

Cognition, Adherence and Stigma in Schizophrenia

The COAST Study

Cecilia Brain

Department of Psychiatry and Neurochemistry
Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg



UNIVERSITY OF GOTHENBURG

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cecilia.brain@neuro.gu.se

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Ale Tryckteam AB

The mind is its own place and in itself,
can make a Heaven of Hell,
a Hell of Heaven.

John Milton, Paradise Lost



ABSTRACT

Schizophrenia is a serious stigmatizing illness. Antipsychotic medication is a cornerstone in treatment. Non-adherence is a predictor of poor outcome leading to relapse, poor functioning, high mortality and costs. Reported adherence rates vary (8-86%). Most adherence studies are small, short and use subjective adherence measures known to underestimate non-adherence. The overall aim of this thesis is to increase knowledge about factors related to adherence to oral antipsychotics and to stigma in a large cohort of patients with schizophrenia or schizophrenia-like psychosis, followed for one year. The specific aims are: to examine adherence to antipsychotics and to compare objective and subjective measures of adherence; to investigate predictors of adherence; to explore stigma and discrimination and to test for potential associations between a) different types of stigma and b) stigma and adherence; to study stigma experiences and the relationship between associated stigma and burden in relatives to persons with schizophrenia.

Adherence was monitored for a year in 117 outpatients at Sahlgrenska University Hospital, Gothenburg, Sweden. Adherence was determined by the Medication Event Monitoring System (MEMS[®]), considered the reference standard, pill count, a composite measure of plasma levels and adherence to lab visits, and patient, staff, psychiatrist and close informant ratings. Symptom burden, insight, cognition, psychosocial function (PSP) and side effects were rated (n=112). Experiences of stigma (n=111) and drug attitude (using the Drug Attitude Inventory, DAI-10) of patients (n=112) and informants (n=65), as well as burden in relatives (n=65) were assessed.

Non-adherence (MEMS[®] adherence \leq 0.80) was observed in 27% of the patients. In *Study I* MEMS[®] adherence was highly correlated with pill count but very poorly correlated with the plasma level measure. In *Study II* low patient-rated DAI-10 scores and poor function emerged as predictors of non-adherence. Positive symptom burden, psychiatric side effects, lack of insight and low DAI-10 informant scores also predicted non-adherence. No association between stigma and adherence could be shown in *Study III*. Almost two-thirds of the patients reported discrimination in social relationships and “anticipated stigma”. One-half felt discriminated against by mental health staff. In *Study IV* a fifth of the relatives avoided situations that might elicit stigma, but there was no association between experienced or anticipated stigma and burden. Stigma impact regarding the relatives’ personal quality of life was associated with overall burden.

In conclusion, structured pill count might be a useful clinical tool to objectively follow adherence. The large discrepancy between MEMS[®] and the plasma level measure needs further study. Positive drug attitude in combination with good psychosocial functioning emerged as predictors of MEMS[®] monitored adherence. Associations were found neither between stigma and adherence nor the relatives’ stigma and burden, and both phenomena need to be investigated further.

Keywords: schizophrenia, adherence, Medication Event Monitoring System, antipsychotics, pill count, drug attitude, stigma, discrimination, relatives’ burden

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SAMMANFATTNING PÅ SVENSKA

Schizofreni är en allvarlig stigmatiserande sjukdom. Antipsykosläkemedel utgör en hörnsten i behandlingen. Bristande läkemedelsföljsamhet (adherence) försämrar prognosen, vilket leder till återfall, funktionsnedsättning, ökad dödlighet och kostnader. Rapporterad grad av adherence varierar (8-86%). I de flesta studier, som är små och korta, används subjektiva mått, vilka ofta överskattar adherence.

Det övergripande syftet med denna doktorsavhandling är att öka kunskapen om faktorer relaterade till adherence till antipsykosläkemedel och till stigma vid schizofreni. De specifika delarbetena avser att: undersöka graden av non-adherence och att jämföra subjektiva och objektiva adherencemått; studera kliniska prediktorer som kan förutsäga non-adherence; skatta stigma och diskriminering och testa eventuella samband mellan a) olika typer av stigma samt b) stigma och adherence; hos närstående till personer med schizofreni studera upplevelsen av stigma och att undersöka associationen mellan stigma och upplevd närståendebörda.

Under ett år följdes adherence hos 117 psykosöppenvårdspatienter vid Sahlgrenska universitetssjukhuset i Göteborg. Elektroniska läkemedelsburkar (MEMS[®]), som anses utgöra referensstandard, och plasmanivåer (kompositmått på plasmanivåer och följsamhet till laboratoriebesök), pillerräkning och skattning av patient, närstående, psykiater och behandlare utgjorde adherencemått. Symtombörda, biverkningar, sjukdomsinsikt, kognition och psykosocial funktion skattades. Läkemedelsattityd (n=112) och upplevelse av stigma hos både patient (n=111) och närstående (n=65) samt närståendebörda mättes.

Sänkt adherence noterades hos 27% av patienterna (MEMS[®] adherence \leq 0.80). Enligt *studie I* hade adherence mätt med pillerräkning mycket hög samstämmighet med MEMS[®] adherence. Däremot hade plasmanivåmåttet lägst samstämmighet. Patientens läkemedelsattityd, i kombination med psykosocial funktion, predicerade adherence i *studie II*. Biverkningar, psykosymtom, bristande insikt och negativ läkemedelsattityd hos närstående var också relaterade till sänkt adherence. Inget direkt samband mellan stigma och adherence sågs i *studie III*. Närmare två tredjedelar av patienterna kände sig socialt diskriminerade och angav att de undviker sådant de förväntar sig kan leda till stigma. Hälften kände sig diskriminerade av psykiatrisk personal. I *studie IV* rapporterade en femte del av de närstående att de undviker situationer som kan föranleda stigma, men inget samband sågs mellan upplevd eller förväntad stigmatisering och närståendebörda. Stigma medförde minskad livskvalitet både för de närstående och för berörda familjer och i bägge fallen sågs en association till närståendebörda.

Sammanfattningsvis antyder den höga samstämmigheten mellan pillerräkning och MEMS[®] att pillerräkning kan vara en enkel och billig objektiv metod för att mäta adherence i kliniken. Plasmanivåmåttet behöver studeras närmare. Kombinationen läkemedelsattityd och psykosocial funktion predicerade MEMS[®] adherence. Ingen relation kunde påvisas mellan stigma och adherence, eller mellan närståendebörda och stigma, och sambanden behöver undersökas närmare.



LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Brain, C., Sameby, B., Allerby, K., Lindström, E., Eberhard, J., Burns, T., Waern, M. Twelve months of electronic monitoring (MEMS[®]) in the Swedish COAST-study: A comparison of methods for the measurement of adherence in schizophrenia. *European Neuropsychopharmacology* 2014; 24(2): 215-222.

- II. Brain, C., Allerby, K., Sameby, B., Quinlan, P., Joas, E., Karilampi, U., Lindström, E., Eberhard, J., Burns, T., Waern, M. Drug attitude and other predictors of medication adherence in schizophrenia: 12 months of electronic monitoring (MEMS[®]) in the Swedish COAST-study. *European Neuropsychopharmacology* 2013; 23(12): 1754-1762.

- III. Brain, C., Sameby, B., Allerby, K., Quinlan, P., Joas, E., Lindström, E., Burns, T., Waern, M. Stigma, discrimination and medication adherence in schizophrenia: Results from the Swedish COAST study. *Psychiatry Research* 2014; 220(3): 811-817.

- IV. Allerby, K*, Sameby, B*, Brain, C., Joas, E., Quinlan, P., Sjöström, N., Burns, T., Waern, M. Associated stigma and burden in relatives to persons with schizophrenia: Results from the Swedish COAST study (Submitted).

* Equal contribution



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ABBREVIATIONS

ACT	Assertive Community Treatment
AIDS	Autoimmune Deficiency Syndrome
AUC	Area Under the Curve
BIRP	Burden Inventory for Relatives to persons with Psychotic disturbance
BMI	Body Mass Index
CGI-S	Clinical Global Impression-Severity
CI	Confidence Interval
COAST	Cognition, Adherence and Stigma in Schizophrenia
CPT-IP	Continuous Performance Test-Identical Pairs Version
DAI	Drug Attitude Inventory
DALYs	Disability Adjusted Life Years
DISC	Discrimination and Stigma Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder, fourth edition
DUP	Duration of Untreated Psychosis
FGA	First Generation Antipsychotics
GAF	Global Assessment of Functioning
HIV	Human Immunodeficiency Virus
INDIGO	International Study of Discrimination and Stigma Outcomes in Mental Health
ISE	Inventory of Stigmatizing Experiences
LAI	Long Acting Injectable
LNS	Letter-Number Sequencing
MEMS	Medication Event Monitoring System
MHP	Mental Health Problem
MHS	Mental Health Service
MPR	Medication Possession Ratio
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NOS	Not Otherwise Specified
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
PSP	Personal and Social Performance Scale

RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
RR	Relative Risk
SCI-SR	Structured Clinical Interview for Symptoms of Remission
SD	Standard Deviation
SGA	Second Generation Antipsychotics
SPSS	Statistical Package for the Social Sciences
TDM	Therapeutic Drug Monitoring
TMT	Trail-Making Test
UKU-SERS-Pat	The Udvalg for Kliniske Undersøgelser Side Effect Self-Rating Scale
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization
VIF	Variance Inflation Factor
WPA	World Psychiatric Association

DEFINITIONS IN SHORT

DALY	Disability-Adjusted Life Years for a disease or health condition (DALYs) are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences.
DUP	The Duration of Untreated Psychosis (DUP) was in this thesis defined as the time from the first documentation of psychotic symptoms in the medical files until registered onset of antipsychotic treatment.
Effectiveness	The ability of an intervention to produce the desired beneficial effect in actual use.
Efficacy	The ability of an intervention to produce the desired beneficial effect in expert hands under ideal circumstances.
NNT	The Number Needed to Treat (NNT) is the number of patients that need to be treated to prevent one additional negative outcome.

1. INTRODUCTION

1.1 The concept of adherence

1.1.1 Therapeutic and medication adherence

According to NICE guidelines [1] between a third and a half of medicines that are prescribed for any long-term conditions are not taken as intended. Furthermore, poor adherence is not limited to medication taking alone and is commonly divided into therapeutic and medication adherence [2]. Therapeutic adherence encompasses non-pharmaceutical treatment recommendations, for example exercise and diet, and this is defined by the World Health Organization (WHO) [3] as “the extent to which a person’s behavior corresponds with agreed recommendations from a health care provider”. Medication adherence, on the other hand, can be defined as the extent to which a patient’s medication-taking matches that which is agreed with the prescriber. Several alternative terms have been used, including treatment compliance, concordance and fidelity. Adherence is currently favored partly because of its neutrality whereas, for example, compliance implies an unequal power balance between the prescriber and patient [4].

1.1.2 Medication non-adherence is common

Non-adherence is a problem in all medical conditions and not only in severe mental illness. Results from a meta-analysis [5] of 569 studies, reporting adherence to medication prescribed by non-psychiatrist physicians, found an average non-adherence rate of 24.8% (Table 1). In physical illness adherence rates were found to be higher in smaller, more recent studies, and in adult samples including medical regimens. A much cited review [6] of non-adherence in schizophrenia, with mean non-adherence rates of 40.5%, is used as a comparison.

Table 1: Non-adherence in various medical conditions and in schizophrenia

Condition	Number of studies	Non-/poor adherence
Schizophrenia	39	40.5%
Medical condition		
Diabetes mellitus	23	32.5%
Pulmonary disease	41	31.2%
End-stage renal disease	20	30.0%
Eye disorder	15	27.4%
Infectious disease	34	26.0%
Obstetric and gynecological disorder	19	25.2%
Ear, nose, throat and mouth disorder	30	24.9%
Cardiovascular disease	129	23.4%
Skin disorder	11	23.1%
Genitourinary/sexually transmitted diseases	17	23.0%
Cancer	65	20.9%
Gastrointestinal disorder	42	19.6%
Arthritis	22	18.8%
HIV/AIDS	8	11.7%

Data based on DiMatteo, M.R. (2004) and Lacro, J.P. (2002).

1.1.3 Cut-off for non-adherence in research

Medication adherence lies on a spectrum ranging from individuals who take no medication, despite agreeing to do so with the prescribing clinician, to those who take each dose precisely on time. Some patients take more than prescribed. This can cause side effects leading to secondary non-adherence as the negative medication experience may cause consequent mistrust of medicines. Varying degrees of adherence, so-called *partial adherence*, where patients take some medication from time to time but not consistently as prescribed is the most common [7].

Adherence is usually dichotomized for research purposes with non-adherence defined as missing $\geq 20\%$ of prescribed medication [8-11]. This cut-off has validity in predicting subsequent hospitalization across several chronic conditions. The 80% cut-off for non-adherence has been challenged in a current study that showed that patients with schizophrenia, with an objectively monitored adherence rate of 80-99.9%, had more somatic concerns, greater psychopathology and were more disoriented compared to patients with full (100%) adherence [12]. The authors claim that full adherence should be a treatment goal for “adherent” patients in order to

optimize outcome. Thus, an adherence rate of 80% is not assumed to equal “adherence”.

For individual patients the degree of non-adherence that affects health outcomes will depend on many factors. These include the condition, its severity and the risk of recurrence, the relative effectiveness of the medication and its dose, mode of delivery and frequency of administration, how the individual patient metabolizes the medication and the effects of concomitant medications, smoking, etc.

Different cut-offs have been used and some, mostly earlier, studies define adherence as taking as low as 75% or as high as 95% of the prescribed medication [11]. This, together with population studied and methods used, should be taken into account when comparing adherence data. Still, the most recent studies use 80% as the cut-off for adherence.

1.1.4 Factors influencing adherence

The Health Belief Model

Theoretical paradigms of adherence, such as the Health Belief Model [13], were developed and adopted in the 70's in order to identify factors that might determine adherence behavior. According to this model, everything revolves around the presumed likelihood that the patient will adhere to treatment recommendations. The patient's decision to adhere to treatment or not is assumed to stem from the implicit, subjective assessment of the pros and cons of medicating. If the advantages are expected to outweigh the disadvantages the patient will most likely be adherent, i.e. the patient's decision is influenced by the assumed individual risks and susceptibility connected to adhering to the treatment. The patient makes decisions based on his or her beliefs about the illness as well as the treatment. With physical illness, it has been shown that patients' beliefs about the medicine are of crucial importance [14]. In line with the Health Belief Model this study found that the necessity of taking medication was weighed against the fear of potential adverse effects from medicating. The patient's beliefs were found to predict adherence significantly better than clinical and sociodemographic factors.

Intentional and unintentional non-adherence

Non-adherence can be divided into *intentional* and *unintentional* non-adherence. In the case of intentional non-adherence the patient has made a deliberate decision not to take the medicine according to the prescription. The patient usually finds the disadvantages of medicating greater than the

advantages. This could be due to poor understanding of the illness or the experience of side-effects (for example those connected to chemotherapy treatment in the final stages of cancer providing only a very limited prolongation of life). Unintentional non-adherence refers to an inability to follow the prescription, for example due to cognitive deficits, unclear instructions, expense of medication or difficulty collecting the medicine at the pharmacy. Unintentional and intentional non-adherence can both occur in the same patient.

1.1.5 The history of non-adherence

The prescription of medicines is a core element of the modern health care system [1]. Non-adherence has existed as long as treatments have been prescribed. As early as the 4th century BC Hippocrates documented that some patients did not take their prescribed medicine and that others complained that their treatment was ineffective [15]. Hippocrates stated the risk of non-adherence with the following words: “Keep watch also on the faults of the patients which often make them lie about the taking of things prescribed” [16]. While Hippocrates may be rather extreme in his wording, our views of the reasons for non-adherence have hopefully evolved. But the problem of non-adherence undoubtedly remains important.

In the 19th century, Robert Koch, the father of modern bacteriology, was critical of patients with tuberculosis who did not follow the instructions given to fight their serious infection [15]. In 1955, not long after the introduction of antibiotics, it was found that approximately one-third of patients with acute pharyngitis or otitis media did not complete a one-week course of oral penicillin [17]. Non-adherence was thus, as already mentioned, found early on to be not only a problem within psychiatry, but a widespread feature of human behavior [18].

The basis for understanding the perhaps even more complex aspects of non-adherence in schizophrenia is familiarity not only with the basic concept of non-adherence in general, but also with the symptomatology and the consequences of the schizophrenia syndrome. Outcomes in schizophrenia, antipsychotics and the stigmatization of and within psychiatry, and of antipsychotics as well as of mental illness itself will also be discussed.

