



OLLI KAMPMAN

Compliance in Psychotic Disorders



ACADEMIC DISSERTATION

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To Ulla, Iiro, Ilari, and Irene

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Introduction

A good doctor-patient relationship is a crucial tool for successful treatment. In psychoses, the formation of this relationship is complex, especially if the patient is unaware of the psychotic illness. Despite the modern psychosocial treatment strategies developed in Finland (Alanen et al. 1991) and elsewhere (Zygmunt et al. 2002) the problems with ensuring collaboration and continuity with prescribed medications have remained. In long-term treatment, approximately half of the patients discontinue or use medications irregularly against doctors' advice (Kane, 1985; Davis et al. 1993).

The psychiatric field has undergone considerable de-institutionalisation in the whole Western world during the past few decades (Geller, 1992; National Agency for Welfare and Health, 1992). In some cases with schizophrenia, this process has led to excessive social problems, and mortality (Brekke et al. 1999; Honkonen, Saarinen & Salokangas, 1999; Munk-Jorgensen, 1999). On the other hand, the development in the pharmacological area has produced new atypical anti-psychotic drugs, which are promising in their beneficial effect on the subjective state of the patient (Gerlach & Larsen, 1999), but their effect on better compliance in maintenance treatment is still questionable (Geddes et al. 2000; Chakos et al. 2001), and they may also produce a number of side-effects in long-term use (Breier et al. 1999; Koro et al. 2002).

During the 1990s, the knowledge about the complex nature of patient compliance has expanded with the development of such new research methods as brain imaging and computerised neuropsychological tests (Laroi et al. 2000). The relationships between awareness of illness, and cognitive processes (Smith et al. 2000; Franck et al. 2001), or with symptoms of psychosis (Schwartz, Skaggs & Petersen, 2000) are examples of completely new approaches in this area of research. On the other hand, careful exploration of previously identified compliance related factors may produce findings that can be implemented in clinical practice in both pharmacological (Gerlach & Larsen, 1999) and psychosocial (Buchkremer et al. 1997) treatment.

Abstract

Problems with non-compliance appear in all areas of medicine. Compliance is a multifactorial phenomenon representing the patient's contribution to the treatment of illness. Problems with non-compliance are closely related with treatment outcome. In psychoses, the patients are often incapable in recognising their symptoms and seeking medical help. On the other hand, many symptoms of psychosis may result in distorted views about the purpose of both medication and other forms of psychiatric treatment.

In general, psychiatric disorders may have a negative stigma among people, and negative attitudes towards psychiatric drugs are common both in patients and their relatives. In previous studies, the medication related factors of compliance in psychoses have been explored comprehensively, whereas the patient-related and other factors, such as the doctor-patient relationship, psychosocial treatment programmes or the accuracy of diagnostics have received less attention.

The aims of the present study were (1) to develop a quantitative rating scale for the assessment of compliance related attitudes and to validate the scale in 106 patients on anti-psychotic medication. (2) Attitudes towards medication; reports of the patients, and of the doctors regarding patient compliance; and (3) factors related to discrepant compliance reports between patients and doctors were explored in the same population.

In a sample of 80 first-episode psychosis patients, the study focused on (4) determining the patient-related factors associated with non-compliance during the first three months of treatment, and (5) exploring the patient related factors associated with diagnostic accuracy in clinical setting in comparison with research diagnoses obtained with a standardised, semi-structured interview (SCAN-2).

The third patient sample comprised 41 long-term schizophrenia patients with recurrent non-compliance and relapses. Eighteen of the patients received ambulatory outpatient care (AOC) and 23 of them conventional outpatient care. The aim of the study was (6) to evaluate treatment outcome during four-year follow-up in both groups.

The self-rating scale developed for attitudes towards neuroleptic medication (ANT) showed high internal consistency and fair test-retest validity. The corresponding items of the Drug Attitude Inventory 10 were in concordance with the results of the ANT. Twenty-seven percent of the patients reported at least 50% non-compliance regarding the prescribed medication. The compliance ratings of the patients and the doctors were in concordance in 79 % of the cases. Manic episode, high neuroleptic dose, and negative view of medication effects among the doctors were predictive of higher patient rating compared with the doctor's view.

In first-episode patients, eleven (19 %) of the 59 patients involved in the three months follow-up showed non-compliance with medications. Medication side-effects, male gender, young age, and lack of social activities were predictive of observed non-compliance over three months.

In the same population, the diagnostic agreement in different diagnostic categories between clinical and research diagnoses varied between 0.46-0.63 being highest in bipolar disorder and equal in the other groups. Minor negative symptoms, low level of education, and high delusion scores predicted diagnostic discrepancy. In the schizophrenia group older age and existing social activities explained the diagnostic discrepancy.

Both groups of long-term schizophrenia patients had significantly lower rates of hospitalisations during follow-up than before it, but no differences between the groups were found. In the AOC group the hospitalisation rate diminished to less than one-thirds. No changes were seen in the levels of functioning. The mortality rate compared with a general mortality in schizophrenia was equal in the AOC group, whereas the non-AOC group showed a tendency on excess mortality.

In psychotic disorders, the levels of non-compliance can be defined and they should be systematically screened during treatment appointments. It is important to inform patients of the possible side-effects of medication; both the patient and the relatives should be given adequate information about them, and possible negative attitudes discussed and intervened. In first-episode psychosis, the patients at risk for non-compliance can be identified. The diagnoses of patients with symptoms of schizophrenia, or solely with delusions should be carefully evaluated during the first months of treatment. Home-based outpatient care may ensure continuity and prevent premature deaths in a certain group of patients with long-term schizophrenia.

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Abbreviations

ACT = assertive community treatment

AOC = ambulatory outpatient care

ANT = Attitudes towards Neuroleptic Treatment Questionnaire

DAI = Drug Attitude Inventory

DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, third revised edition

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition

G1...N = Number of items on the general psychopathology scale

GAF = Global Assessment of Functioning Scale

ICD-10 = International Classification of Diseases, tenth edition

P1...N = Number of items on the positive symptoms scale

PANSS = The Positive And Negative Symptoms Scale

PSE = Present State Examination

SCAN-2 = Schedules for Clinical Assessment in Neuropsychiatry, version 2.0

UKU = Udvalg for Kliniske Undersøgelser (Committee of Clinical Trials)

VAS = Visual Analogue Scale

CI = confidence interval

CMR = crude mortality rate

SD = standard deviation

OR = odds ratio

List of original publications

The thesis is based on the following original publications, which are referred in the text by Roman numerals I-V.

