list of top ten causes of disability in the coming years.

5.2. Adherence to medication

5.2.1. Historical perspectives

Through centuries and in different cultures men have turned to those with knowledge of medicines and healing with their ailments. Remedies and potions have been mixed and prescribed, but alongside the desire to get well is the behaviour of being noncompliant and not following advice, by not taking what was prescribed, or not taking it as was recommended and even taking too much. Perhaps the first example of nonadherence was when Eve ate the apple in the garden of Eden. Hippocrates stated that physicians should keep aware of the fact that patients often lie when they state that they have taken certain medicines.

5.2.2. Definitions

The subject of medication-taking has generated extensive literature and considerable controversy. The complexity of the topic is illustrated by the fact that at least three terms are commonly used in relation to medication-taking, with little apparent consensus (Horne *et al*, 2005). In 1976 Sackett introduced the term *"compliance"* into medicine. The meaning of the term according to the English dictionary is: The act or process of complying to a desire, demand or proposal or, to coercion. In the medical context the term is used to describe the extent to which a patient takes the medication as prescribed. In Haynes *et al´s* Compliance in health care, the term is defined as "The extent to which the patients´ behavior in terms of taking medication, following diets, executing life style changes, coincides with medical or health advice (Haynes *et al*, 1979). This term has been widely used in the past, for the act of following treatment instructions. The use of the term has been criticized (Stimson, 1974) as it gives the patient a passive role and makes him submissive in his relationship to the physician. Based on this argument the term *adherence/nonadherence* (Barofsky, 1978) has been adopted by many in the past few years. According to the English dictionary this term means: "Quality of adhering; fidelity, steady attachment". In a therapeutic alliance the term is defined as: Patient acceptance of recommended health behaviours. By using the term adherence it is implied that the patient is more active in his own therapy and there is more focus on building a good therapeutic alliance. Some have meant there is still a way to go and introduced a third term; *Concordance* (Royal Pharmaceutical Society of Great, 1997), which has a more complex definition: "a new approach to the prescribing and taking of medicines. It is an

agreement reached after negotiation between a patient and a health care professional that respects the beliefs and wishes of the patient in determining whether, when and how medicines are to be taken. Although reciprocal, this is an alliance in which the health care professionals recognize the primacy of the patient's decisions about taking the recommended medications." This term is predominantly used in the UK and has not been adopted into mental health studies when addressing the behaviour of taking medication. The term adherence has by some experts in the field been recommended as the term of choice to describe patients' medicine taking behaviour (Horne *et al*, 2005). The WHO has taken the same standpoint in their definition: "Strong emphasis was placed on the need to differentiate adherence from compliance. The main difference is that adherence requires the patient's agreement to the recommendations. We believe that patients should be active partners with health professionals in their own care and that good communication between patient and health professional is a must for an effective clinical practice" (WHO: Adherence to long-term therapies. Evidence for action 2003). In spite of the debate of terms, the terms noncompliance and nonadherence have comprised a generally consistent set of core elements and include the failure of patients to follow the direction of the health care providers. This includes entering treatment programmes, premature termination of therapy and incomplete implementation of instructions, including prescriptions and that the goal of the health care provider is to treat or prevent a disorder. The main focus of this thesis is on the failure to follow medical treatment.

Another important definition is that of the extent of adherence or nonadherence. When is a patient partially adherent or nonadherent? How many doses of medication does a person need to leave out or not take to be categorized as not fully adherent? The weakness of the proposed definition of adherence fails to acknowledge that it is not an "all or nothing" phenomenon. The term partial adherence acknowledges the common situation in which a patient takes some, but not all, of their prescribed medication (Weiden *et al*, 2004). Many patients display a range of adherence behaviours. They may take an amount that is less than recommended, taking the correct dose at the incorrect time, taking irregularly (on and off), taking gaps or "drug" holidays and stopping the treatment prematurely. Then there are some that may take too much. Nonadherence can be intentional (primary) or unintentional (secondary) i.e. some patients forget and others decide not to take. When considering long-term disorders it is unlikely that many patients are 100% adherent at all times, but at what level of adherence does the medication not reach the desired effect? This is what is important

for the clinical result of the treatment. Not all types of medication are dependent on the patient being fully adherent for clinical response. In studies, an adherence rate of 80-90% is considered satisfactory, but it is important to bear in mind that adherence behaviour is in its nature not a constant but a dynamic phenomenon. A patient that is fully adherent in certain circumstances can be partially adherent in other circumstances. Adherence and nonadherence behaviour is so dynamic and varied that perhaps we can never define it properly. Those that have worked as clinicians will grasp the variety of the problem, that patient characteristic and behaviours are very different and that it is not always easy to find a reason for different types of behaviours and that those reasons are not always rational to health professional.

5.2.3. Previous adherence estimates

Patient's follow-up of treatment is an important factor for the effectiveness within the mental health system. For many years we have had medication that has proven effective in schizophrenia and bipolar disorder, but it has been a challenge to motivate the patients to stay on the medication. Treatment nonadherence has a major impact on the effectiveness of therapeutic interventions and presents many problems in clinical practise (Haynes *et al*, 2005).

Schizophrenia

In 1997 Fenton *et al* published a review of studies of medication adherence in schizophrenia (Fenton *et al*, 1997). They reported a median nonadherence rate of 55% in 15 studies, with the range of 24-88%. In the review of Lacro *et al* (Lacro *et al*, 2002), the range of non-adherence in 10 studies was 20-56%, with a mean rate of 41%. Lacro *et al* set strict inclusion criteria for studies accepted in the review, where the definition of being adherent was "regularly taking medication as prescribed" and if the adherent measure was a self-report, another source was needed to estimate adherence. When adopting even stricter criteria for the included studies, corresponding to only five study reports, the mean nonadherence rate was 49%. Nosé *et al* reanalyzed data from 86 studies involving a more heterogeneous sample of patients with schizophrenia, psychosis and severe mental disorder (Nosé *et al*, 2003). They found that around 1 in 4 patients failed to adhere to medication or scheduled appointments. Gilmer *et al* studied adherence to antipsychotic medications among Medicaid beneficiaries with schizophrenia, between 1998 and 2000, using prescription fills for oral antipsychotic medication as a basis for the adherence analysis. They found that 41% were fully adherent,

16% were partially adherent, 24% were nonadherent and 19% were excess fillers (Gilmer *et al*, 2004). Valenstein *et al* found that 40% of patients with schizophrenia or schizoaffective disorder, being prescribed with one antipsychotic, had MPR (Medication Possession Ratio) <0.80 (Valenstein *et al*, 2004). The study included 49.003 patients from the Veteran Affairs system.

A number of studies have looked especially at patients with first-episode psychosis and adherence to medication. In the early stages of the disorder, patients seem to be more responsive to treatment, irrespective of the antipsychotic medication used (Frangou & Byrne, 2000). Coldham *et al* followed 186 patients included in an Early Psychosis Program for one year (Coldham *et al*, 2002). Thirty nine percent dropped out of the program or stopped taking their medication, 20% took irregularly and 41% rarely or never missed doses of medication. Verdoux *et al* followed 65 first admitted patients with psychosis for two years (Verdoux *et al*, 2000). This was a naturalistic study and 53% interrupted their medication treatment for 2 weeks or more, against medical advice, during the follow-up. Mojtabai *et al* followed 182 patients diagnosed with schizophrenia for two years after first admission (Mojtabai *et al*, 2002). Thirty seven percent used antipsychotic medication throughout the first year without any gaps in the treatment. Fifty one percent had gaps of 30 days or longer during the first year and the mean number of days not taking medication was 204 for that group. In Robinson *et al´s* follow-up of 112 first episode schizophrenia patients, 26% stopped taking antipsychotics during the first year of treatment and 30% stopped during maintenance treatment following the first relapse (Robinson *et al*, 2002). The authors emphasized that there were ongoing efforts by the research team to educate patients and families with the goal of maintaining treatment adherence and that in standard clinical practise such resources were usually less. In addition they emphasized that the patients stopped taking antipsychotics despite very good overall response to treatment. Data from the West London first episode study, examining cross-sectionally 101 patients, 89 of which were still in-patients at the time of admission into the study, showed that 44% had poor adherence as defined by the Compliance Rating Scale (Mutsatsa *et al*, 2003).

In summary, studies of nonadherence in patients with schizophrenia show a wide range of adherence. The design of the studies, the definition of adherence and the measures used are different. When the study populations are better defined as in the studies of first-episode patients the rates of nonadherence are more similar. Further studies, where the concept of nonadherence is clearer and the study populations are better defined, are needed to establish nonadherence rates in schizophrenia.

Bipolar disorder

In bipolar disorder, nonadherence to long-term prophylactic pharmacotherapy ranges from 20%-66% according to a review by Lingam and Scott, that is commonly referred to in studies on adherence in bipolar disorder (Lingam & Scott, 2002). They base this range on two studies on adherence in lithium maintenance treatment, conducted in the years 1976 and 1982 (Bech, *et al*, 1976; Connelly *et al*, 1982) and on an earlier review based on studies from the years 1966 to 1986 (Cochran, 1986). In the study of Bech *et al* 76 patients were studied retrospectively, and in the study of Connelly *et al* 48 patients were followed for 12 months. In both studies 25% discontinued lithium treatment. The review of Cochran is based on 13 studies examining lithium efficacy or lithium compliance. The definition and measures are very different from study to study, but in conclusion the rate of nonadherence was 9%-57% and the author comments that this range probably underestimated the true problem (Cochran, 1986). Keck *et al* found that 64% of a sample of 101 patients admitted for acute mania were partially or totally nonadherent in the month prior to admission (Keck *et al*, 1996). The same group followed 140 bipolar patients after discharge from hospital and during the follow-up period of one year, 51% were partially or totally non-adherent with prescribed medication (Keck *et al*, 1997). A more recent study accounting for all types of psychiatric medication and using a combination of adherence measures found that 60% of euthymic bipolar disorder patients were fully adherent over a follow-up for two years, and there was no difference in adherence with regards to type of medication (Colom *et al*, 2000).

In a large scale study of over 1500 patients followed for 6 years, Johnson and McFarland reported that the median continuous use of lithium after first being prescribed was 76 days and that lithium used by the sample studied, was more often sporadic than continuous (Johnson & McFarland, 1996). In a sample of 98 patients being treated with mood stabilizers (72 of which took lithium), Scott and Pope found that almost 50% of the patients admitted some degree of medication nonadherence in the preceding two years and 32% reported missing ≥30% in the preceding month (Scott & Pope, 2002). In a study from 1979 more than one-third of patients had stopped their medication two or more times, without proper consultation with their psychiatrist, and nine of every 10 patients had at some point considered medication withdrawal (Jamison *et al*, 1979). Sajatovic *et al* have studied treatment adherence to lithium and anticonvulsants and to antipsychotic medication in patients with bipolar disorder (Sajatovic *et al*, 2006; Sajatovic *et al*, 2007). The study on lithium and anticonvulsants involved data on 44,637 bipolar patients identified using the Veterans Affairs National Psychosis Registry in the USA. Medication adherence was assessed by using the

MPR for lithium, valproate, carbamazepine and lamotrigin. A slight majority of individuals, 54%, had MPR greater than 0.8 and were considered fully adherent. 25% were partially adherent and 21% nonadherent. The same procedure was used in the study of antipsychotic medication, where the population counted 73,964 patients and of those 45% were prescribed with an antipsychotic. Fifty two percent of this group were fully adherent, 21% were partially adherent and 27% were nonadherent. The last two studies mentioned are interesting in many ways. The groups are very large and there are no exclusion criteria, here everyone that has been in this database system in the year of the study, is included. There is no study-intervention that might influence adherence. The adherence measure is pharmacy records showing whether the patients are in possession of the prescribed medication or not. There are only about half of the patients that possess more than 80% of their prescribed medications, be it lithium, an antiepileptic or antipsychotic. We can probably predict that partial adherence and nonadherence in this group is even higher, as possessing the medication does not guarantee it being taken.

As a whole, the studies of adherence in bipolar disorder suggest high rates of nonadherence. The design of the studies, the definition of adherence and the measures used are different. Also in bipolar disorder further studies with clearer definitions and better described patients' populations are needed to learn more about nonadherence to medication.

General Medicine

Partial and nonadherence is not an isolated problem within the mental health system, but is widespread throughout medicine. Cramer and Rosenheck reviewed 10 studies reporting adherence rates for antidepressive medication, 24 studies for antipsychotic medication and 12 reports for medication adherence in a range of nonpsychiatric disorders (Cramer & Rosenheck, 1998). They found that in patients with psychiatric disorders adherence is lower than among patients with physical disorders. Patients receiving antipsychotics took an average of 58% of the recommended amount with a range of 24-90%. Patients receiving antidepressants took 65% of the recommended amount, with a range from 40-90%. The mean adherence rate for patients with physical disorders was 76%, with a range from 60-92%. In their review of the studies they compared the measures used and concluded that the difference might be largely attributable to the different measures used for estimating adherence. Despite this finding, the problem of nonadherence is big throughout medicine, especially in chronic conditions (Osterberg & Blaschke, 2005). Examples of this are diseases like hypertension,

asthma and HIV infection. Adherence to therapeutic recommendations in asthma has been shown to have a range between 30 and 70% (Bender *et al*, 1997). For children the average medication adherence rate of 48% was compiled in a review of 10 studies (Creer & Bender 1993). Patients with hypertension are often asymptomatic and experience no immediate physical symptoms resulting from missing a dose on occasion or on permanent basis. In the longer term however, the inadequate control of elevated blood pressure that is a result of poor adherence, increases significantly the risk for costly complications such as stroke, myocardial infarction and kidney disease (Burnier, 2006). The range of adherence in studies is wide, but they indicate that within a year of antihypertensive therapy, 50% have discontinued the treatment (Burnier, 2006). In the treatment of patients with HIV infection or the acquired immunodeficiency syndrome, it is essential to achieve 95% adherence to highly active antiretroviral therapy. These studies of nonpsychiatric patients show the global nature of partial and nonadherence and reflect its complexity and that it is inherent in human nature.

5.2.4. Methodological problems

The variation in reported adherence in severe mental disorders seems to reflect inconsistency of study design and methods, which in turn makes it difficult to compare results and limits the generalizability of the findings (Lacro *et al*, 2002; Lingam & Scott, 2002; Awad, 2004; Colom *et al,* 2005; Velligan *et al*, 2006). This is a complex problem, as we see discrepancies in the *definition of adherence* in each study, or differences in the way non-adherence is addressed (Lacro *et al*, 2002). Some studies use dichotomous rating (adherent or nonadherent) and other use continuous scales. Cut off levels vary and this makes it difficult to find any consistent pattern. In one study patients who took 80% of their medication were considered adherent (Duncan & Rogers, 1998). In another study, those who reported having stopped their medication for 1 week or longer after hospital discharge were deemed non-adherent (Olfson *et al*, 2000). This indicates that a patient that is considered adherent in one study can be considered nonadherent in another. Recently it has been proposed that studies investigating adherence, report an estimate of the mean percentage of medication taken, even though the primary measure of adherence is operationalized otherwise (Velligan *et al*, 2006). This would allow studies to be compared on a common variable.

Then there is the long standing challenge of how to best *measure adherence* and non-adherence. There are several methods used for adherence measurements, both direct methods such as observing the patient swallowing tablets or measuring serum levels of medication and

indirect methods such as self-reports and electronic monitoring. Measures of medication adherence fall into two basic categories: 1) Objective measures such as pharmacy records, pill counts, electronic monitoring and blood plasma levels and 2) Subjective measures based on self-rating of the patients, or an interviewer, asking family members or care givers.

Self-reports and care-giver reports are the most common ways used to assess adherence in studies. Velligan *et al* reviewed literature published between 1971 and 2006 on adherence to oral antipsychotic medication in schizophrenia patients and found that more than 66% (107/161) of studies, used self-report alone or in combination with other measures. Of those, 51 used only self-report (Velligan *et al*., 2006). The self-report measures used varied greatly among studies and included ad hoc measures, unspecified interviews, semi structured interviews unspecified or specified such as the Rating of Medication Influences, Treatment Compliance Interview, Drug Attitude Inventory (DAI), the medication compliance item from the Multinomah Community Ability Scale, Medication Aherence Rating Scale (MARS), knowledge level, attitudes and insight and asking if they had stopped taking in the past one or two weeks. The subjective measures including provider report, significant other report, and chart review were used 218 times and were the only measures used in 124 studies (77%). Self-report is often criticized as being the least valid measure of adherence due to biases of recall and self-presentation (Byerly *et al*, 2007; Kennedy *et al*, 1991). Velligan *et al* found that patients and physicians were not able to identify adherence when compared to data from electronic monitoring with MEMS (Medication Event Monitoring System, pill bottle caps that record the time and date of bottle opening) and pill count (Velligan *et al*, 2007). Byerly *et al* found that clinicians underestimated levels of nonadherence when compared to MEMS (Byerly *et al*, 2005). It is clear from the review of Velligan *et al*, that there are many different self-report measures in use and it is questionable if they all measure the same thing (Velligan *et al*, 2006).

There seem to be at least two types of self-report that measure different behavioural constructs. The first type takes the form of retrospective recall of actual medication taking events (e.g., “How many times did you take your pills over the past week or month?”) while the second is a more general adherence rating (“I took my medication as prescribed” or “I often forget to take my medication.” With response assessed as strongly disagree to strongly agree). The structure of the self-report is also different. Garber *et al*, found that the concordance of self-report and other measures of medication adherence varied widely based on the construct of the measures used (Garber *et al*, 2004). Questionnaires and diaries had moderate to high concordance with objective measures, but interviews were not concordant

with objective measures. The reason that self-report is most widely used is the fact that it is simple, non-intrusive and not costly. Because self-report is inaccurate, it has been suggested that it should be used in combination with an objective measure (Velligan *et al*, 2006). According to Velligan *et al´s* review of adherence measures, pill count is the objective method most widely used (Velligan *et al*, 2006). Pill counts determine how many pills are missing from a container and an estimate of adherence percentage is found. The patients are needed to bring their pill bottles in for counting or a more reliable method, unannounced home visits are scheduled. In recent years the MEMS caps have been increasingly used in adherence studies (Diaz *et al*, 2004; Byerly *et al*, 2005; Frangou *et al*, 2005; Nakonezny & Byerly, 2006). They have been considered by some to be the gold standard for measuring adherence (Velligan *et al*, 2006), but even so, they only monitor opening and closing of medication bottles, not actual pill ingestion. Patients may take out more than one dose at a time, not take any out at all, or fail to replace the cap. Then there is considerable expense in obtaining the devices. Thus, the instrument is likely to remain in use only in research, but a more general use clinically to monitor adherence is less likely.