1.2 Outcome in schizophrenia

Schizophrenia is a complex and debilitating mental illness [19]. The clinical syndrome of variable, but profoundly disruptive, psychopathology involves cognition, emotion, perception, and other aspects of behavior. Multiple

factors, such as drug abuse, stigma, discrimination and social deprivation, which are all common in schizophrenia, contribute to a poor prognosis [20]. Relapses do not only seem to be associated with a considerable psychosocial risk, but also to morphological changes of the brain and to treatment refractoriness [21].

Schizophrenia is seen as a severe neurodegenerative disorder involving recurring and chronic psychotic episodes with relapses leading to deterioration of cognition and psychosocial functioning. This widespread view that schizophrenia causes progressive brain changes and cognitive deficits makes *outcome* a key concern [22]. One consequence of the gloomy Kraepelinian estimate of the long-term outcome, based on institutional experiences before the introduction of antipsychotics, is a persisting negative outlook on the prognosis of schizophrenia [23]. This view has influenced the development of diagnostic manuals as well as the content of textbooks, lectures and psycho-education. Together with the frequently negative public view of psychiatry, this may have both compromised social inclusion and rehabilitation of patients and added to the burden and stigmatization of patients and families. It may also have negatively impacted the implementation of modern evidence based psychiatric practices and treatments, including the optimal use of psychiatric medications.

The way antipsychotics have been viewed has been influenced by earlier pessimistic views of outcome, the anti-psychiatry movements and a lack of trust in evidence based treatments [24]. Psychiatrists and psychiatric staff are themselves stigmatized. In a newly published international survey [25] of stigmatization of psychiatrists (n=1,893) and general practitioners (n=1,238), the psychiatrists reported significantly more perceived stigma and discrimination. This may affect recruitment, funding and consequently quality of psychiatric care and these are directly connected to outcome in schizophrenia [26].

1.2.1 Psychiatric outcome measures

There is a need for improvement in psychiatric outcome measures [27]. Psychiatry is often criticized for using “soft” subjective measures and rating scales as opposed to “hard” outcomes, such as death or major events (for example heart attack) often used in other medical specialties [28]. In this meta-analysis it was pointed out that neither high blood pressure nor cholesterol levels lead to suffering and thus should not be the primary outcome, but instead their long-term consequences. Other somatic drugs directly reduce primary symptoms from the disease (for example oesophagitis or migraine) but the pathophysiological disease progress in these somatic

illnesses is not death. This is unlike medications for many severe psychiatric conditions where the disease progress is fatal.

Traditionally in psychiatric research, unlike somatic medicine, death (such as suicide) has not generally been seen as an outcome to be measured but has more often been reported as an adverse event. Instead, common primary outcome measures for schizophrenia are reduction of illness severity, degree of hallucinations and hospitalizations. With recent increased recognition of the reduced life expectancy in severe mental illness of more than 20 years [29], mortality is now proposed as a routine and legitimate outcome measure in psychiatric studies. Thus, death and suicide should always be reported along with further improvements of psychiatric outcome measures [27].

1.2.2 Is adherence an outcome measure?

Antipsychotic medication is a cornerstone in treatment of schizophrenia [4, 30, 31] and the basis for psychosocial interventions [11]. Despite the increased availability of evidence based treatments and pharmacological treatment options during the last decades, the recovery rates have not improved, as shown by a recent Finnish systematic review and meta-analysis [32]. Only 1 in 7 individuals with schizophrenia met the study criteria for recovery (both clinical and social recovery for at least two years and absence of, or only mild, symptoms).

This might partly be due to the known association between non-adherence and poor prognosis, where missed medication leads to a significantly increased risk of relapse and suicide [33, 34]. A large Cochrane review [35] showed that continuous treatment with antipsychotics was superior to intermittent treatment in regard to relapse prevention. Despite this, several studies with non-adherence as a primary intervention target have shown that even if adherence improved, clinical outcome did not get better [36]. Thus, adherence in itself is not a sufficient treatment goal. Instead adherence should be considered as an important tool to achieve the treatment goals [37]. Accordingly, adherence to antipsychotics is a *predictor of outcome* and is only of interest as it affects outcome.

1.3 Modern schizophrenia treatment

Antipsychotic medication is acknowledged as the basis in schizophrenia treatment. However, it has been established that medication alone is not sufficient [11]. For optimal outcome antipsychotics need to be combined with

psychosocial interventions in community based psychiatry. Treatments should be prioritized, selected and followed-up based on structured ratings and clinical interviews. Patients' attitudes, insights and subjective experiences (for example of medication and potential side effects) need to be acknowledged. These treatment components are all crucial for alliance, treatment adherence and optimal outcome [31] and are part of a tailor-made, person-centered approach to evidence based community mental health [38].

Assertive Community Treatment (ACT) with case management has previously been shown to improve medication adherence [39]. This care delivery system, the continuity and (if called for) the higher frequency of contacts with the patients and the social network are all of importance [7]. These facilitate the patients' adjustment and problem solving in everyday life as the basis for finding alternative strategies despite cognitive deficits or withdrawal symptoms of schizophrenia. The strategies are assumed to be of use both when having to cope with stigma and when taking medication [40]. Still, the question of which pharmacological and psychosocial interventions specifically improve outcome within integrated care models (and for whom) is still largely unanswered.

One Swedish study found that an integrated care model improved social function and consumer satisfaction [38]. In a review [41] of eight randomized controlled trials (RCTs) and 21 non-RCT studies published between 2011 to 2013, the authors suggest that person-centered integrated care models should be offered for treatment of complications, such as non-adherence to antipsychotics, continuous psychopathology or service disengagement. This mode of working was associated with improvement of symptoms, better functioning, quality of life, adherence, patient satisfaction and reduced caregiver's stress. This is in line with the suggestion of a further review [42] that a shared discussion between patients and health care professionals about the patient's beliefs and attitudes about medication could facilitate the integration of psychopharmacology and psychological treatments and help reduce the stigma of having to medicate.

A recent systematic review [43] concluded that the evidence supports a team-oriented approach as it improves adherence and reduces relapse rates, hospitalization and costs. The multidisciplinary team thus plays an important role in identifying and overcoming patients' barriers to adherence. Finally, medication, outcome and quality of life can be optimized by also involving the informal caregivers as their burden [44], and most likely their impact on the outcome, is quite substantial in schizophrenia.

1.3.1 Is antipsychotic medication efficacious?

Psychotropics versus somatic medication

Responding to frequent claims that psychotropic drug efficacy (i.e. the degree to which an antipsychotic brings about a specific result) is very small or altogether non-existent, Leucht and coworkers recently reviewed 94 meta-analyses [28]. They aimed to compare the efficacy of major somatic drugs versus psychotropic medications. The review found that effect sizes obtained by psychiatric pharmacotherapy were in the same range as most general medical drugs and this was also the case for antipsychotics. Still, it is underlined that with differences in both outcomes and diseases the results can only be interpreted qualitatively and in the light of percentage of patients helped by a specific drug.

The efficacy of antipsychotics

Large meta-analyses of placebo controlled trials show that antipsychotics in acute and maintenance treatment of schizophrenia are efficacious. A meta-analysis [45] of 38 RCTs that compared second generation antipsychotics (SGA) to placebo in the acute phase showed a moderate effect size of approximately 0.5 with a number needed to treat (NNT) of 6 for response (NNT=the number of patients that need to be treated to prevent one additional negative outcome). In another meta-analysis [30] of 65 trials, patients were stabilized on antipsychotics before being randomized to continued medication or switched to placebo. Antipsychotics reduced the rate of relapse from between 7 and 12 months compared to placebo with a NNT to benefit of 3. Patients treated with antipsychotic medication were re-hospitalized to a lesser extent and they were not as likely to drop out as a consequence of lack of effect or for any other reason.

1.3.2 Compound and mode of delivery

The differences in efficacy between the first generation antipsychotics (FGA) and SGA are small, but the metabolic, extrapyramidal and sedating side effect profiles generally differ considerably. Previous studies regarding differences in non-adherence rates for SGA and FGA are inconclusive, but often show no significant difference [45-47]. A more recent systematic review [48] and meta-analysis of relapse prevention found a difference in relapse rates between SGA (29.0%) versus FGA (37.5%) treatment. The SGAs were more likely to prevent hospitalization and relapse at the 3, 6 and 12 month follow-up and fewer dropped out due to medication intolerance.

Findings regarding the cost effectiveness of SGAs are contradictory. The results and clinical implications of two large clinical trials, CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and CULASS (Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study), were analyzed in one study [49]. In CATIE the all-cause discontinuation rate was 74% before 18 months, with a median time to discontinuation of 4.6 months. The overall efficacy of FGAs and SGAs in both study populations was similar and few differences between the groups were detected. Still, it is concluded that there is no single optimal antipsychotic suitable for all patients, but the lower risk of tardive dyskinesia and the better subjective effects favor SGAs.

During the last decade there has been an increasing focus on the metabolic side effects of antipsychotics and a concern that concomitant use of several antipsychotics, discussed below, might increase mortality among patients with psychotic disorders [50]. Data regarding the mortality rate associated with FGA versus SGA are inconclusive [51]. A ten-year follow up study of more than 1,600 patients found FGAs to be associated with doubled mortality [52], even if SGAs have been shown to be associated with more weight gain and worsening of metabolic parameters [53]. Pharmacoepidemiological research that includes all individuals residing in a country is made possible by the unique personal identity codes used in Finland, Denmark and Sweden. Nationwide register studies were performed in Finland to investigate the relationship between antipsychotics and mortality more thoroughly [29, 54-56]. Tiihonen and co-workers found that the use of any antipsychotic lowered mortality rates compared to no antipsychotic, and clozapine appeared superior. However the SGAs are a highly heterogeneous group [29], as shown in a meta-analysis [57] that questions the division between FGA and SGA altogether proposing a division based on side effect profiles.

An additional concern, apart from the profile of the actual compound is the treatment regimen and delivery system. Prescribed dose frequency is an important factor for predicting medication adherence to antipsychotics [58]. The number of daily doses have been found to be inversely associated with adherence [59] and single daily dosage to be preferred.

The administration of long acting injectables (LAI) has been shown to be associated with lower risk of hospitalizations compared to use of the same compound as an oral formulation [55]. With LAIs there is clear evidence of whether the patient has received the prescribed medication or not. If the patient misses an appointment to receive an LAI the professional caregiver is given an immediate opportunity to act in order to facilitate adherence by offering psychoeducation, cognitive support or home visits, etc. [60].

Similarly, the informal caregiver will have a window of opportunity to act as well as seek the support of the professional health care system to hopefully avoid an exacerbation.

Nevertheless, many patients are not offered or informed about the option of an LAI. The reasons might be the attitudes of the psychiatrists and other health care professionals towards LAIs or the prescribers' beliefs that patients might be negative to injectables [61, 62]. Some patients prefer oral medication and in the clinic the available medication options need to be readily available and the optimal treatment tailor made for each patient.

1.3.3 Polypharmacy

Clinicians have, for some decades, been advised against polypharmacy. However, a recent Finnish database study [56] revealed that concomitant use of several antipsychotics did not increase mortality in comparison with antipsychotic monotherapy. Instead a two-fold risk of death was observed for patients who did not use any antipsychotic. These results confirmed findings in earlier database studies by Tiihonen and coworkers [29, 54, 55]. An additional finding was that antidepressants did not increase mortality, but instead decreased the risk of suicide. On the other hand, a two-fold increase of overall mortality was seen during treatment with benzodiazepines with long elimination half-life regardless of other concomitant medication. In line with the Finnish results, a current US study [63] in a large integrated health care setting found that benzodiazepines used for insomnia were associated with a three-fold mortality rate compared to no benzodiazepine use. The observed excess mortality could not be explained by control of selective prescription of benzodiazepines for patients in poor health. The results from the Finnish register studies are also supported by a large Danish register study [64] of 28,000 patients with schizophrenia and treatment with antipsychotics, where adjunctive benzodiazepine use was associated with a 1.8-fold risk of natural death. In the same study it was also shown that the use of antipsychotics reduced the risk of death due to natural causes in middle-aged patients with schizophrenia.

1.4 Schizophrenia

1.4.1 The history of schizophrenia

In general, illnesses are defined in terms of their clinical presentation plus their course and outcome. The identification of what was later to be called schizophrenia was distinguished in 1896 as “dementia praecox” by Emil Kraepelin (1856-1926). He identified it as a distinct syndrome separate from the broad spectrum of psychoses he studied in his mental hospital [65]. The major distinction was made between dementia praecox and recurring affective episodes or manic depressive disorder, now known as bipolar disorder [66]. Kraepelin thus laid the foundation for a rational classification of psychiatric disorders. Interestingly enough he could not speak the language of his patients at the hospital where he conducted his research in Dorpat, in what is today Estonia. Therefore, his identification of dementia praecox rested primarily on his observations of the course and outcome alone [22]. According to his observations recovery was extremely rare and deterioration inevitable.

In 1911 Eugen Bleuler (1857-1939) renamed the illness schizophrenia [67] and published *Dementia praecox oder die Gruppe der Schizophrenien* [68]. The title refers to the heterogeneity of persons with schizophrenia and to his famous “four A’s”, i.e. Autism (withdrawal), Ambivalence (lack of direction and motivation), Association disturbance (thought disorder, i.e. different associations or meanings being attached to words) and Affective flattening (mood disturbances). This is the first report of the importance of psychosocial functioning in schizophrenia. None of these symptoms are, however, mandatory or specific for a diagnosis of schizophrenia today. Bleuler’s approach has been superseded by an emphasis on the so-called positive symptoms of schizophrenia (delusions, hallucinations, thought disorder) due to their easy and reliable identification and responsiveness to antipsychotic medication.

Contrary to Kraepelin, who spent his work life treating chronic inpatients without recovery in sight, Bleuler had extensive conversations with both discharged and partially recovered patients. This might have been the start of understanding the importance of building relationships in psychiatric care [24]. He was able to capture not only the course and outcome of a wider variety of the schizophrenia spectrum, but also more of the various clinical presentations. Bleuler presented a more optimistic outlook on outcome in schizophrenia. This development, of incorporating various aspects of the illness, has lead some researchers of today to present the trajectory of

schizophrenia as an *integrated sociodevelopmental-cognitive model* [69]. This takes into consideration not only the possible impact of neurodevelopment, dopamine and cognition, but also integrates them as a basis for successful treatment.

1.4.2 The epidemiology of schizophrenia

Epidemiological research on psychosis has to date focused primarily on the incidence, prevalence, risk factors and etiology, course and outcome [70]. The disorder exhibits substantial heterogeneity with regard to severity and course of illness [71], but the typical features of its natural history support the theory of a neurodevelopment genesis with an important genetic contribution [72]. The liability to develop the disorder is inherited rather than the certainty of developing it [70].

In chronic disorders such as schizophrenia, categorical outcome measures (e.g., recovered vs. persistent illness) are less operational [73]. Dimensional symptom outcomes (e.g., positive or negative symptoms of schizophrenia with hallucinations, affective flattening, or impoverishment of speech and language) and measures of disability (e.g., employment, social functioning) tend to fluctuate over time and show divergent trajectories. Compared with measuring incidence and prevalence, assessing clinical outcomes in schizophrenia is much more of a challenge.

Incidence and prevalence of schizophrenia

The *prevalence* is the existing number of cases of a condition at a single point in time as a percentage of that population. The prevalence of schizophrenia is about 0.7% with estimates in various countries ranging from 0.2-2.0% [74]. The one-year prevalence of schizophrenia was 3.7/1,000 in a recent Swedish population-based study [75] using comprehensive health care registers in Stockholm County. This can be compared to a reported prevalence of 6.7/1,000 for non-affective psychoses.

The modal age of onset is between 18 and 25 years in men, and between 25 and 35 in women [76]. The *incidence* is defined as the number of new cases of a condition over a given period of time as a percentage of the population. Geographical differences in the incidence of schizophrenia may be due to variations in definitions as well as different ratings or diagnostic manuals used. In a Swedish multi-generation register study [77] which contained information about all children, their parents and the hospital discharge register (all public psychiatric inpatient admissions), an average incidence rate of 0.2% per year was estimated. The incidence rate appeared to be fairly

stable across a wide range of cultures, climates and ethnic groups. The general lifetime risk of schizophrenia was approximated as less than 1%. Heredity increased the relative risk (RR) for schizophrenia when the proband had schizophrenia: RR 9.9, (95% CI 8.5-11.6) for parent to offspring and RR 9.0, (95% CI 8.1-9.9) for sibling to sibling.

Opposite to the findings in the Swedish multi-generation study a large review [73] found that the incidence rate fluctuated due to key variables, such as migrant status and latitude. Compared with native-born persons, migrants had an increased incidence and prevalence of schizophrenia. The distribution of incidence rates differed significantly and the migrant versus native-born rate ratio median was 4.6. The illness was found to be more frequent in men, with a male:female ratio of 1.4:1. The frequency measures also varied with urbanicity, economic status and latitude.