- I Kampman O, Lehtinen K, Lassila V, Leinonen E, Poutanen O, Koivisto A (2000): Attitudes towards neuroleptic treatment: reliability and validity of the attitudes towards neuroleptic treatment (ANT) questionnaire. *Schizophr Res* 45:223-34 (Copyright 2003, with permission from Elsevier).

- II Kampman O, Lehtinen K, Lassila V (2001): The reliability of compliance assessments performed by doctors and patients during neuroleptic treatment: a comparison of compliance ratings. *Acta Psychiatr Scand* 104:299-304 (Copyright 2003, with permission from Blackwell Publishing).

- III Kampman O, Laippala P, Väänänen J, Koivisto E, Kiviniemi P, Kilkku N, Lehtinen K (2002): Indicators of medication compliance in first-episode psychosis. *Psychiatry Res* 110:39-48 (Copyright 2003, with permission from Elsevier).

- IV Kampman O, Kiviniemi P, Koivisto E, Väänänen J, Kilkku N, Leinonen E, Lehtinen K (2003): Patient characteristics and diagnostic discrepancy in first-episode psychosis. (submitted)

- V Kampman O, Illi A, Poutanen P, Leinonen E (2003): Four-year outcome in non-compliant schizophrenia patients treated with or without home-based ambulatory care. *Eur Psychiatry* 18:1-5 (Copyright 2003, with permission from Elsevier).

1 Review of the literature

1.1 Definitions of compliance

Problems with compliance are common in all areas of medicine (Blackwell, 1976). Compliance has been defined as the extent to which a person's behaviour is in line with the medical advice given (Sackett & Haynes, 1976). It is a complex phenomenon representing a patient's contribution to the management of illness (Sackett & Haynes, 1976; Babiker, 1986). It comprehends a wide variety of behaviours: failure to enter a treatment programme, premature termination of therapy, and incomplete implementation of instructions, like drug prescriptions. Factors associated with non-compliance can be identified in the patient, his network, the illness, the physician, the treatment setting and the medication itself (Blackwell, 1976). Non-compliance is closely related to treatment outcome (McEvoy et al. 1989c; Frank & Gunderson, 1990; Drake et al. 1991; Kent & Yellowlees, 1994).

Compliance behaviour has been explained by two different theories. The role theory is based on assumptions relating to the sick role (Parsons, 1967). Accordingly the patient is obliged to seek the help of the doctor and to follow his rational and competent instructions. The responsibility for non-compliance lies solely with the patient, and it is deemed abnormal and irrational (Babiker, 1986). The health belief model offers a more credible explanation. This view determines health behaviour as a "readiness to act", which is based on the perception of a threat to health and the belief that a certain action will reduce the threat. The decision to act depends on weighing the advantages and negative consequences of the proposed action (Sackett & Haynes, 1976; Ludwig et al. 1990). This process is often complex and may cause dysfunctional behaviour in the patient (Babiker, 1986).

1.2 The problem of non-compliance in psychotic disorders

Adherence to treatment is often incorrectly seen only as a trait of the patient, or related to motivation or resistance, rather than as collaboration between the patient and a doctor (Corrigan, Liberman & Engel, 1990). Models of compliance borrowed from physical medicine (Sackett & Haynes, 1976) do not fit properly in the treatment of psychoses, where the perception of illness is often distorted (Kane, 1985).

Studies evaluating compliance or adherence issues in psychiatry have focused on drug treatment, non-attendance in outpatient treatment and rehabilitation programmes, and self-discharge from hospital against medical advice. Rates of non-compliance in psychotic

disorders have been reported to vary between 11 and 80% (Johnson, 1984; Kane, 1985; Ayuso-Gutierrez & del Rio Vega, 1997). The contributing factors of compliance in psychotic disorders can be divided in medication-related, patient-related and environmental components (Fenton, Blyler & Heinssen, 1997; Kampman & Lehtinen, 1999). Most of the studies deal with schizophrenia and related disorders, and a few with unselected groups of psychotic patients.

1.3 Assessment of medication compliance

Compliance assessment methods have included inquiries, tablet counting and drug identification in body fluids (Blackwell, 1976). Their reliability is quite problematic. More invasive assessment methods, like drug serum concentrations tend to reduce non-compliance by two different mechanisms. The most non-compliant patients may decline from the studies, or some of the patients may change their medication-taking during observation (Kane, 1983). Moreover, as non-compliance is most often partial, it is difficult to detect even with tracer techniques (Young, Zonana & Shepler, 1986). For example, there may be 10-15 fold differences between individuals with the same dosage in the mean steady-state neuroleptic plasma levels. This method can thus only be used as a criterion for complete non-compliance (Pietzcker & Muller-Oerlinghausen, 1984; Babiker, 1986). Pill counts have shown to be a fairly accurate method (Seltzer, Roncari & Garfinkel, 1980). A fluorescence analysis of riboflavin that was prescribed in tablet form has been used in one study to control patients' medication-taking behaviour (Kapur et al. 1991).

When compliance has been assessed by questionnaires or interviews, the most common practices have been either to divide the patients as compliant or non-compliant according to selected criteria (Van Putten, Crumpton & Yale, 1976; McEvoy, Howe & Hogarty, 1984; Gaebel & Pietzcker, 1985; Kent & Yellowlees, 1994), or to use a five-point scale measuring the level of compliance (Miklowitz et al. 1986; Adams & Howe, 1993; Cuffel et al. 1996). Reliability has been improved with additional information from relatives or medical staff (Adams & Howe, 1993; Cuffel et al. 1996). Attitudes towards medication are closely related to medication-taking behaviour (Awad et al. 1996; Gallhofer et al. 1996). Hogan and co-authors have developed an attitude scale, Drug Attitude Inventory (DAI), which has showed high predictive value with compliance (Hogan, Awad & Eastwood, 1983).

1.4 Medication-related factors

Problems in drug adherence include errors of omission, purpose, dosage and timing. (Blackwell, 1976). Medication compliance is reduced by complex treatment regimens (Blackwell, 1976; Kane, 1983; Razali & Yahya, 1995) and by neuroleptic side-effects (Blackwell, 1976; Van Putten, 1978; Young, Zonana & Shepler, 1986; Buchanan, 1992; Kemp et al. 1996; Tran et al. 1997), most notably akathisia (Van Putten, 1978; Seltzer,

Roncari & Garfinkel, 1980) and akinesia (Van Putten, 1978). Patients recently discharged from hospital may be careful with compliance, but this is likely to decline over time with the symptom relief (Kane, 1985).