Electronic pharmacy records are an objective, unobtrusive method to determine level of adherence. As the availability of electronic pharmacy records is increasing, this opens the possibility to study larger groups, but electronic records should not be assumed to be accurate or complete. An interesting measure derived from pharmacy data is the MPR. This has in recent years been used to estimate adherence in large populations (Valenstein *et al*, 2002; Sajatovic *et al*, 2007; Sajatovic *et al*, 2006). Measuring the level of medicine in the blood is an objective method that is regarded as highly reliable but it depends on a strict protocol and is costly (Baumann *et al*, 2004; Osterberg & Blaschke, 2005). It is surprising that the method has rarely been used in adherence studies, and in the review of Velligan *et al*, only 7 of 161 studies used blood levels as part of adherence evaluation (Velligan *et al*, 2006). Serum concentrations are a necessary tool in lithium treatment and are often used to follow up the treatment with valproate. Even so, structured interviews and pharmacy records are the most widely used instruments in adherence studies of mood stabilizers in bipolar disorder (Manwani *et al*, 2007; Sajatovic *et al*, 2007; Zeber *et al*, 2008). Plasma levels of medicine indicate if the medication has been taken or not, but do not predict future adherence. It is therefore interesting to use plasma levels in combination with a simple self-report to measure adherence and this would provide new information. The availability of plasma measurements of different psychotropic medicines varies between countries as there has been lack of easily defined therapeutic windows for the newer antidepressants and the second generation

antipsychotics (Bengtsson, 2004). In Norway the situation is somewhat special as this has been a readily available tool in clinical practice for many years and there exists some expertise with regards to reference levels of the different medications (Castberg *et al,* 2007). Thus, in Norway the background for using plasma measurements of psychotropic medications in the study of adherence is very good. From the overview of available data on adherence and nonadherence in schizophrenia and bipolar disorder it seems that the rate of nonadherence is alarmingly high. Even so further studies are needed were adherence measures are better defined and multiple measures are used. This has rarely been practised before.

Selection of patients is a general concern with adherence studies, as those patients that deny all treatment usually do not consent to participate in studies. Ethically, this is a problem that is impossible to reduce. Even so, it is important to study patient samples that are representative of real clinical populations, and naturalistic studies with unselected patients are needed to do this. In addition, there is a need of an overview of adherence problems in differently organized health care systems. Psychiatric services in Norway are catchment area based and publicly funded. Mental health care and treatment is available for anyone suffering from severe mental disorder. Studies of adherence in patients with severe mental disorder in Scandinavia are sparse.

From the overview of available data on adherence and nonadherence in schizophrenia and bipolar disorder it seems that the rate of nonadherence is alarmingly high, but with a large variation between studies and among different patient groups. Further studies are needed where available health services in the area, representativity of samples, and adherence measures are better defined. Along with this multiple measures of adherence should be used.

5.2.5. Clinical consequences

Poor adherence with medical treatment has a major impact on clinical outcome and greatly increases health care costs (Osterberg & Blaschke, 2005). Many factors affect the outcome in schizophrenia treatment. Partial adherence or nonadherence is considered to be one of the most important factors (Bebbington, 1995), being strongly associated with an increased risk of relapse (Fenton *et al*, 1997; Robinson *et al*, 1999). In patients with schizophrenia, partial and nonadherence can set in motion a “downward spiral” of events resulting in inconsistent symptom control, relapse and rehospitalisation, which in turn can lead to long-term functional disabilities, loss of autonomy, education or employment possibilities, homelessness, a likelihood of dropping out of care completely and even suicide (Llorca, 2008). Robinson *et al*

reflect that relapse prevention is a major challenge in the care of patients with schizophrenia (Robinson *et al*, 1999), and in their study of first episode patients they found that five years after initial recovery the relapse rate was 82%. With increased relapse rates, the likelihood of hospitalization is greater as well. Those who discontinued treatment with antipsychotic medication had five times increased risk of relapse. In a sample of 67,000 U.S. veterans with schizophrenia who received antipsychotic medication over a 12-month period, those with MPR closest to 1.0 had the lowest hospital admissions, and the rates increased with smaller MPRs (Valenstein *et al*, 2002). Poorly adherent patients also had longer duration of hospitalization. Gilmer *et al* also found lower rates of hospitalization in adherent patients (14%) than in those who were nonadherent (35%) or partially adherent (24%) (Gilmer *et al*, 2004). A study of "revolving door" schizophrenia patients in the USA found that nonadherence to medication was the most common reason for hospital admission, cited as the cause of admission for 50% of patients (Weiden & Glazer, 1997). Similar results were reported from the United Kingdom with medication nonadherence being the reason for admission for 55% of patients (Jeffreys *et al*, 1997). Moreover data from a 1-year cohort study of over 4000 patients demonstrated that even small gaps in medication (1-10) days, increased the likelihood of hospitalization two-fold, and larger gaps (≥ 30 days) increased the likelihood four-fold (Weiden *et al*, 2004). Law *et al* reported similar findings (Law *et al*, 2008). Verdoux *et al* looked especially at involuntary readmissions and found them to be six times greater in patients with a history of poor medication adherence (Verdoux *et al*, 2000). The negative impact of nonadherence was demonstrated convincingly in a 20-year follow-up of patients with schizophrenia in Iceland (Helgason, 1990). Only 54% of patients considered to require inpatient care at first contact, accepted hospital admission. Patients that had declined at first contact and were admitted later and after further progression in their illness were in the end admitted more often and stayed longer in hospital. A recent 3-year prospective, naturalistic study examined the relationship between medication adherence and long-term functional outcome in schizophrenia (Ascher-Svanum *et al*, 2006). Adherence was assessed using self-report and MPR. Nonadherence was associated with poorer functional outcomes, including greater risks of hospitalization, use of emergency psychiatric services, arrests, violence, victimizations, poorer mental functioning and greater substance and alcohol abuse. Recent data from Denmark indicate that treatment nonadherence is associated with increased suicide risk in schizophrenia (Nordentoft, 2007). As it has been shown that long-term treatment with antipsychotic medication is associated with lower mortality in patients

with schizophrenia (Tiihonen *et al*, 2009), it is likely that improved adherence could lower the mortality even further.

Poor adherence also increases the risk of relapse and rehospitalization in bipolar disorder. In the study of lithium maintenance treatment of Johnson and McFarland, they found that discontinuation of lithium was associated with increased hospitalization (Johnson & McFarland, 1996). In the study of Scott and Pope from 2002, admission rates were 90% in those who were nonadherent compared with 10% in those who were adherent (Scott & Pope, 2002). Keck *et al* demonstrated that 64% of individuals admitted with manic episode had been nonadherent to prescribed mood stabilizers in the month prior to hospitalization and with the nonadherent group the severity of mania was greater (Keck *et al*, 1996). Colom *et al* followed 200 bipolar disorder patients for a period of 2 years and reported that those with good adherence had fewer hospitalizations over the study period (Colom *et al*, 2000). Scott and Pope explored the relationship between medication adherence, plasma levels of mood stabilizers and psychiatric hospitalizations in 98 individuals with mood disorders (Scott & Pope, 2002). They found significantly higher admission rates in partially adherent patients with sub therapeutic plasma levels. Müller-Oerlinghausen *et al* have published data demonstrating that continuous use of lithium may reduce the risk of attempted or actual suicide and that stopping lithium increases the risk of death from suicide or physical disorders, particularly cardiovascular disorders (Müller-Oerlinghausen *et al*, 1996; Müller-Oerlinghausen, 2001). They reported that adequate long-term lithium treatment significantly reduces and even normalizes excess mortality rates in patients with mood disorders. Furthermore, a meta-analysis of pooled data from 17,000 patients in 28 studies demonstrated that the rate of suicidal acts was 8.6 times higher in patients not receiving regular lithium treatment (Müller-Oerlinghausen, 2001). These data show the benefits of long-term treatments with lithium, and offer indirect evidence of the potential benefits of adherence to mood stabilizers. Gonzalez-Pinto *et al* confirmed these findings in 2006 reporting a lower risk of suicidal acts during closely monitored, highly adherent, long-term lithium treatment (Gonzalez-Pinto *et al*, 2006).

When partial or nonadherent patients are not identified in the clinic, this can lead to unnecessary increases in dosage, a switch in the type of medication or addition of unnecessary adjunctive medication. These patients may be incorrectly labelled as having treatment resistant illness.

Adherence is very important in clinical trials as we base our knowledge of medical treatment on them. An estimated average adherence of 50% rather than 100% in a trial would increase the required sample size fivefold in order to maintain the same power (Vermeire *et al,* 2001).

5.2.6. Economical consequences

When severe chronic illnesses like schizophrenia and bipolar disorder are inadequately treated, this increases direct costs of the health care system and indirect costs with lost productivity and with the economical burden of disability. Wu *et al* examined the costs of schizophrenia in the United States in 2002 (Wu *et al*, 2005). They calculated the excess annual health care costs to society as the difference in costs between schizophrenia patients and their nonschizophrenia controls matched on age, sex and geographic region. Results were calculated using a modest prevalence rate of 5.1 per 1000. According to their calculations the total excess costs of schizophrenia patients in the United States in 2002 was $62.7 billion. Sun *et al* estimated that the national rehospitalisation cost related to nonadherence to antipsychotics was $1479 million in the United States in 2005 (Sun *et al*, 2007). Given that adherence problems are the most common cause of relapse in schizophrenia (Schooler, 2006), nonadherence is a significant contributor to increased cost in this population.

In bipolar disorder the estimated total annual cost in the United States was about $45 billion in 1991 for the 2 to 2.5 million prevalent cases in the country (Wyatt & Henter, 1995). Another study based on the incidence data (95 000 cases) from 1998, estimated total lifetime costs of $24 billion (Begley *et al*, 2001). Durrenberger *et al* demonstrated in a case series, that the cost of care over a period of six years for one nonadherent patient with frequent manic relapses was equal to that of 13 patients who adhered to their mood stabilizers (Durrenberger *et al*, 1999).

It is clear from the last section on clinical consequences that higher relapse rates, more frequent hospitalizations and longer duration of relapse is related to partial adherence and nonadherence. All this in turn leads to increased cost of the health care system directly as well as indirect costs linked to disability and loss of productivity.

5.3. Factors predisposing nonadherence

It has been difficult to identify predictors of medication nonadherence. As with all adherence studies, these studies vary in design, definitions and measures as well as in the study samples. Even so, there are predictors that seem so be consistently related to adherence, although the evidence is still weak for several of them. Factors that have been linked to nonadherence in schizophrenia and bipolar disorder are commonly divided into four groups (Fenton *et al*, 1997; Goodwin and Jamison 2007): 1) Patient related factors; including insight, beliefs and attitudes towards illness and treatment, history of adherence problems, duration of illness and substance use. This group also includes factors like age, gender, ethnicity, marital status and education. 2) Illness related factors; including degree of symptoms and cognitive impairment. 3) Medication related factors; including type and dose of medication and adverse effects. 4) Environmental factors; including therapeutic alliance, inadequate out-patient care and the involvement of family.

5.3.1. Insight

There has been considerable interest in the concept of insight in schizophrenia, but less in bipolar disorder. In the last twenty years the understanding and definitions of having insight into one's own pathology have changed and there seems to be a consensus among researchers that insight is multidimensional and should be measured along a continuum that includes awareness of illness, awareness of symptoms and the perceived need for treatment David 1990). In the DSM-IV-TR the following is stated: A majority of patients with schizophrenia have poor insight regarding the fact that they have a psychotic illness. Evidence suggests that poor insight is a manifestation of the illness rather than a coping strategy. It may be comparable to the lack of awareness of neurological deficits seen in stroke, termed anosognosia. This symptom predisposes the individual to noncompliance with treatment and has been found to be predictive of higher relapse rates, increased number of involuntary hospital admissions, poorer psychological functioning, and a poorer course of illness (*Diagnostic and statistical manual of mental disorders : DSM-IV-TR*, 2000). As is stated in the DSM-IV-TR, schizophrenia patients with poor insight are predisposed to nonadherence. In adherence studies insight is the risk factor most consistently associated with nonadherence in patients with schizophrenia (Fenton *et al*, 1997; Lacro *et al*, 2002). In their review of risk factors for nonadherence in schizophrenia Lacro *et al* found that poor insight was related to nonadherence in 10 out of 14 studies addressing the issue (Lacro *et al*, 2002). Even though

there has been a lot of focus on insight in schizophrenia, much less is known about insight in bipolar disorder.

The relationship between insight and nonadherence in bipolar disorder remains unclear and few studies have addressed it (McEvoy & Wilkinson, 2000). A recent study showed a positive correlation between all 3 dimensions of insight and adherence to medication in bipolar disorder (Yen *et al*, 2005). The few studies that have compared the levels of insight in schizophrenia and bipolar disorder found no substantial difference between patients with bipolar disorder and schizophrenia, neither during psychotic episode (Amador *et al*, 1994; Pini *et al*, 2001) nor in remission (Yen *et al*, 2002). However, the instruments used for measuring insight were not validated for patients with bipolar disorder in the mentioned studies. Thus there is need for a validated instrument to measure insight in bipolar disorder and for studies looking at the relationship between adherence and insight in bipolar disorder. Insight has mostly been assessed using semi-structured interview based measures. The Scale to Assess Unawareness of Mental Disorders (SUMD) (Amador *et al*, 1993) is perhaps the most widespread scale. It is time consuming and depends on the subjective clinical evaluation of the interviewer. It has been proposed that self-report scales might have the benefit of obtaining the same information in less time and may provide better control for cofounding variables that are conceivably inherent in patient-examiner interaction (Young *et al*, 2003).

5.3.2. Beliefs about medication

Theoretical paradigms of adherence, such as the Health Belief Model (figure 1, p.31) have been developed and adapted to model factors that may determine adherence behaviour (Becker & Maiman, 1975). The model provides a useful perspective for understanding how patients' beliefs and attitudes can affect adherence. At the centre of the model is the likelihood that a patient will adhere to treatment recommendations. A decision to be partially or nonadherent stems from an implicit, subjective assessment of the relative costs and benefits (pros and cons) of treatment. If the patient concludes that the benefits of treatment are greater than its costs, they will adhere to it. The process is influenced by what patients believe about their illness, what its bad effects are and how susceptible they themselves are to those effects. Patients´ beliefs and attitudes towards medication have been shown to influence adherence in chronically ill patients (Horne & Weinman, 1999). To better understand the reasons for nonadherence to medication, Horne *et al* developed the Beliefs about Medicines Questionnaire (BMQ) (Horne *et al*, 1999). The scale was intended to assess commonly held

beliefs about medicines and to simplify the broad range of beliefs people have about specific and general medication into "core themes" which are relevant across illnesses and cultural groups. These themes could then be evaluated as psychometric scales. Beliefs about specific medications prescribed for a certain illness were grouped into two core themes. These were their beliefs about the *necessity* of the prescribed medication for maintaining health now and in the future and *concerns* about the potential adverse effect of taking it. Commonly held beliefs about medicines in general were also grouped under two themes. These were general beliefs about the intrinsic nature of medicines and the extent to which they are perceived as essentially harmful substances that should be avoided if possible and general beliefs about the way in which medicines are used by doctors. Horne *et al* reported that necessity correlated positively with adherence to medication, while concern correlated negatively (Horne *et al*, 1999). They also found that medication beliefs were more powerful predictors of reported adherence than clinical and sociodemographic factors. Horne *et al* validated the scale. The sample in the validation comprised patients with chronic somatic illnesses and a small group of patients with psychiatric disorders not otherwise specified (Horne *et al*, 1999). Hence the scale had not been validated in patients with severe mental disorders.

Attitudes towards medication have been shown to influence adherence to medication in schizophrenia (Lacro *et al*, 2002; Perkins, 2002). In the review of Lacro *et al*, 8 of 10 studies addressing negative attitudes towards medication, demonstrated an association (Lacro, *et al*, 2002). In a study of Cabeza *et al*, the positive subjective response to antipsychotic medication measured by the DAI was significantly correlated to adherence (Cabeza *et al,* 2000). There was also a significant correlation between the subjective response and insight. In a sample of schizophrenia patients living in supported housing facilities, negative attitudes towards medication were associated with nonadherence (Grunebaum *et al*, 2001).

In bipolar disorder, attitudes and beliefs towards medication are listed in review articles analyzing factors influencing adherence (Lingam & Scott, 2002). In 1979 Jamison *et al* explored the attitudes of 42 patients receiving lithium and the reasons for nonadherence (Jamison *et al*, 1979). Two of the major reasons for nonadherence were that patients disliked the idea that their moods were controlled by medication and disliked taking medication as it reminded them that they had a chronic illness. In a study of nonadherence with mood stabilizers, where attitudes were measured using the Lithium Attitudes Questionnaire (Harvey, 1991) with adjustments, partially adherent subjects demonstrated more negative attitudes towards the medical treatment (Scott & Pope, 2002). A recent study using Horne´s

Necessity/Concerns framework, but utilizing a semi-structured interview in 16 bipolar patients, found that patients´ concerns about the medication were associated with both intentional and unintentional nonadherence (Clatworthy *et al*, 2007).

In earlier studies of attitudes to medication in patients with schizophrenia the DAI was most commonly used (Hogan *et al*, 1983; Hofer *et al*, 2002; Day *et al*, 2005; Adewuya *et al*, 2006). A newer scale, the Attitudes towards Neuroleptic Treatment questionnaire, was introduced a few years back (Kampman *et al*, 2000). These scales are developed especially for patients with schizophrenia. One of the goals of Horne *et al*, when developing the BMQ, was to construct a scale that could be used broadly across illnesses and cultures. We find this a useful goal, which enables researchers to compare different patient groups within both psychiatric and medical illness populations. It will enable us to help identify factors that are specific for the attitudes of particular groups and this may gain new knowledge to be used for improving the effect of pharmacotherapy.

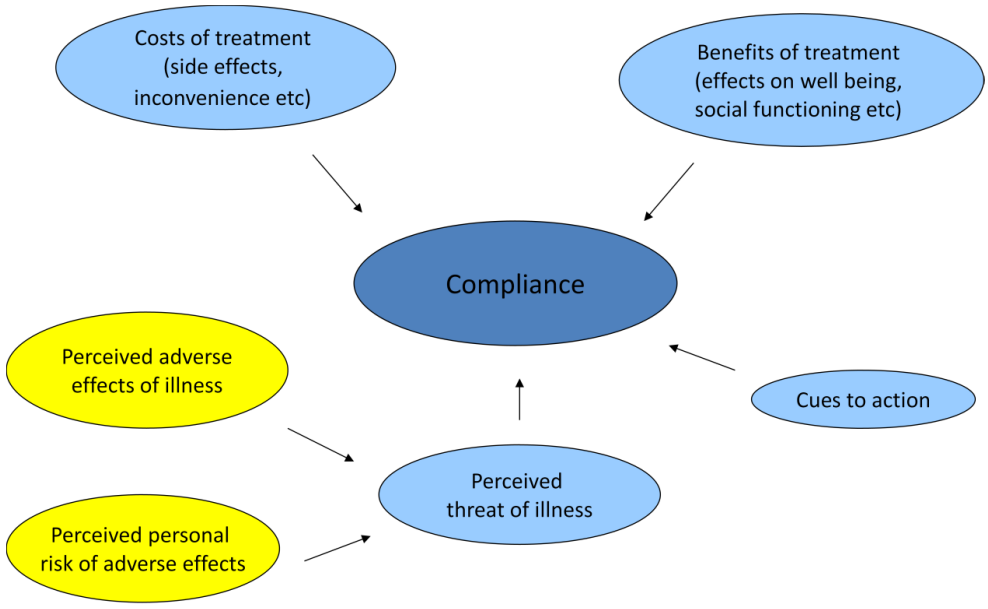

Figure 1. THE HEALTH BELIEF MODEL OF COMPLIANCE
(Becker and Mainman 1975)

5.3.3. Substance abuse

Research has supported an association between co-occurring substance abuse and adherence problems. In Lacro *et al´s* review of predictors of nonadherence in schizophrenia, an association of past or current substance abuse and nonadherence was found in 5 of 9 studies analysing this (Lacro *et al*, 2002). The authors comment that the studies employing a more rigorous methodology were more likely to find an association. In the review of Nosé *et al* it is mentioned that substance abuse is related to nonadherence in 8 studies, but the studies are not listed (Nosé *et al*, 2003). Some studies of first episode psychosis or schizophrenia have looked at the relationship between substance abuse and adherence problems. In a study following 200 patients in an Early Psychosis Program, nonadherent patients demonstrated more alcohol and cannabis use than those who were adherent (Coldham *et al*, 2002) and continued cannabis use at one year was one of the most significant determinants of nonadherence. In a one year follow-up of first-episode patients, Perkins *et al* likewise found that ongoing substance abuse significantly predicted poor adherence to medication (Perkins *et al*, 2008). In a prospective study that looks specifically at the use of cannabis as a risk factor for nonadherence and treatment dropout in 112 first-episode schizophrenia, the results indicated that cannabis use increased the hazard of nonadherence by a factor of 2.4 and the hazard of treatment dropout by a factor of 6.4 (Miller *et al*, 2009).