In an earlier review [78] the distribution of estimates did not differ according to economic status. The median incidence rates per 100,000 people for the least developed countries of 20.0 (0.4-35.0), emerging economies 11.0 (5.0-26.0), and developed countries 16.0 (8.0-48.0) showed no significant differences. Urbanicity was shown to be associated with an increased incidence of schizophrenia in a more recent review [20]. It was concluded that social drift alone could not account for these findings, where differences were found even between different neighborhoods. The variability of incidence and prevalence in schizophrenia should be taken into account when interpreting research results, as conclusions drawn need to be interpreted in the light of the sociodemographics of the population studied.

1.4.3 Disability and cost of schizophrenia

The World Health Organization has rated schizophrenia as the eighth leading cause of *disability-adjusted life years* (DALYs) worldwide in the group of 15-44 year olds [79]. DALYs are calculated as the sum of lost years of life due to premature mortality in the population and years lost due to disability. In 2004, the World Health Organization [19] estimated that over 26 million people suffered from schizophrenia and was in the top 20 illnesses contributing to the global burden of illness. In addition to the direct burden there is a substantial burden on the relatives of persons with schizophrenia [80]. In a European review schizophrenia and schizophrenia-like psychoses were among the most expensive “disorders of the brain”, with the highest yearly and lifetime costs [81]. The unemployment rate for patients with schizophrenia was almost 90%. Schizophrenia, due to both short-and long-term impairments and disabilities, was considered a great emotional, financial

and social burden to both patients and their families. The recommendation was to optimize schizophrenia treatment as it would be highly beneficial for both health- and socioeconomic reasons [41].

Reported costs of schizophrenia vary depending on methods used and expenses included. In one WHO report [19] the cumulative cost of schizophrenia was 39.0%, a cost larger than for example war (32.9%) or for road traffic accidents (19.6%). In a recent Swedish study [82] that combined hospital-based registry data with national registry data, an average annual (in 2008) cost of 42,700 € per patient with schizophrenia was found. For community mental health care an additional cost of 12,400 € was to be added, giving a total cost of 55,100 €. Improving the psychosocial functioning of the patient and avoiding hospitalizations would, according to the authors, not only reduce the suffering and burden of the patient and relatives or other informal caregivers, but directly cut the societal costs of schizophrenia.

1.4.4 Mortality and reduced life expectancy

Based on the standardized mortality ratio (a ratio between the observed number of deaths in a study population and the expected number of deaths based on age and gender), people with schizophrenia have a two to three-fold increased risk of premature death [73]. This differential gap in mortality has increased over the last decades. In a national Swedish cohort study [83] that included more than 8,000 people with schizophrenia who were followed for seven years, men died 15 and women 12 years earlier than the rest of the population. This was not accounted for by unnatural deaths (such as suicide and accidents). The main cause of the markedly premature mortality in this study was ischemic heart disease and cancer. These conditions were largely underdiagnosed in patients with schizophrenia (diagnostic overshadowing), despite having more health care contacts than average. The physical symptoms were mistakenly assumed to be accounted for by the mental illness, overseen or not prioritized. Stigma of mental illness is also known to contribute to diagnostic overshadowing and lack of treatment (treatment overshadowing) [84]. These findings were supported by a review [51] where the main causes of mortality in schizophrenia were suicide, cancer and cardiovascular disease.

Lack of antipsychotic medication was also associated with increased mortality in the Swedish cohort study [83]. These data are in line with the results from a previous large population-based 11-year follow-up cohort study [29] of almost 67,000 Finnish patients with schizophrenia. In this study long-term treatment with any antipsychotic was associated with lower mortality compared with no antipsychotic. It was also concluded that the

newer SGAs are a heterogeneous group of drugs and their association with mortality needs further study. The use of clozapine was associated with a substantially lower mortality compared to any other antipsychotic medication. These mortality data showed a decreased life expectancy of 25 years in 1996 and 22.5 years in 2006, compared to the general public.

1.4.5 Suicide

Following cardiovascular disorders, suicide is the second most common cause of mortality in schizophrenia [85], but the contribution of suicide to mortality varies dependent on type of study, age of the study cohort and length of follow-up [51]. A recent systematic literature review [86] found that suicide risk in schizophrenia was mainly related to affective symptoms, previous suicide attempts and number of psychiatric hospitalizations. Additional risk factors were younger age, male gender, early phase of the illness, having a first episode later in life, substance abuse and proximity to time of discharge. Additionally, mortality due to suicide can be assumed to be higher than measured as about 25% of undetermined or accidental deaths are suicides [87].

In a Swedish study [88] the one-year prevalence of suicide was high (3.6/1,000). The odds ratio (OR) corrected for gender and age was around 10, which was compatible with another recent estimate in the literature, 8.5 [89]. An earlier review [90] found that 10% of patients with schizophrenia eventually will commit suicide and that the rate of suicide attempts were two to five times that of the completed suicides. In a more recent meta-analysis [91] the lifetime risk of suicide was found to be half (4.9%) of that previously reported, with an increased risk near the onset of illness. A similar result was found in a later review [92] where the lifetime risk of suicide in schizophrenia also was approximately 5%.

The authors claim that suicide prevention is complex and that increased efforts need to be put into adherence to medication, as the only consistent protective factor for suicide was being both offered medication and being adherent to effective treatment. This result is in line with a finding of a current population-based cohort study [93] of all patients in Sweden who had received treatment for schizophrenia between 2006 and 2009. The longer a patient refrained from taking an antipsychotic the greater the risk of death by suicide.

1.5 Stigmatization and mental illness

1.5.1 A mark of shame

Schizophrenia is not only a severe chronic illness with high mortality rates. It is also one of the most stigmatized mental disorders [94, 95]. Stigma places a significant burden on patients and their relatives or other informal caregivers [96-98].

The word stigma originally referred to the mark left on the skin after a sharp sting, sometimes used to mark slaves and vagabonds [84]. Furthermore, the marks left in the hands of Jesus Christ after the crucifixion have been referred to as *stigmata*. These various kinds of marks led to today's metaphorical use of the word stigma, referring to stained or marked individuals who somehow are considered morally diminished. The word stigma has come to mean "any attribute, trait or disorder that marks an individual as being unacceptably different from the 'normal' people with whom he or she routinely interacts, and that elicits some form of community sanction" [99, 100]. Stigma is thus closely tied to feelings of shame and of being of lesser worth.

1.5.2 Different types of stigma

The term stigma overarches problems of knowledge (ignorance), attitudes (prejudice) and behavior (discrimination) [101]. The concept is divided into various types of stigma [102]: *Public stigma* refers to the negative views of mental illness by the general public and this has been the most common type of stigma studied in psychiatric research, where patients traditionally have not been asked about their own experiences; *self-stigma* describes the phenomenon when a patient, due to stigmatizing and discriminatory experiences related to the mental illness, incorporates the stigma as being a true reflection of themselves and starts feeling shame; *anticipated stigma*, on the other hand, refers to when stigmatizing experiences lead to avoidance of situations that might elicit stigma.

Similarly, relatives and others with close social connections can experience stigma and this is called *associated stigma*. Various studies show different results with 50 [103] to 80% [104] of the relatives reporting associated stigma. Experiences of associated stigma increase the overall burden of both the patient and the entire family and thus leads to poor function and exacerbates recovery [105]. Furthermore, *structural stigma and discrimination* encompasses the widespread exclusion and rejection of

persons with mental illness affecting every aspect of personal, social and occupational life. Structural discrimination refers to, for example, unfair legislation, unevenly distributed medical research funds not prioritizing psychiatric research projects, budget cuts and politically under-dimensioned financial plans concerning psychiatric hospital beds and expenses for optimal medication.

1.5.3 Is a diagnosis of schizophrenia stigmatizing?

The recent more strictly biogenetic view of schizophrenia has in a review [96] been claimed to negatively label the illness as being caused by definite and perhaps treatment refractory brain changes. This has been thought of as a reason for the stigmatization of schizophrenia. However, a later study showed that mentioning schizophrenia as a *mental illness* and using the word *schizophrenia* in itself did not increase social distance and stigma [98]. On the other hand a recent review and meta-analysis [106] concluded that the acceptance of mental illness by the general public has not improved despite a greater understanding of the biological correlates. More research in this field is needed.

1.5.4 Social consequences of stigma

According to the World Psychiatric Association [107] stigma creates a vicious cycle of discrimination and social exclusion for those who suffer from a mental illness and all of those who are associated with them “Stigma is the single most important barrier to quality of life of mental health consumers and family members-more so than the illness itself-and is a major impediment to mental health reform and development”.

Negative public opinions are assumed to potentially have even more potent consequences for patients and their families since the shift from psychiatric care in mental institutions to treatment in community settings [84]. This is, at least partially, caused by the demand for more frequent social interactions and for independent living. Additionally, the consequences of stigma, such as unemployment, lack of housing, diminished self-esteem and weak social support, can be major obstacles to recovery, influence long term prognosis and promote disability. Stigma and the expectation of stigma is also assumed to cause serious disruptions in family relationships and reduce normal social interactions because of a desire for secrecy.

1.5.5 Stigma and help-seeking

Regardless of the high prevalence of discrimination and the need to conceal the diagnosis, more patients with schizophrenia than with other mental disorders still receive protracted care and are prescribed medication [108]. Despite this almost half of patients with schizophrenia experience considerable levels of stigma and two-thirds report perceived discrimination due to their mental illness [109]. Stigma reduces the rate of seeking help and contributes to diminished access to care, deficient treatment, social exclusion and financial hardship [110, 111]. The lack of social networks is likely to be aggravated by stigma and discrimination [112]. A recent study [113] found that self-stigmatization, especially the feeling of being alienated from society, contributed to a negative attitude towards taking prescribed antipsychotic medication.

1.5.6 Stigma and health care

Negative attitudes towards the mentally ill, as well as towards their antipsychotic medication, may also be present in the individual's social environment and might even be found among health care providers [114]. Additionally, psychiatric medication is commonly stigmatized and often considered ineffective by the general public [95]. In a recent large international multicenter survey [25], psychiatrists reported significantly higher levels of experienced stigma and discrimination than general practitioners. This negative image of both psychiatrists and psychiatry reveals multiple layers of problems regarding the improvement of access to care and treatment itself in psychiatry [115].

To conclude, for the benefit of the patients the reputation of psychiatry and psychiatric treatments need to be improved. The specialty should be able to attract and keep qualified staff, receive an adequate (i.e. larger) proportion of the hospital budget, and continuously conduct clinical research as a basis for improved services [84]. Patients with schizophrenia would benefit directly by reduced stigma and better psychiatric and physical health [116]. The common delay in getting appropriate medical diagnoses (diagnostic overshadowing) and adequate treatment (treatment overshadowing) due to stigma would most likely be reduced [117].

1.6 Symptomatology and functioning in schizophrenia

In this doctoral thesis the DSM-IV diagnostic system (Diagnostic and statistical manual of mental disorders) [76] was used to define schizophrenia. In order to fulfill DSM criteria the disorder has to last for at least six months with a minimum set of characteristic signs and symptoms present for at least one month (active phase). Schizophrenia is characterized by *positive symptoms* (such as overt delusions and perceptual abnormalities with hallucinations, thought disorders, paranoid ideation and hostility), as well as *negative symptoms* (such as avolition, blunted affects and social withdrawal), often paralleled by *general psychiatric symptoms* (such as anxiety and depression). Additionally, cognitive impairment commonly occurs in individuals with schizophrenia contributing to the decline of occupational and social functioning. A majority of individuals with schizophrenia are not able to sustain full time competitive employment or complete higher education. Many patients need supported living and assistance in activities of daily living.

In spite of remarkable progress in the field of psychopharmacology for treating positive symptoms, clinical challenges remain in the management of negative and cognitive symptoms. These are at least equally as important as the successful treatment of positive symptoms when it comes to predicting real world functional outcome and subjective quality of life. Finally, the management of non-adherence is crucial in schizophrenia treatment [31].

1.7 Non-adherence in schizophrenia

The phenomenon of non-adherence is especially challenging in schizophrenia. The reasons are several: lack of illness awareness (including lack of insight as well as attitudes and beliefs about the nature of schizophrenia itself); direct and debilitating impact of symptoms (psychotic symptoms and cognitive deficits); further social exclusion; stigma; co-morbid disorders (such as substance abuse); and finally, the frequent fragmentation of psychiatric health care services. Also, studies on medication adherence in psychosis are limited by mostly including multi-episode patients and the demand for an informed consent, and thus a certain degree of medication adherence at study entry [118].

The key factors associated with non-adherence can further be summarized from research findings [4, 31, 119]. They encompass the illness, the treatment and medication, the organization of the health care services as well as attributes of the patient, the health care providers and the relatives or other informal caregivers. Use of compulsory supervision and inclusion in clinical trials can also affect adherence rates.

Factors associated with non-adherence in schizophrenia, based on a current review [4], are shown in Fig 1. Most of these factors are, in a slightly modified form (such as type of symptomatology or medication prescribed), valid in all medical conditions.

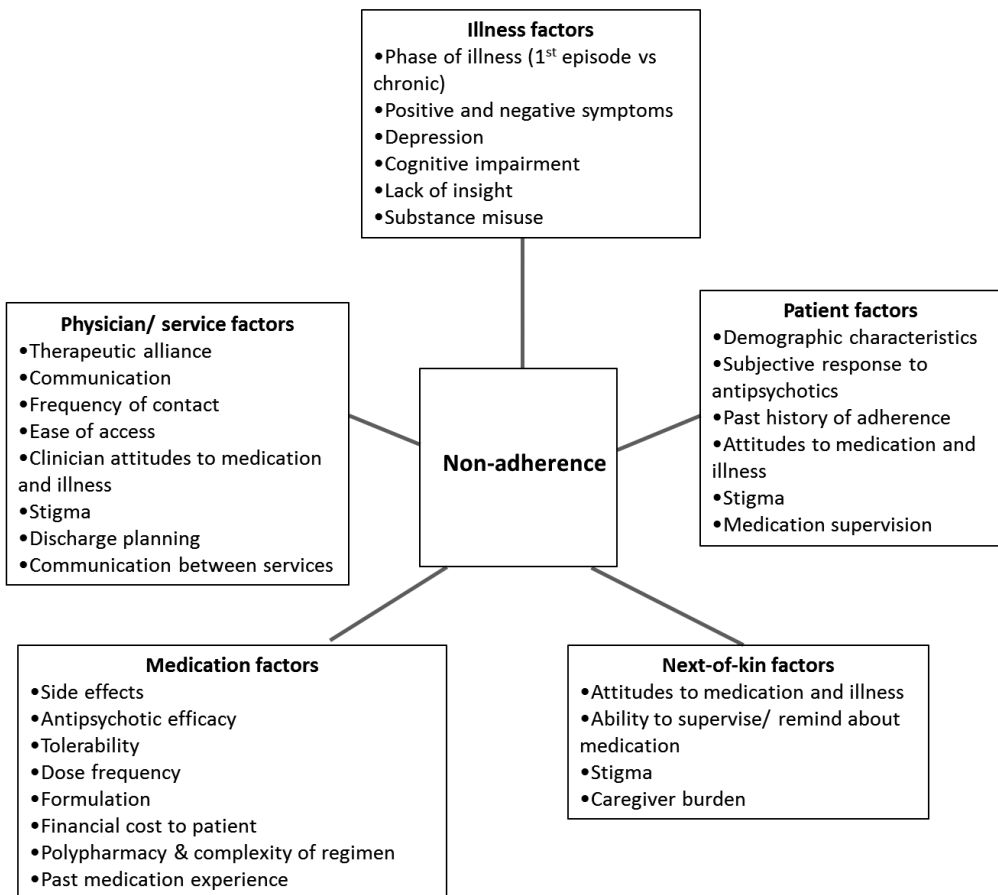


Figure 1. Key factors associated with non-adherence in schizophrenia. Modified from Haddad, Brain, Scott (2014).

1.7.1 Prevalence of antipsychotic non-adherence

Antipsychotic medication is the first-line treatment in schizophrenia [30, 120]. The optimal medication, dose, and route of administration vary according to stage of illness, individual patient characteristics and the clinical and social situation. In out-patient clinics up to 55% of first-episode patients are non-adherent to prescribed medication [46], which is associated with a five-fold risk of relapse [121, 122]. In general higher rates of non-adherence are more common in first-episode patients and a 3-year follow-up study of this population found medication non-adherence to be the only factor predictive of relapse [123]. Relapses are deleterious as recurrent psychotic episodes at all stages of illness are associated with aggravation of functional disability, cognitive decline, brain atrophy, hospitalization and higher risk of suicide [46, 88, 124, 125]. In multi-episode schizophrenia only about half of patients take their antipsychotic medication as prescribed [11] and non-adherence is associated with five year relapse rates of 80% [18, 126]. Partial adherence with medication gaps as short as 1-10 continuous days during a 12-month period is associated with a two-fold increase in hospitalization and increased risk of cognitive decline and poor outcome [112]. Frequently relapsing patients are often referred to as “revolving door” patients as they keep being readmitted.