A negative change in the subjective state during medication has been associated with negative attitudes and impaired compliance (Awad, 1993). Negative attitudes towards antipsychotic medication predict non-compliance (Serban & Thomas, 1974; Falloon, 1984; Mantonakis et al. 1985; Ludwig et al. 1990; Fenton, Blyler & Heinssen, 1997).

The label, package or form of the medication or the type of drug may also alter medication compliance (Blackwell, 1976; Young, Zonana & Shepler, 1986; Schwartz & Brotman, 1992). For example in a sample of 35 studies the relapse rate during depot medication was lower compared to oral medication. The authors (Davis et al. 1993) suggested that this was due to compliance. On the other hand, a systematic meta-review showed no difference in relapse rates or adverse events between oral and depot forms, but a better global outcome with depot drugs (Adams et al. 2001). In a review of 26 studies comparing depot and oral medications mean compliance rates were higher with depot medications (Young, Zonana & Shepler, 1986). A recent meta-analysis by Walburn et al. (2001) concluded that patients showed more positive attitudes to depot medication compared with oral administration. Nevertheless, there is need for quality improvement with prescribing guidelines of depot medications (Marland & Sharkey, 1999; Valenstein et al. 2001).

Atypical antipsychotic agents, such as clozapine, olanzapine, risperidone or quetiapine have shown superiority over conventional antipsychotic drugs by producing less extrapyramidal side-effects (Leucht et al. 1999; Geddes et al. 2000) and enhancing cognitive functioning (Keefe et al. 1999; Meyer et al. 2002). So far the evidence regarding atypical antipsychotics and better compliance in schizophrenia has been inconclusive (Young et al. 1999; Allison & Casey, 2001; Chakos et al. 2001).

1.5 Patient-related factors

1.5.1 Sociodemographic factors

Supportive family environment has been reported to have a positive effect on compliance (Bebbington & Kuipers, 1994). The family members' awareness of the patient's illness is also connected to better compliance (Smith, Barzman & Pristach, 1997). Social activity has been related to more positive attitudes towards medication in outpatient care (Draine & Solomon, 1994), but to poorer compliance with long-term rehabilitation patients (Taylor & Perkins, 1991). Living alone (Seltzer, Roncari & Garfinkel, 1980) and poor housing (Drake et al. 1991) increase the risk of medication non-compliance. In most studies, gender has not been associated with compliance (Fenton, Blyler & Heinssen, 1997), but male patients had lower adherence compared with women in a skills training programme for chronic schizophrenia patients after relapse (Smith et al. 1997).

1.5.2 Symptoms and course of illness

Certain symptoms, or the course of a psychotic illness may affect compliance (Johnson, 1984; Awad, 1993). During manic episodes patients typically deny their illness and actively resist the need for medication (Zito et al. 1985; Peralta & Cuesta, 1998). In hypomanic state the patient usually experiences increased productivity and is therefore at risk of missing the option for treatment (Seltzer, Roncari & Garfinkel, 1980). Delusional patients may interpret side-effects as particularly threatening or invasive (Young, Zonana & Shepler, 1986). In two follow-up studies delusions predicted non-compliance (Seltzer, Roncari & Garfinkel, 1980; Gaebel & Pietzcker, 1985). Grandiose delusions have been associated with high rate of non-compliance (Van Putten, Crumpton & Yale, 1976). Depressive symptoms in psychosis may also result in poor compliance (McEvoy, Howe & Hogarty, 1984; Pan & Tantom, 1989). Non-compliant patients have been found to have a longer history of treatment than compliant patients (Razali & Yahya, 1995), but not a longer duration of illness (Buchanan, 1992).

Substance abuse seems to be a strong predictor of non-compliance in psychosis, especially in men (Miner et al. 1997). In schizophrenia, any substance abuse is associated with markedly elevated risk for non-compliance (Kashner et al. 1991), and re-hospitalisation (Pristach & Smith, 1990). More specifically, non-compliance has correlated more clearly with heavy than with slight alcohol use (Drake, Osher & Wallach, 1989), and with the use of marijuana (Smith, Barzman & Pristach, 1997).

1.5.3 Insight on psychotic symptoms

Amador and co-authors (1993) define insight as awareness or recognition of illness, and perception of the progress or origin of symptoms. David (1990) and David et al. (1992) divide insight into three dimensions: 1) the patient's recognition or awareness of the illness and the realisation that the illness is mental; 2) the ability to re-label the experience of certain mental events as pathological, e.g. realising that hearing voices could be an auditory hallucination; and 3) treatment compliance.

Lack of insight is a specific phenomenon in psychoses, and particularly in schizophrenia (Amador et al. 1994) and bipolar disorder (Pini et al. 2001) it often leads to problems in collaboration between patient and doctor, and poor outcome (Rossi et al. 2000). There has been ample interest in investigating both the manifestation and negative consequences of lack of insight in psychoses. A study by McEvoy et al. reported poorer insight in committed than voluntarily hospitalised patients with schizophrenia (McEvoy et al. 1989a, b, c). Several studies have proposed an association between poor compliance and lack of insight in schizophrenia (Lysaker et al. 1994; Peralta & Cuesta, 1994; Kemp et al. 1996; Ayuso-Gutierrez & del Rio Vega, 1997; Nageotte et al. 1997). A recent study by Pyne et al. (2001) characterised the typical patient at risk of poor insight as young, experiencing a minimal medication effect and having few depressive symptoms. Social support has found to contribute to awareness of illness in schizophrenia (White et al. 2000).

1.5.4 Disturbances in cognitive and memory functions

Approximately half of the patients with a diagnosis of schizophrenia who present with chronic psychotic symptoms experience a significant decline in intellectual abilities. The cognitive deficits may emerge in the domains of attention, memory, executive function, language, oculomotor speed and visuospatial perception (Weickert & Goldberg, 2000). The linkage between cognitive disturbances and compliance in schizophrenia is still somewhat obscure.