In bipolar disorder substance abuse has been found to have a relationship to nonadherence (Lingam & Scott, 2002; Sajatovic *et al*, 2006; Sajatovic *et al*, 2007). In a follow-up study of 134 bipolar patients, medication adherence was inversely associated with the presence of comorbid substance use disorder (Keck *et al*, 1998). In a study of 115 patients with bipolar disorder, lifetime adherence with mood stabilizers was 65.5% in the 58 patients with comorbid substance abuse, compared with 82.5% in the 57 patients without substance abuse disorders. A couple of interesting studies have also been published during the work with the current thesis. A one year follow-up of 3459 bipolar in- and outpatients showed that over the study period, cannabis users exhibited less adherence and had higher overall illness severity (van Rossum *et al*, 2009). In a study of 429 bipolar patients in the US, Baldessarini *et al* found that alcohol dependence was significantly associated with nonadherence and more so than other factors (Baldessarini *et al*, 2008).

It is important to continue the work in this field as substance abuse in general and in severe mental illnesses is widespread and a serious health problem. Targeting substance abuse especially should probably be a priority when developing interventions to improve adherence.

5.3.4. Adverse effects

The burden of side effects and its relationship to nonadherence have got considerable attention in research. Side effects are a recognized problem clinically and are often the reason for switching to another medication (Weiden & Buckley, 2007). Even so, there does not seem to be a clear relationship between more severe side effects and nonadherence. In systematic reviews, there is not a consensus regarding this. In a review by Fenton *et al*, 4 studies are mentioned where between one quarter and two thirds of those who discontinue their medication unilaterally, cite side effects as their primary reason (Fenton *et al*, 1997). In a review of studies covering the years 1974-1997, Kampman *et al* mention 6 studies finding that side effects reduce adherence, most notably akathisia and akinesia (Kampman & Lehtinen, 1999). Nosé *et al* reviewed 103 studies that reported nonadherene with medication and scheduled appointments by psychotic patients. In their list of factors associated with adherence and nonadherence, there is no mention of side effects as a predictor of nonadherence (Nosé *et al*, 2003). Lacro *et al* reviewed 39 adherence articles and found 9 that looked especially at side effects (Lacro *et al*, 2002). Only 1 of the 9 demonstrated an association to nonadherence. This came as a surprise to the authors that noted that in the reviewed studies systematic ratings of side effects were rarely obtained. Some of the first-episode studies have examined the relationship of side effects and nonadherence. Robinson *et al* found that parkinsonian side effects significantly increased the likelihood that patients would discontinue medication during the first year of treatment (Robinson *et al*, 2002).

With the introduction of the second generation antipsychotics, the spectrum of side effects has changed. There are as yet, not many studies that have looked at side effects like weight gain and sexual side effects and their relationship to nonadherence. Results from a survey of 239 schizophrenia patients demonstrated a strong correlation between body mass index (BMI) and nonadherence , which was defined by self-report as missing any medication in the previous month (Weiden *et al*, 2004). Further studies are needed that focus on side effects of second generation antipsychotics.

When studying the literature on predictors for nonadherence in bipolar disorder, side effects of medication are not among the factors most often mentioned as predictors. Jamison *et al* suggested that lithium side effects may predict nonadherence (Jamison & Akiskal, 1983). A Danish study from 1976, showed that 16 of 74 patients discontinued lithium treatment (Bech *et al*, 1976). The stated reason for discontinuing was side effects with 12 patients and insufficient effect with 4 of the patients. A study of Scott and Pope highlights that it was not the actual side effects but the fear of side effects that increased the risk of nonadherence

(Scott & Pope, 2002). In a European survey of over 3000 patients, side effects were ranked only seventh on a list of patients concerns about treatment (Morselli *et al* 2003).

5.3.5. Neurocognitive factors

Neurocognition is an important predictor of functional outcome in schizophrenia (Green, 1996, 2006; Green *et al*, 2004) and the same relationship seems to exist for bipolar disorder (Green, 2006; Martinez-Aran *et al*, 2007; Burdick *et al*, 2010). It is reasonable to assume that cognitive functions may be related to adherence behaviour, but the relationship between neurocognitive dysfunction and nonadherence is still unclear. The studies are sparse, but there have been reports from general medicine pointing in the direction that better IQ predicts better adherence (Stilley *et al* ,2004). In studies focusing on schizophrenia, results are mixed (Buchanan, 1992; Cuffel *et al*, 1996; Kemp & David, 1996; Smith *et al*, 1999; Donohoe *et al* 2001; Robinson *et al,* 2002; Jeste *et al,* 2003; Maeda *et al* 2006; Perkins *et al* 2008; Lepage, *et al* 2010;) and few use extensive neurocognitive testing when measuring cognitive impairment. In bipolar disorder there is one study pointing at a relationship between poor treatment adherence and cognitive impairment (Martinez-Aran *et al*, 2009). It is important to explore this relationship further.

5.3.6. Other factors

The relationship of adherence to psychopathology in schizophrenia remains unclear, both in terms of significance and the direction of effect. In the review of Lacro *et al* 4 of 8 studies addressing psychotic symptoms found that there was an association between more severe psychotic symptoms and nonadherence (Lacro *et al*, 2002). The presence of mood symptoms was associated with nonadherence in 3 of 7 studies. In a study following 400 first-episode patients for a year, ongoing depression predicted poor adherence (Perkins *et al*, 2008). In bipolar disorder there is evidence suggesting that there is an association between affective symptoms and nonadherence. In a study of 429 bipolar disorder patients, greater numbers of affective symptoms and recent mania or hypomania were associated with treatment nonadherence. Keck v found that 64% of individuals admitted with manic episode had been nonadherent to prescribed mood stabilizers in the month prior to hospitalization and with the nonadherent group the severity of mania was greater (Keck *et al*, 1996). This however does

not prove cause and effect as nonadherence may lead to mania or mania may increase the likelihood of nonadherence.

There was hope that with the second generation antipsychotics, adherence to medication would improve, but to date, data is inconclusive regarding this. There are not many studies addressing this issue, and those that do, often compare only a few of the antipsychotics and not always list the different medication in each group. Rosenheck *et al* found that patients taking clozapine continued their medication for a significantly longer time compared to patients taking haloperidol (Rosenheck *et al*, 2000). In the study of Olfson *et al,* there was a nonsignificant trend suggesting that patients taking SGA (clozapine or risperidone) were less likely to become nonadherent than those taking FGA (not described which) (Olfson *et al*, 2000). Cabeza *et al* found no association between type of antipsychotic medication and medication adherence (Cabeza *et al*, 2000). In the study of Grunebaum *et al*, patients prescribed with SGA had significantly more days of missed medication compared with those receiving FGA (Grunebaum *et al*, 2001). In a 12 month follow-up of Dolder *et al*, patients receiving SGA had significantly smaller gaps in therapy, where patients on FGA had approximately 7 days a month without medication and patients on SGA had approximately 4 days a month (Dolder *et al,* 2002). Mean adherence rate at 12 months was 55% for the SGA group and 50% for the FGA. This difference was not significant and it is clear that adherence remained a problem regardless of the type of antipsychotic agent. A study of 298 California Medicaid recipients found that antipsychotic medication was available for 60% of the days over a 1 year follow-up and there was no difference in the availability between FGA and SGA (Menzin *et al*, 2003). In the EUFEST study the group taking low-dose haloperidol discontinued significantly more often than the groups taking SGA, even though there was no difference in efficacy (Kahn *et al*, 2008). The above mentioned data suggest that there is no clear difference in adherence with regards to FGA or SGA, even though the trend seems to favour SGA. In only two of the above mentioned studies, comparing FGA and SGA was a primary outcome topic (Dolder *et al,* 2002; Menzin *et al*, 2003).

Regarding the relationship of adherence and sociodemographic factors such as age, gender, ethnicity, marital status and education level the results of studies in schizophrenia are inconclusive. A majority of studies reviewed by Lacro *et al*, found no association (Lacro *et al*, 2002), but in the review of Nosé *et al* some studies found a relationship between nonadherence and younger age and being male (Nosé *et al*, 2003). Some studies of first-episode schizophrenia patients have found that younger age and earlier onset of illness predict nonadherence (Coldham *et al,* 2002), while others have not found this association (Robinson

et al, 2002; Perkins *et al*, 2008). As in schizophrenia, the findings in bipolar disorder are contradictory on sociodemographic factors and adherence to medication (Colom *et al*, 2005). It remains unclear whether male gender is linked to nonadherence, as some studies support this (Danion *et al*, 1987; Keck *et al*, 1997), but others do not (Colom *et al*, 2000; Scott & Pope, 2002) and some have found that being female predicts nonadherence (Copeland *et al*, 2008). Some studies also support that younger age and minority ethnicity are associated with nonadherence (Sajatovic *et al*, 2007), but others do not (Keck *et al*, 1997).

5.4. Unresolved issues and rationale for the thesis

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

- Studies with well defined multiple adherent measures (both direct and indirect) are sparse and much needed.
- Adherence studies from representative and well described patient groups are needed. There are no such studies from Scandinavia.
- It is important to continue the work of defining adherence behaviour and establishing what characterises partially and nonadherent patients. There are no such studies from Scandinavia.
- Studies investigating the relationship of adherence and neurocognition are sparse.
- Instruments used to determine factors such as insight and beliefs about medication need to be simplified and validated in patients with bipolar disorder.

6. Aims of the study

Overall aim

The overall aim of the thesis was to determine adherence rates in a Norwegian catchment area population of patients with severe mental illnesses and to identify predictors for nonadherence in this population.

Subaims

To study the psychometric properties of the Birchwood Insight Scale (IS) in patients with severe mental disorders (schizophrenia and bipolar disorder). Furthermore, to determine the level of insight in the two patient populations (Paper I).

To evaluate the psychometric properties of the Beliefs about Medicines Questionnaire (BMQ) in patients with schizophrenia and bipolar disorder. To examine if beliefs about medicines are related to medication adherence in those patients and to explore differences in these beliefs between patients with schizophrenia and bipolar disorder. Further, to compare the scores of patients with schizophrenia and bipolar disorder to those of patients with severe medical disorders (Paper II).

To determine the level of adherence in a representative outpatient sample of patients with severe mental disorders based on blood concentration of psychopharmacological agents. Furthermore to evaluate the sensitivity and specificity of a short and simple self-report method for adherence measurement and compare this with the 5-item Medication Adherence Rating Scale (MARS) and provider reports (Paper III).

To identify potential risk factors associated with medication nonadherence in a well-described group of patients with schizophrenia and bipolar disorder. Furthermore, to investigate if there were different risk factors related to the two diagnostic groups. We included factors suggested in earlier studies; including insight, substance abuse, psychiatric symptoms, side effects and sociodemographic factors as well as factors not investigated much earlier, such as neurocognitive functioning and adverse effects (Paper IV).

7. Material and methods

7.1. Design

This thesis is part of the TOP (Thematically Organized Psychosis) Study. The Oslo TOP study is a large, multisite research study, carried out by the University of Oslo in joint collaboration with all four University Hospitals in Oslo on the basis of the specialist psychiatric services. Patients with SMI from all health care sectors in Oslo are included, the main diagnostic groups being schizophrenia and bipolar disorder. Inclusion of patients is ongoing. In this thesis, data are based on patients included in the study from May 2003 through October 2006. The study design is naturalistic, with a translational approach. Thus, a number of biological and clinical characteristics of SMI are investigated in order to gain more knowledge about the underlying pathophysiological mechanisms of disease.

The inclusion area covers practically the whole city of Oslo, with a total of 550.000 inhabitants, living in urban and suburban parts of the capital. The treatment system is catchment area based and publicly funded. Patients are referred from primary care. The core basis of the psychiatric specialist treatment system is subsector catchment area-based outpatient units, with the addition of acute, intermediate and long treatment units. Eligible patients were all those meeting study criteria and giving informed written consent of participation. The Regional Ethics Committee and the Norwegian Data Protection Agency approved the study, and the biobank was approved by the Norwegian Health Directorate.

7.2. Participants

Inclusion criteria for the TOP Study are broad, consisting of 1) being registered in the psychiatric services of any of the 4 University Hospitals in Oslo; 2) aged 18 to 65 years; 3) meeting the DSM-IV criteria for any major psychotic or bipolar disorder; 4) understanding and speaking a Scandinavian language; 5) having no history of severe head trauma or neurological disease; and 6) having an Intelligence Coefficient (IQ) score over 70.

Patients are included mainly from the outpatient units of each health care sector, but also from intermediate and long treatment units. Patients in acute ward treatment are considered not currently capable of participation. These patients are instead approached after release from hospital**,** when their mental condition is stabilized. All participants are invited

into the study by the clinician responsible for their treatment. Those willing to participate receive thorough information of the study aims and procedures from one of the PhD students responsible for the assessments, all of them trained psychologists or psychiatrists. The inclusion procedure itself is divided into several sessions and in total comprises eight hours or more of assessment, including clinical interviews, a physical examination and neuropsychological testing. The interviews take place partially at the patient's regular treatment unit, and partially at Oslo University Hospital.

Participants were continuously being included in the study throughout the study period and the study is still ongoing. As a result of this the number of participants grew throughout the study period. The purpose of this thesis was to investigate patients with diagnoses of bipolar disorder (bipolar I and bipolar II), schizophrenia and schizoaffective disorder (the schizoaffective patients were grouped with the schizophrenia patients in analysis). Patients with diagnoses of other psychotic disorders were thus excluded from this study. In total 385 patients were evaluated during the inclusion period. Eighty eight patients did not meet the diagnostic criteria. Fifteen patients had not started treatment with medication at the time of inclusion and were thus excluded, and two patients withdrew their data after inclusion.

In paper I the study group consists of patients included from May 2003 to November 2005. There are 201 patients in this sample, that met the diagnostic criteria for schizophrenia, schizoaffective disorder, bipolar I and bipolar II disorder.

In paper II, III and IV the study group consists of patients included from May 2003 to October 2006. There were 280 patients in this sample, patients with bipolar I (n=66) and II (n=48) disorders (bipolar group, n= 114), schizophrenia (n=126), schizoaffective (n=30) and schizophreniform (n=10) disorder (schizophrenia group, n=166). Patients included in study II, III and IV were outpatients.

Table 1. Demographic and clinical characteristics of study samples.

	Study I			Study II- IV	
Samples	Sch.	BD I	BD II	Sch.	BD
N	101	57	37	166	114
Male, N (%)	61(60)	24(42)	13(35)	95(57)	46(40)
Age, mean(y)	33	40	37	33	38
PANSS pos, mean	15	9	10	15	10
PANSS neg, mean	16	10	11	15	11

Sch.; Schizophrenia, BD; bipolar disorder, PANSS; Positive and Negative Symptoms Scale, neg; negative, pos; positive

In study samples II, III and IV serum concentrations of medicines were obtained from 255 of 280 participants. For these 255 a primary therapeutic agent (PTA) was defined. In the schizophrenia group 146 patients (94.8%) were prescribed an antipsychotic agent as the primary therapeutic agent. Of those, 55 patients (37.7%) were on monotherapy and 91 (62.3%) on combined therapy with other antipsychotics, antiepileptics or lithium, or antidepressants. Forty nine (33.6%) took two medications, 29 (19.9%) took three, 9 (6.2%) took four, 2 (1.4%) took five medications and 2 (1.4%) were taking six different types of medications. In the bipolar group 60 patients (59.4%) were prescribed an antiepileptic or lithium as their primary therapeutic agent, 23 (22.8%) antipsychotics and 9 patients (8.9%) had an antidepressant as their primary therapeutic agent. In this group 34 patients (33.7%) were on monotherapy, 34 (33.7%) took two medications, 20 (19.8%) took three medications and 4 patients (4.0%) took four medications. In addition, benzodiazepines were prescribed to 24% of the sample.

Table 2. Distribution of Primary Therapeutic Agents (PTA)

	Schizophrenia (n=154)	Bipolar disorder g(n=101)	Total (n=255)
First Generation Antipsychotics	15	3	18
Perphenazine	10	2	
Zuclopenthixol	4		
Flupenthixol	1		
Levomepromazin		1	
Second Generation Antipsychotics	131	20	151
Olanzapine	65	13	
Quetiapine	17	1	
Risperidone	16	2	
Ziprasidone	13	1	
Aripiprazole	10	2	
Clozapine	6	1	
Amisulpride	4		
Lithium	0	19	19
Antiepileptics	2	41	43
Lamotrigine	2	26	
Valproic Acid		12	
Carbamazepine		2	
Topiramate		1	
Antidepressants	2	9	11
Venlafaxine	1	1	
Ecitalopram	1	5	
Citalopram		2	
Fluoxetine		1	
Non-adherent patients not wishing to report medication last prescribed	4	9	13

Within the schizophrenia group, there were 28 patients with schizoaffective disorder. Of those 22 were prescribed a second generation antipsychotic as the PTA, 2 a first generation antipsychotic, 1 lamotrigine and 2 antidepressants. One was nonadherent and did not wish to report what was last prescribed.

7.3. Methods

7.3.1. Diagnosis

Diagnosis was established using the Structured Clinical Interview for DSM-IV-TR-Axis I Disorders (SCID-I) (Spitzer *et al*, 1992). The SCID-I is a semi-structured interview, making use of all available information on the patient. In addition to direct information from the interviewees and the clinical staff responsible for treatment, the interviewers had access to the patient's complete clinical file. All interviewers finished a training course in SCID assessment based on the training program at the University of California Los Angeles (Ventura *et al*, 1998). All interviewers participated in regular diagnostic consensus meetings led by a clinically experienced professor of psychiatry. To assess reliability for actual study interviews a stratified random sample was drawn, consisting of cases from every interviewer. 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 0.77 (95 % CI: 0.60-0.94).