Antipsychotic medication is no panacea. It has several drawbacks, such as side effects, a main medication effect only on positive symptoms and treatment resistance. Maintenance antipsychotic treatment does not eliminate the risk of psychotic relapses, but there is strong evidence that the risk is substantially reduced. A systematic Cochrane database review showed that continuous antipsychotic treatment decreased the risk of relapse by about two-fold or more in all stages of schizophrenia compared to intermittent treatment [35]. This data underlines the importance of adherence enhancing interventions in the clinic as well as the consideration of LAIs to improve adherence and reduce the risk of rehospitalization in schizophrenia [55].

1.7.2 The measurement of adherence

The magnitude of reported non-adherence in schizophrenia varies widely in research studies depending on definition of adherence, cohorts studied and methods employed for the measurement [6, 127]. Adherence rates as high as 86% [2] and as low as 8% [128] have been reported when defining adherence as $\geq 80\%$ of the prescribed dose correctly taken.

Various adherence measurements have been used in schizophrenia studies and the most common are self-reports and clinician ratings. Some studies also use diaries and rating scales. These subjective measurements are often quick and easy to use, but tend to overestimate adherence rates [129]. The Expert Consensus Guideline [11] recommends the use of objective measures, including electronic monitoring, pill count, plasma levels and pharmacy refill records. As objective measures are more time consuming and expensive, the literature regarding these measures is sparse. Most studies of adherence in schizophrenia in general, and especially studies using objective measures, are short and use small samples.

The Medication Event Monitoring System ([MEMS[®]], Apex Corporation, Fremont, CA, USA) [130, 131] is generally considered the reference standard for recording adherence. The MEMS[®] has a medication bottle cap equipped with a microprocessor that records the occurrence and time of each bottle opening. The reliability and predictive validity for MEMS[®] has been shown to be high [132]. However, the approach has its drawbacks. It requires regular monitorings and cannot detect discarding of pills [121, 133].

Two other objective adherence measures are pill count and plasma levels. Studies that have either used pill count as an adherence measure or have compared adherence measured by pill count and MEMS[®] have yielded disparate results [2, 128]. Plasma levels of antipsychotics are commonly used in the clinic to monitor adherence. The interpretation of the results is problematic as it may not reflect long-term adherence but be influenced disproportionately by recent use [134]. Intra-individual variability in plasma levels is considerable. A complicating factor in the clinical setting is that the time of last intake of the antipsychotic might not be recorded at the laboratory, making the interpretation of the result impossible. Patients may also increase their medication intake prior to the assay by taking so called *loading doses* to conceal poor adherence (“white coat adherence”). Additional factors such as concomitant medications, medication metabolism and smoking can affect the result. Data regarding what therapeutic plasma levels to use is limited regarding SGA [135].

1.7.3 Predictors of adherence

The reasons for non-adherence are multifactorial. In one study the risk of relapse following treatment for first episode psychosis was significantly increased by most of all non-adherence to antipsychotics, but also by persistent substance use, caregivers’ criticism and poorer pre-morbid adjustment [136]. Medication tolerability, including side effects, as well as

drug effectiveness have previously been shown to contribute to non-adherence [137]. One study showed that all previous or present antipsychotic side effects can have a durable negative impact on drug attitude and adherence [138]. Several other studies have shown inconclusive results where side effects have had no influence on adherence [8, 132, 139]. Several antipsychotics cause metabolic side effects with weight gain. The findings are mixed regarding the association between body mass index (BMI) and non-adherence. High correlations have been found both between high BMI and poor adherence [140] and high BMI and good adherence [141].

A negative drug attitude in both first [142] and multiple episode schizophrenia [128] is a known risk factor for non-adherence, but the extent to which the frequently used 10-item Drug Attitude Inventory (DAI-10) [143] can be used as a proxy measure for adherence remains unclear [144]. A prolonged structured assessment of drug attitude has to date not been performed using MEMS[®] as an objective measure of adherence. Furthermore, knowledge is lacking regarding the influence of informant (relative or other significant relationship) drug attitude on the medication regimen of the patient. One previous study showed that in patients with poorer executive function the attitude of the informant, rather than the patient's executive function, affected subjectively approximated adherence [145].

Clinical factors [146] including non-adherence [147] have been shown to be associated with lack of insight. Studies exploring the relationship between neurocognitive dysfunction and non-adherence on the other hand have been inconclusive [148]. Specific cognitive domains have been associated with non-adherence in some studies [149], but not in others [128]. Some suggest that cognitive deficits of schizophrenia may interfere with the complexity of medication taking [150]. However, a more recent study found individuals with higher cognitive function more likely to be non-adherent [141]. The findings underline the need for further studies using objective adherence measures in combination with standardized test of neurocognition.

1.8 Summary

The complexity of schizophrenia itself and the stigmatization of the illness and its treatments require special attention. Mortality rates and societal costs are high. Medication non-adherence is common due to illness, patient and treatment related factors and leads to relapse and poor psychosocial

functioning. Further, evidence based treatment methods may be difficult to employ in non-adherent, unremitted patients with psychotic symptoms and cognitive decline. Patients and their families are faced with burden and stigma. Increased knowledge and future clinical research within the field of schizophrenia is needed, to improve psychiatry and to improve the lives of those affected.

2. AIMS OF THE THESIS

The overall aim of this thesis is to increase knowledge about factors related to adherence to oral antipsychotic medication and to stigma in a large cohort of outpatients with schizophrenia and schizophrenia-like psychosis, followed for one year. The specific aims are:

Study I

To examine adherence to antipsychotics and to compare objective and subjective measures of adherence.

Study II

To investigate predictors of adherence to antipsychotics.

Study III

To explore stigma and discrimination and to test for potential associations between a) different types of stigma and b) stigma and adherence to antipsychotics.

Study IV

To study experiences of stigma in relatives to persons with schizophrenia in a treatment setting where outpatient practices include components of Assertive Community Treatment. Further, to examine the relationship between relatives' stigma experiences and overall burden.

3. MATERIAL AND METHODS

3.1 Subjects Study I-III

Studies I-III of this doctoral thesis are based on preplanned analyses of patient data from the naturalistic, prospective study Cognition, Adherence and Stigma in Schizophrenia (COAST). All patients in the COAST study were treated at state-financed urban psychiatric outpatient clinics specializing in psychotic disorders. The clinics are geographically distributed and, as customary in Sweden, located throughout the city and each with its own catchment area. This organization can facilitate collaborations between local authorities, social services, physical health care (through general practitioners) and the community mental health care.

Two hundred and fifty consecutive patients at eight psychiatric outpatient clinics at Sahlgrenska University Hospital in Gothenburg, Sweden were approached. The patients were initially identified by their psychiatrists and case managers as fulfilling the inclusion criteria of this study and they were asked if they would be interested in receiving additional information about the study.

The inclusion criteria were: age 18-65, prescription of unsupervised oral antipsychotics and a clinical diagnosis by the prescribing psychiatrists of schizophrenia or schizophrenia-like psychosis according to the DSM-IV (Table 2). The term “schizophrenia-like” was used in cases where the psychiatrist described psychopathology in accordance with DSM-IV criteria for schizophrenia without having formally made the diagnosis. Schizophrenia-like also refers to delusional disorders and psychotic disorders NOS (i.e. not otherwise specified). Delusional disorders were included, but not schizoaffective disorders due to frequent diagnostic difficulties differentiating them from bipolar disorder in the clinic. All diagnoses are henceforth referred to as schizophrenia. Exclusion criteria were: hospitalization for substance abuse in the year preceding the study, acute suicide risk, need for an interpreter, severe learning difficulties leading to special educational needs, treatment with LAIs and dispensation of antipsychotics by pillbox.

In the next step the patients were approached and informed, both orally and with written information, about the study by the research psychiatrist and one of the two study nurses. Out of the 250 approached patients, 131 eligible patients chose to participate, and gave written informed consent. However, 14

of the enrolled declined to use the electronic medication bottle (MEMS[®]) and thus 117 initiated medication monitoring (Figure 2). All initially included patients (n=131) were asked if they had a close informant (family member, close friend or other significant person) who might be willing to fill out a postal questionnaire at baseline. The informants received written information about the study and signed an informed consent.

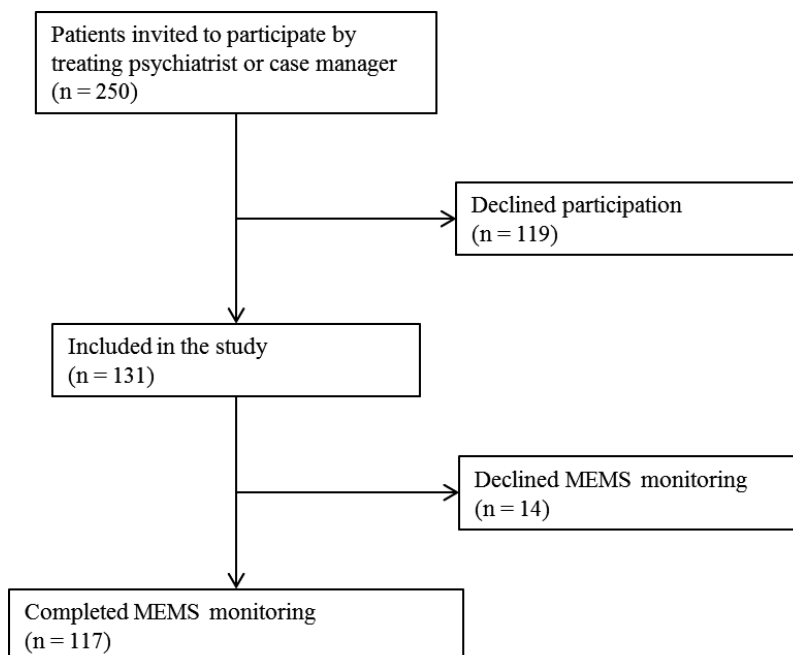


Figure 2. Flow Chart for Participants and MEMS[®]

Study I (comparison of adherence measures study): Of the 117 patients, five discontinued MEMS[®] monitoring at some point during the study. Three of these were deemed as adherent using a last-value-carried-forward procedure. One other adherent patient died a natural death (cardiac arrest) after the 10-month monitoring. Five patients were hospitalized during the study and only one of these was deemed as adherent based on case records and data from the previous MEMS[®] monitoring. Three patients were switched to LAIs by their psychiatrists and were regarded as non-adherent for the purpose of this study.

Study II (predictors of adherence study): Five of the 117 patients who were MEMS[®] monitored for a year were excluded due to missing data on various

adherence predictors, leaving a total cohort of 112 patients for inclusion in this study. Demographic and clinical characteristics of the study cohort at baseline are shown in Table 2. Mean duration of illness was 19.5 years defined as the time from the first documentation of psychotic symptoms in the medical files until the study inclusion. The mean Duration of Untreated Psychosis (DUP) was 3.4 years and defined as the time from the first documentation of psychotic symptoms in the medical files until registered onset of antipsychotic treatment. Ninety-nine of the included MEMS[®] monitored patients (n=117) identified a close informant willing to participate and 61 (62%) returned their questionnaires.

Study III (adherence and stigma study): Of the initial 117 patients who started the MEMS[®] monitoring, five discontinued and did not provide stigma data. One other patient gave incomplete responses in the stigma rating. A total of 111 patients provided a full year of MEMS[®] monitorings and completed stigma ratings.

3.2 Subjects Study IV

Study IV (associated stigma and burden in relatives): Of the 131 eligible patients in the COAST study, 111 (85%) gave contact information to a close informant who might be willing to respond to a postal questionnaire. In the next step questionnaires were sent out to the 111 persons and returned by 75 (68%). Three of these were excluded because the respondents were the patient's professional caregiver and a further seven were excluded due to missing data, leaving a cohort of 65 (59%). Table 3 shows sociodemographic characteristics of the 65 respondents (henceforth referred to as relatives), as well as data pertaining to the patients.

Table 2: Characteristics of patients at baseline: The COAST study.

Variable	Patients (<i>n</i> = 131)
Gender (male/female), n	83/48
Age, years	46 (21 - 65)
Education, years n (<12 / >12)	60/71
Marital status, n (%)	
Single	99 (75.6)
Married	4 (3.1)
Divorced/separated	18 (13.7)
Relationship	10 (7.6)
Living situation, n (%)	
Independent	68 (51.9)
Custodial care	39 (29.8)
Institution	24 (18.3)
Employment, n (%)	
Regular	17 (13.0)
Supported/sheltered/volunteer	20 (15.3)
No employment	94 (71.8)
Sick-leave, disability retirement	109 (83.2)
Duration of illness, years	19.5 (0 - 55)
Duration of untreated psychosis, years	3.3 (0 - 31)
Exacerbations	7.6 (0 - 38)
Diagnosis (DSM-IV), n (%)	
Paranoid schizophrenia	23 (17.6)
Undifferentiated schizophrenia	56 (42.7)
Residual schizophrenia	12 (9.2)
Delusional Disorder	10 (7.6)
Psychotic Disorder NOS	30 (22.9)
Symptom and function ratings	
PANSS, total	62.3 (35 - 122)
PANSS, positive symptoms	15.5 (7 - 33)
PANSS, negative symptoms	17.6 (7 - 37)
GAF, total	44.6 (25 - 76)
CGI-S, median	3 (1 - 5)

Values denote mean (range) if not specified otherwise.
Impression-Severity.

Table 3: Characteristics of the participating relatives and their ill family members (patients)

Variable	n	%	Mean	SD
Relatives (n=65)				
Male	22	33.8		
Age			61	±14.4
Education, ≤ 12 years	21	32.3		
Parent	34	52.3		
Sibling	13	20		
Child	3	4.6		
Other relative	3	4.6		
Other relationship	12	18.5		
Living together	6	9.2		
Time spent together, hours/week			14.5	±14.9
Practical help, hours/week			1.9	±5.4
Patients (n=65)				
Male	46	70.7		
Age			45.6	±10.9
Education ≤ 12 years	23	35.3		
Regular employment	10	15.4		
Supported/sheltered/volunteer	11	16.9		
No employment	44	67.7		
Independent living	38	58.4		
Duration of illness, years			19.2	±12.7
Diagnosis (DSM-IV)				
Paranoid schizophrenia	10	15.4		
Undifferentiated schizophrenia	30	46.2		
Residual schizophrenia	5	7.7		
Delusional Disorder	4	6.2		
Psychotic Disorder NOS	16	24.6		
Symptom and function ratings				
PANSS total			58.7	±13.7
PANSS positive			13.6	±5.0
PANSS negative			15.8	±5.5
GAF function			48.1	±9.4

SD = Standard deviation

4. STUDY PROCEDURES

4.1 Procedures Study I-IV

Patients were fully informed by the research psychiatrist and one of the two research nurses about the study protocol, monitoring procedures and about the plasma sampling at the university hospital lab at baseline, at 6 months and at the 12-month endpoint rating. Eligible patients were entered into the study between October 2008 and June 2011, and followed over a period of one year. Data regarding current and history of substance and alcohol abuse, DUP, duration of illness, number of previous exacerbations and hospitalizations as well as sociodemographic information was retrieved from medical records. At baseline a medical examination was performed by the research psychiatrist and BMI was calculated. Present antipsychotic medication was registered.

Patients brought their oral antipsychotics, prescribed by their psychiatrists, to the study clinic. The medication possession ratio (MPR), i.e. percentage with a valid antipsychotic prescription the day of inclusion, was thus 100% at the MEMS[®] baseline monitoring. The research psychiatrist rated the symptom level and other clinical characteristics at baseline and endpoint.

The patients, informants, staff and prescribing psychiatrists filled in ratings according protocol. The rating frequency and the MEMS[®] monitoring procedure is more closely described below.

Postal questionnaires to the informants (i.e. relatives in Study IV) were distributed at baseline. Up to two postal reminders were sent when questionnaires were not returned on time.

4.2 Measurements

4.2.1 Research psychiatrist-rated instruments

Symptom severity was rated using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) [151]. The scale consists of 30 items; each is rated from 1 (absent) to 7 (extreme). The PANSS item G12 was used to assess insight. A person was considered to be in remission if none of the 8

items, derived from PANSS and used to identify cases of symptomatic remission in accordance with the Structured Clinical Interview for Symptoms of Remission (SCI-SR) [71], were scored above 3. The time criterion of 6 months was unattainable in this study.