Neuro-psychological test performance has been found to be associated with compliance during 6 months follow-up (Cuffel et al. 1996), although not in acute psychosis (Kemp & David, 1996). Nonverbal problem-solving ability test performance has been related to attitudes towards current medication among outpatients with chronic schizophrenia (Todman, Gordon-Leeds & Taylor, 1997). A number of studies have shown a connection between neuro-psychological test performance and insight regarding psychotic symptoms (Lysaker & Bell, 1994; Cuffel et al. 1996; MacPherson, Jerrom & Hughes, 1996; McEvoy et al. 1996). There is also evidence of a connection between frontal atrophy, poor performance in executive functions and lack of insight (Laroi et al. 2000). In addition to the lack of insight, the possible mechanisms between cognitive disturbance and non-compliance include selective encoding of threat-related stimuli in delusional states (Blackwood et al. 2001), misattribution of one's own actions (Franck et al. 2001), or energetic or motivational deficits (Schmand et al. 1994).

1.6 Environmental factors

1.6.1 Compliance, therapeutic alliance and different treatment models

In any treatment, it is essential to prepare and inform the patient about the forthcoming treatment procedure. In psychiatry, the effect of patient education as improved outpatient attendance was noted and published in the early and mid 1970's (Donlon & Rada, 1976; Goldstein, 1992). Comprehensive psycho-educational and behaviour-oriented treatment models were described ten years later (Beels & McFarlane, 1982).

The psycho-educational treatment programmes are based on the vulnerability-stress model, or the stress-diathesis hypothesis. According to this, schizophrenia is dynamically a product of interacting forces, some genetic or biological and some psychological, some innate or constitutional and some learned through experience (Nuechterlein et al. 1992, 1994; McGlashan & Hoffman, 1995). In follow-up studies, the psycho-educational programmes have resulted in improved outpatient compliance and lower re-hospitalisation rates (Falloon, 1984; Falloon et al. 1985; Liberman & Evans, 1985; Kelly, Scott & Mamon, 1990; Fowler, 1992; Wallace et al. 1992). The compliance improving methods used in these programmes are: 1) informing the patient and the family about the purpose and side-effects of medication, 2) cognitive reformulation of family attitudes towards psychiatric illness, 3) home-based outpatient appointments, and 4) flexible dosage in

maintenance treatment to avoid neuroleptic side-effects (Falloon, 1984; Falloon et al. 1985; Liberman & Evans, 1985; Clary, Dever & Schweizer, 1992; Goldstein, 1992; Wallace et al. 1992; Falloon & Fadden, 1993). A systematic review summarizes the effects of psycho-education in schizophrenia as fewer readmissions and some evidence towards better compliance (Walburn et al. 2001). Nevertheless, psycho-educational interventions without cognitive reformulation and focusing on patients' attitudes to medication have not been successful in improving patient adherence (Zygmunt et al. 2002).

Individual, cognitive-behavioural interventions have also resulted in improved compliance in controlled follow-up studies (Kemp et al. 1996; Lecompte & Pelc, 1996). Frank and Gunderson (1990) found an association between a good alliance in individual therapy and medication compliance during 6-month follow-up. In the Finnish clinical tradition, a positive experience of the use of the need-adapted treatment model has yielded treatment recommendations comprising family and environment-oriented practice in the treatment of acute psychosis (Alanen et al. 1991). A combination of psycho-education, counselling and cognitive therapy resulted in more positive attitudes, but not compliance in schizophrenia patients in a controlled multi-centre study (Buchkremer et al. 1997). In refractory schizophrenia, the use of assertive community treatment programmes resulted in fewer relapses and hospitalisations and improved patient satisfaction (Marshall & Lockwood, 2001).

1.6.2 Reliability of diagnosis

Diagnoses in psychiatry are based on selected clinical symptoms, with every diagnostic category having determined symptom criteria. The current worldwide diagnostic system, the ICD-10, which is also used in Finland, (World Health Organization, 1992) has shown high predictive validity for long-term outcome (Mason et al. 1997). On the other hand, there is evidence in studies both from Finland (Isohanni et al. 1997; Taiminen et al. 2001) and other countries (Fennig et al. 1994; Loffler et al. 1994) that the clinical diagnoses are not stated according to the diagnostic criteria. In psychotic disorders unspecified diagnoses are frequently used, and clinical practices in diagnostics may include national biases (Fennig et al. 1994; Taiminen et al. 2001; Dalman et al. 2002). Inappropriate diagnoses may result in inadequate treatment or insufficient follow-up (Honer et al. 1994; Hellewell, 1999). This is likely, especially if the patient is unaware of current psychotic symptoms, for example in first-episode psychosis.

There is little data about the connection between reliable diagnosis and treatment compliance. Some previous studies have, however, presented a connection between lack of insight and psychopathology of a certain type. It is evident that patients with manic symptoms are at risk for both poor insight and misdiagnosis (Peralta & Cuesta, 1998; Pini et al. 2001). This may also be true with patients suffering from schizophrenia of disorganised type or presenting with predominantly negative symptom cluster (Cuesta, Peralta & Zarzuela, 1998; Schwartz et al. 2000).

1.7 Conclusions based on the literature

Being clinically common and crucial in relation to outcome, problems with compliance arise from multiple reasons. In psychotic disorders compliance involves specific factors, such as side-effects of anti-psychotic medication, attitudes towards treatment, insight regarding symptoms, or disturbances in cognitive functioning. Most of the previous studies have focused on the weight of medication effects and side-effects. Similarly, attitudes towards medication, and the roles of psychopathology, insight and substance abuse are all well established as important factors regarding non-compliance. There is evidence of better compliance using specific psychosocial treatment methods, such as cognitive-behavioural interventions and assertive community treatment. The results with some socio-demographic factors, especially living circumstances, need further studies to confirm the present findings. Cognitive functioning has shown some connection with insight, but its role in compliance is still unclear.

Most of the previous studies suffer from methodological shortcomings. These include insufficient study samples, lack of structured diagnostic and symptom assessments, and narrow-viewed designs and statistical analyses. The issues of cognitive functioning, the benefits of new generation anti-psychotic medications, and the weight of different components in integrated psycho-social treatment programmes need further evaluation in the context of compliance. The present study provides an extension towards better methodology in both developing a new, advanced assessment scale for attitudes, and also retaining practical designs that still make comprehensive hypotheses and data analyses possible. The study presents prospective data on first-episode psychoses, in which the management of compliance may have long-acting consequences when considering the prognosis and outcome of the psychotic illness.