7.3.2 General assessments

Participants were interviewed regarding their history of mental illness, present symptoms, sociodemographics, life style and pharmacological treatment. Symptoms were assessed by the following clinical instruments: Inventory of Depressive Symptomatology (IDS) (Rush *et al*, 1996), Young Mania Rating Scale (YMRS) (Young *et al*, 1978) and the Positive and Negative Symptoms Scale (PANSS) (Kay *et al*, 1987). Higher scores on the symptom scales signify more symptoms. All interviewers participated in inter rater reliability testing which entailed rating of patient videos. An intra class correlation (Shrout & Fleiss, 1979) of 0.73 was obtained for the PANSS scale. Global symptoms and psychosocial functioning were measured by the Global Assessment of Functioning Scale (GAF), (Pedersen *et al*, 2007). Side effects were measured using the "Udvalg for Kliniske Undersøkelser" (UKU) side effect rating scale (Lingjaerde *et al,* 1987) This scale measures a wide range of side effects divided in the categories: psychological, neurological, autonomic and others. After going through the different side effects, the patient and the caregiver separately assessed the effect of side effects on the patients' daily life, on a scale from 0-3. All patients were weighed, height was measured and BMI calculated.

7.3.3 Assessments of adherence

Three independent types of measures were used: serum concentration, self-report and provider-report.

Serum concentrations

Fasting blood samples were routinely collected between 9 and 11 am from all patients. Patients were instructed not to take their morning dose of prescribed medication prior to the blood sampling, according to standard protocol. Serum concentrations of medications were analyzed at the Department of Clinical Pharmacology, St. Olav's Hospital, Trondheim. To simplify the analysis, a primary therapeutic agent was defined for patients taking more than one medicine. When more than one psychotropic medicine from the same class was used, the primary therapeutic agent was defined as the medicine with the highest dose. If the dose range was similar, the medicine which had been used for the longest duration was selected as the primary therapeutic agent. The reference range for each drug has been derived at the laboratory based on their extensive database and long experience with measuring each psychotropic drug (Castberg *et al*, 2007). Of the 280 patients in study samples II, III and IV, serum concentrations were missing for 25 and they were excluded from analysis. Reasons for the missing data were that some patients refrained from giving blood samples, and some samples were not analyzed due to technical problems.

When considering serum concentrations of psychotropic medicines the concentration/dose ratio was used as this gives the best picture of drug intake (Castberg *et al*, 2007). An exception from this was lithium, where the serum concentration was used. By using the concentration/dose ratio the serum concentration is divided by daily dosage and thus corresponds to the serum concentration per mg of the medication taken daily by the individual. By using this measure, the values can be compared directly between subjects independently of different drug treatment regimens. To simplify the analysis, the patients were grouped into clusters, as suggested by Velligan *et al* (Velligan *et al*, 2006). Three groups were defined with regards to the concentration/dose ratio provided by the Trondheim laboratory: 1) Not detectable, 2) Low and 3) Within reference range or higher.

Self-report

Self-report of adherence was obtained from all patients. They were given a questionnaire by the research fellow and marked on a visual analogue scale from 0 – 100% how much of their

prescribed medication they had taken the past week. The scale had tick marks with corresponding numbers indicating 0, 25, 50, 75 and 100 % level. The patients marked on the scale the % intake for each medication they were taking at the time of assessment (see appendix fig 1.).

In order to compare the current simple self-report with other measures, the Medication Adherence Report Scale (MARS) was administered. The version used here, MARS-5, is a five-item self-report scale developed in the U.K. (Horne & Weinman, 2002). It was translated into Norwegian, with the back translation approved by the original author. MARS-5 has been used in earlier studies as a questionnaire to measure self-reported adherence (Horne & Weinman, 2002; George *et al*, 2005; Bowskill *et al*, 2007). The scale consists of general statements about medicines and is not specifically developed for psychiatric patients. The five items are: "I forget to take my medicines", "I change the dose of my medicines", "I stop taking my medicines for a while at times", "I decide not to take a dose" and "I take less than I am instructed to." There is no time frame specified in this scale (see appendix fig 2.). The item responses are scored on a five-point Likert scale where 1 = always, 2 = often, 3 = sometimes, 4 = rarely, 5 = never. Scores range from 5-25 with higher scores indicating higher adherence. There exist longer versions of the scale that include questions about specific types of medication, i.e. for lung diseases. The internal validity of the MARS-5 version used here was tested, and Cronbach´s alpha was 0.78. The internal validity in our sample is similar to other studies using this version (George *et al*, 2005).

Provider report

In order to compare self-report with information from the providers, a provider-report of adherence was obtained from the patients' case workers who filled in a scale from 0 – 100% indicating how much of the prescribed medication they estimated their patients had taken the past week.

Based on the self-report and serum concentrations the study sample in study IV was divided into adherence groups: 1) Fully adherent patients who with certainty had 100% adherence the past week (reported that they took 100% of their medication and the serum concentration was within reference level and in correct ratio with the dose) and into, 2) Partially adherent group (reported adherence between 12% and 95 %, and/or the concentration/dose ratio was lower than the recommended reference values, but with detectable medication), 3) No adherence group, that included patients who with certainty had

not taken anything (reported that they did not take their medication and/or the serum analysis showed no detectable medicines). In the study sample in study II the partial adherence group does not include patients that have reported 100% adherence on self-report, but have a concentration dose ratio that is lower than the recommended values, but not very low.

7.3.4 Assessment of insight

The Birchwood Insight Scale (IS) (Birchwood *et al*, 1994) was used in the assessment of insight (see appendix figure 3.). This self report inventory consists of eight questions which are easy to complete and represent three subscales; awareness of illness (2 items), relabelling of symptoms (2 items) and need for treatment (4 items). Due to low internal consistency for the subscales (study 1), the usage of the scale was restricted to the total score (see discussion 9.1.1., p 55). The total score has a range of 0-12, with a score of 9 or more indicating good insight. The original 3-point Likert scale (agree-unsure-disagree) was transformed to a 5-point scale (agree very much-agree-unsure-disagree-disagree very much).

The scale was translated into Norwegian and back into English. The authors of the scale had no objections to the translation.

In paper I the PANSS G12 insight item was used to validate the IS scale.

7.3.5 Assessment of beliefs about medicines

The Beliefs about Medicines Questionnaire (BMQ) (Horne *et al*, 1999) was used to assess patients' beliefs about their medication (see appendix figure 4.).This questionnaire has been validated in patients with chronic illnesses (Horne *et al*, 1999). The BMQ comprises a specific and a general scale and each has two subscales. The BMQ-Specific scale assesses the patients' beliefs about the medication he is prescribed for a specific illness in terms of the necessity of taking them and concern about taking them. The scale includes 11 items in two subscales, the *concern* subscale and the *necessity* subscale. Examples from the 6 item *concern* scale include: "I sometimes worry about the long term effect of my medicines" and "I sometimes worry about becoming too dependent on my medicines". Examples from the 5 item *necessity* scale include "My health at present depends on my medicines" and "My medicines protect me from becoming worse". The degree of agreement with each statement is indicated on a five point Likert scale, ranging from 1= strongly disagree to 5 = strongly agree. Thus the total scores for the *concern* and *necessity* scales range from 6-30 and 5-25. The *necessity* and *concern* scale assess positive and negative attitudes toward medication. An indication of the relative

importance of these attitudes for individual patients was obtained by calculating the necessity-concerns differential, calculated as the difference between necessity and concern scores (Horne *et al*, 1999). The BMQ-General scale assesses more general beliefs or social representations of pharmaceuticals as a class of treatment: beliefs that medicines in general are overused by doctors and beliefs that medicines in general are harmful, addictive, poisons that should not be taken continuously. The scale includes 8 items in two subscales, the *overuse* subscale and the *harm* subscale. Examples from the 4 item *overuse* scale include: "Doctors use too many medicines" and "Natural remedies are safer than medicines". Examples from the 4 item *harm* scale include: "Most medicines are addictive" and "Medicines do more harm than good". The total scores for the *overuse* and *harm* scales range from 4-16.

The scale was translated into Norwegian and back into English. The authors of the scale had no objections to the translation. One of the co-authors of paper II, Kjell Ingar Pettersen was responsible for the adaptation process.

7.3.6 Neurocognitive assessments

A comprehensive neuropsychological test battery was administered to all participants by psychologists trained by a specialist in clinical neuropsychology. Tests from domains found to be sensitive to dysfunction in groups with bipolar disorder or schizophrenia were included. These were tests of psychomotor speed, attention, working memory, executive functioning, verbal learning and tests of intellectual capacity. In paper IV test results are from five neurocognitive domains are used in analysis.

General cognitive functioning

Premorbid IQ was assessed with the Norwegian research version of the National Adult Reading Test (NART) (Sundet & Vaskinn, 2008). The numbers of errors on the NART were calculated into the NART premorbid IQ (Sundet & Vaskinn, 2008). Current IQ was measured with Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007a). All participants showed adequate neuropsychological test effort by scoring less than two errors on the forced recognition trial of the California Verbal Learning Test (CVLT-II) (Delis *et al*, 2004). NART was only administered to patients who had gone through their primary schooling in Norway, and as such were fluent in the Norwegian language. All analyses of neurocognitive variables were limited to these patients. They counted 104 in the schizophrenia group and 90 in the

bipolar disorder group. The distribution in the adherence groups was the same after excluding patients for the neurocognitive analyses. This was also true for the mean age and gender.

Domains

Psychomotor speed. The Digit Symbol test from Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 2003) was included as a measure of psychomotor speed.

Attention and Working Memory. Digit Span-forwards from WAIS-III (Wechsler, 2003) was used as a measure of focused attention. The test requires the person to repeat an increasing number of digits in the same order as the test administrator. Score reported here is the maximum number of digits repeated. The Bergen n-back test (Haatveit *et al*, 2010) is a computer-based test requiring that a button is pressed every time the two numbers displayed on the screen are the same as the numbers displayed two screen pictures back ('2-back'). Number of correct responses minus the number of false positives (commissions) was used as a measure of working memory.

Executive functioning. Executive functioning was assessed with the Verbal Fluency test from the Delis-Kaplan Executive Function System (D-KEFS) (Delis *et al*, 2005). Phonetic fluency was assessed with the Letter Fluency subtest, where the score is the number of words beginning with the letters 'F', 'A', and 'S' generated separately within 60 seconds. Semantic fluency was measured with the Category Fluency subtest. The person is given 2 x 60 seconds to name first as many animals, then as many boys' names as possible. Finally, semantic set shifting was measured with the Category Switching subtest where the participant is instructed to switch between naming fruits and furniture. Number of correct switches within 60 seconds is the score reported.

Verbal learning and Memory. The Logical Memory test from Wechsler Memory Scale (WMS-III) (Wechsler, 2007b), was used to assess verbal learning. Two short stories were read aloud to the participant who was instructed to repeat them immediately. Score reported is the total number of story units recalled. From the CVLT-II (Delis *et al*, 2004) the total number of words repeated immediately after five reading trials of a list of 16 words was used as a measure verbal learning.

Higher scores on the neuropsychological tests signify better performance on all tests.

7.4. Statistical analyses

Statistical analyses were carried out using the software Statistical Package for the Social Sciences (SPSS) version 13.0 and 14.0 for Windows.

In paper I reliability analyses of the Birchwood Insight Scale (IS) were performed by calculating the internal consistency (method of Chronbach´s alpha) for the 3 subscales and the total score in patients with schizophrenia, bipolar I and bipolar II disorder. Bivariate correlations between subscales and between subscales and the PANSS G1 insight item were calculated using Pearson correlation tests. The same method was applied in paper II when analysing the internal consistency for the BMQ-subscales and their intercorrelations. Cronbach's alpha ≥ 0.70 was considered satisfactory, as this has been regarded the necessary level for reliable individual comparisons (Perrin *et al*, 1995). For comparison of continuous data (symptom scores, insight scores, scores on BMQ, scores on nevropsychological tests and of side effects) between groups, we used a one way analysis of variance (ANOVA) and post hoc Bonferroni tests were applied to control for multiple testing when considered appropriate. The sensitivity and specificity of the specific and general BMQ scales was tested by performing an ROC analysis.

In paper III mean rates of all adherence measures were calculated. Group differences in categorical variables were explored with Chi-square. Correlations were calculated when comparing the different adherence measures. This method was chosen to add statistical power to the analysis. Due to skewed distribution correlations were calculated as Spearman's rho. Analyses were conducted first for the whole group and then separately for the two diagnostic groups (schizophrenia vs. bipolar disorder).

In paper IV, some variables were dichotomous (using or not using alcohol and/or illegal substances), and when looking at the relationship of these variables to the different adherence groups, Chi square was calculated, for two of the adherence groups at a time. For continuous data ANOVA was used as before.

7.5. Ethical aspects and patients perspective

Ethics had a special relevance in this project as it implied research involving sensitive personal information and use of biological materials from patients with severe psychiatric disorders. The potential ethical aspects of the research were paid attention to regarding its objectives, the methodology and the possible implications of the results. The central issue was that of informed consent and confidentiality – that participants knew how their information and blood samples would be used, and that measures to ensure confidentiality were secure. All data collection was performed with the approval of the Regional Ethics Committee (ref # 493-03-01179), and written informed consent was obtained prior to study participation. The following procedures were followed: Each participant had the study explained by a health professional 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 their own data, and their right to have all data deleted at any occasion. Written informed consent was obtained prior to study participation. It they were not able to give informed consent, they were contacted later after the acute affective or psychotic episode. 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. 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.

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 Oslo University Hospital, Ulleval. 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 are 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. The biobank was approved by the Norwegian Health Directorate (Sosial- og helsedirektoratet, # 05/5851).

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. Participants did not receive compensation for their participation, but in some cases transportation to and from the research centre was provided. After blood sampling participants were provided with a light meal as fasting was a necessary part of the blood sampling. T

Throughout the study, we, as clinical investigators, were impressed by the interest, co-operability and tenacity of the participants, without which this research would not have been possible.

8. Results

Paper I

The IS scale works well for patients with schizophrenia and bipolar I disorder when the total score is used, with Cronbach´s alpha of 0.80 and 0.70 respectively. However it works poorly for patients with bipolar II disorder. The subscales showed poor to marginal internal consistency, except for "need for treatment" indicating that the usage of the instrument should be restricted to the total score. For validation purposes the relationship between the IS total score and the PANSS G12 insight item was investigated. A moderate to high correlation was found for patients with schizophrenia ($r= -0.54$, $p<0.01$) as well as for patients with bipolar I disorder ($r= -0.49$, $p<0.01$). For patients with bipolar II disorder however, a low to moderate correlation was found ($r= -0.27$), indicating a poor validity of the scale for this diagnostic group. The cut off score on the IS total score was set to 9 by the authors. In this study the mean IS total scores were similar in the groups with schizophrenia and bipolar I disorder, 8.2 and 8.5 respectively, reflecting a general attenuated insight in the groups. In the schizophrenia group 62% of patients scored below 9 and 56% in the bipolar I disorder group.

In conclusion, the IS showed good psychometric properties in schizophrenia, moderate properties in bipolar I disorder, and the scale did not work for patients with bipolar II disorder. This suggests a cautious use of the scale across different diagnostic groups.

Paper II

The BMQ works for patients with severe mental disorders. Cronbach's alpha was satisfactory for all subscales, being 0.76 for the BMQ-Specific Concern scale, 0.90 for the BMQ-Specific Necessity scale, 0.73 for the BMQ-General Overuse scale and 0.69 for the BMQ-General Harm scale. The Concern and Necessity scales seem to measure fairly independent dimensions, whereas the Overuse and Harm scales are strongly intercorrelated.

The Full adherence group scored significantly higher on the Necessity and lower on Concern, Harm and Overuse subscales than the No adherence group. The patients with partial adherence had scores in between on all subscales except for general harm, where they had a

slightly higher score than the two other groups. The necessity subscale score was much lower in the No adherence group than in the other two groups. The mean necessity-concern differential for the three groups was: 0.4 for the Full adherence group, -1.5 for the Partial adherent group and - 6.0 for the No adherence group, the difference between the No adherence groups and the two others was significant (p=0.002). ROC analysis for the BMQ necessity subscale showed area under the curve of 0.735. An optimal discrimination was found with a cut off score of 17.5, giving a sensitivity of 0.76 and a specificity of 0.56 respectively.

The mean self reported adherence was 88 % in the schizophrenia-group and 86 % the bipolar group. The schizophrenia-group scored higher on concern and lower on necessity, and there was a significant difference in the necessity-concern differential, –1.9 in the schizophrenia group and 1.0 in the bipolar group (p=0.002), suggesting that, for the former group, medication concerns were more likely to outweigh beliefs about necessity. Comparison of BMQ-General scores between the schizophrenia and bipolar groups showed that patients with schizophrenia had more negative attitudes to medicines as a whole. They were significantly more likely to perceive medicines as addictive, harmful poisons (higher scores on the General Harm scale) and more likely to believe that medicines are overused by doctors (higher scores on the General-Overuse scale), although the latter did not reach significance. When comparing the BMQ scores of our sample of patients with SMI to that of patients with chronic medical illnesses, the patients with schizophrenia had significantly lower scores on BMQ-Specific Necessity than the patients with chronic medical illnesses.

In conclusion, the BMQ had satisfactory psychometric properties for use in patients with severe mental disorders. Nonadherent patients felt medication to be less necessary and were more concerned about it than adherent patients.

Paper III

Adherence rate defined by serum concentrations within reference level was 61.6 % in the total sample, 58.4% for schizophrenia and 66.3% for bipolar disorder, the difference between the diagnostic groups was not significant. The patients' self report scores overestimated adherence, but correlated significantly to health personnel scores (r=0.50), to MARS-5 (r=0.39) and to serum concentration of medication (r=0.52). The sensitivity for the self-report scale for determining adherence using concentration/dose ratio as the objective measure was

98% and the specificity was 33%. The positive predictive value was 70 % and the negative predictive value was 91 %.

The MARS-5 mean score in the total sample was 22.0 (SD 2.9, range 13-25). The mean adherence last week according to the Provider-report was 85.2%.

In conclusion, outpatients with severe mental disorders showed relatively good adherence to prescribed medication, and self report questionnaires seem to be a valid method for measuring adherence.

Paper IV

In the schizophrenia group, 11 (12.9 %) had a lifetime diagnosis of addiction or abuse in the Full adherence group, 25 (48.1 %) in the Partial adherence group and 2 (11.8 %) in the No adherence group. The difference between the Full adherence group and the Partial adherence group was statistically significant ($p < 0.001$). In the bipolar group, 11 (18.6 %) had a lifetime diagnosis of addiction or abuse in the Full adherence group, 4 (14.8 %) in the Partial adherence group and 7 (46.7 %) in the No adherence group. The difference between the bipolar Full adherence group and the No adherence group was statistically significant ($p = 0.024$). In the schizophrenia group the Partial adherence group used significantly more illegal substances in the past 2 weeks and 6 months and alcohol in the last six months. In the bipolar group it was the Nonadherence group that used significantly more illicit drugs and alcohol in the last two weeks and six months.