The current level of severity of the psychotic disorder was rated using the 7-point scale (1=normal/not at all ill, 7=extremely ill) Clinical Global Impression scale-Severity of illness (CGI-S) [152]. Psychosocial function was evaluated using the Personal and Social Performance Scale (PSP) [40] and the Global Assessment of Functioning (GAF) [153]. Both GAF and PSP are 100-point rating scales, where a higher score indicates better functioning. The PSP scale measures functioning in four areas of life: self-care, social activities, personal and social relations, disturbing and aggressive behavior.

The Discrimination and Stigma Scale (DISC 12) [154, 155] is a structured interview for assessing all the patient's past experiences or anticipation of stigma and discrimination since the first appearance of a mental illness. The scale developers gave access to the scale at the time of the endpoint visit and the scale was translated into Swedish and back translated. A focus group (patients with schizophrenia not included in the study) ensured that the terminology was well adapted to both Swedish language and context. DISC was used in Study III and the 32 items were scored according to the scale developers [155] on a 4-point scale and anchored at 0 (not at all) and 3 (a lot). A not applicable category was included for questions irrelevant to the patient, such as in relation to having children. The scale has four subscales: patient experienced discrimination (item 1-21), anticipated discrimination (item 22-25), overcoming stigma (item 26: "Have you made friends with people who don't use mental health services?", and item 27: "Have you been able to use your personal skills or abilities in coping with stigma and discrimination?"), and positive treatment due to mental illness (item 28-32). Discrimination refers to unfair treatment and unjust distinction in how different people are being treated by others. Anticipated discrimination was defined as to which extent the patients limit their involvement in important aspects of daily life due to the anticipation of stigma. Subscale mean scores were calculated by summing the rating (0-3) for each item and dividing by the number of applicable items responded to. For frequency reports of the DISC items a rating of ≥ 1 (i.e. a little or more) was used to define endorsed discrimination.

4.2.2 Self-rated instruments

Patient self-ratings were performed at baseline and endpoint. The patients' attitude, experience and beliefs about antipsychotics were assessed using the

10-item self-report Drug Attitude Inventory (DAI-10) [143]. Scores ranged from -10 (very poor attitude) to +10 (best possible attitude).

Unwanted side effects were rated 0-3 using the Udvalg for Kliniske Undersøgelser side effect self-rating scale (UKU-SERS-Pat) [156] examining four categories: psychiatric (including sedation, depression and sleep disorders), neurological (including movement disorders, tremor and akathisia), autonomic (including gastrointestinal symptoms, dry mouth or hyper salivation) and others (including sexual and metabolic side effects).

4.2.3 Informant questionnaires

In order to assess the informants' attitudes, experiences and beliefs regarding antipsychotics the research psychiatrist slightly modified the DAI-10 [143]. The same questions and the rating described above for the patient version of DAI were used, but the questions addressed the informant instead of the patient.

Further, a close informant version of the Inventory of Stigmatizing Experiences (ISE) [157] was translated into Swedish and back translated and used in study IV. The ISE consists 15 sociodemographic items followed by the Stigma Experience Scale (item 16-32) and the Stigma Impact Scale (item 33-34). The Stigma Experience Scale measures the frequency of personal experiences of stigma, both actual and anticipated stigma, along with thoughts on public views on mental illness and coping strategies. Responses for items 16-20 are ascertained with a 5-point Likert-type scale (never/rarely/sometimes/often/always for 5 items), and items 25-27, 29-32 have categorical responses (yes/no/unsure). There are also five items with qualitative free text answers but these were not analyzed in this thesis. Responses on the Stigma Experience Scale were recoded into binary variables where 1 reflects high expectancy of stigma (sometimes, often, always or yes) and 0 reflects low expectation (never, rarely or no). The Stigma Impact Scale quantifies the impact of stigma on quality of life, social contexts, family relations and self-esteem. Item 33 focuses on personal impact and item 34 on familial impact. Responses for the Stigma Impact Scale range from 0 (no impact) to 10 (highest amount of impact).

In study IV the relatives' perceived burden was rated with the Burden Inventory for Relatives to persons with Psychotic disturbance (BIRP) [158], a 10-item instrument focusing on both practical and emotional burden, and own health. Each item has four response alternatives (1=no, 2=sometimes,

3=often, 4=always); scores are summed to yield a total score (10-40 points), where a higher score reflects a higher burden.

4.2.4 Measurements of adherence

Medication Event Monitoring System (MEMS®)

The 117 patients that initiated MEMS® monitoring were instructed to take their medication as prescribed by their psychiatrists. The MEMS® bottle was monitored 6 times and refilled by a study nurse at approximately 2, 4, 6, 8, 10 and 12 months (no refill at endpoint). For patients prescribed several antipsychotics, separate bottles were employed for the monitored antipsychotics (Table 4).

Table 4: Antipsychotic medication monitored by MEMS® across study period.

MEMS® medication, n (%)	Patients
	(n = 117)
Aripiprazole	26 (19.8)
Olanzapine	25 (19.1)
Clozapine	24 (18.3)
Risperidone	17 (13.0)
Quetiapine	16 (12.2)
Paliperidone	13 (9.9)
Flupentixol	7 (5.3)
Haloperidol	6 (4.6)
Ziprasidone	5 (3.8)
Zuclopenthixol	5 (3.8)
Perphenazine	1 (0.8)
Sertindole	1 (0.8)

Percentages do not sum up to 100 percent because of polypharmacy and change of medication during study period.

Patients unable to attend the study center were monitored by the study nurse at their ordinary outpatient clinic or in their home. Antipsychotic dosing regimens varied from once (n=91, 76%), twice (n=26, 22%) to three (n=2, 2%) times daily. Patients who received treatment with depot injectables at any point of the study were regarded as non-adherent, i.e. they were not excluded from the sample but were rated as non-adherent in terms of the outcome measure.

MEMS[®] adherence was mathematically defined as the number of days which the patient took *at least* the prescribed dose divided by the number of dosing days. The possible range of this continuous measure is 0.00 to 1.00. A value of 1.00 is given for more than prescribed bottle openings. In cases with more than one bottle, the MEMS[®] adherence measure for the bottle with the lowest adherence was used. Calculations of adherence were made for every calendar day with a cut-off at midnight. Mean adherence was calculated based on all six two-month periods. MEMS[®] adherence was dichotomized into two categories, adherent (> 0.80) vs. non-adherent (≤ 0.80) [8].

Pill count

Pills remaining in the MEMS[®] device at each monitoring were counted prior to refill. Pill counts were calculated by means of inter- and extrapolations if intervals between monitoring visits deviated from the intended two months. Mean pill count over the study period was calculated and dichotomized at the same cut-off as that used for MEMS[®], i.e. ≤ 0.80 vs. > 0.80 . It should be noted that pill count is a more global measure of adherence for the whole two month period and not restricted to a single day as MEMS[®].

Plasma level measure

At least one plasma sample was available for 96 of the patients with MEMS[®] recordings. A composite measure of plasma levels and adherence to lab visits was used. Two senior psychiatrists independently rated whether plasma levels for each lab visit were in accordance with the prescribed dosage (a “No”/“Yes” rating for each sample). The number of samples with adequate levels was summed (0-3), with a value of 3 indicating adherence. Inadequately low plasma levels at any of the three lab visits and/or two missed laboratory visits were assumed to indicate non-adherence. For those with one missing visit (n=32), a revised last-value-carried-forward procedure was applied. For example, if two levels were adequate, the missing value was also regarded as adequate and the patient received an assumed value of “3”. If one or two levels were inadequate, the missing value was also regarded as inadequate. The inter-rater reliability for the plasma level adherence measure was very high (K= 0.92, $p < 0.001$). An inconsistency was found for four patients and this was solved by consensus to use the lower value. Three blood samples were collected from 51 patients. Two samples were collected from 32 patients, out of which 17 (53%) patients were considered adherent. Fifteen patients left only one blood sample. A drop-out analysis revealed that 52% of those without any blood sample and 22 % of those with blood samples were found to be non-adherent according to MEMS[®] ($\chi^2=8.07$, $p=0.005$).

Subjective ratings of adherence

The patients were asked to rate their adherence at each monitoring visit and a mean rating was calculated. Ratings of adherence were also made by the patients', clinical staff (case manager) and prescribing psychiatrist at baseline and endpoint and once by an informant. A 5-point scale (1="0-20%", 2="21-40%", 3="41-60%", 4="61-80%", and 5="81-100%") was used. For the dichotomous adherence variable, category 5 was considered adherent.

Adherence class

With the division similar to the 5-point subjective scale of adherence (1="0-20%", 2="21-40%", 3="41-60%", 4="61-80%", and 5="81-100%") adherence classes were created (Table 3). The values in each of the five classes denote percentages of patients classified by prescribed dosages correctly taken. The highest class (81-100%) represents the adherent group. All adherence measures were divided into five classes except the plasma level measure, which was rated in four classes (0-3) with 3 indicating adherence.

4.2.5 Cognitive Assessment

The semi-computerized neuropsychological test battery consisted of standard neuropsychological tests, comprising tests of speed and attention, learning, memory and executive function. The test battery was administered at baseline and endpoint. All cognitive tests were administered in a standardized sequence [159-161] and conducted in one to two sessions each lasting 60-120 minutes.

The Rey Auditory Verbal Learning Test (RAVLT) [159] was used to measure verbal learning and memory. The test consists of a 15-word list that was presented by the rater and the patient was asked to recall as many words as possible. This was repeated five times; thereafter an interference list was presented, followed by a request to recall the original list without further presentation. Finally, a delayed recall test was presented after 20 minutes. The number of words correctly recalled was summarized as a measure of the verbal learning memory.

The Continuous Performance Test-Identical Pairs version (CPT-IP) [161, 162] is a computerized vigilance test. Stimulus (the second of a pair of a four-digit number) was flashed on the computer screen at a constant rate. The patient was asked to respond as fast as possible to the stimulus using the mouse button, measuring the participants' ability to discriminate targets from

non-targets. The test is constructed in three sequences, each with 150 trials. The total score for the 450 trials was used as a measure of vigilance.

The Trail-Making Test (TMT) [163] consists of two subtests. The TMT-A was used to measure visuomotor processing speed and efficacy, while TMT-B was used to measure cognitive flexibility. The patient was asked to, as fast as possible, connect numbers (TMT-A) or number and letters (TMT-B) on a paper. The time for completing the test correctly is the scoring point [164].

The Letter-Number Sequencing test (LNS), now a subtest in the *Wechsler Adult Intelligence Scale-Third Edition* (WAIS-III) [165], is often used to assess the auditory working memory performance [166]. The patient was verbally presented with a row of numbers and letters and asked to sort them out in a specific order and to separately recall the letters and numbers in successive order. The test starts with a series of two digits; the next level is three digits, etc.

The *Vocabulary* subtest of the *Wechsler Adult Intelligence Scale-Revised* (WAIS-R) [167] has been recognized to measure both verbal and general mental abilities. The patient was presented with a word and asked to describe its meaning, starting with easy words and proceeding with increasing difficulty. Answers were assessed and graded (0 point=no or incorrect description, 1 point =partially correct description, 2 points=correct description). The sum of all points was used to measure the verbal facility.

Executive functions were measured with The Wisconsin Card Sorting Test (WCST) [168]. The test consists of 4 stimulus cards that depict figures, colors, and numbers. The patient was given 128 response cards with the task to match each response card with one of the stimulus cards. The computer lets the patient know whether the match is correct or not. The computer will change the sorting principle during the test, varying among the three possible ways to sort according to a predetermined pattern. Scores on Categories Completed, Total Errors, Preservative Responses, and Conceptual Level Responses are used to describe test performance.

A *global composite score* for cognitive function [169] was created from tests within the following cognitive domains: verbal learning [159]; sustained attention [161]; visuomotor processing speed and cognitive flexibility [163]; working memory [166]; verbal facility [167]; and executive functioning [168]. The composite cognition score was created by transforming individual test scores to z-scores using the patient sample and then averaging across tests [170].

4.3 Statistical methods used

Study I: All variables were summarized with standard descriptive statistics. Categorical variables including adherence (non-adherent vs. adherent) were analyzed with Pearson's χ^2 -method or with Fisher's exact test. Kappa ("K") coefficients describe the agreement between MEMS[®] and another adherence measure, as well as inter-rater reliability for the plasma level adherence measure. Means of MEMS[®], pill count, the plasma level measure and patient ratings were calculated in order to capture adherence across the entire period. Concordance was measured, i.e. the frequency of patients that were identified as adherent according to both MEMS[®] monitoring and another specified measure of adherence. Differences between groups regarding symptom scores, CGI-S, and GAF were analyzed with Mann-Whitney U tests. Change in adherence over the study year was analyzed with an analysis of variance for repeated measurements. The continuous measures of adherence were also entered in a principal component analysis with Oblimin rotation, assuming a relationship between the variables. SPSS 20.0 was used.

Study II: Group comparisons were carried out using the Student's t-test for continuous variables. The χ^2 test was used for categorical variables. Spearman's rank correlation coefficient was employed to estimate the correlation between variables. Univariate logistic regression analyses were performed to estimate the odds of MEMS[®] non-adherence by each predictor variable. In order to reduce the number of variables a composite score for cognitive function, regarded as a measurement of the global level of cognitive performance, was created. Individual test scores were transformed to z-scores using the patient sample and then averaging across tests. The composite score was also stratified by tertiles, which were entered in a separate univariate logistic regression model as a categorical variable to test for non-linear associations. The method of purposeful selection was used [171] when building a multivariate logistic regression model for adherence according to MEMS[®]. To assess performance of the identified predictors of adherence, a receiver-operating characteristic curve (ROC) was used. The area under the curve (AUC) was calculated and compared to a curve obtained by chance using the Wilcoxon statistic. R version 2.15.2 and SAS 9.3 were used for all statistical analyses.

Study III: Group comparisons were carried out using the Student's t-test for continuous variables. The χ^2 test was used for categorical variables. Spearman's rank correlation coefficient was employed to estimate the

correlation between variables. Univariate logistic regression analyses were performed to estimate associations between DISC mean subscale scores and MEMS[®] non-adherence. In a second step multivariate logistic regression models were fitted for each DISC subscale mean score, adjusted for DAI-10 and PSP. The latter two were included as it was previously shown (in Study II, the predictors of adherence study) that drug attitude (DAI-10) and psychosocial function (PSP) are associated with non-adherence after analyzing a broad range of candidate factors. The number of confounders was limited to two due to the relatively small number of non-adherent patients. All measures included in the analyses were from the endpoint rating. Multicollinearity was tested for in the multivariate models using the Variance inflation factor (VIF). A VIF-value of 2.5 or higher was used as a cut-off indicating problematic multicollinearity. R 3.0.1. and IBM SPSS 21.0 was used for all analyses.

Study IV: Group comparisons were carried out using the Student's t-test for continuous variables. For categorical variables differences in proportions were tested with the χ^2 test. Ordinal logistic regression was used to analyze associations between specific ISE items and BIRP score tertiles. For the analysis of the relationship between associated stigma and relatives' overall burden focus was put on an item that captured the relatives' own experience of stigma. Item 19 ("Have you experienced stigma due to your relative's illness?") was deemed to be the item that best captured this phenomenon, and those who responded "sometimes/often/always" were considered to be the exposed group. Similarly, item 29 ("Do you avoid situations that might be stigmatizing for the family?") was considered to be the item that best captured anticipated stigma on the part of the relative. As frequency but not severity is quantified for both these items, measures of impact were included. Therefore, as items 33 and 34 deal directly with the impact of stigma on the individual (item 33) and on the entire family (item 34), these items were considered to be of particular interest when testing for associations with relative's burden. In a first step individual ISE variables were analyzed in univariate ordinal logistic regression models. In a second step they were analyzed in separate ordinal logistic regression models, adjusting for confounders. The potential confounders age, gender, symptom burden in patients (PANSS total) and patient function (GAF) were screened separately in univariate ordinal logistic regression models and variables with p-values lower than 0.2 were used as confounders. R 3.0.1. and IBM SPSS 21.0 were used for all analyses.

5. ETHICAL CONSIDERATIONS

All patients, independent of diagnosis, are in a subordinate position in relation to the health care system. Special caution is a necessity when asking persons with schizophrenia to take part in a research study. Many have previously been subject to involuntary treatment and may suffer from debilitating psychotic or cognitive symptoms, as well as poor self-esteem due to stigma and discrimination. With these aspects in mind patients were first approached through, and thus with the approval of, their staff or treating psychiatrists in the outpatient clinics. This procedure might have introduced a selection bias towards more well-functioning and adherent patients, but was considered to be the most ethical.