2 Aims of the study

The study was designed to obtain information on several questions. One of the main problems in previous studies has been the validity of assessing medication compliance with non-invasive methods. The data on the validity of direct compliance inquiries was scant, but measuring the drug-related attitudes has shown good validity in relation with medication compliance. A questionnaire with ten dichotomous items, The Drug Attitude 10, appeared as a robust scale for following-up compliance-related attitudes of different types, and gathering more information on the factors associated with unreliable compliance assessments. For these two reasons it was necessary to develop a quantitative scale, which was theoretically based on the DAI-10 (I).

Simultaneously with the implementation of the new, quantitative scale the patients on neuroleptic medication made direct compliance assessments and these were compared with the doctors' compliance assessments. With this design, it was also possible to evaluate the patient, doctor and treatment-related factors associated with both good compliance and discrepancies between the ratings of patients and doctors, and thus identify the patients at risk for non-compliance and unreliable compliance assessments (II).

In first-episode psychoses, many patients experience harmful side-effects during anti-psychotic medication. On the other hand, most of the patients are treatment-naïve, representing attitudes towards psychiatric treatment comparable with attitudes in general population. The patient and treatment-related factors associated with patient compliance had not been systematically examined during first-onset psychosis, which was thus important to ascertain in the present study (III).

A careful clinical evaluation of the patient's illness includes an accurate diagnosis from the early stage of the treatment. The doctor-patient relationship may be disrupted during psychosis, and this may possibly lead to misdiagnosis and faulty clinical decisions. The patient-related factors, including insight regarding psychotic symptoms, and associated with discrepancies between clinical and research diagnoses in first-episode psychosis were of interest in this sense (IV).

Finally, patients with schizophrenia and non-compliance may have poor outcome. It was important to evaluate the long-term outcome in a group of those patients treated either with or without home-based outpatient care (V).

The aims of the present study comprised:

1. Developing and testing a quantitative scale for attitudes towards anti-psychotic medication (I)

2. Assessing attitudes towards drugs in a population currently using anti-psychotic medication (II)
3. Finding reasons leading to discrepancies between patient and doctor compliance assessments by using the developed attitude scale (II)
4. Examining compliance-related factors during first psychotic episode (III)
5. Defining patient-related factors associated with differences between clinical and symptom-criteria based research diagnoses in first-episode psychosis (IV)
6. Evaluating outcome in long-term schizophrenia patients treated with or without home-based outpatient care (V)

3 Patients and methods

3.1 Study samples

The study included three different patient samples. The samples were gathered in the City of Tampere (samples 1, 2 and 3), and in the municipalities of Pirkkala and Nokia (samples 1 and 2) located in Tampere region, at south-western part of Finland. The population of the area is 250,000. All patients had attended either psychiatric inpatient or outpatient care in the public health care system. The results are presented in detail in the five original publications (I-V).

3.1.1 Patient sample 1 (Patients on neuroleptic medication; I, II)

Sample 1 consisted of 106 consecutive patients (57 men and 49 women) 16-63 years of age (mean 37.6 years) from the inpatient (n=54) and outpatient (n=52) services at the Tampere University Hospital, Department of Psychiatry during the period January-March 1996. The inclusion criteria were 1) 18-65 years of age, 2) current neuroleptic medication (daily dose 100 mg of chlorpromazine equivalents or more), 3) informed consent. Twenty of the patients originally selected for the study declined to give their consent.

Patient characteristics are presented in Table 1.

Table 1. Patients on neuroleptic medication: characteristics

Type of neuroleptic medication:	N	%
Conventional neuroleptics	84	79.2
Risperidone	15	14.1
Clozapine	6	5.7
Clinical diagnoses (DSM-III-R):	N	%
Schizophrenia group	48	45.3
Brief or non-specified psychosis	22	20.8
Delusional disorder	10	9.4
Bipolar disorder	7	6.6
Psychotic depression	5	4.7
Other ¹	14	13.2
	Mean	SD
Mean neuroleptic dose ²	334	215
Time from first contact in psychiatric services, years	4.9	4.3

1 Non-psychotic depression, personality disorder or substance abuse-induced mental disorder

2 Daily chlorpromazine equivalents in milligrams

3.1.2 Patient sample 2 (Patients with first-episode psychosis; III, IV)

The patient sample 2 consisted of 80 people (37 women and 43 men) 33 ± 11 years of age (mean \pm SD) living in the catchment area of Tampere University Hospital, Department of Psychiatry. All patients had their first treatment period due to a psychotic episode. The sample was collected during the period 1995-98. The patient inclusion criteria were 1) 18-65 years of age 2) first-episode psychosis and 3) resident in the study area. Five other patients had been selected for the study, but four declined and one moved away.

Fifty-nine of the patients gave their consent to a follow-up interview after three months. Approximately half of those patients (n=33, 56%) received outpatient treatment according to the Buckingham family-based psycho-educational model (Falloon & Fadden, 1993). This involves two trained therapists, home visits and family appointments. The rest of this sample (n=26, 44%) received standard individual outpatient treatment at the local mental health care centre. The home address of the patient determined the treatment model, as trained therapists were available at about 50% of the local mental health centres during the study.

Half of the patients were living alone, less than half of them had at least vocational training, and most of them were hospitalised in the initial phase of treatment (Table 2).

Table 2. First-episode psychosis: patient characteristics

	N	%
Living alone	40	50.0
Vocational training or higher educational level	35	43.8
Hospitalisation during first three months	72	90.0
SCAN-2 ¹ diagnosis (ICD-10)	N	%
Schizophrenia group	42	52.5
Acute polymorphic or unspecified psychotic disorder	14	17.5
Severe depressive episode with psychotic symptoms	9	11.3
Manic episode	11	13.7
Delusional disorder	4	5.0
	Median	Quartiles
Duration of untreated psychosis, weeks	11	4/26
	Mean	SD
PANSS ² , total score	74	18
PANSS, positive subscale score	19	5
PANSS, negative subscale score	18	8
GAF ³ score	36	14
Neuroleptic dose at onset of outpatient treatment ⁴	160	109

1 Schedules for Clinical Assessment in Neuropsychiatry, version 2.0

2 The Positive And Negative Symptoms Scale

3 Global Assessment of Functioning

4 Daily chlorpromazine equivalents in milligrams

3.1.3 Patient sample 3 (Patients with long-term schizophrenia; V)

The sample for screening was selected from the hospital discharge register. The inclusion criteria were 1) living in the City of Tampere (population of 200,000) 2) 18-65 years of age, 3) schizophrenia as discharge diagnosis, and 4) at least three hospitalisations during the four-year period 1986-1989. The screening sample included 78 patients. The final study sample (n=41) was extracted from this sample according to the information in medical records. The selection criteria included that 1) the patient met the DSM-IV criteria for schizophrenia and 2) the patient had a prolonged history of outpatient non-compliance,

defined as repeated relapses and hospitalisations due to non-compliance or continuous failure in outpatient attendance between hospitalisations.