The mean (SD) insight score measured on the IS in the schizophrenia group was 8.16 (2.20) in the Full adherence group, 7.70 (2.15) in the Partial adherence group and 6.38 (2.15) in the No adherent group. The difference between the full adherence group and the nonadherent group was statistically significant ($p<0.05$). In the bipolar group the scores were: 8.28 (1.67) in the Full adherence group, 8.24 (1.62) in the Partial adherence group and 7.69 (1.68) in the Nonadherence group. The bipolar group as a whole scored higher than the schizophrenia group, but the difference was not significant.

Schizophrenia patients with no adherence did better on tests of executive functioning, verbal learning and memory and had higher IQ than patients with better adherence.

There was a significant association between poor adherence and some autonomic side effects; diarrhea, nausea and orthostatism in schizophrenia patients and with orthostatism and urine retention in bipolar disorder patients. Otherwise there was no significant relationship between side effects and adherence.

Schizophrenia patients in the Full adherence group had statistically significant higher BMI (27.1) than those in the Partial adherence group (24.8). In the bipolar disorder patients there were no statistically significant differences of mean BMI between the groups.

In conclusion, substance use is an important risk factor for nonadherence in our patients with schizophrenia and bipolar disorder. Poor insight is also a risk factor, especially in schizophrenia. Further, the results suggest that cognitive dysfunction is not a risk factor for nonadherence in these diagnostic groups. This supports interventions that focus on reducing substance abuse and improving insight in order to increase adherence.

9. Discussion

9.1. Discussion of main results

9.1.1. Psychometric properties of the Birchwood insight scale across diagnoses

An aim of the current thesis was to study insight in patients with schizophrenia and bipolar disorder and its relationship to adherence. To be able to do this an insight measure was necessary. The TOP study is a large study, examining many aspects of severe illnesses. There are many assessments and the inclusion process is time consuming. It was therefore important to use instruments that were simple, easy to complete and not time consuming. In addition it was important to limit the subjective assessment of raters to reduce bias of data. There exist several instruments for insight measurement. The Insight and Treatment Attitude Questionnaire (McEvoy *et al*, 1989), the Scale to Assess Unawareness of Mental Disorder (SUMD) (Amador *et al*, 1993), the Schedule of Assessment of Insight (SAI and SAI-E) (Kemp & David, 1997) are structured or semi-structured researcher-rated interviews. The extensive rater-based scale SUMD is widely used and is translated to Norwegian. The use of SUMD was evaluated, but the scale was found to be time consuming and thus unpractical for use in the TOP Study.

The use of self-report in psychosis research has become more frequent. Self-reports may provide a better control for confounding variables conceivably inherent in the patient-examiner interaction (Young *et al*, 2003). Young *et al* compared the interview based and the self-report method in the assessment of insight and postulated that the attendance of a rater may add many complexities to the process of self-reflection due to exacerbated cognitive problem (Young *et al*, 2003). In two studies comparing researcher rated (SUMD) and self-report measures of insight, significant correlations were found in insight scores only when self report measures were administered first (Young *et al*, 2003; Jovanovski *et al*, 2007). The authors offered the explanation that the presence of an active examiner exacerbates cognitive problems and social skill deficits and that data are more reliable when the individual makes the initial decision regarding his beliefs, without the effect of social influence.

In this thesis, the Birchwood Insight Scale (IS) was used to assess insight. The results indicate that this scale works well for patients with schizophrenia and patients with bipolar I

disorder. However, the scale seems to work poorly for patients with bipolar II disorder. This suggests that data obtained with the IS in bipolar II disorder are difficult to interpret.

Another finding of the current study, is that the subscales of the IS seem to have poor to marginal reliability. In the original article of Birchwood *et al* reliability and validity was explored in a mixed psychiatric sample of 133 patients (Birchwood *et al*, 1994). The authors found that the 8 items of the scale could be accounted for by a common factor, therein obtaining acceptable construct validity. Cronbach´s alpha was high to very high for the total scale, indicating a good internal consistency for the total scale. However, Birchwood *et al* reported subscale inter-item correlation that indicated a fairly low Cronbach´s alpha. This taken together with the results of this thesis and the high internal consistency for the total score, leads to the conclusion that the scale measures one dimension, and subsequently, the usage of the IS should be restricted to the total score.

The literature on insight and its measurement has focused on schizophrenia, with few studies on bipolar disorders. In studies that have compared insight in schizophrenia and bipolar disorder, researchers have used instruments developed and validated in schizophrenia (Yen *et al*, 2002; Braw *et al*, 2011) and studies assessing insight in bipolar disorder patients have done the same (Ghaemi *et al*, 1995; Dell'Osso *et al*, 2002). The current data suggest that if instruments assessing insight in bipolar patients are not validated for that group, the results may be questionable. The IS doesn't include items that measure insight into mood symptoms. Recently, the IS has been developed into a scale more specifically designed for patients with mood disorders (Sturman & Sproule, 2003). The authors argue that insight scales already in use are validated in schizophrenia, schizoaffective or mixed psychiatric samples. These often do not reflect the symptomatology and course of illness for patients with mood disorders who have not experienced psychotic symptoms.

There was no difference between the bipolar I disorder and schizophrenia group in the total insight score. Yen *et al* studied insight in patients with schizophrenia and bipolar disorder, who were in remission (Yen *et al*, 2002), using the SAI-E to assess insight. Bipolar disorder patients with history of psychosis did not differ from those with schizophrenia. However bipolar disorder patients without past history of psychosis had significantly better insight than the other two groups (Yen *et al*, 2002). Others have found the same (Peralta & Cuesta, 1998). A new study comparing insight among schizophrenia and bipolar disorder patients in remission, found that there was a difference, but this became nonsignificant when

adjusting for age (Braw *et al*, 2011). We cannot exclude the possibility that the poorer performance on the IS especially for the bipolar II disorder patients is due to lack of psychotic experiences. In our sample of bipolar II disorder patients, 8 individuals had experienced psychosis. Eliminating these patients from the analysis did not change the results, which suggests that the performance of the bipolar II disorder group was not related to previous psychotic episodes. The group of bipolar II disorder patients in our sample is relatively small which makes our findings in this group somewhat uncertain. There has not been much interest in the study of insight in bipolar disorder patients and we have not found studies that differentiate between bipolar I and II disorders when assessing insight. Our results indicate that this could be called for. This thesis mainly addresses issues involved in adherence to medication. Insight was studied as a factor related of adherence. We did not look at the relationships of insight and symptomology or if this had an effect on our results regarding insight. Severity of psychopathology has been shown to be significantly related to insight in some studies but not others (McEvoy *et al*, 1989; David *et al*, 1992; Amador *et al*, 1993; Birchwood *et al*, 1994; Michalakeas *et al*, 1994; Ghaemi *et al*, 1995; Mathew *et al*, 2010; Cassidy, 2010).

To our knowledge this is the first study to compare insight in schizophrenia and bipolar disorder, using an insight measure validated in both groups.

9.1.2. Psychometric properties of the Beliefs about Medicines Questionnaire adherence

One of the study aims of this thesis was to assess the beliefs and attitudes of patients towards their medication. Here a measure was needed. The Beliefs about Medicines Questionnaire (BMQ) is a simple self-report scale that had already been translated and adapted into Norwegian. The scale has been used in patients with chronic somatic disorders, but has not been used in patients with severe mental illnesses until now. In previous studies of attitudes to medication in schizophrenia the DAI was most commonly used (Hofer *et al*, 2002; Day *et al*, 2005; Adewuya *et al*, 2006) and a newer scale was introduced a few years back, the Attitudes Towards Neuroleptic Treatment (Kampman *et al*, 2000). Both are developed especially for patients with schizophrenia and the DAI is in some studies used not only as a measure of attitudes to medication, but also as an adherence measure (Thompson *et al*, 2000). One of the goals of Horne *et al* when developing the BMQ was to construct a scale that could be used broadly across illnesses and cultures (Horne *et al*, 1999). In addition the scale is a self-report, it

is simple to administer and not time consuming. As the BMQ had not been validated in a population with severe mental disorders, this was necessary in the current study. The result was that the scale works for this patient group. The psychometric properties proved satisfactory, especially for the specific subscales Concern and Necessity. These two subscales seem to measure independent dimensions, and consequently the necessity-concerns differential seems to give reliable scores. In contrast to the specific subscales, the two general subscales Harm and Overuse, were strongly intercorrelated. They were also fairly strongly correlated with both the two specific subscales. We cannot exclude the possibility that the high intercorrelations reflect characteristics of our sample, as they were higher in our sample than in Horne's original sample (Horne *et al*, 1999). The BMQ is a simple tool and the necessity-concerns framework it assesses might be of use in clinical practise, to identify patients who have negative perceptions of their treatment. This would provide the clinician with valuable information that could trigger a more detailed discussion in the clinical setting or other interventions aimed at improving adherence.

To our knowledge this is the first study to validate the BMQ-scale in a sample of patients with severe mental disorders.

9.1.3. Medication adherence in outpatients with severe mental disorder

The overall aim of the thesis was to investigate adherence rates in a representative outpatient sample with severe mental disorders. Multiple measures of adherence were used to arrive at a consensus measure. The adherence rate was 61.6% in a sample of 255 outpatients with severe mental disorders, with 58.4% in schizophrenia and 66.3% in bipolar disorder (paper III). As pointed out in the introduction of this thesis, the methodology of adherence measures has been questioned. We have in this study used multiple measures of adherence as recommended and find that this strengthens the validity of the measure. Thus, the present results seem to indicate a reasonably high adherence level in the present outpatient sample. However, this is a cross-sectional study and as such it is difficult to predict the long-term adherence behaviour. In addition, the blood levels only represent adherence levels in the last few days before blood draw, and it can be discussed how representative they are for more extended periods (Velligan *et al*, 2006). However, blood level measurements are considered better than most other methods, but are difficult to do as routine clinical assessment in most countries.

In addition to the assessment methods, the adherence level depends on the characteristics of the patient sample. In the present study we investigated patients who attend outpatient clinics on a regular basis. Other studies of adherence in schizophrenia outpatients have also found relatively high adherence (Garavan *et al*, 1998; Weiss *et al*, 2002; Rettenbacher *et al*, 2004; *et al*, 2006) using self-report or provider report. In the past years some studies have focused on first-episode schizophrenia patients in naturalistic, follow-up studies. Such studies are interesting because of the characteristics of the samples and the observation that in the early stages of the disorder, patients seem to be more responsive to treatment, irrespective of the antipsychotic medication used (Frangou & Byrne, 2000; Kahn *et al*, 2008). When reviewing these studies of first-episode patients (Verdoux *et al*, 2000; Coldham *et al*, 2002; Robinson *et al*, 2002; Mojtabai *et al*, 2002; Mutsatsa *et al*, 2003; Perkins *et al*, 2006), they show that by 6 months of treatment, as many as 33% to 44% of patients are nonadherent, and by 1 year, as many as 59% (Perkins *et al*, 2008). It is also interesting to look at two recent effect studies in first episode patients. McEvoy *et al* did a RCT of a total of 400 early psychosis patients randomly assigned to olanzapine, quetiapine or risperidone and at week 52, all-cause discontinuation rates were 68%, 71% and 71% for all three antipsychotics (McEvoy *et al*, 2007). Overall 41.5% of the 400 patients, discontinued against medical advice. In an open RCT conducted by the EUFEST study group, the aim was to compare haloperidol to SGA in first-episode patients (Kahn *et al*, 2008). In all 498 patients from 14 European countries were randomly assigned to treatment with haloperidol, amisulpride, olanzapine, quetiapine or ziprasidone and were followed for one year. At week 52, all-cause discontinuation rate was 72% for haloperidol, 40% for amisulpride, 33% for olanzapine, 53% for quetiapine and 45% for ziprasidone. Only 13% of the 498 patients discontinued because of nonadherence, but other reasons where insufficient efficacy and side effects. There are no obvious reasons for these differences in the discontinuation rate in these two studies and the study groups are similar. But there is one other marked difference in outcome, namely that in the EUFEST study the mean improvement on the PANSS scale was considerably better than in the McEvoy study. A recent survey asking 41 leading experts about the extent of the problem in schizophrenia and bipolar disorder, showed them to believe that these patients in their practises took 51-70% their prescribed medication (Velligan *et al*, 2009).

The health care services are different internationally and this should be taken into account when comparing studies of adherence. This study is naturalistic, but in our opinion

fairly representative of SMI patients in an outpatient clinic in the Norwegian health care system. In Norway the government owns and runs all psychiatric hospitals and outpatient departments. The service is based on catchment areas, and is practically free, and the treatment is integrated with community based public health care. An important additional factor is the high level of therapeutic medication monitoring in clinical practice in Norway. Serum measurement of medication is a routine clinical practice in most hospitals, also outside University clinics, and for the patients with schizophrenia and bipolar disorder this can be expected when attending outpatient clinics. Thus, one might argue that in a well-organized health care system, with close collaboration with community services, where the follow-up of the patients is careful and extensive including regular blood level measurements, a favourable basis for good adherence in this patient group is obtained. Thus, it seems reasonable that the current high adherence rates are correct, and it could be speculated that this is due to extensive blood serum measurements. However, more studies are needed to answer this question.

Even though the current findings indicate higher adherence rates than most previous studies, an adherence rate of around 60% should be considered far from acceptable in clinical practise. There is need of continuous adherence assessments in clinical practise and simple measures such as self-report can be a useful tool in such an assessment. However, direct measures such as blood-level measurement of medication should be available for patients who seem resistant to treatment or have a history of nonadherence. When partial or nonadherence is identified, it is important for clinicians to initiate strategies to improve adherence. Factors contributing to patient´s adherence problems need to be identified, and the interventions should target these factors specially.

To our knowledge no previous study has reported adherence levels in a Norwegian sample of out-patients with SMI.

9.1.4. Predictors of medication adherence in patients with schizophrenia and bipolar disorder

We have so far established that there is a relatively high adherence in the current sample, which is probably reflecting the situation in clinical practice. In addition we have used multiple measures in establishing adherence levels and validated instruments used to measure insight and beliefs about medication in both diagnostic groups. Having done this, we

addressed another of the main aims of the current thesis, namely to identify predictors for nonadherence in the study population. An association between poor adherence and reduced insight, and the use of illegal substances and alcohol in patients with schizophrenia was found. This was similar to the findings in bipolar disorder patients where poor adherence was associated with the use of illegal substances and alcohol, while the association to reduced insight was on a trend level. Some autonomic side effects were associated with poor adherence in both groups, but current symptom levels were not. Better neurocognitive functioning was related to decreased adherence in schizophrenia.

Insight

Poor insight has been considered one of the main predictors of nonadherence in schizophrenia (Buckley *et al*, 2007; Lacro *et al*, 2002; Perkins, 2002). Our results (paper IV) support this. Few studies have directly investigated the relationship between insight and adherence in bipolar disorder. Our data suggest that nonadherence in patients with bipolar disorder could be associated with poor insight. The nonadherent bipolar disorder patients had lower insight than both the fully adherent and the partially adherent patients, but the difference did not reach significance. Further research is needed to clarify this. Two previous studies have found a relationship between insight and adherence to medication in bipolar patients (Yen *et al*, 2005; Copeland *et al*, 2008). As discussed earlier we used the IS to measure insight after validating the scale. A drawback of the validation was that the scale did not work well in patients with bipolar II disorder. Despite this, these patients were included in the analysis of adherence and insight. This might affect our results on insight. Another factor it that the bipolar disorder patients were mostly euthymic at inclusion in the study. Insight in bipolar disorder fluctuates and has been shown to be worse in mania and in psychotic depression (Peralta & Cuesta, 1998). Follow-up studies of bipolar disorder patients are needed in order to evaluate this further.

Beliefs about medication

In paper II the relationship of the beliefs about medicines, measured with the BMQ, to patients' adherence to medication was investigated. We found that beliefs about necessity and the concerns about taking medication were related to adherence in patients with SMI. This is a parallel to the finding that patients' beliefs about medication are a strong predictor of adherence in patients with different kinds of chronic illnesses (Horne & Weinman, 1999). Two recent studies on patients' adherence to maintenance antidepressants used the BMQ

specific scale and found that adherence was lowest when concern about taking medication exceeded the perceived need to take them and highest when perceived need exceeded the concerns (Aikens *et al*, 2005; Brown *et al*, 2005). The same was found in a study of 223 bipolar disorder patients (Clatworthy *et al*, 2009). A study comparing factors affecting adherence to antipsychotics in schizophrenia patients on either depot or oral medication did not find that side effects predicted nonadherence in either group, but rather beliefs and attitudes towards the medication (Patel *et al*, 2008) A new study following 112 patients in early-episode schizophrenia found that attitudes towards medication predicted medication adherence (Baloush-Kleinman *et al*, 2011). In our sample the schizophrenia group had the greatest variation in scores, but the necessity-concern difference was much lower in the schizophrenia group than in bipolar disorder group and the groups from Horne *et al´s* original sample. The scores on BMQ-Specific Necessity were lower in our sample of patients with SMI and in the psychiatric group in the original sample, than in the sample of patients with somatic illnesses. This might reflect that the psychiatric patients have lower insight into their illness than the patients with somatic disorders.

Even though our study is not a longitudinal one, the results support the Health Belief Model and the role of attitudes towards medication as a predictor of adherence.

Substance abuse and alcohol

We found a relationship between poorer adherence and the use of illegal substances and alcohol, in both patient groups (paper IV). Interestingly there is a difference in these results. In the schizophrenia group it is the Partial adherence group that uses significantly more illicit substances and alcohol than the Full adherence group, and more often has a lifetime diagnoses of addiction or abuse. In the bipolar disorder group, the nonadherent patients abuse illicit substances more often than those who were fully adherent. In a recent study of first episode psychotic patients, substance abuse was one of the three strongest predictors of poor medication adherence (Perkins *et al*, 2008). A recent study found a significant increase in nonadherence and treatment dropout associated with cannabis use among patients with first-episode schizophrenia followed over 12 months (Miller *et al*, 2009). The same was found with bipolar disorder patients in a large study of the effect of cannabis on outcome (van Rossum *et al*, 2009). Manwani *et al* found that lifetime adherence with mood stabilizers was lower in patients with co-morbid substance use disorder (van Rossum *et al*, 2009). Our results

are in line with earlier findings that the use of illicit substances and alcohol is a risk factor for nonadherence of medication, both in schizophrenia and bipolar disorder. This is of large clinical importance, as many clinicians experience that the use of illegal substances is a growing problem with young patients suffering from schizophrenia and bipolar disorder.