The Ethics Committee for Medical Research at the University of Gothenburg approved of the COAST study. In accordance with the provisions of the Helsinki Declaration, informed consent was obtained from the patients after they had received oral and written information about the study. Informants were only approached after the approval of the patients. Thereafter the informants received written information and an offer to receive additional oral information. Informants willing to fill in study related questionnaires also gave their written informed consent. Both patients and informants were assured that they could withdraw from the study at any time without having to explain the reason for withdrawal and that this would not in any aspect affect their care.

The baseline and endpoint clinical investigations, including the sessions for cognitive testing, were time-consuming and often strenuous for the patients. Most patients needed one or several breaks during sessions and sometimes the investigations had to be scheduled in several consecutive sessions. Patients were therefore offered a light meal of a total value of 60 Swedish crowns (about 6 €) and single tickets for the city public transportation system at these visits.

6. RESULTS

6.1 Results Study I

6.1.1 Drop-out analysis

The group of 14 patients who declined MEMS[®] monitoring did not differ from those who participated with regard to gender ($\chi^2=0.44$, $p=.507$) and age ($\chi^2=0.001$, $p=.976$). A larger proportion of the participants had education beyond 12 years ($\chi^2=6.781$, $p=.009$). The drop-outs had a more severe illness (CGI-S: $z=2.10$, $p=.035$; and PANSS total: $z=2.538$, $p=.011$), but no significant difference in functioning as measured by GAF ($z=1.412$, $p=.158$).

6.1.2 Subjectively and objectively measured adherence

Non-adherence (MEMS[®] ≤ 0.80) was observed in 27% of the patients, which was almost identical to the pill count non-adherence (29%). Half (56%) of the patients were judged to be adherent with the plasma based measure that included adherence to lab visits. Among the subjective measurements, the highest figure was observed for the self-rated measure (mean adherence 92%), and the lowest for the psychiatrist-rated measure (58%) (Table 5). As adherence class does not apply to the composite plasma measure, the values denoting the percentages of patients classified are not evenly distributed in the table format.

Table 5: Adherence across study period and agreement between adherence measures.

Variable	Adherence ratings						
	MEMS [®]	Pill count	Plasma level ^b	Patient	Informant	Staff	Psychiatrist
Adherence class ^a							
0.00-0.20	4%	8%	6%	1%	0%	2%	0%
0.21-0.40	3%	6%	22%	1%	3%	0%	4%
0.41-0.60	6%	2%	15%	0%	3%	6%	10%
0.61-0.80	14%	14%		6%	7%	16%	28%
0.81-1.00	73%	71%	57%	92%	87%	77%	58%
Concordance with MEMS [®] adherence	-	89%	56%	79%	77%	80%	68%
K (kappa) for MEMS [®] adherence	-	0.72	0.05	0.30	0.35	0.46	0.31

^a Values denote percentages of patients classified by prescribed dosages correctly taken.

^b Adherence class does not apply for plasma level adherence which was rated 0-3 with 3 indicating adherence.

6.1.3 Relationship between adherence measures

The relationships between MEMS[®] adherence and each of the other measures are shown in Table 5. MEMS[®] adherence was highly correlated with pill count (concordance=89% and $K=0.72$, $p < .001$). Only 13 patients were differently classified: six patients as adherent according to pill count and non-adherent according to MEMS[®], and vice versa for seven patients. Concordance and K were lower for all other adherence measures and very low for the relationship between MEMS[®] adherence and the plasma level measure (concordance=56% and $K=0.05$, $p=.607$). Forty-four percent of the patients were differently classified, 31(32%) were classified as adherent according to MEMS[®] and non-adherent according to the plasma level measure, and vice versa for 11 (12%). Adherence measures were also entered into a principal component analysis in order to analyze interrelationships between all measures. Three components were yielded (Table 6). MEMS[®] recordings, pill count and informant ratings had their highest loadings in the first component, the plasma level measure alone in the second and patient, psychiatrist and staff ratings in the third. The component analysis confirms the results from the analysis of concordance.

Table 6: Principal component analysis with Oblimin rotation of adherence measures.

Measure of adherence	Component			h^2
	I	II	III	
Adherence, pill count	0.93	0.24	0.43	0.87
Adherence, MEMS [®]	0.85	0.03	<i>0.57</i>	0.77
Adherence rating, informant	0.79	0.21	0.32	0.63
Adherence, plasma levels, consensus	0.25	0.99	0.10	0.98
Adherence rating, staff	<i>0.51</i>	0.02	0.90	0.82
Adherence rating, psychiatrist	0.31	0.08	0.85	0.73
Adherence rating, patient	<i>0.65</i>	-0.01	0.82	0.77
Total variance explained	0.52	0.16	0.12	0.82

The highest component loading is in bold, and loadings above 0.50 in italics. h^2 is the communality or the proportion of the variance of the variable that is explained by the components.

6.1.4 One year MEMS[®] and pill count adherence

A comparison between MEMS[®] and pill count mean adherence over time is shown in Figure 3. Mean adherence across the study period for MEMS[®] was 84% (95% C.I. 73 to 88%) and as measured by pill count 82% (95% C.I. 77 to 87%). Mean adherence for MEMS[®] and for pill count both showed non-significant drops during the last monitoring period.

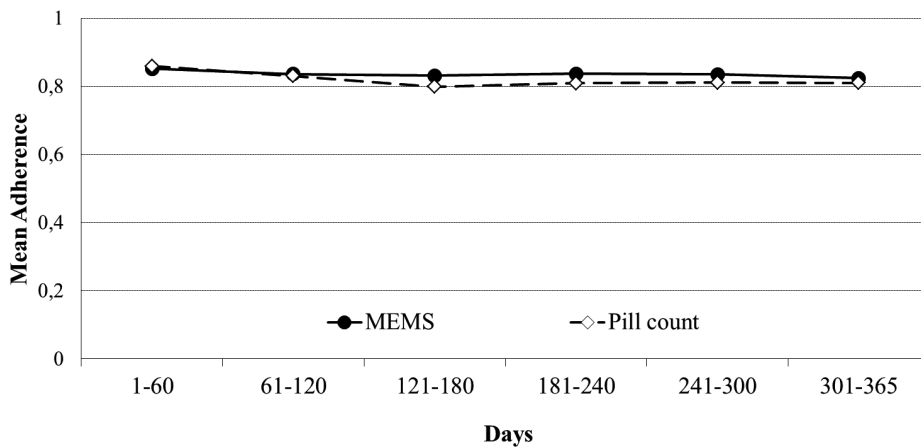


Figure 3. Comparison between mean adherence as measured by MEMS[®] and pill count at each two month assessment across study period.

6.2 Results Study II

6.2.1 Drop-out analysis

Nineteen of the initially recruited 131 patients either declined to use the MEMS[®] bottle or lacked sufficient data for the predictor analyses. They did not differ from the 112 included patients in terms of age, gender or education. However they had lower level of function (GAF, $t=2.75$; $p=.009$; PSP, $t=3.10$; $p=.004$) and greater symptom severity (PANSS positive, $t=-2.16$; $p=.040$; PANSS negative, $t=-2.44$; $p=.023$; PANSS general, $t=-2.16$; $p=.042$).

6.2.2 Predictors of MEMS® non-adherence

Non-adherence (MEMS® adherence ≤ 0.80) was observed in 31 of the 112 patients (27%). Sixty-five of the adherent patients (80.2%) had antipsychotic monotherapy at baseline and 16 (19.7%) had ≥ 2 different MEMS® monitored antipsychotics at baseline. Of the 31 non-adherent patients, 21 (67.7%) had monotherapy and 10 (32.3%) had ≥ 2 antipsychotics.

In univariate regression models (Table 7) a more negative drug attitude (low scores on DAI-10), higher positive symptom burden (PANSS positive subscale), poor function (PSP), psychiatric side effects (UKU-SERS-Pat) and lack of insight (G12) predicted non-adherence. There was no association between global cognitive function, substance abuse, BMI, DUP, duration of illness, number of exacerbations, type of antipsychotic (FGA/SGA) or medication regimen and non-adherence. In the adherent sub-group 49 (60.5%) were in remission compared to 15 (48.4%) in the non-adherent group, but no association with adherence was found.

In the informant subsample (n=61), where ratings with the slightly modified DAI-10 were performed, a more negative drug attitude in informants was associated with non-adherence in a univariate logistic regression analysis, with an OR (0.82; 95% CI: 0.68-0.97; p=.024) similar to that observed for the DAI-10 patient version. A weak, though significant correlation ($\rho=.350$; p=.006) was observed between DAI-10 informant and patient ratings.

Table 7: Univariate logistic regression models predicting MEMS® non-adherence by demographic and clinical measurements

Variable	Adherent (n = 81)	Non-adherent (n = 31)	OR (CI95%)
Male, n (%)	47 (58)	22 (71)	0.57 (0.23 - 1.38)
Age	46.9 (21.5 - 65.9)	43.5 (22.4 - 65.7)	0.97 (0.94 - 1.01)
Body mass index	30 (20.0 - 63.6)	28.7 (16.4 - 43.5)	0.97 (0.91 - 1.02)
Living situation, n (%)			
Custodial care	19 (23.5)	7 (22.6)	1.24 (0.44 - 3.49)
Institution	8 (9.9)	8 (25.8)	3.38 (1.09 - 10.42)
Substance and alcohol abuse, n (%)	24 (29.6)	11 (35.5)	1.32 (0.44 - 3.93)
Duration of untreated psychosis	3.3 (0 - 22)	4.1 (0 - 31)	1.02 (0.96 - 1.10)
Duration of illness	19.4 (1 - 52)	19.8 (0 - 55)	1.00 (0.97 - 1.04)
Exacerbations	7.3 (1 - 38)	7.5 (2 - 19)	1.01 (0.93 - 1.09)
First generation antipsychotics, n (%)	14 (17.3)	2 (6.5)	3.30 (0.71 - 15.35)
Medication regimen (1/ ≥2 per day), n (%)	58 (72)/23 (28)	22 (71)/9 (29)	1.03 (0.41 - 2.57)
PANSS subscale			
positive	20.4 (14 - 37)	22.5 (15 - 33)	1.01 (1.01 - 1.20)
negative	22.5 (14 - 36)	24.5 (14 - 36)	1.10 (1.00 - 1.17)
general psychopathology	45.3 (35 - 62)	46.8 (34 - 58)	1.06 (0.98 - 1.14)
Judgment and insight	3.6 (2 - 6)	4.1 (2 - 6)	1.61 (1.08 - 2.42)
DAI-10	6.2 (-4 - 10)	2.4 (-10 - 10)	0.79 (0.70 - 0.90)
PSP	49.2 (30 - 75)	42.8 (30 - 68)	0.94 (0.91 - 0.99)
SCI-SR, n (%)	49 (60.5)	15 (48.4)	0.61 (0.27 - 1.41)
Side effects			
psychiatric	1.6 (1.0 - 3.0)	1.9 (1.0 - 3.20)	3.95 (1.60 - 9.80)
neurological	1.4 (1.0 - 2.88)	1.5 (1.0 - 2.25)	1.35 (0.50 - 3.64)
autonomic	1.4 (1.0 - 2.91)	1.4 (1.0 - 2.18)	0.96 (0.30 - 3.10)
other	1.4 (1.0 - 2.5)	1.3 (1.0 - 2.25)	0.98 (0.35 - 2.80)
Cognitive composite score	0.14 (-1.6 - 1.3)	0.12 (-1.2 - 1.2)	0.95 (0.45 - 1.99)

Values denote mean (range) if not specified otherwise.

In multivariate regression models, low patient-rated DAI-10 and PSP scores emerged as predictors of non-adherence (Table 8).

Table 8: Age and gender adjusted multivariate logistic regression model predicting MEMS[®] non-adherence by clinical measurements.

Variable	OR	CI95%	p-value
Age	0.96	0.92 - 1.03	.070
Gender	1.77	0.60 - 4.99	.269
DAI-10	0.71	0.69 - 0.89	<.001
PSP	0.94	0.90 - 0.98	.007

The drug attitude of the patient emerged as a significant predictor of adherence in all model configurations and thus an ROC analysis was performed to determine the ability of the instrument to correctly diagnose adherence status. Figure 4 shows the sensitivity (i.e. the proportion of non-adherent patients correctly identified as non-adherent) and 1-specificity (i.e. the proportion of adherent patients falsely identified as non-adherent) of the DAI. The area under the curve (AUC) was 0.73, indicating a performance significantly better than chance ($p < .001$). At the “optimal” cut-off of 4 the sensitivity was 0.68 and the specificity was 0.32.

A somewhat larger AUC (0.78, $p < .001$) was observed when the ROC procedure was applied to the multivariate regression model including DAI-10, PSP, age and gender. For the subgroup with informant data ($n=61$), the AUC for the DAI-10 informant version was 0.68 ($p=.021$).

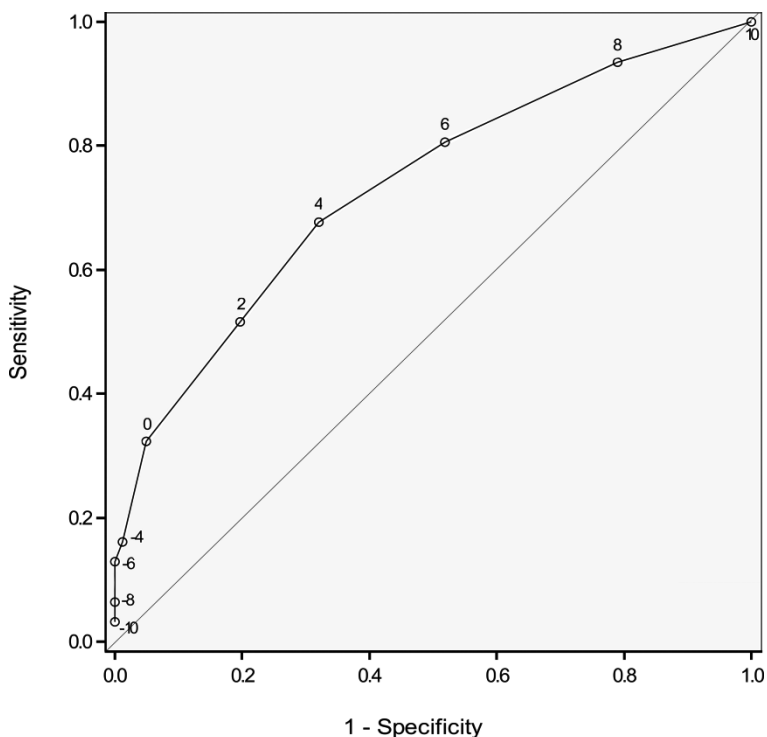


Figure 4. ROC-curve demonstrating the accuracy of the DAI-10 to predict non-adherence to antipsychotic treatment (mean MEMS[®] \leq .80) across the one year study period ($n = 112$, $AUC = 0.73$). Markers on the curve denote DAI-10 scores.

6.3 Results Study III

The 20 drop-outs who had initially accepted participation in the COAST study did not differ from the 111 patients with both stigma and adherence data in terms of age, gender or education. However they had greater total and general symptom severity, as has been described in the drop-out analysis (section 6.2.1) for Study II. Out of the 112 patients included in Study II one patient left incomplete DISC responses, leaving a cohort of 111 patients for Study III.

6.3.1 Level of stigma and discrimination

Of the 111 included patients the proportions with a rating of “a little”, “moderate” or “a lot” (≥ 1) per DISC subscale were as follows: experienced discrimination 31.5% (n=35), anticipated discrimination 64.8% (n=72), overcoming stigma 63.1% (n=70), and positive treatment 5.4% (n=6). The mean DISC subscale scores (SD) were: experienced discrimination 0.7 (0.4), anticipated discrimination 1.4 (0.7), overcoming stigma 1.1 (0.8), and positive treatment 0.3 (0.3).

The reported proportion of experienced stigma and discrimination on the single DISC item level is shown in Figure 5. The highest proportion included experienced discrimination in social relationships and mostly in making/keeping friends (71%) and in the neighborhood (69%). Almost two-thirds (62%) of the patients reported having been avoided because of their mental health problems. About half of the patients experienced discrimination by their families, in intimate relationships, regarding employment and by mental health staff. More than one-third (36%) had been treated unfairly when seeking medical attention for physical health issues. Due to anticipated stigma most patients (88%) wanted to conceal their mental health problems from others and 70% stated that anticipated discrimination resulted in avoidance of close personal relationships. About half reported that they avoided applying for work (51%) or education (43%) for fear of unjust treatment because of their mental illness. Most patients (78%) claimed to have at least some personal strategy and skill to overcome and cope with stigma. Experiences of positive treatment by family or other significant person because of the patient’s mental illness was experienced by 51%.