The study group was divided into two subgroups retrospectively according to information in the patient records. Group 1 (n=18) included patients receiving ambulatory outpatient care (AOC) and Group 2 (n=23) those receiving conventional outpatient treatment (non-AOC).

In AOC, one of the hospital nurses at a time made regular visits to patients' homes to ensure the continuation of intra-muscular depot neuroleptic medication. The conventional outpatient treatment (non-AOC) comprised regular appointments at a mental health care centre with a psychiatric nurse every 2-4 weeks, and with a psychiatrist when necessary.

Baseline characteristics of the AOC and non-AOC groups are presented in Table 3. In the AOC group, two patients lived in a nursing or rehabilitation home and two with their parents. Five patients had previously been prescribed depot neuroleptics and all of them had discontinued the injection visits in mental health outpatient care. Two patients had previously been treated with clozapine, but in both cases the medication was discontinued due to non-response.

In the non-AOC group, two patients were living in a nursing or rehabilitation home and four patients with their parents or spouse. None of the patients in the non-AOC group had been treated with clozapine.

The only difference between groups at baseline was the greater lifetime number of days hospitalised in the AOC group compared with the non-AOC group.

Table 3. Long-term schizophrenia patients: baseline characteristics of the AOC and non-AOC groups.

	AOC group (n=18)	Non-AOC group (n=23)		
Proportion of males	14/18	13/23		
At least tertiary education	2/18	5/23		
Living alone	14/18	17/23		
Harmful alcohol use or alcohol dependency	3/18	5/23		
	Mean	SD	Mean	SD
Age in years	41.1	9.9	37.8	8.0
Time in years from first hospitalisation	14.5	6.8	12.2	7.3
Total number of hospitalisations	11	7	10	6
Neuroleptic dose ¹	322	212	377	185
	Median	Quartiles	Median	Quartiles
Total number of days hospitalised	921 ²	564/1202	677	410/976
Number of days hospitalised in the preceding four years	368	252/633	324	113/450

1 Chlorpromazine equivalents mg/day

2 P=0.036 compared with controls

3.2 Methods

3.2.1 *The ANT scale (I, II)*

Before the study, a new assessment scale for attitudes towards psychopharmacological treatment was developed. The scale was named the Attitudes towards Neuroleptic Treatment Questionnaire (ANT), (I, Appendix 1). Structurally the scale was based on 12 Visual Analogue Scale (VAS) items (Aitken, 1969, 1970), in which the statements were formulated and grouped to correspond with the structures of the Drug Attitude Inventory 30 and the DAI-10 (Hogan, Awad & Eastwood, 1983). These scales consist of a number of statements regarding subjective positive and negative feelings, and attitudes towards medication, which are rated by the patients as “yes” or “no” to each item. In addition to items of these two types, two insight items were added to the ANT scale. The questions in ANT-items concerning subjective state (4, 7, 10, 11 and 12) were formulated so that they measured the patient’s expectations about his/her subjective state during medication. This was done in order to make the scale equally suitable for drug-naïve or previously medicated patients. All patients on neuroleptic medication (sample 1) filled in the ANT scale and the 10-item Drug Attitude Inventory (DAI-10), simultaneously. The ANT and the DAI-10 were filled in again 1-2 weeks later by 75 patients for test-retest validity estimation. The doctors also rated two additional items on their attitudes to prescribing medication.

3.2.2 *Compliance assessments (I-IV)*

With the patients on neuroleptic medication (sample 1), the patients and their treating doctors estimated the level of patients’ compliance on a five-point scale (0, 25, 50, 75 or 100% of prescribed medication). Reassessments of compliance were made after 1-2 weeks (n=53). In the questions on compliance, no particular time period was set. By leaving this open the purpose was to be able to assess the use of medications over the long term. Hospitalised patients and their doctors were instructed to rate compliance prior to the patients’ admission.

With first-episode patients (sample 2) the patients’ prediction of their compliance was assessed using a four point Likert scale. This was classified as 1) regular use of medication 2) irregular use 3) occasional use 4) will not use medication at all. Information on medication compliance over the first three months was collected from medical records. The data was obtained retrospectively and all information from the first year of treatment was used when estimating compliance during the first three months.

3.2.3 SCAN-2 interview (III, IV)

With the patients with first-episode psychosis (sample 2), a trained psychiatrist or a psychiatric nurse completed the SCAN-2 diagnostic interview (World Health Organization, 1994) in the initial assessment. The SCAN-2 is a standardised, semi-structured diagnostic interview, which is designed to give diagnoses in mental disorders according to the diagnostic criteria in ICD-10 and DSM-IV classifications. The SCAN-2 interview has been developed from the Present State Examination (PSE) (Wing, Cooper & Sartorius, 1974). All five interviewers had completed a four-day training session with a trainer from the Institute of Psychiatry in London. Fifty-nine of the patients gave their consent to a follow-up interview after three months. Another researcher checked the interview records and a consensus diagnosis was made between the two researchers.

The clinical diagnoses were collected from the hospital discharge and outpatient registers during the first three months of treatment. Some of the patients had more than one psychosis diagnosis. In such cases the most concordant code with the SCAN-2 diagnosis was chosen as the clinical diagnosis.

3.2.4 Assessments of psychopathology (III, IV)

For the first-episode patients (sample 2), the interviewers completed the ratings of symptom severity in the initial interview with the Positive and Negative Symptom Scale (PANSS), (Kay, Fiszbein & Opler, 1987). The scale has thirty items, with each of them rated as 1-7 points according to symptom severity in positive and negative psychotic symptoms, and general psychopathology. The Hamilton Depression Scale (Hamilton, 1960) with 21 items was used to assess the severity of depressive symptoms. The Global Assessment of Functioning Scale (GAF), (American Psychiatric Association, 1987), in which the range for scoring is 0-100 points, was used as a measure of overall functioning. The Strauss-Carpenter Scale (Strauss & Carpenter, 1974) has four 4-point Likert items, and was used for the ratings of outcome during the past year.