Adverse effects

Conflicting evidence exists regarding the role of adverse effects of medication in nonadherence (Young *et al*, 1986; Fenton *et al*, 1997; Lacro *et al*, 2002). Our results indicate that except for some autonomic side effects, side effects in general cannot be considered a main risk factor for nonadherence in our sample. Two recent studies of first-episode patients found that neurological side effects increased the likelihood of discontinuation of antipsychotics (Robinson *et al*, 2002; Opjordsmoen *et al*, 2009). Two other recent studies of first-episode patients did not find an association between perceived side effects and treatment nonadherence (Mutsatsa *et al*, 2003; Perkins *et al*, 2008). With increased use of SGA, metabolic side effects have gained more attention, but few have as yet investigated specifically the relationship of metabolic side effects and nonadherence. Weiden *et al* reported that in a group of 239 schizophrenia patients, obese individuals were more than twice as likely as those with normal BMI to report missing their medication (Weiden *et al*, 2004). In the current study, the Full adherence schizophrenia group had the highest mean BMI and the partial adherence group the lowest. This could be due to the naturalistic design, since those that stay on the medication are more likely to gain weight and keep it, than those that take medication irregularly or stop completely. We do not have data on former weight gain. In the bipolar disorder group BMI was not significantly different between the adherence groups. This could be due to differences in the type of medication between these two groups, with more lithium and antiepileptics used in bipolar disorder. However, these medications also cause weight gain.

Overall, results are still somewhat conflicting. The differences in the literature may be related to differently selected patient groups, assessment methods and study design. An alternative explanation for the different results regarding side effects could be related to attitudes. Nonadherence is more related to the fear of side effects (the concerns), than the actual side effects themselves. Adverse effects are one of the factors of the Health Belief

Model, but perhaps they affect adherence to medication indirectly through attitudes and beliefs.

Neurocognitive factors

Few studies using extensive neurocognitive testing have looked at the relationship of neurocognition and adherence. In the current study patients were tested with a comprehensive cognitive test battery. An interesting finding of our study (paper IV) was that schizophrenia patients with no adherence did significantly better on tests of verbal learning and memory and executive function and had significantly higher IQ than adherent patients. Neurocognition is an important predictor of functional outcome in schizophrenia (Green, 1996; Green *et al*, 2004) and the same relationship seems to exist for bipolar disorder (Green, 2006; Martinez-Aran *et al*, 2007; Burdick *et al*, 2010). Early onset of schizophrenia and poor premorbid functioning are 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 (Cahill *et al*, 2006; Daban *et al*, 2006), but is thought to be partly responsible for the poor functional outcome in bipolar disorder (Martinez-Aran *et al*, 2009; Burdick *et al*, 2010). In studies that have looked at the relationship between neurocognition and adherence in schizophrenia, results are mixed (Lepage *et al*, 2010), but mostly indicate no relationship (Adams & Howe, 1993; Buchanan, 1992; Kemp & David, 1996; Smith *et al*, 1999; Lepage *et al*, 2010). However, a recent study found that higher baseline neurocognitive performance was associated with lower medication adherence (Perkins *et al*, 2008), which is in line with our findings. Others have found an association between poor adherence and some form of poorer outcome on neurocognitive tests (Cuffel *et al*, 1996; Donohoe *et al*, 2001; Robinson *et al*, 2002). Robinson *et al* found that during the first year of treatment patients with poorer premorbid cognitive functioning were more likely to stop antipsychotics and that executive functioning was significantly associated with nonadherence after first relapse (Robinson *et al*, 2002). The same team had earlier presented data showing that patients who repeatedly went off antipsychotics tended to have better premorbid adjustment and better neurocognitive performance and suggested that better functioning patients were more likely to deny treatment (Robinson *et al*, 1999). A recent Japanese study suggests that executive functioning, education and general IQ may be important factors in individual motivation for medication adherence. We found only one study, of Jeste *et al*, that reported neurocognitive functions to be the strongest patient related predictor of the ability to manage medication (Jeste *et al*,

2003). This study used different measures of adherence and neurocognition than the other studies discussed here. Although nonadherent schizophrenia patients seem to perform better on neurocognitive tests, their insight is worse than that of either fully or partially adherent. The underlying mechanisms of this somewhat surprising relationship in schizophrenia need to be further explored. One could speculate that schizophrenia patients with higher neurocognitive functions have higher beliefs in their abilities to cope without using medication, especially when in remission. One study explored the relationship between adherence and neurocognition in bipolar disorder (Martinez-Aran *et al*, 2009) using both extensive neurocognitive tests and multiple adherence measures. In this study both the adherent and poorly adherent group showed impairments in attention, psychomotor speed and verbal fluency compared to healthy controls. In addition the poor adherence group showed worse performance on frontal executive tasks, some of which became nonsignificant when controlling for covariates. In the current study there was no difference in neurocognitive performance with regards to the adherent groups in the bipolar disorder patients. The bipolar disorder group in our study had significantly higher IQ than the schizophrenia group and this could affect the results. The current findings have contributed to the much needed data on the relationship of neurocognition and adherence and found that cognitive dysfunction does not seem to be a risk factor for nonadherence in these diagnostic groups.

We have found, in line with other investigators that the use of illicit substances and alcohol is an important risk factor for nonadherence in both schizophrenia and bipolar disorder. In addition, lack of insight is a risk factor, especially in schizophrenia. Beliefs about medications, reflected in the concerns about taking them and the feeling of the necessity of taking them are an important predictor of adherence in both these SMI, just like has been established in somatic disorders. The direct role of side effects is more unclear in both disorders, even though we did find a relationship between autonomous side effects and nonadherence.

Diagnostic differences

An aim of our study was to compare risk factors for nonadherence in schizophrenia and bipolar disorder and if those were the same. The relationship to potential risk factors was stronger in the

schizophrenia group. Moreover, the patients in the bipolar disorder group were older, more often female, they had longer education, more often held jobs and were more often in a relationship. They also had higher IQ. This could affect the results, but is probably also reflecting the differences commonly found between these diagnostic groups. And as our sample is naturalistic, the results are fairly representative of patients being treated at Norwegian out-patient clinics.

9.2. Methodology

9.2.1. Sample representativity

Psychiatric services in Norway are catchment area based and publicly funded. Outpatient clinics are equally distributed and offer a similar quality of care across all districts of the city, regardless of socio-economic and socio-cultural differences. Thus, the expectation was that the sample would be representative for people with severe mental disorders who live in social democratic urban societies, where treatment and care is available for anyone suffering from severe mental disorder. The inclusion area for the TOP Study covered practically the whole city of Oslo. The study sample represents an unselected cohort, which was examined within a time interval of approximately three and a half years, assuring concordance in time for variables susceptible of rapid changes within any given society.

In Norway, unlike other Scandinavian countries, there was no national Hospital Discharge Register with available diagnoses. Thus, it was no impossible to trace patients with relevant diagnoses who had not been included, Due to the person data security act, information on invitees declining to participate was inaccessible. It was thus not possible to estimate the participation rate. However, some degree of selection bias can be assumed. Very impaired patients, lacking capacity of informed consent, would not be approached. It also seems likely that individuals suffering from severe cognitive deficits, massive negative symptoms, or paranoid ideation, would tend to decline participation, even when invited, or may not be capable of completing the inclusion procedures. It is also clear from paper IV, that the TOP sample turned out to be relatively high-functioning with mean IQ-score within the normal range. The mean age of the schizophrenia sample is somewhat lower than that of the bipolar disorder sample. In Norway there are specialized clinics for patients with first-episode

psychosis where these patients are followed for 5 years. One such clinic recruited patients to the TOP and the younger age of the schizophrenia patients might reflect this fact.

A general concern with adherence studies based on informed consent is the implicit selection of patients, as those patients that deny all treatment usually do not consent to participate in studies. One must assume that a proportion of patients that are referred to further treatment at the outpatient clinics from in-patient wards, never follow-up the treatment and are therefore never selected in studies. 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 better insight into need for treatment and more positive attitudes towards the treatment in general and its necessity. More specifically for our study, we cannot rule out that the clinicians who referred patients selected candidates that were more adherent and had less extensive psychopathology. Thus, the TOP sample in the present study is probably skewed towards a better functioning and better adherent group than a randomized sample of patients with severe mental disorders, taken from the general patient population.

9.2.2. Validity and reliability of assessments

General assessments

The instruments used to determine diagnoses and measure symptoms are all widely used in clinical psychiatric research and thoroughly tested (see Methods for details). 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 & Kallert, 2007).

The TOP investigators were all clinically experienced psychologists or psychiatrists. They received ongoing supervision and participated in regular consensus meetings. In addition, all clinical investigators underwent an extensive and structured training program led by a well recognized American researcher within the field of diagnostics (Ventura *et al*, 1998). To assure inter-rater reliability of the test battery employed, testing was performed, yielding very good to excellent results.

Adherence measures

An aim of this thesis was to investigate adherence rate in a population of patients with severe mental disorders. After reviewing the literature it became clear that there does not exist a simple and widely used measure to assess adherence. A range of measures are available and all have limitations. It has therefore been recommended that two or more adherence measures should be combined and that at least one of these should be a direct or objective method (Sajatovic *et al,* 2006). As measurements of serum concentrations of psychotropic medicines are readily available in Norway, this was an obvious choice of a direct measure. The main limitation of using blood levels is that they only represent adherence level in the last few days before blood is drawn and cannot be used to determine adherence over an extended period of time, unless repeated samples are taken. In addition the actual blood sampling is burdensome to the patient and the analysis is expensive. In the current study we used a laboratory with extensive experience in blood level measurements (Castberg *et al*, 2007), and used established values for normal range based on a database of several hundred cases. We also used the dose/concentration ratio which controls for the dose of the medication (Castberg *et al*, 2007), but got comparable results using concentration alone.

Self-report was the other choice of adherence measure. This self report was constructed by the research team with the goal that it should be simple and easy for the participants to use (for the detailed scale see appendix figure 1). The time frame for the self-report was the past week. We found that this was more reliable than asking about the past month or the past 3 months as some studies have done (Garavan *et al*, 1998; Velligan *et al*, 2007). In addition keeping the time frame short makes the combined measure of serum concentration and self-report more reliable. In addition to the two measures mentioned we used the MARS-5 a short self-report that measures more general adherence behaviour where no time frame is specified. We tested the internal validity of the MARS-5 and Cronbach´s alpha was 0.78. The internal validity in our sample was similar to other studies using the same version of MARS-5 (Mårdby *et al*, 2007). We also compared the self-report to provider report of adherence. This was available for 182 of the 255 participants used in the adherence analysis. In study III the correlation between self-report and serum concentration was 0.52. This was highly significant. The sensitivity of the self-report was very good (98%), and so was the negative predictive value (89%). However the specificity was poor (33%), whereas the positive predictive value was moderate (70%). Our validation of the self-report used, suggests that it is a reasonably valid method for measuring adherence (paper III). The

correlation between the self-report and the provider report was reasonably good, but less between the self-report and the MARS-5. The MARS-5 is as mentioned a more general type of scale and as such measures a different construct of adherence. To be able to measure adherence more accurately it seems that multiple measures are required and also multiple constructs of measure. The measure should not only be able to estimate recent adherence, but also adherence or non-adherence in the past. Thus, a more general scale like the MARS-5 could be useful in this.

9.2.3. Strengths and weaknesses of the studies

The studies included in this thesis have several strengths. The work was financially supported by public grants and was independent of sponsorship from the pharmaceutical industry. The design is naturalistic and cross-sectional, with a multi-site approach and broad inclusion criteria. Thus, the sample is fairly representative of patients in an outpatient clinic in the Norwegian health care system. The sample was well characterized and reliability testing was performed for all central items. The study had significant power to obtain statistically significant answers to clinically important questions. Psychometric properties of the clinical instruments not used before in the current patient groups, were tested in both groups. Multiple adherence measures were used with the direct measure of serum concentration of medication used to ascertain adherence.

However, the studies have some weaknesses. The study is cross-sectional and we do not have adherence measures over time. The sample of psychiatric patients consisted of patients who gave informed consent to participate in a comprehensive research project. As pointed out earlier, a general concern with adherence studies based on informed consent is the implicit selection of patients, as those patients that deny all treatment usually do not consent to participate in studies. This is an important limitation, which due to ethical reasons is impossible to reduce. However, the same limitation is present in all the studies in the field requiring informed consent. More specifically for the current thesis, one cannot rule out that the clinicians who referred patients selected candidates that were more adherent. In addition, participating in a study can be considered an intervention and as such may also improve adherence. The study sample consists of out-patients that mostly follow their treatment and come to their appointments at the clinic. As a consequence of this the No adherence group is small and we might miss some important differences.

The patients were aware of the fact that blood samples would be taken and serum level of medication measured. This might influence the patients' adherence to the better. However, the current blood level measurement protocol is similar to routine clinical practice in many clinics in Norway. We have not controlled for factors that could affect medicine blood level measurements, such as interactions with other medication or intra and inter individual differences in the medication metabolism, but this is probably of less importance because it only affects a minority of the results.

In study II we had no possibility to match our patients with the medical sample which was studied 10 years ago, and cannot exclude the possibility that general attitudes to medications may have changed somewhat during the 10 year period.

9.3. Clinical implications

Compared to other studies of adherence the present results seem to indicate a reasonably high adherence level in the present outpatient sample (58-66%). Although we concluded that this rate is "reasonably" high, it is clear that there is still a long way to go and this should not be an acceptable adherence rate in clinical practice.

There is a need of continuous adherence assessments in clinical practice and simple measures such as self-report can be a useful tool in such an assessment. This is easy to do in everyday practice, and there are no formal limitations for clinical use of a simple self-report in line with the one used in this thesis. However, direct measures such as blood-level concentrations of medication should be available for patients who seem resistant to treatment or have a history of nonadherence. In addition, mental health services in general should prioritize interventions to enhance treatment adherence.

Our findings support the need to address adherence from the full range of influencing factors (patient, illness, medication and environment). The predictive factors were insight, beliefs about medication, substance abuse and possibly side effects. Despite not perfect sensitivity and specificity, clinicians will be more able to predict adherence if these factors are assessed. Clinicians also need to use a collaborative approach in working together with patients in order to identify the meaning that patients attribute to the symptoms, prognosis and medication. Understanding the patients' perceptions and accepting these may facilitate greater treatment adherence and consequent improved clinical outcomes.

It is very important to reduce nonadherence. Based on the current findings together with literature, the most effective interventions should focus on reducing substance abuse, improving insight and understanding patients' perceptions and beliefs. Adherence interventions are called for and much needed as has been stated by the World Health Organization:"Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments" (WHO: Adherence to long-term therapies. Evidence for action 2003).

10. Conclusions

- The Birchwood Insight Scale, a simple self-report scale to assess insight, showed good psychometric properties in schizophrenia, medium properties in bipolar I disorder, and seems not to work in patients with bipolar II disorder.
- The level of insight was similar in patients with schizophrenia and bipolar I disorder.
- The Beliefs about Medication Questionnaire had satisfactory psychometric properties for use in patients with severe mental disorders.
- Nonadherent patients felt medication to be less necessary and were more concerned about it than adherent patients.
- Outpatients with severe mental disorders showed relatively good adherence to prescribed medication.
- Simple self report questionnaires seem to be a valid method for measuring adherence.
- Substance use is an important risk factor for nonadherence in our patients with schizophrenia and bipolar disorder.
- Poor insight is a risk factor for nonadherence, especially in schizophrenia.
- Autonomic side effects of medication might be a risk factor for nonadherence.
- The present findings suggest that reduced cognitive function is not a risk factor for nonadherence in patients with schizophrenia and bipolar disorder.

11. Errata

The printed version of this thesis is a reprint of the originally submitted thesis to the University of Oslo.

The following changes have been made:

Thesis

a) In the Appendix, figure 3, page 90, Birchwood Insight Scale. In the original version the column reading, Disagree stood in the middle and the column, reading Unsure to the left. The order of these two columns has now been changed according to the order in the Norwegian version used when including patients in the study.
b) In the Appendix, figure 4, page 91, Beliefs about Medicines Questionnaire – Specific. In the first column the heading Strongly disagree, has been changed for Strongly agree, which is the right version.

Errata in published papers:

Paper II

In the description of adherence measures it says: In 20 cases, we did not have blood samples and in 51 cases the serum analysis did not give conclusive results regarding adherence. This should read: In 25 cases, we did not have blood samples and in 46 cases the serum analysis did not give conclusive results regarding adherence.

Paper III

a) In the introduction it says: In bipolar disorder, adherence to long-term prophylactic pharmacotherapy ranges from 20-66%. This should read: In bipolar disorder, non-adherence to long-term prophylactic pharmacotherapy ranges from 20-66%.

b) Reference section, reference 35 should read:
George J, Kong DCM, Thoman R et al. Factors associated with medication nonadherence in patients with COPD. Chest 2005;128:3198-3204

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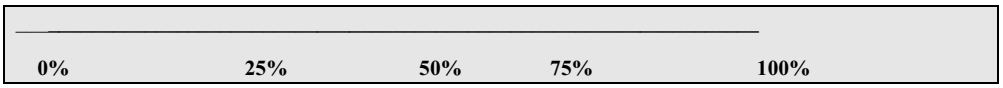
Appendix

Figure 1. Self-report of adherence in the past week

How much of your medication do you take?

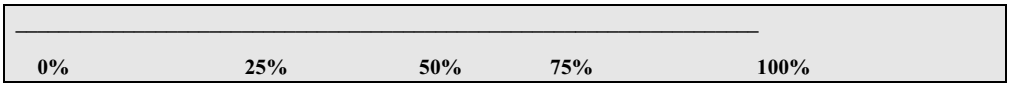
1. How much of medicine 1 did you take in the past week?

Cross on the line:



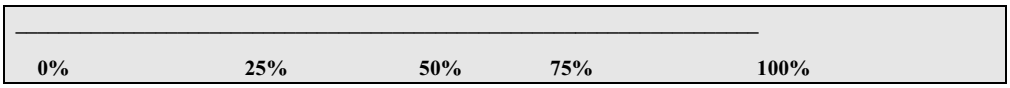
2. How much of medicine 2 did you take in the past week?

Cross on the line:



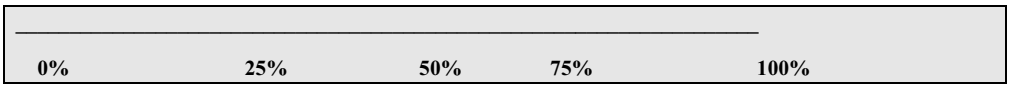
3. How much of medicine 3 did you take in the past week?

Cross on the line:



4. How much of medicine 4 did you take in the past week?

Cross on the line:



5. How much of medicine 5 did you take in the past week?

Cross on the line:

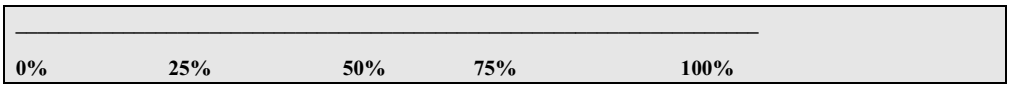


Figure 2. Medication Adherence Rating Scale – 5

Questions about your use of medicines

- Many people find a way to use their medication that suits them.
- This can be different from the instructions that follow, or what your physician has advised.
- We would like to ask some questions about how you use your medicines.

Below are statements about how people use their medicines. Please tick for each statement in the appropriate box

	Always	Often	Sometimes	Rarely	Never
I forget to take my medicines					
I change the dose of my medicines					
I stop taking my medicines for a while at times					
I decide not to take a dose					
I take less than I am instructed to					

Figure 3. Birchwood Insight Scale

Please read the following statements carefully and then tick the box which best applies to you.