The experienced and anticipated discrimination subscales were positively correlated ($\rho=.503$; $p < .001$), while anticipated discrimination was observed to be inversely associated with overcoming stigma ($\rho=-.365$; $p < .001$). Moderate correlations were observed between PSP and anticipated discrimination ($\rho=.311$; $p=.001$) and PSP and overcoming stigma ($\rho=.487$; $p < .001$). The correlation between DAI-10 and overcoming stigma ($\rho=.242$; $p=.010$) was also moderate. No other correlation between independent variables reached significance.

6.3.2 Association between stigma and adherence

Non-adherence (MEMS[®] adherence ≤ 0.80) was observed in 30 patients (27.3%). When DISC subscale mean scores were entered in separate regression models (including all 111 patients in Study III) neither experienced nor anticipated stigma was associated with adherence. An

inverse association was shown between overcoming stigma and non-adherence, i.e. patients who reported lower skills in coping with stigma were more likely classified as non-adherent.

After adjusting the logistic regression models for DAI-10 and PSP, none of the DISC subscale mean scores reached significance in association with non-adherence in the multivariate model.

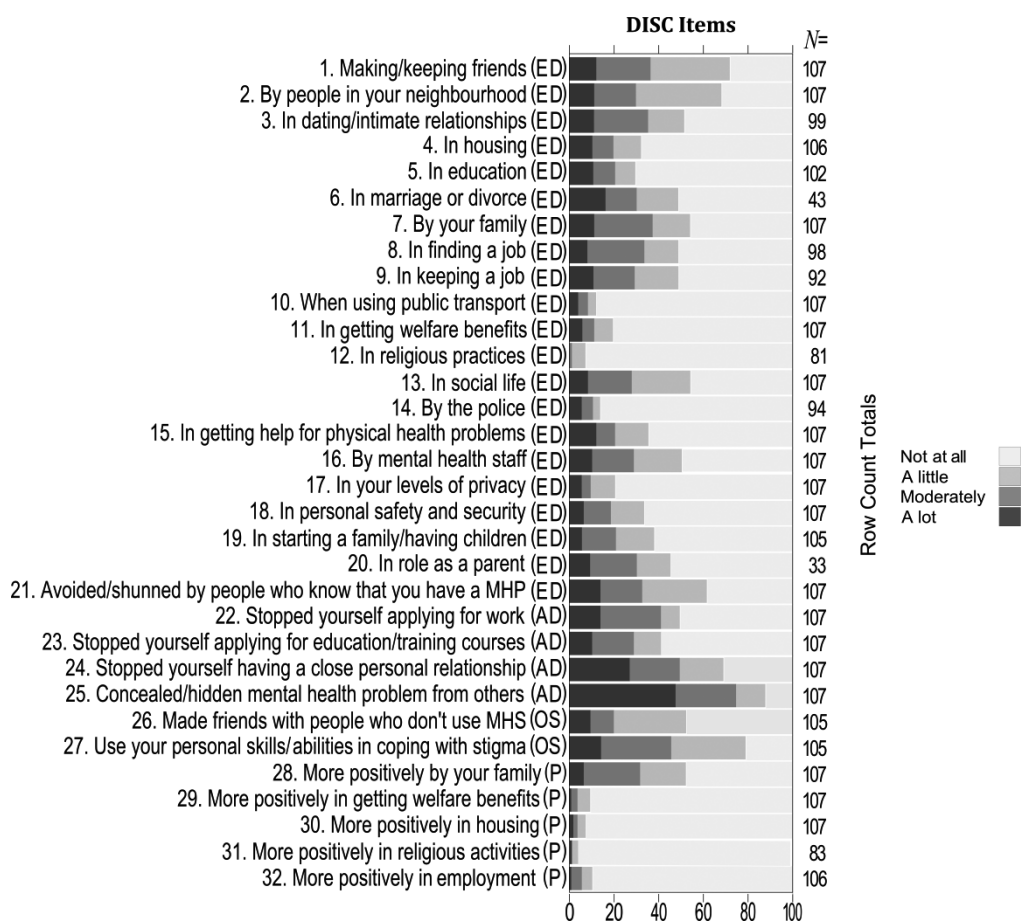


Figure 5. Proportions of DISC items. N refers to applicable/valid item responses. ED = Experienced discrimination subscale; AD = Anticipated discrimination subscale; OS = Overcoming stigma subscale; P = Positive treatment subscale; MHP = Mental health problem; MHS = Mental health service

6.4 Results Study IV

6.4.1 Drop-out analysis

Patients with (n=65) and without (n=66) participating relatives did not differ in terms of age, gender or function. However, patients without data from relatives had fewer years of education ($\chi^2=5.6$; $p=.028$) and higher total scores on the PANSS (63.8 vs. 58.7 $t=2.1$; $p=.037$).

6.4.2 Ratings of stigmatizing experiences

According to the first part of the ISE (Stigma Experience Scale) most relatives, (n=56, 93%) thought that “people think less of those who have mental illness.” An identical proportion responded that they thought that “the average person is afraid of someone with serious mental illness.” Almost half of the responding relatives (n=30) reported that their relative with schizophrenia was sometimes, often or always stigmatized. Own experiences of stigma (item 19) were reported sometimes, often or always by 11 (18%). Slightly over one quarter (n=16) acknowledged that other family members had been stigmatized. Anticipated stigma (item 29) was experienced by one fifth (n=13) of the relatives. One quarter (n=15) stated that their “experiences with stigma had stimulated a family member to speak out for the rights of the mentally ill” and 9 (15%) actually took part in programs to increase public knowledge about stigma.

The second part of the ISE (Stigma Impact Scale) showed that for both the impact of stigma on the personal level (item 33) and on the family as a whole (item 34), the highest impact was found on family relations and quality of life.

6.4.3 Ratings of relatives' burden

Relatives' responses to each BIRP item are shown by frequency category in Figure 6. The mean total per respondent (all ten items) was 14.2; the range was broad (10-30). The highest burden ratings (on a single item level) were expressed in item 2, i.e. the area of needing to help the mentally ill relative to occupy him/herself (mean 1.72), and in item 7, i.e. in feeling strain because of his/her mental problem (mean 1.83). Relatively few expressed worry that the patient would harm someone (item 5, mean 1.03) or commit suicide (item 6, mean 1.18).

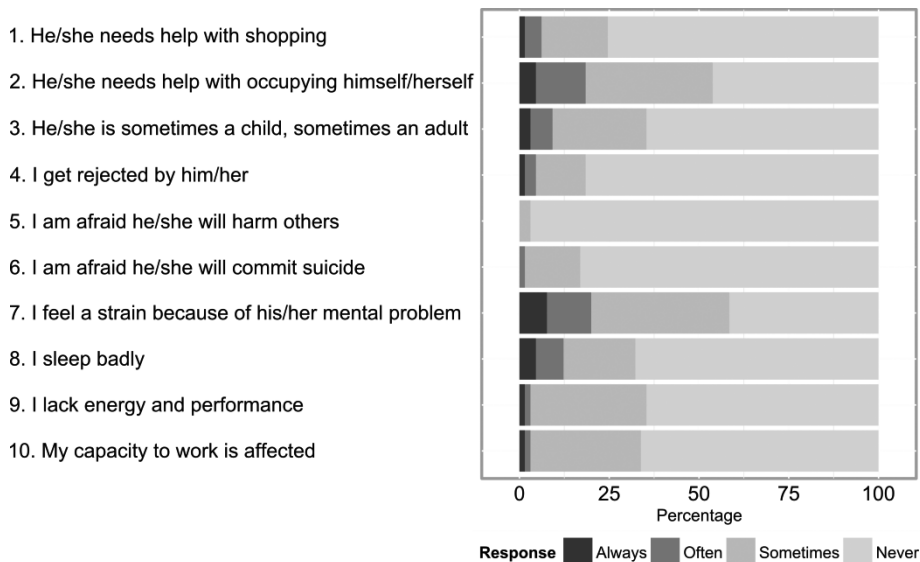


Figure 6. Proportions of respondents reporting burden by frequency categories in accordance with the Burden Inventory for Relatives of persons with Psychotic disturbances.

6.4.4 Relationships between stigma and burden

Neither experienced nor anticipated stigma was associated with level of burden (Table 9). Higher stigma impact ratings on items related to personal quality of life and self-esteem were associated with higher overall burden, as were higher ratings on familial impact on quality of life, social contacts and family relation. Findings from adjusted models are also shown in Table 8. Out of potential confounders, PANSS and GAF were strongly correlated ($\rho = -.60$) and due to the small sample size PANSS was left out and only GAF and patient age were included as confounders. Both personal and familial stigma impact on quality of life remained associated with relatives' burden after adjustment for patient age and level of functioning (GAF).

Table 9: Ordinal regression models demonstrating relationships between selected ISE^a variables and levels of burden (BIRP^b) in relatives to persons with schizophrenia.

Variables	Univariate			Adjusted ^c		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Experienced stigma (n=60)	2.71	0.78 – 9.39	.116	1.89	0.52 - 6.94	.337
Anticipated stigma (n=57)	0.26	0.04 – 1.71	.162	0.31	0.04 - 2.14	.232
Personal impact (n=59)						
Quality of life	1.30	1.08 - 1.56	.006	1.24	1.03 - 1.50	.024
Social contacts	1.08	0.91 - 1.29	.355	1.03	0.86 - 1.24	.740
Family relations	1.14	0.97 - 1.35	.103	1.11	0.94 - 1.31	.226
Self-esteem	1.18	1.00 - 1.39	.041	1.13	0.96 - 1.34	.136
Family impact (n=53)						
Quality of life	1.35	1.11 - 1.66	.003	1.26	1.03 - 1.56	.026
Social contacts	1.20	1.00 - 1.43	.047	1.11	0.92 - 1.33	.277
Family relations	1.26	1.04 - 1.52	.017	1.16	0.95 - 1.42	.135

^aInventory of Stigmatizing Experiences

^bBurden Inventory for Relatives to Persons with psychotic disturbance

^cAdjusted for patient age and GAF (function)

7. DISCUSSION

7.1 Main findings of the COAST study

Almost one-third of the patients taking part in the COAST study were non-adherent to their oral antipsychotics according to the reference standard MEMS[®].

In the study comparing adherence measures (Study I), MEMS[®] and pill count were found to be highly correlated. The poorest concordance was found between MEMS[®] and the plasma level measure. Adherence was underestimated by the prescribing psychiatrists, whereas patients and informants overestimated it.

In the predictors of adherence study (Study II) a positive drug attitude, in combination with good psychosocial function, emerged as the best predictors of MEMS[®] monitored adherence across the 12-month study period in adjusted models. Higher positive symptom burden, poor insight, psychiatric side effects and negative informant drug attitude were also related to non-adherence.

Almost two-thirds of the patients in the stigma and adherence study (Study III) reported experienced or anticipated stigma and discrimination, especially in social relationships. Half felt discrimination by mental health staff. Coping with stigma was associated with adherence in univariate analysis, but no association was found between stigma and adherence in adjusted models.

In the associated stigma and burden in relatives study (Study IV) one-fifth of the relatives avoided situations that might elicit stigma, but there was no association between experienced and anticipated stigma and burden. Stigma impact regarding both the relative's personal quality of life and quality of life for the whole family were both significantly associated with overall burden in adjusted models.

7.2 Strengths of this study

We believe that this is the largest and longest study of any medical diagnosis measuring adherence using MEMS[®] for a full year. Also, it is to our knowledge the first study to combine an objective measure of adherence and the use of a valid and psychometrically strong measure of patient experienced stigma and discrimination, and to employ structured instruments to examine

the relationship between experiences of both stigma and burden in relatives to persons with schizophrenia.

The overall strengths of this naturalistic non-interventional study were the long observation period of a whole year and the multiple monitorings with an objective measure of adherence. As adherence fluctuates over time due to clinical and environmental factors, the clinical variations of adherence might be more adequately captured by a prolonged monitoring period. Other strengths were the few exclusion criteria, home visits to reduce the risk of missing data, the same research psychiatrist performed all the clinical ratings and few patients lost to follow-up. Also, plasma levels are commonly used in clinical practice but to date only a few studies have compared plasma level adherence measures with other objective measures of adherence.

Finally this is, as far as we know, the first study to include a structured rating of close informant drug attitude to test if the drug attitude of the informant is a potential predictor of patient adherence. Informants were also asked to rate the patients' adherence and to fill in questionnaires regarding their own experiences of stigma and burden in relation to having a relative with schizophrenia. This approach is in line with modern evidence based community psychiatry emphasizing the importance of including informal caregivers, such as relatives [172].

7.3 Limitations of this study

7.3.1 Considerations regarding the adherence rate

The power of the COAST study to detect potential predictors of non-adherence might have been affected by the relatively low number of patients with non-adherence (n=31; 27%). MEMS[®] is generally considered the reference standard for adherence measurement [134] and the ≤ 0.8 cut-off for MEMS[®] non-adherence was chosen as it is commonly used for research purposes [8]. Nevertheless it might not be a true reflection of real world non-adherence. Also, eligible patients were identified by their case managers or clinical psychiatrists and this might have introduced a selection bias towards more adherent patients. These patients may therefore also have reported less experiences of stigma. Another consideration is that staff might have been less likely to suggest the inclusion of patients with a previous record of non-adherence and several relapses due to fear of introducing study related stress and increased risk of exacerbations.

At baseline all patients had filled prescriptions from their psychiatrists and came to the first monitoring with their medication. Also, the regular monitorings of adherence could have increased adherence rates. Similarly, the heightened focus on adherence, like in any other adherence study, might have decreased the overall non-adherence rates of the study patients. On the other hand this would not be expected to impact differently on the various adherence measures. Further, due to inclusion of only baseline data and mean adherence of the twelve month study period, no conclusion about the temporal relationship between the predictors of adherence and the medication taking behavior can be made.

7.3.2 Adherence measure considerations

There are some obvious limitations concerning the adherence measures. MEMS[®] and pill count cannot detect discarding of pills, but by also including other frequently used subjective and objective adherence measures in the same study the likelihood of capturing non-adherence increased.

One important limitation concerns the plasma level measure. Plasma was sampled only three times because four samplings were not considered realistic as the patients had to travel to the lab at the university hospital. Also, plasma level adherence was rated in four categories (0-3) rather than five for the other adherence measures and therefore the adherence class (percentage of patients classified by prescribed dosages correctly taken) does not apply for plasma level adherence. In some previous studies adherence has been defined as a plasma level variability of less than 30% between samples [11]. This definition captures stability over time, but does not reflect whether the levels are appropriate in regard to the prescribed dosage. Further, partial non-adherence may be missed. Since there is no reference standard for the evaluation of plasma levels as a long term adherence measure, we constructed a composite measure to take into consideration not only the plasma level as such but also adherence to lab visits.

There are several general drawbacks in the interpretation of plasma levels, [11, 135] such as what therapeutic plasma level to use as criterion for SGA, concomitant medication, metabolism, smoking and loading doses (increasing intake before a lab visit to hide non-adherence). Intra-individual variability in plasma levels is considerable. Additionally, a composite measure that includes deciding the adequacy of plasma levels in accordance to prescribed dose might be difficult to replicate in future studies.

Nevertheless, the present study is to our knowledge not only the longest and largest study measuring adherence also with objective measures but one of

few [2, 119] comparing a plasma level adherence measure to another objective measure.

7.3.3 Instrument related concerns

Several scale related considerations deserve attention. While the sensitivity of DAI-10 was moderate, the specificity was rather low. As sensitivity increases the trade off with false positives becomes larger. According to our data a DAI-10 cut-off at 4 can identify the maximum number of true non-adherent patients while minimizing the number of false positives. Still, one-third of the adherent patients would be falsely identified as non-adherent.

Alliance was not assessed and a more extensive measure of insight is lacking. Data regarding substance and alcohol use was retrieved from the medical records only as data from the patient self-rated scales (AUDIT [173], DUDIT [174]) lacked power due to missing values and thus could not be included in the study. Alcohol and illicit drugs have been previously been shown to be associated with non-adherence [141].

Global cognitive function did not predict non-adherence in our study. The use of composite scores may obscure an association between non-adherence and specific cognitive domains. A composite score was used as the power of the study did not allow for additional co-variates in the analyses. Further studies are needed to explore the various cognitive domains and their association to non-adherence.

The stigma scale (DISC) provides a subjective measure of the degree to which a range of everyday situations are experienced as stigmatizing, but does not capture the frequency of these experiences. Also, the scale does not address the impact of discriminative experiences on the individual. On the other hand DISC is a valid and psychometrically strong measure of patient experienced stigma and discrimination.