3.2.5 Self-report scales (III, IV)

In order to assess insight, perceived side-effects of medication and need for treatment, the first-episode patients (sample 2) were asked to rate these aspects on three different scales designed for this particular study. The first self-report scale was modified from the Brief Psychiatric Rating Scale (Overall & Gorham, 1962) and includes thirteen dichotomous items for assessing insight into symptoms. Five of the items address positive psychotic symptoms, one item negative symptoms, and seven items general psychopathology (Appendix 2).

The second self-report scale, an 11-point dichotomous questionnaire, is based on the Scale of the Udvalg for Kliniske Undersøgelser (Committee of Clinical Trials), UKU (Lingjaerde et al. 1987), to assess perceived side-effects. It includes one item for mental

side-effects, three items for neurological side-effects, and seven items for autonomic side-effects (Appendix 2).

The patients rated the overall harm from perceived side-effects using a 4-point Likert item. The subjective need for treatment was assessed with four 4-point Likert items (Appendix 2).

3.2.6 *Assessments of outcome (V)*

Of the long-term schizophrenia patients (sample 3), the follow-up in the AOC group lasted four years before and after starting the ambulatory care. In the non-AOC group the corresponding periods covered four years before and after December 1991. This was the median month of starting the ambulatory care in the AOC group. Days of hospitalisation, mortality rates and levels of functioning (GAF) during follow-up were compared between the two subgroups. A researcher blind to the study design performed the GAF assessments. The mortality rates in each group were compared with general mortality in schizophrenia patients by using the result of a meta-analysis as a reference. The meta-analysis by Brown (1997) produced an aggregate crude mortality rate (CMR) of 1.89 deaths/100 population per year.

3.3 Statistical methods

For the ANT scale, data analysis was performed using reliability testing, test-retest validity using the Wilcoxon test for paired samples and the Spearman correlation coefficients. Factor analysis was performed using principal component as extraction model with eigenvalues > 1 . In keeping with the structure of the Drug Attitude Inventory Scales (Hogan, Awad & Eastwood, 1983), the equivalent items in the ANT and the DAI-10 were grouped for reliability testing, as items of subjective state, and items of attitudes. The comparisons between the DAI-10 and ANT subjective items were made by using analysis of variance and the Kruskal-Wallis test.

With patients on neuroleptic medication (sample 1), the test-retest validity and correlations for the patients' and the doctors' compliance ratings were evaluated using the Spearman correlation coefficient. Backward stepwise model of logistic regression analysis was used in determining factors related to patient and doctor compliance ratings separately, and in explaining the discrepancy between them. Explanatory variables comprised subjective states and attitudes on the ANT scale; and demographic, treatment and symptom-related factors including age, sex, education, living conditions, neuroleptic dose, diagnostic category, hostility, suspiciousness and the existence of delusions. In the model, the p-value limits to enter and to remove variables were 0.10 and 0.15 respectively.

With first-episode patients (sample 2), data analysis was performed using reliability testing for self-report scales, binomial test in comparison between the patients' and the clinicians' ratings of symptom and side-effects measure, and kappa statistics for agreement

between research and clinical diagnoses. Sensitivity and specificity were calculated for each diagnostic group using research diagnosis as a reference. Backward stepwise model of logistic regression analysis was used to analyse the indicators of patients' prediction as to their compliance and the observed medication compliance during the first three months. The following subsets of variables were used prior to the final analyses: 1) insight, 2) psychopathology and level of functioning, 3) side-effects of medication and 4) content of the treatment. Significant variables were then extracted from each subset for the final analysis.

Logistic regression analysis was also used with the first-episode patients (sample 2) in determining the explanatory variables for disagreements between the diagnostic categories of clinical and research diagnoses for the total sample and for the schizophrenia group separately. The explanatory variables in the model included: 1. demographic variables (gender, age, living conditions, education and social activities); 2. measures of psychopathology (PANSS total, positive and negative subscale scores, delusions (P1), suspiciousness (P6) and lack of judgment and insight (G12) as separate items in the PANSS scale, Hamilton Depression Scale); 3. level of functioning (GAF, Strauss-Carpenter Scale); 4. duration of untreated psychosis and 5. diagnostic category according to SCAN-2 interview in the analysis for the total sample. In all three models, the p-value limits to enter and to remove variables were set equal to 0.10 and 0.15 respectively. Bivariate analyses were performed with chi-square, and Mann-Whitney U-tests.

In the long-term schizophrenia patients (sample 3), the differences in hospitalisations within groups were analysed with the Wilcoxon test. The differences between groups were analysed with chi-square and Mann-Whitney U-tests. Mortality rates were analysed with the Kaplan-Meier survival analysis. In comparison with the CMR, odds ratios with 95% confidence intervals were used in each group.

In all analyses, SPSS statistical software was used for computation (versions 7.5, 9.0 and 10.1) (SPSS Inc., 1996).

4 Results

4.1 Psychometric properties of different scales

4.1.1 *The ANT-scale with patients on neuroleptic medication (I)*

There were no significant changes in single VAS items between two different time-points, except in Item 4 (effect on personality). This difference was explained by significantly more positive expectations in the affective disorders group (n=8; p=0.015) in the reassessment. Cronbach's alpha between all items was 0.798. In the schizophrenia group, Cronbach's alpha between all items was 0.707.

The factor analysis comprised three different factors (Table 4). The first consisted of items concerning the patients' expectations regarding their medication and subjective state. The second factor consisted of items on general attitudes. The third, a weak component, consisted of the two insight items, and item 1 (importance of medical treatment), which had a weak loading on this factor. The first two factors explained approximately 50% of the variance of single items. In the factor analysis for the schizophrenia group the item concerning the effect of medication on ability to do things (12) was excluded from the first factor. Furthermore, the item assessing reaction to possible side-effects (6) was excluded from the third factor. These two items together loaded on a weak fourth factor. The first three factors together explained 58.6% and the fourth factor additional 8.5% of the variance.

Factor 1 items were separately compared with the results of the questions concerning subjective state in the DAI-10 (questions 1, 2, 4, 5, 7 and 9). The patients were divided into three categories according to the sum of DAI-10 subjective items scores (0-1, 2-3, and 4-6 points; Figure 1). In all items, the group with the lowest DAI-10 subjective sum scores (0-1) had significantly lower VAS item scores than the two other groups (p<0.01). Item 11 also showed differences between the groups where DAI-10 subjective sum points were 2-3 or 4-6 (p=0.001). In the schizophrenia group, two subgroups were used in the corresponding analysis (patients with 0-2, and 3-6 points). The difference between subgroups was significant in Items 7 (p=0.018), 10 (p=0.003) and 12 (p=0.021). The difference was almost significant in Item 11 (p=0.065) and non-significant in Item 4 (p=0.172, Mann-Whitney U-test).