	Agree very much	**Agree**	**Unsure**	**Disagree**	**Disagree very much**
1. Some of my symptoms were made by my mind					
2. I have always been mentally well					
3. I did not need medication					
4. My stay in hospital was necessary					
5. The doctor was right in prescribing medication for me					
6. I did not need to be seen by a psychiatrist					
7. If someone said I had a nervous or mental illness they would be right					
8. None of the unusual things I experienced were due to an illness					

Figure 4a. Beliefs about Medicines Questionnaire - Specific.

Your views about medicines prescribed for you

- We would like to ask you about your personal views about medicines prescribed for you.
- These are statements other people made about their medicines
- Please show how much you agree or disagree with them by ticking the appropriate box.

Your views about medicines prescribed for you	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
My health, at present, depends on my medicines					
Having to take medicines worries me					
My life would be impossible without my medicines					
I sometimes worry about the long-term effect of my medicines					
Without my medicines I would be very ill					
My medicines are a mystery to me					
My health in future depends on my medicines					
My medicines disrupt my life					
I sometimes worry about becoming too dependent on my medicines					
My medicines protect me from becoming worse					
These medicines give me uncomfortable side effects					

Figure 4b. Beliefs about Medicines Questionnaire - General.

Your views about medicines in general

- These are statements other people have made about medicines in general.
- Please show how much you agree or disagree with them by ticking the appropriate box.

Your views about medicines in general	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
Doctors use too many medicines					
People who take medicines should stop their treatment for a while every now and a again					
Most medicines are addictive					
Natural remedies are safer than medicines					
Medicines do more harm than good					
All medicines are poisons					
Doctors place too much trust on medicines					
If doctors had more time with patients they would prescribe fewer medicines					

I

II

III

IV

Predictors of medication adherence in patients with schizophrenia and bipolar disorder

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Abstract

Objective: To investigate potential risk factors for medication nonadherence in patients with schizophrenia and bipolar disorder.

Method: A total of 255 patients (154 with schizophrenia and 101 with bipolar disorder) underwent clinical assessments, neurocognitive testing and blood sampling. The patients were divided into groups of No, Partial or Full adherence. Relationships to different risk factors were analyzed.

Results: In schizophrenia, use of illegal substances, alcohol and poor insight were related to worse adherence. Schizophrenia patients with No adherence did better on tests of executive functioning, verbal learning and memory and had higher IQ than patients with better adherence. There were higher levels of autonomic side effects in the nonadherence group, but body mass index (BMI) was lower in the Partial adherence group than in the Full adherence group. In the bipolar disorder patients, there was an association between the use of illegal substances and alcohol and poor adherence. There was a nonsignificant trend for poorer insight in bipolar patients with No adherence. We found no relationship between adherence behavior and neurocognition in the bipolar disorder group.

Conclusion: Substance use is an important risk factor for nonadherence in patients with schizophrenia and bipolar disorder. Poor insight is also a risk factor, especially in schizophrenia. Further, the results suggest that cognitive dysfunction is not a risk factor for nonadherence in these diagnostic groups. This supports interventions that focus on reducing substance abuse and improving insight in order to increase adherence.

Key word: Adherence, predictors, schizophrenia, bipolar disorder

Significant outcomes

- Substance abuse is an important risk factor for partial or nonadherence in patients with schizophrenia and bipolar disorder.
- Poor insight is related to nonadherence in schizophrenia.
- Neurocognitive impairment is not a risk factor for nonadherence in schizophrenia and bipolar disorder.

Limitations

- The study had a cross-sectional design where adherence was measured at one time-point.
- The sample had a high level of adherence, which makes the nonadherence group small.
- Because of a naturalistic design, nonadherent patients may be underrepresented.

Introduction

In recent years the problem of nonadherence to medication has received increased attention. For clinicians to deal with the problem, it is important to identify factors associated with nonadherence (1). Understanding these factors is especially important in chronic disorders, as it has been shown that adherence is lower when the condition is prolonged (2-4). It is widely recognized that nonadherence is a big problem in patients with chronic psychiatric disorders (5-10). Schizophrenia and bipolar disorder are two of the most severe psychiatric disorders and medication nonadherence is strongly related to the course of illness in these disorders (10-12).

The risk factors most consistently associated with nonadherence in patients with schizophrenia are poor insight and lack of therapeutic alliance (2, 7). Other important factors are negative attitudes towards medication, previous nonadherence, shorter illness duration for first-episode patients, substance abuse and inadequate discharge planning and aftercare environment (11-13). In bipolar disorder, attitudes toward illness and health beliefs are strongly related to nonadherence (8-10, 14). Other important factors are substance and alcohol abuse and a comorbid personality disorder. Sosiodemographic factors such as younger age and male gender are more disputed as is the role of side effects (10).

There are some consistencies between the different studies with regards to the different risk factors for nonadherence, but some inconsistencies as well, and it is still unclear which clinical predictors are most important in schizophrenia and bipolar disorder (7, 8, 10, 15-17). One of the reasons for this could be the differences in design and methods in the different studies of adherence (7, 8, 10, 18, 19). The measurement of adherence/nonadherence is a long standing methodological problem (18). There are several available methods. Direct measures include observing patients swallowing tablets and the measurement of level of medicine or metabolites in the blood. Indirect measures cover self reports and electronic

medication monitors (1, 20). Few studies have previously used adherence measures based on blood levels of a range of medicines in a large well-characterized sample of patients with severe mental disorders (20). A recent review of the literature proposed that all studies of adherence should include at least 2 measurements of adherence of which one should be a direct or an objective measure (18).

Neurocognitive dysfunction is a characteristic of both schizophrenia and bipolar disorder (21, 22) and an important predictor of functional outcome in schizophrenia (23-26). Some studies have found the same relationship in bipolar disorder (25, 27, 28). It is reasonable to assume that neurocognition may be related to adherence behavior, but the relationship between neurocognitive dysfunction and nonadherence is still unclear. The studies are sparse, but there have been reports from general medicine pointing in the direction that better IQ predicts better adherence (29). In studies focusing on schizophrenia, results are mixed (30-40) and in bipolar disorder there is one study pointing at a close relationship between poor treatment adherence and cognitive impairment (41). It is important to explore this relationship further.

In a previous study we found outpatients with schizophrenia and bipolar disorder to have relatively good adherence to their medication(20). In that study, four different measures of adherence, including serum level analysis, were utilized. The aim of the current study was to investigate the association of medication nonadherence with a range of potential risk factors in this well described group of patients with schizophrenia and bipolar disorder. Another aim was to investigate if there were different risk factors related to the two diagnostic groups. We investigated factors identified in several earlier studies; including insight, substance abuse, symptoms, side effects and sociodemographic factors (2, 7-12, 14), as well as factors less investigated earlier, such as neurocognition and body weight (40-42). Based on previous literature, we hypothesized that poor insight and the use of illegal substances or

alcohol would predict poorer adherence. We also hypothesized that there would be an association between degree of neurocognitive dysfunction and poor adherence.

Materials and Methods

Sample

This study is a part of the ongoing Norwegian Thematically Organized Psychosis (TOP) Study of patients with schizophrenia and bipolar disorders. It is carried out by the University and the four university hospitals in Oslo, Norway (20, 43). Patients were recruited from the psychiatric departments at these hospitals. Informed consent was obtained by all participants, and the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. Exclusion criteria were presence of a diagnosis of developmental disorder (IQ<70) or brain damage and age below 18 or above 65 years. The sample comprises patients who were consecutively referred to the study from outpatient clinics from May 2003 to October 2006. In total 385 patients were evaluated during the inclusion period. Eighty eight patients did not meet the diagnostic criteria. Fifteen patients had not started treatment with medication at the time of inclusion and were thus excluded, and two patients withdrew their data after inclusion. The sample used in the current study consisted of 280 patients with bipolar I (n=66) and II (n=48) disorders (bipolar group, n= 114), schizophrenia (n=126), schizoaffective (n=30) and schizophreniform (n=10) disorder (schizophrenia group, n=166). The sample consisted of 141 men and 139 women; the mean age was 35.1 years. The patients were recruited by their clinicians, and thus we do not know the exact number of eligible patients who were not referred to the study based on the clinicians' decisions. However, there were 48 clearly eligible patients who were referred but refused to participate.

All patients underwent a SCID-I diagnostic interview by an experienced clinician (44). All interviewers participated in regular diagnostic consensus meetings led by a clinically experienced professor of psychiatry. Inter-rater reliability of DSM-IV diagnoses was adequate, with a Kappa of 0.77 (95% CI: 0.60 – 0.94) ref. Sixty four patients (22.9 %) had a lifetime diagnosis of alcohol or substance abuse or dependency and within that group 56 (87.5%) had used alcohol and 34 (53.1%) had used illicit drugs within the last 6 months. In the whole group 90 (32.1%) patients had used illegal substances in the past two years and 75 (26.8%) of those had used cannabis. Of the 280 patients included, serum concentrations were missing for 25, and they were excluded from analysis. Reasons for the missing data were that some patients refused to give blood samples, and some samples were not analyzed due to technical problems. Thus, a total of 255 participants were included in the analysis, with n=154 in the schizophrenia and n=101 in the bipolar group. The excluded patients did not differ significantly from the group included in the analysis on the following variables: age, gender, education, ethnicity or symptoms scores. Demographic and clinical characteristics of patients within the study are summarized in Table 1 and the use of illicit drugs and alcohol in the past 2 weeks, 6 months and two years is shown in table 2.

Adherence Measures

All measures were obtained at the time of inclusion in the study. Fasting blood samples were routinely collected between 9 and 11 am from all patients. Serum concentrations of medications were analyzed at the Department of Clinical Pharmacology, St. Olav's Hospital, Trondheim. To simplify the analysis, a primary therapeutic agent (PTA) was defined for patients taking more than one medicine. When more than 1 psychotropic medicine from the same class was used, the primary therapeutic agent was defined as the one with the highest dose. The PTA in the schizophrenia group were second generation antipsychotics for 131

patients, first generation antipsychotics for 15 patients, antiepileptics for 2 patients, antidepressants for 2 patients and 4 patients who were nonadherent did not wish to report the medication last prescribed to them. The PTA in the bipolar disorder group were antiepileptics for 41 patients, lithium for 19 patients, second generation antipsychotics for 20 patients, first generation antipsychotics for 3 patients, antidepressants for 9 patients and 9 patients did who were nonadherent did not wish to report the medication last prescribed to them. The reference range for each drug has been derived at the laboratory based on their extensive database and long experience with measuring each psychotropic drug (45).

When considering serum concentrations of psychotropic medicines the concentration/dose ratio was used as this gives the best picture of drug intake (45). An exception from this was lithium, where the serum concentration was used. To simplify the analysis, the patients were grouped into clusters, as suggested by Velligan (18). We defined three groups with regards to the concentration/dose ratio provided by the laboratory: 1) Not detectable, 2) Low levels and 3) Within reference range or higher.

Self-report of adherence was obtained from all patients. They were given a questionnaire by the research fellow and marked on a Likert scale from 0 – 100% how much of their prescribed medication they had taken the past week. Based on both measures we divided the sample into a "Full adherence" group; patients who with certainty had 100% adherence the past week (reported that they took 100% of their medication and the serum concentration was within reference level and in correct ratio with the dose) and into a "No adherence" group; patients who with certainty had not taken anything (reported that they did not take their medication and/or the serum analysis showed no detectable drugs). The Full adherence group counted 144 patients and the No adherence group counted 32. The rest of the sample was assigned to the Partial Adherence group which reported adherence between 12% and 95 %, and/or the concentration/dose ratio was lower than the recommended reference values, but with detectable

medication. Thus the Partial adherence group counted 79 patients. In the schizophrenia group there were 85 patients in the Full adherence group, 52 in the Partial adherence group and 17 in the No adherence group. In the bipolar disorder group the numbers were 59, 27 and 15.

Risk factor measures

Symptoms were assessed by the following clinical instruments: Inventory of Depressive Symptomatology (IDS) (46), Positive and Negative Symptoms Scale (PANSS) (47) and Young Mania Rating Scale (YMRS) (48). For IDS and YMRS the sum score was used and for PANSS the sum score and five different components where calculated, the negative, positive, cognitive, excitement and depression (49, 50).

Insight was measured using the Birchwood Insight Scale (IS) (51). This self report scale has been validated for a Norwegian sample with mental illness (52).

Side effects were measured using the Udvalg for Kliniske Undersøkelser (UKU) side effect rating scale (53). This scale measures a wide range of side effects divided in the categories: psychological, neurological, autonomic and others. After going through the different side effects, the patient and the caregiver separately assessed the effect of side effects on the patients' daily life, on a scale from 0-3. All patients were weighed, height was measured and BMI calculated.

The use of different illicit substances and alcohol use for the last 2 weeks and 6 months was obtained with specific questionnaires. The amount of alcohol use was registered and how often which type of substance had been used.

Neurocognitive assessment

A comprehensive neuropsychological test battery was administered to all participants by psychologists trained by a specialist in clinical neuropsychology. Tests from domains found to be sensitive to dysfunction in groups with bipolar disorder or schizophrenia were included.

National Adult Reading Test (NART) was only administered to patients who had gone through their primary schooling in Norway, and as such were fluent in the Norwegian language. All analyses of neurocognitive variables were limited to these patients. They counted 104 in the schizophrenia group and 90 in the bipolar group. The distribution in the adherence groups was the same after excluding patients for the neurocognitive analyses. This was also true for the mean age and gender.

General cognitive functioning

Premorbid IQ was assessed with the Norwegian research version of the *National Adult Reading Test* (NART)(54) . The number of errors on the NART were calculated into the NART premorbid IQ (54). Current IQ was measured with *Wechsler Abbreviated Scale of Intelligence* (55). All participants showed adequate neuropsychological test effort by scoring less than two errors on the forced recognition trial of the California Verbal Learning Test (CVLT-II) (56).

Domains

Psychomotor speed. The Digit Symbol test from *Wechsler Adult Intelligence Scale* (WAIS-III) (57) was included as a measure of psychomotor speed.

Attention and Working Memory. Digit Span-forwards from WAIS-III (57) was used as a measure of focused attention. The test requires the person to repeat an increasing number of digits in the same order as the test administrator. Score reported here is the maximum number of digits repeated. The Bergen n-back test (58) is a computer-based test requiring that a button is pressed every time the two numbers displayed on the screen are the same as the

numbers displayed two screen pictures back ('2-back'). Number of correct responses minus the number of false positives (commissions) was used as a measure of working memory.

Executive functioning. Executive functioning was assessed with the *Verbal Fluency* test from the Delis-Kaplan Executive Function System (D-KEFS)(59). Phonetic fluency was assessed with the Letter Fluency subtest, where the score is the number of words beginning with the letters 'F', 'A', and 'S' generated separately within 60 seconds. Semantic fluency was measured with the Category Fluency subtest. The person is given 2 x 60 seconds to name first as many animals, then as many boys' names as possible. Finally, semantic set shifting was measured with the Category Switching subtest where the participant is instructed to switch between naming fruits and furniture. Number of correct switches within 60 seconds is the score reported.

Verbal learning and Memory. The Logical Memory test from Wechsler Memory Scale (WMS-III) (60), was used to assess verbal learning. Two short stories were read aloud to the participant who was instructed to repeat them immediately. Score reported is the total number of story units recalled. From the CVLT-II (56) the total number of words repeated immediately after five reading trials of a list of 16 words was used as an measure verbal learning.

Higher scores on the neuropsychological tests signify better performance on all tests.

Data analysis

Statistical analyses were carried out using the software Statistical Package for the Social Sciences version 14.0 for Windows (SPSS Inc., Chicago, Ill.)

When looking at the dichotomous variable of using or not using alcohol and/or illegal substances, and the relationship to the different adherence groups, Chi square was calculated, for two of the adherence groups at a time. For continuous data (symptom scores, insight scores, scores on nevropsychological tests and of side effects) ANOVA was used when comparing means in the three different groups.

Results

Illicit drug use and alcohol use. In the schizophrenia group, 11 (12.9 %) had a lifetime diagnosis of addiction or abuse in the Full adherence group, 25 (48.1 %) in the Partial adherence group and 2 (11.8 %) in the No adherence group. The difference between the Full adherence group and the Partial adherence group was statistically significant ($p < 0.001$). In the bipolar group, 11 (18.6 %) had a lifetime diagnosis of addiction or abuse in the Full adherence group, 4 (14.8 %) in the Partial adherence group and 7 (46.7 %) in the No adherence group. The difference between the bipolar Full adherence group and the No adherence group was statistically significant ($p = 0.024$) (Table 3). Table 4 shows the relationship of the different adherence groups to the use of all illegal substances, cannabis or alcohol in the past 2 weeks and 6 months showing less use of illegal drugs and alcohol in the Full adherence groups for both diagnostic categories.

Symptomology. Within the schizophrenia group, there was a tendency to higher scores on PANSS, IDS and YMRS in the Partial and No adherence groups, but the difference was not statistically significant. Within the bipolar disorder group, the scores on the positive and excitement component were higher in the Partial and No adherence groups, than in the Full

adherence group, but the difference was not statistically significant. This was also the case for YMRS. The symptom scores are shown in table 3.

Insight. The mean (SD) insight score measured on the Bircwood Insight Scale in the schizophrenia group was 8.16 (2.20) in the Full adherence group, 7.70 (2.15) in the Partial adherence group and 6.38 (2.15) in the No adherent group. The difference between the full adherence group and the non adherent group was statistically significant ($p<0.05$). In the bipolar group the scores were: 8.28 (1.67) in the full adherence group, 8.24 (1.62) in the partial adherence group and 7.69 (1.68) in the non adherent group. The bipolar group as a whole scored higher in the insight scale, but the difference was not significant.

Neurocognition

In the schizophrenia sample, the patients in the No adherence group had significantly higher WASI IQ and better verbal learning and verbal fluency. In the bipolar sample, the results of the Partial adherence group where intermediate to the other two groups, but there were no statistically significant differences. The results are shown in Table 5.

Demographics

Age, sex, marital status or education was not associated with adherence to medication.

Side effects

There was a significant association between poor adherence and some autonomic side effects; diarrhea, nausea and orthostatism in schizophrenia patients and with orthostatism and urine retention in bipolar disorder patients. Otherwise there was no significant relationship between side effects and adherence. Schizophrenia patients in the Full adherence group had higher BMI than those in the Partial adherence group (table 3) and this was statistically significant. In the bipolar patients there were no statistically significant differences of mean BMI between the groups. When dividing the patients into weight groups based on the BMI (normal weight, overweight and obese), we found no differences in adherence between the groups.

Discussion

In the present study we used a reliable measure of adherence and directly compared schizophrenia and bipolar disorder patients. The main finding was an association between poor adherence and reduced insight, and the use of illegal substances and alcohol in patients with schizophrenia. This was similar to the findings in bipolar disorder patients where poor adherence was associated with the use of illegal substances and alcohol, while the association to reduced insight was on a trend level. Some autonomic side effects were associated with adherence in both groups, but current symptom levels were not. Better neurocognitive functioning was related to decreased adherence in schizophrenia.