The ISE family version was originally validated for persons with various diagnoses and not only for families of persons with psychotic disorders, whereas the family burden scale (BIRP) was developed and validated specifically for relatives to persons with psychotic disorders. Furthermore, it can be argued that relatives' objective burden is underestimated with instruments based on recall [44]. An alternative method, such as continuous report by diary might not be as suited to the quantification of mental strain and other phenomena captured with the BIRP. Both ISE and BIRP ratings may be underestimates as patients without data for relatives had higher PANSS scores. Symptom severity may impact on relatives' stigma [103] and

burden [175, 176]. Further, relatives of patients with lower education levels were underrepresented. It is however unclear how this might affect our results. Also, our data is limited to one single relative or close friend chosen by the patient him or herself. A person who was not chosen to be the “key” person to respond to our questionnaires could experience significant levels of stigma and/or burden and no conclusion can be made regarding these. Due to the limited sample size gender differences could not be studied. This would be of relevance since female and male relatives perceive burden differently [177].

The absence of patients receiving LAI antipsychotics may have resulted in an underestimation of both non-adherence and stigma as depot injections are traditionally more frequently prescribed to patients with apparent difficulties following an oral medication regimen [4]. Similarly, patients prescribed an LAI often suffer from more severe psychopathological symptoms, which might increase the experienced and anticipated stigma in their relatives [178].

7.3.4 Potential influence of the health care setting

Most patients were treated in a community psychiatry setting inspired by ACT [38, 179]. This mode of working is known to increase adherence to antipsychotics [39, 43] and might partly explain the rather high adherence rates in this study as well as the relatively high concordance with several subjective measures [180]. The majority of patients were treated with active case management, including shared decision making and empowerment of the patient. Structured psychoeducation (about mental illness and prognosis, psychopharmacology, use of illicit substances, stress reduction and strategies for recovery and reintegration) is offered to both patients and their relatives (or other persons with a significant relation). Case management and ACT approaches might reduce symptom burden and thereby stigma [11]. Also, ACT has previously been shown to affect relatives in a positive manner regarding both burden and satisfaction with care [191, 192]. Still, the influence of ACT components on the results of this study is unknown and the relationships were not investigated.

7.4 Discussion of the results

7.4.1 Discussion Study I

The adherence rate was in the higher end of previously reported adherence rates [31], but similar to results shown in studies performed in other settings using active ACT strategies such as medication management and shared decision making [43].

The high concordance between pill count and MEMS[®] adherence is comparable to results from a smaller 12-week study [2], suggesting that pill count has potential as a routine clinical tool. Pill count could be an easy and inexpensive tool for monitoring adherence in the clinic. Even if it would seem expected that calculations on the two objective methods based on the same medication bottle would be similar, other studies have shown low correlations [8, 128].

The low concordance between MEMS[®] and the plasma level measure is of special interest as the use of plasma levels as a sole measure of adherence is common in clinical practice. Also, therapeutic drug monitoring (TDM), where plasma levels are used to monitor adherence over time is recommended by some [181], but most studies supporting TDM are based on the use of FGA only. With the increasing use of SGA due to the often more acceptable side effect profile, there is an additional concern as very little data on what therapeutic plasma levels to use as a criterion is available [135]. Previously it has been shown in a shorter study that plasma levels-to-medication dose ratios were not consistent over time [2]. Misinterpretation of low plasma levels due to non-adherence can lead to an increase in dosage, switching or the prescription of additional medications. Patients might also run the risk of being falsely identified as treatment resistant. In order to conceal complete or partial non-adherence, patients might take their medication (i.e. loading doses) only prior to plasma sampling. The large discrepancy found between the MEMS[®] and the plasma level measure in the COAST study points to the complexity of interpreting plasma levels. The reasons for the observed discordance could be several as explained in the limitations section.

Most of the subjective measures showed fairly good concordance with MEMS[®] adherence, but as expected the adherence rates were overestimated. A surprising finding, contrary to previous research [129], was that adherence was underestimated by the prescribing psychiatrists. Approximately half of the participants were treated at the same outpatient clinic where the research

psychiatrist was clinically active at the time of the study. For about half of those study patients (25%) the research psychiatrist was also the treating psychiatrist and this may have increased adherence rates.

The high correlations between MEMS[®] and pill count and the fairly high correlation between the MEMS[®] and the informant and patient ratings indicate the usefulness of combining objective and subjective measures as well as the value of close informant involvement.

7.4.2 Discussion Study II

Positive drug attitude, as measured by DAI-10, in combination with psychosocial functioning (PSP) emerged as the best predictors of MEMS[®] monitored adherence across the 12-month study period. Furthermore, this is to the best of our knowledge the first study to analyze the predictive validity of the DAI-10 in multiple episode psychosis using an objective adherence measure. The DAI-10 had a moderate sensitivity, i.e. the ability to correctly identify non-adherent patients, whereas the specificity was rather low. According to the data a maximum number of patients can be correctly identified as being truly non-adherent at a cut-off of 4, while the number of false positives is minimized. Still, one-third of the adherent would falsely be identified as non-adherent. Thus, according to our data, more patients with a negative drug attitude should have been expected to be non-adherent according to MEMS[®]. Perhaps other compensatory mechanisms, such as treatment alliance and shared decision making, increased the adherence rates despite negative medication attitude, but this needs to be studied further.

Psychiatric side effects and positive symptoms increased the odds of non-adherence. Other studies have shown inconclusive results with either no relationship between symptom severity and adherence [141] or relation to various PANSS items or domains [182, 183]. Poor insight and non-adherence were associated, confirming the findings of others [11, 184]. Insight is an unstable and multidimensional trait, and recognizing lack of insight as a contributor to non-adherence underlines the importance of regular monitoring. Insight can be measured in various ways, including using the PANSS (G 12) item [185] as in the COAST study. Our research group has previously performed a pilot study comparing PANSS (G 12) to a Swedish translation of the Scale to Assess Unawareness of Mental Disorder [184], which is a more comprehensive scale. The PANSS came out favorably and was much preferred by patients, but further study is needed.

Global cognitive function did not predict adherence in our study. The global score was used due to a need to reduce the number of variables and the risk of false positives, but it might have obscured an association between non-adherence and specific cognitive domains. Also, it is conceivable that cognitive performance fluctuates over time due to disease progress and remission status, which in turn may affect adherence. Perhaps cognitive decline, rather than level of cognitive function, may be associated with non-adherence. Even though complex cognitive tasks may be compromised, patients with schizophrenia might manage the practicalities of taking their medication by developing compensating strategies if the support system is sufficient. However, no measure of premorbid cognitive function was available. According to the initial protocol it was intended to gather high school report cards from the participating patients as a measure for premorbid cognitive function. Unfortunately there were numerous obstacles rendering this undoable. Report cards that had been lost by the patients were often not obtainable from the central archives or from the specific schools where they sometimes were supposed to still be on file. Also, the overall grading system had undergone several changes over the years, which made comparisons difficult. In addition, a number of patients did not attend Swedish schools.

The informant version of the DAI-10 might provide a useful additional assessment. However, the number of close informants who responded to the postal questionnaire was limited and further studies are needed.

7.4.3 Discussion Study III

To our knowledge this is the first study to employ an objective measure of adherence (MEMS[®]) and a validated stigma scale (DISC). A high proportion of the participants reported at least some experienced and anticipated stigma and discrimination, especially within the field of social and intimate relationships. Stigma and discrimination changes during the course of schizophrenia and more stigma has been found as the illness progresses. This was confirmed in a very recent international cross-sectional survey of first-episode schizophrenia [186]. Nine of the 25 first-episode patients from Sweden included in that study were also taking part in the COAST study.

In univariate analysis overcoming stigma was associated with adherence, but none of the DISC mean subscale scores were associated with adherence in adjusted models when psychosocial function and drug attitude was taken into consideration. As in any adherence study, the inclusion criteria and the regular monitorings might have introduced a selection bias towards more adherent patients. The relatively high adherence rate of 73% might have

affected the power of the study to identify an association between stigma and non-adherence.

More than half of the patients reported that they had felt shunned or socially excluded. Most of them felt that they had at least some skills to overcome stigma. Still, the most common coping strategy seemed to be avoidance of social and occupational interactions and concealing the diagnosis due to fear of discrimination. This ostensible coping strategy can be an obstacle in patient centered rehabilitation, where social integration is considered to be central for both work and family life. Social withdrawal due to fear of stigma in combination with poor insight into the psychotic illness underlines the importance of psychoeducation and flexible approaches and treatment strategies in the psychiatric treatment team.

Discriminatory and stigmatizing views held by psychiatric and general medical staff need further study as they affect quality of care [114]. In line with the findings of another recent study [154] we found that one-third of the patients felt discriminated against when seeking physical health care and approximately half of the patients felt stigmatized by mental health staff. This result is concerning as patients with schizophrenia have increased mortality rates and are in great need of both access to and trust in psychiatric and physical health care. The difficulties encountered in contact with somatic care might be partially explained by a lack of knowledge from those professional caregivers as well as by fear and misunderstanding of psychiatric symptomatology.

The mean DISC subscale scores were low and similar to those previously reported in a study with mixed diagnoses [154]. The need to conceal the diagnosis was higher in our study (88%), perhaps partly due to the higher education level in the COAST study, as it has been shown that more highly educated patients prefer to conceal their diagnosis to a greater degree than those with lower education [187].

7.4.4 Discussion Study IV

To the best of our knowledge, this is the first study to employ structured instruments to examine the relationship between experiences of both stigma and burden in relatives to persons with schizophrenia. Surprisingly few relatives (18%) reported personal experiences of stigma, even if almost half thought that their ill relative had been stigmatized at least to some extent. Our results showed that the impact of stigma on quality of life of the relatives

themselves and the family as a whole was associated with higher overall burden in adjusted models.

In the current study the frequencies of associated stigma was relatively low. There are numerous possible explanations to this result. Patients were recruited from outpatient clinics and most of them were undergoing voluntary treatment in a stable phase of their illness both at the time of inclusion and during the study year. The remission rate was 60% in the adherent group of patients and almost 50% in the non-adherent group as shown in the predictors of adherence study (Study II). The relatives that responded to the questionnaires might have been less likely to acknowledge stigma than relatives of patients in emergency psychiatric treatment settings or members of advocacy groups [104, 188]. Study IV is a preplanned part of the larger COAST study, which is primarily focused on medication adherence in schizophrenia. Therefore there is a likely selection bias towards including more adherent, well functioning and less stigmatized patients in Study IV. Further, treatment with LAI is traditionally administered to more severely ill patients and being on a depot injection was an exclusion criterion in the COAST study.

Also, as was shown in the drop-out analysis, relatives of patients with a more severe burden of illness did not participate either due to the patient's unwillingness to identify relatives that might be able to participate, or refusal on the part of the relatives themselves. Some patients could not identify a relative suitable for participation. Additionally, the mean duration of illness in this study was long (almost two decades), and this would be expected to influence the relatives' experiences of stigma. However, due to the limited sample size, it was not feasible to test for interactions with patient age or illness duration. Mostly multiple episode patients were included and thus it is expected that they would be both more adherent to their medication [6] and perhaps report less stigmatizing experiences [186]. Further, less than one-tenth of the relatives in our study lived together with their ill relative, a proportion considerably smaller than (50%) in the ISE test family sample [189]. The likelihood of encountering potentially stigmatizing experiences will decrease if less time is spent with the ill person, possibly explaining the relatively low rate of anticipated stigma in our study.

Regarding burden in relatives, the mean BIRP score in the current study (14.2) was similar to that (14.8) reported for the "moderate burden" group of relatives to persons with psychosis in a study carried out by developers of the scale in a neighboring region of Sweden [175]. Relatives' burden was related to stigma impact on a variety of psychosocial factors including family

relations, social contacts and self-esteem. The mechanisms of these associations cannot be clarified with the present study design. The lack of association between experienced stigma and burden was unexpected and might in part be a power issue, but also related to the fact that the ISE question picks up on frequency but not intensity. Data for relatives was available for only half of the patients who took part in the COAST study and among these the number acknowledging stigma experiences was lower than anticipated. This further reduced the possibility of detecting significant associations. Finally, many of the participating relatives were part of case management programs with ACT approaches, such as psychoeducation and stress management [190], which are known to decrease burden and positively affect satisfaction with care [191, 192].

8. CONCLUSIONS

In order to help improve the lives of persons with schizophrenia and their relatives or other informal caregivers there is a need for an increased understanding of both adherence and the impact of stigma and discrimination on the course of the illness. The consequences of stigma, such as social exclusion, shame and denial of optimal care, seriously impacts on the lives of those affected. Also, patients need to receive optimal and individualized antipsychotic medication as part of person-centered treatment to improve outcome. Oral medication is still preferred by many patients and professionals alike, even though the introduction of long-acting depot injectables in most cases is superior for adherence. Further research in this field is needed to optimize medical treatment and to continuously improve psychiatric care.

The COAST study showed that pill count has obvious advantages for measuring adherence, whereas occasional plasma samples probably are not true reflections of adherence. The high correlation between pill count and MEMS[®] underlines the importance of continuous clinical monitoring of antipsychotics in outpatient settings. Pill count is inexpensive and requires no advanced technical equipment. Regular visits to a health care professional can promote patient alliance, and may include not only pill count but also special focus on side effects and psychoeducation regarding adherence. Pill counts can be conducted in all health care settings in conjunction with self-rated adherence. Smart pill-boxes with reminder functions could also be of clinical value as they are similar to the MEMS[®] bottle, which most patients in the study found positive to use. Many study participants expressed that they wanted to continue using the MEMS[®] bottle even after the study ended.

The study showed that DAI-10 is a predictor of adherence together with psychosocial function, but that DAI alone or even combined with measures of function, symptoms or psychiatric side effects achieved only a moderate level of discrimination between adherence and non-adherence to antipsychotic treatment. No conclusion can be made about the temporal relationship between the predictors of adherence and medication taking due to the inclusion of only baseline data. Still, the DAI-10 inventory is an easily performed self-rating scale that patients in the clinical setting appreciate as it focuses on potential and otherwise often neglected adverse experiences of antipsychotics. It might be used as a screening tool indicating the need for more extensive ratings, such as regarding side effects, symptomatology, etc. Drug attitude, together with other clinical predictors identified to be related to non-adherence, might also indicate when patients need to be offered

adherence promoting strategies, for example through motivational interviewing, alliance enhancing methods, pill counts and computerized reminders.

Furthermore, the study showed that almost two-thirds of the participants felt discriminated against within the area of social relationships and half felt discriminated by mental health staff and in employment-related situations. Anticipated discrimination caused more than half of the participants to limit their activities and to conceal their diagnosis. An association between stigma and adherence was not found in the current study, but the relationship needs to be investigated further in other contexts.

Stigma was not only shown to impact patients with schizophrenia, but also the quality of life of their relatives and this was associated with overall burden. Increased awareness on the part of service providers may decrease the impact of stigma in relatives, but relationships need to be examined in larger studies in diverse cultures and treatment settings.

In conclusion, measuring and predicting non-adherence is complex. Regular monitorings of adherence using an objective measure, such as pill count, might be of clinical use. The large discrepancy between MEMS[®] and the plasma level measure needs to be studied further. Positive drug attitude, in combination with good psychosocial function, emerged as the best predictors of MEMS[®] monitored adherence across the one-year study period. Associations were found neither between stigma and adherence nor relatives' stigma and burden, and further studies are needed.

9. FUTURE PERSPECTIVES

Based on the results presented in this thesis the following proposed future avenues should be pursued:

- The relationship between schizophrenia, adherence and various aspects of cognition needs to be investigated further based on the COAST database and other datasets.
- Further study and validation of the modified informant version of DAI-10 in larger populations and in various social and cultural contexts need to be undertaken. The same version of the informant scale is currently being used in the UK as part of collaborative studies between the respondent/University of Gothenburg and the University of Manchester.
- The respondent is an elected member of the World Psychiatric Association (WPA), Scientific Section of Stigma and Mental Health. The main focus of the WPA network is research within the areas of stigma and the evaluation, promotion and implementation of evidence based practices in psychiatry. Collaborative studies are ongoing with the WPA group through the Institute of Psychiatry in London and the Association for Improvement of the Mental Health Programmes, Geneva.
- The impact of the Swedish version of ACT used at the clinics taking part in the COAST study (so-called Integrated Psychiatry with the Resource Group as a central component for person-centered case management) on non-adherence rates and cost of schizophrenia need to be investigated further. Such studies would be in line with the increasing international interest in person-centered care, where persons with chronic illnesses are placed in a context at the center of health care rather than being considered just as carriers of illness. According to the 2012 Geneva Declaration on Person-centered Care for Chronic Diseases [193] this view may also help de-stigmatize persons affected and those who care for them. The ingredients of ACT thus need to be studied in various settings.

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