Lack of insight is a fundamental attribute of schizophrenia (61) and it makes sense that patients who do not realize that they are ill, do not find it sensible to take medication for something they do not have. Poor insight has been considered one of the main predictors of nonadherence, especially in schizophrenia (7, 15, 61). Our results support this. The literature on insight and its measurement has focused on schizophrenia, with few studies on bipolar disorder (62, 63). As predictors of nonadherence in bipolar disorder patients, attitudes, beliefs and expectations are mentioned, but seldom insight as such (8, 17, 64). Our data

suggest that nonadherence in patients with bipolar disorder could be associated with poor insight, but further research is needed to establish this. Two previous studies have found a relationship between insight and adherence to medication in bipolar patients (62, 65). In our study we used Birchwood insight scale, which is developed for patients with schizophrenia (51). In a validation study in bipolar disorder we found that the scale worked well in patients with bipolar I disorder, but not so well in patients with bipolar II disorder (52). This might affect our results on insight. Another factor it that the bipolar disorder patients were mostly euthymic at inclusion in the study. Insight in bipolar disorder fluctuates and has been shown to be worse in mania and in psychotic depression (63). Follow-up studies of bipolar patients need to be done in order to evaluate this further. We have in earlier studies looked at beliefs about medication and adherence in patients with severe mental illness and found that patients with doubts about their need for medication were less adherent (66).

We found a relationship between poorer adherence and the use of illegal substances and alcohol, in both patient groups. Interestingly there is a difference in these results. In the schizophrenia group it is the Partial adherence group that uses significantly more illicit drugs and alcohol than the Full adherence group, and more often has a lifetime diagnoses of addiction or abuse. In the bipolar disorder group, the nonadherent patients abuse illicit drugs more often than those who were fully adherent. Many clinicians would claim that the use of illegal substances is a growing problem with young patients suffering from schizophrenia and bipolar disorder. In a recent study of first episode psychotic patients, substance abuse was one of the three strongest predictors of poor medication adherence (34). A recent study found a significant increase in nonadherence and treatment dropout associated with cannabis use among patients with first-episode schizophrenia followed over 12 months (67). The same was found with bipolar disorder patients in a large study of the effect of cannabis on outcome (68). Manwani et al found that lifetime adherence with mood stabilizers was lower in patients with

co-morbid substance use disorder (69). Our study supports earlier findings that the use of illicit substances and alcohol is a risk factor for nonadherence of medication, both in schizophrenia and bipolar disorder.

An interesting finding of our study is that schizophrenia patients with no adherence did significantly better on tests of verbal learning and memory, executive function and had significantly higher IQ. There is a shortage of adequate studies examining the association between adherence to medication and neurocognition. The results in schizophrenia are mixed (40), but mostly indicate no relationship (30-33, 40). However a recent study has found that higher baseline neurocognitive performance was associated with lower medication adherence (34), which is in line with our findings. Even in patients with acute symptoms, neurocognitive impairment seems to play little or no role for adherence. Kemp et al concluded that clinical variables and attitudes to treatment appeared to be more relevant to adherence in acute psychosis than neuropsychological impairment (32). Others have found an association between poor adherence and some form of poorer outcome on neurocognitive tests, like reduced facial recognition memory (35) and executive functioning (36) as well as a more generalized impairment (37). A recent Japanese study suggests that executive functioning, education and general IQ may be important factors in individual motivation for medication adherence (38). We found only one study, of Jeste et al, that reported neurocognitive functions to be the strongest patient related predictor of the ability to manage medication (39). This study used different measures of adherence and neurocognition than other similar studies we have mentioned.

Despite the lack of studies showing a relationship, the recently published Expert Consensus Guidelines mentioned cognitive impairment as one of the main factors influencing medication adherence in schizophrenia. (70). We argue that more studies are needed before such claims can be made. In the current study, using extensive neuropsychological test

batteries, we found that patients with schizophrenia that do not adhere to medication do significantly better on tests of verbal learning and memory, executive function and have a higher IQ than adherent patients. This is in line with recently published work of Perkins et al (34). Although nonadherent patients seem to perform better on neurocognitive tests, their insight is worse than that of either fully or partially adherent. In the bipolar group there was no difference in neurocognitive performance with regards to the adherent groups. The underlying mechanisms of this somewhat surprising relationship in schizophrenia need to be further explored. One could speculate that schizophrenic patients with higher neurocognitive functions have higher beliefs in their abilities to cope without using medication, especially when in remission.

We found no relationship between adherence and symptom severity in the schizophrenia group. This finding is in line with earlier findings in schizophrenia (7), even though some have found an association between psychotic symptoms (71), or depressive symptoms (34) and lower adherence. In the bipolar disorder group the nonadherent patients scored higher on the excitative and positive component on PANSS and on the YMRS scale. The difference did not reach significance, but goes in the same direction as found in earlier studies (72).

Many clinicians would claim that patients complain of side effects as a reason for discontinuing medication, but despite several studies, there is still conflicting empirical evidence. Lacro et al reported in their review that only one of nine studies found that the severity of side effects predicted adherence problems (7). Fenton et al and Young et al found that in the majority of studies they reviewed there was a direct association (2, 7, 73). Our results indicate that except for some autonomic side effects, side effects in general cannot be considered a main risk factor for nonadherence. In a recent study of first-episode patients, parkinsonian side effects significantly increased the likelihood of discontinuation during the first year of treatment. (36). Another first episode study suggested the same, namely that

patients found neurological side effects worse than weight gain and sedation,, leading to more discontinuation among those who used first-generation antipsychotics (74). Two other recent studies of first-episode patients did not find an association between perceived side effects and treatment nonadherence (34, 75). Metabolic side effects have gained attention recently and Weiden et al reported that in a group of 239 schizophrenia patients, obese individuals were more than twice as likely as those with normal BMI to report missing their medication (42). In our study, the Full adherence schizophrenia group had the highest mean BMI and the partial adherence group the lowest. This could be due to the naturalistic design, since those that stay on the medication are more likely to gain weight and keep it, than those that take them irregularly or stop completely. We do not have data on former weight gain. In the bipolar disorder group BMI was not significantly different between the adherence groups. This could be due to differences in the type of medication between these two groups, with more lithium and antiepileptics used in bipolar disorder. However, these medications also cause weight gain. Overall, results are conflicting. The differences in the literature are most likely related to differently selected patient groups, assessment methods and study design.

An aim of our study was to compare risk factors for nonadherence in schizophrenia and bipolar disorder and if those were the same. The relationship to potential risk factors was stronger in the schizophrenia group, but this could be due to higher number of patients. Moreover, the patients in the bipolar disorder group were older, more often female, they have longer education,

more often hold jobs and are more often in a relationship. They also have higher IQ. This could affect the results, but as our study is naturalistic, this sample represents the features of fairly representative patients being treated at Norwegian out-patient clinics.

The present study has several limitations. The study is cross-sectional, and we do not have observations over time. A general concern with adherence studies based on informed consent is

the implicit selection of patients, as those patients who deny all treatment usually do not consent to participate in studies. In addition we cannot rule out that the referring clinicians selected more adherent candidates. Participating in a study can in itself be considered an intervention and may improve adherence. The patients were aware of the fact that blood samples would be taken and might therefore have been more adherent at the time of the study. We have pointed out earlier that adherence in general is good in this group and therefore we might have a biased group with regards to nonadherence and the relationship to neurocognitive factors (20). Our group consists of out-patients that mostly follow their treatment and come to their appointments at the clinic. As a consequence of this the No adherence group is small and we might miss some important differences.

In conclusion, the use of illicit substances and alcohol is an important risk factor for nonadherence in both schizophrenia and bipolar disorder. Insight is also a risk factor, especially in schizophrenia. Side effects of medication might be a risk factor for nonadherence. This supports interventions that focus on reducing substance abuse, improving insight and using medications with few side effects. The relationship to psychiatric symptoms is more unclear, and it is important to study adherence in different phases of bipolar disorder. Further, cognitive dysfunction does not seem to be a risk factor for nonadherence in these diagnostic groups.

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Legends

Table 1. Table 1. Demographic and clinical characteristics of the study sample.

Table 2. Use of illicit drugs and in the past 2 weeks, 6 months and 24 months

Table 3. Relationship to age, gender, diagnosis of abuse or addiction, symptoms insight and weight.

Table 4. Relationship between adherence and the use of illegal substances and alcohol in the past 2 weeks and 6 months.

Table 5. Neurocognitive performance within the different adherence groups.

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Table 1. Demographic and clinical characteristics of the study sample.

	Schizophrenia (n=154)	Bipolar Disorder (N=101)	
Male gender, n (%)	84 (54)	41 (41)	*
Age, mean (SD)	33.2 (9.3)	38.8 (12.1)	**
European origin, n (%)	122 (79.2)	94 (93)	**
Married or cohabiting, n (%)	25 (16.2)	33 (32.7)	**
Education, mean years (SD)	12.6 (2.7)	14.8 (3.1)	**
Currently employed, n (%)	16 (10.4)	32 (31.7)	**
Co-morbid addiction n (%)	38 (21.4)	22 (21.8)	
PANSS positive symptoms (SD)	15.2 (5.6)	9.4 (2.4)	**
PANSS negative symptoms (SD)	15.3 (6.0)	10.4 (3.6)	**
PANSS positive component (SD)	12.9 (5.0)	6.9 (2.4)	**
PANSS negative component (SD)	20.2 (7.4)	14.5 (4.8)	**
PANSS excitement component (SD)	7.6 (2.6)	7.1 (2.0)	
PANSS depressive component (SD)	11.8 (4.3)	10.4 (3.6)	**
PANSS cognitive component (SD)	5.3 (2.1)	3.8 (1.2)	**
YMRS mania symptoms (SD)	5.7 (4.9)	2.4 (3.2)	**
IDS depressive symptoms (SD)	17.9 (12.5)	16.0 (11.8)	
IS (SD)	7.8 (2.2)	8.2 (1.6)	
NART pre-morbid IQ (SD)	112.1 (4.1)	113.2 (4.2)	*

PANSS, Positive and negative Syndrome Scale; YMRS, Young Mania Rating Scale; IDS, Inventory of Depressive Symptomatology; IS, Birchwood Insight Scale; NART, National Adult Reading Test.
* $p<0.05$, ** $p<0.01$ (Means compared using One way ANOVA and Chi-square used when dichotomous variables)

Table 2. Use of illicit drugs and alcohol in the past 2 weeks, 6 months and 24 months

Use of illicit drugs (%)	Past 2 weeks		Past 6 months		Past 24 months	
	Schiz	Bipolar	Schiz	Bipolar	Schiz	Bipolar
Cannabis	12.1	4.4	21.7	12.3	27.1	26.3
Amphetamine	2.4	0	10.2	1.8	17.5	2.6
Other	1.2	0	8.4	1.8	9.6	3.5
All use	12.8	5.3	26.8	15.8	34.5	28.9
Use of alcohol (%)	48.2	69.3	76.5	83.2	81.3	88.6

Schiz; Schizophrenia, Bipolar; Bipolar disorder

Table 3. Relationship to age, gender, diagnosis of abuse or addiction, symptoms insight and weight.

	Schizophrenia			p	Bipolar disorder			p
	1. Full Adherence (n=85)	2. Partial Adherence (n=52)	3. No Adherence (n=17)		1. Full Adherence (n=59)	2. Partial Adherence (n=27)	3. No Adherence (n=17)	
1.Age, mean years (SD)	33.3 (9.6)	32.6 (8.5)	35.1(10.3)		36.7 (13.0)	35.4(10.6)	41.3(10.7)	
Male gender, n (%)	49 (57.6)	24 (46.2)	11 (64.7)		21 (35.6)	12 (44.4)	8 (53.3)	
2. Lifetime diagnosis abuse or addiction, n (%)	11 (12.9)	25 (46.3)*	2 (18.2)	2>1 (0.000)	11 (18.6)	4 (14.8)	7 (46.7)*	3>1 (0.024)
3. Symptoms:								
PANSS, mean (SD)								
Positive	14.2 (5.6)	16.0 (5.6)	15.7 (6.1)		9.2 (2.1)	9.6 (2.7)	10.3 (2.9)	
Negative	14.9 (5.9)	15.6 (5.8)	16.7 (6.8)		10.9 (3.8)	9.6 (2.7)	9.9 (3.1)	
Positive component	12.5 (5.1)	13.5 (4.8)	13.7 (5.4)		6.5 (1.9)	7.1 (2.4)	8.0 (3.4)	
Negative component	19.5 (7.4)	20.5 (7.4)	22.8 (7.5)		14.9 (4.9)	13.4 (4.5)	14.7 (5.3)	
Excitement component	7.5 (2.5)	7.9 (2.8)	7.2 (2.3)		6.7 (1.7)	7.5 (2,2)	7.9 (2.4)	
Depressive component	11.9 (4.2)	11.5 (4.4)	12.4 (4.4)		10.1 (3.9)	11.5 (3.3)	9.7 (2.9)	
Cognitive component	5.1 (2.0)	5.6 (2.2)	5.3 (2.5)		3.9 (1.3)	3.7 (1.0)	3.8 (1.1)	
IDS	17.5(12.2)	18.4(12.8)	18.8(14.4)		16.3 (12.3)	12.0 (2.4)	14.7 (9.8)	
YMRS	5.1 (4.6)	6.3 (5.3)	6.8 (4.6)		2.0 (2.8)	2.6 (3.4)	3.8 (3.2)	
4. Insight (Birchwood), mean (SD)	8.16(2.20)	7.70(2.15)	6.38(2.15)	3>1 (0.013)	8.28 (1.67)	8.24 (1.62)	7.69 (1.68)	
5. BMI, mean (SD) [1]	27.1(4.7)	24.8(4,2)*	26.7 (3.9)	1>2 (0.012)	26.1 (5.0)	27.9 (4.6)	26.1 (4.4)	

[1]N = 149 in the Schizophrenia group (5 missing) and n = 99 in the bipolar group (2 missing). PANSS, Positive and negative Syndrome Scale; YMRS, Young Mania Rating Scale; IDS, Inventory of Depressive Symptomatology; IS, Birchwood Insight Scale; BMI (Body Max Index).
(Means compared using Oneway ANOVA and Chi-square used when dichotomous variables).

Table 4. Relationship between adherence and the use of illegal substances and alcohol in the past 2 weeks and 6 months.

	Schizophrenia			p	Bipolar			p
	1. Full Adherence (n=85)	2. Partial Adherence (n=52)	3. No Adherence (n=17)		1. Full Adherence (n=59)	2. Partial Adherence (n=27)	3. No Adherence (n=17)	
Narcotics								
Last 2 weeks								
No use	79 (93)	43 (83)	15 (88)	1 < 2 (p<0.05)	58 (98)	25 (93)	12 (80)	1 < 3 (p<0.01)
Use	5 (6)	9 (17)	2 (12)		1 (2)	2 (7)	3 (20)	
Last 6 months								
No use	72 (85)	28 (54)	14 (82)	1 < 2 (p<0.01)	53 (90)	22 (81)	9 (60)	1 < 3 (p<0.01)
Use	11 (13)	24 (46)	3 (18)	3 < 2[1] (p<0.05)	6 (10)	5 (19)	6 (40)	
Cannabis								
Last 2 weeks								
No use	79 (93)	43 (83)	15 (88)	1 < 2 (p<0.05)	58 (98)	25 (93)	13 (87)	3>1 (0.05)
Use	5 (6)	9 (17)	2 (12)		1 (2)	2 (7)	2 (13)	
Last 6 months								
No use	76 (89)	31 (60)	14 (82)	1 < 2 (p<0.01)	54 (92)	22 (81)	11 (73)	
Use	9 (11)	21 (40)	3 (18)		5 (8)	5 (19	4 (27)	
Alcohol								
Last 2 weeks								
No use	44 (52)	27 (52)	11 (65)		21 (36)	9 (33)	0	1 < 3 (p<0.01)
Use	41 (48)	25 (48)	6 (35)		38 (64)	18 (67)	15	2 < 3 (p<0.05)
Last 6 months								
No use	25 (29)	7 (13)	5 (29)	1 < 2 (p<0.05)	10 (17)	6 (22)	0	2< 3 (p<0.05)
Use	60 (71)	45 (87)	12 (71)		49 (83)	20 (78)	15	

[1] Significant difference in groups 2 and 3, with group 2 being the group using significantly more narcotics.
Chi-square used to evaluate group differences.

Table 5. Neurocognitive performance within the different adherence groups.

	Schizophrenia			p	Bipolar disorder			p
	1. Full Adherence (n=59)	2. Partial Adherence (n=34)	3. No Adherence (n=11)		1.Full Adherence (n=56)	2. Partial Adherence (n=22)	3. No Adherence (n=12)	
1. Psychomotor speed Digit symbol (WAIS III)	54.5 (15.6)	54.2 (33.8)	63.9 (21.6)		65.9 (18.1)	60.5 (14.7)	67.5 (18.2)	
2. Attention/working memory (WAIS III) Digit span	14.6 (2.6)	14.9 (3.3)	15.4 (3.0)		15.1 (3.3)	15.1 (3.9)	15.0 (3.5)	
3. Executive functioning Verbal fluency (D-KEFS) Phonetic Semantic Set shifting	 36.4 (12.2) 37.1 (9.8) 11.4 (2.4)	 37.7 (13.7) 38.7 (9.7) 12.4 (2.5)	 48.1 (10.5)* 45.8 (8.7)* 13.4 (2.1)*	 3>1 0.017 3>1 0.021 3>1 0.043	 41.0 (10.5) 42.8 (10.6) 13.2 (3.3)	 38.6 (10.9) 39.3 (10.3) 12.8 (2.7)	 48.3 (16.0) 46.2 (11.5) 13.7 (3.5)	
4. Verbal learning and memory Logical memory (WMS-III) LM-I CVLT-II (Total 1-5)	 20.1 (6.7) 45.8 (11.6)	 21.7 (7.0) 48.7 (10.2)	 28.7 (6.1)* 59.3 (9.6)*	 3>1 0.001, 3>2 0.011 3>1 0.001, 3>2 0.020	 25.6 (7.3) 55.6 (11.1)	 23.7 (6.2) 52.6 (10.8)	 22.2 (4.3) 56.3 (11.2)	
5. Current IQ (WASI) Verbal IQ Performance IQ	 101.4 (11.9) 103.2 (11.4)	 103.2 (11.6) 103.1 (15.3)	 113.2 (14.5)* 114.3 (15.6)*	 3>1 0.012 3>1 0.040	 107.4 (12.6) 107.5 (15.1)	 106.4 (14.8) 106.4 (11.3)	 103.6 (8.8) 109.1 (14.2)	
6. Premorbid IQ (NART)	111.9 (4.2)	111.9 (4.1)	113.4 (3.7)		114.0 (4.3)	112.5 (3.9)	111.0 (2.9)	

Values are given as mean (standard deviation). Higher scores signify better performance on all tests. Means compared using Oneway ANOVA.
WAIS, Wechsler Adult Intelligence Scale; D-KEFS, Delis-Kaplan Executive Function System; WMS-III, Wechsler Memory Scale; CVLT-II, California Verbal Learning Test; WASI, Wechsler Abbreviated Scale of Intelligence; NART, National Adult Reading Test.