The means of single VAS items were significantly lower (p<0.05) in the non-compliant group (0-50%; n=27) compared with the compliant group (75-100%; n=79) in all other items except in Items 4 (effect on personality; p=0.165) and 12 (effect on ability to do things; p=0.056). In a comparison with the doctors' assessments of patients' compliance

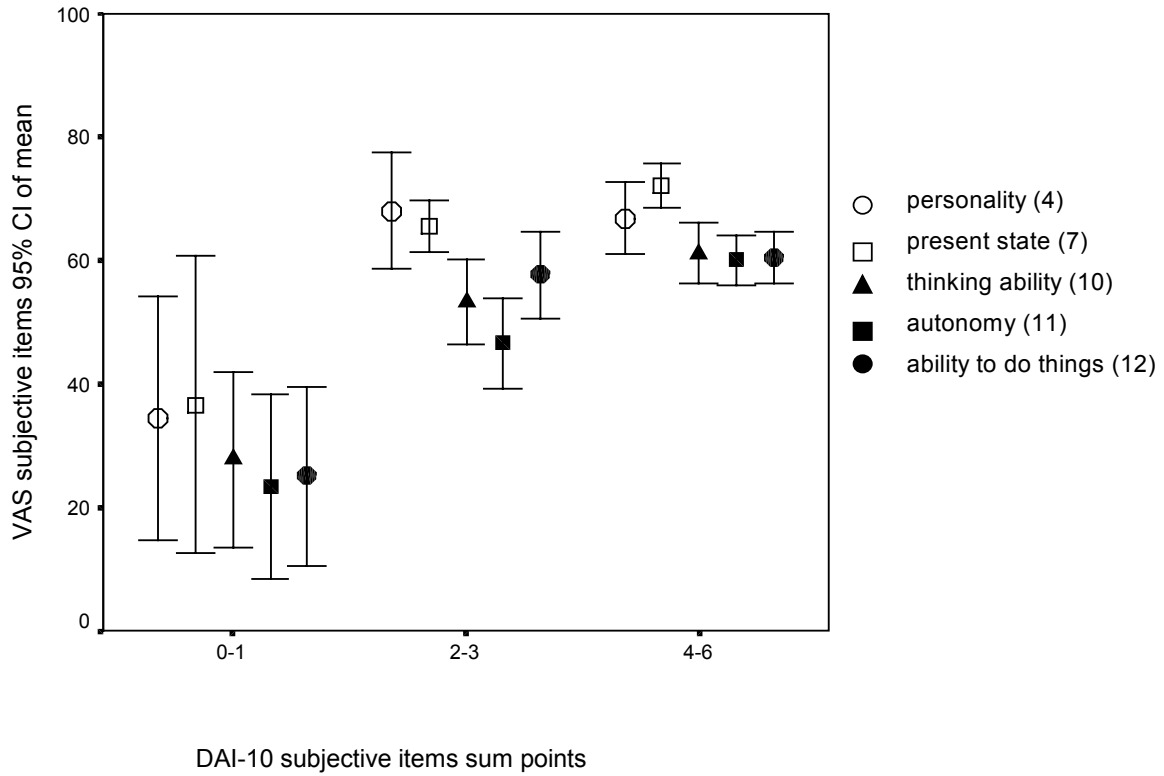
the difference between groups was significant in all other items except in Item 11 (effect on autonomy; $p=0.073$). No corresponding analysis was possible in the schizophrenia group as only five patients in this group reported their compliance as 50 % or less.

Table 4. Patients on neuroleptic medication: results of factor analysis of the ANT-scale for the total sample.

Factor	1 Subjective feeling and expectations	2 General attitudes	3 Insight
Total variance explained %	34.6%	14.9%	10.3%
Loadings of single ANT items ¹			
Importance of medication		0.545	0.454
Medication compared with psychosocial treatment		0.625	
Length of maintenance treatment		0.609	
Effect on personality	0.584		
Willingness in taking medication		0.613	
Reaction to side-effects		0.775	
Expected effect on present state	0.730		
Level of mental problems			0.900
Need for help			0.913
Expected effect on thinking ability	0.765		
Effect on autonomy	0.817		
Effect on ability to do things	0.486		

1 Including loadings > 0.45

Figure 1. Patients with neuroleptic medication: comparison between sum points of DAI-10 subjective items and ANT subjective VAS items.



4.1.2 Self-rating scales for assessing insight, side-effects and need for treatment in patients with first-episode psychosis (III)

The Cronbach alpha coefficients between all items in the self-report scales measuring insight into symptoms, perceived side-effects and need for treatment were 0.764, 0.642 and 0.735, respectively. The item-by-item significances of sensitivity and specificity in the self-rating scales for insight and side-effects are presented in Table 5.

Table 5. First-episode psychosis: item-by-item sensitivity and specificity of the patients' ratings compared with the clinicians' ratings in the self-rating scales for assessing insight and perceived side-effects.

A. Self-rating scale for assessing insight into symptoms

Item	Specificity, p	Sensitivity, p
Hallucinations	0.08	0.50
Agitated or aggressive behaviour	0.02	0.08 ¹
Delusions	<0.01	<0.01 ¹
Disorganisation of thoughts	0.04	0.08 ¹
Elevation of mood	0.04	<0.01
Apathy and social withdrawal	0.04	0.24
Depressive mood	0.24	<0.01
Anxiety	0.24	0.36
Tension	0.14	<0.01
Abnormal movements and posture	0.04	<0.01
Slowness or lack of motor activity	0.02	0.08
Somatic concern	0.50	<0.01
Sleep problems	0.50	0.14

B. Self-rating scale for perceived side-effects

Item	Specificity, p	Sensitivity, p
Excessive fatigue or sluggishness	0.50	0.36
Muscular cramps	<0.01	0.14
Stiffness	0.26	0.09
Physical restlessness	0.04 ¹	0.02
Dizziness	0.12	0.02
Palpitation	0.14	<0.01
Dry mouth	0.14	0.04
Excessive salivation	0.02	<0.01
Nausea	<0.01	<0.01
Constipation	0.08	<0.01
Urination problems	<0.01	<0.01

¹ The expected value of discordant ratings is exceeded.

4.2 Compliance assessments (II, III)

4.2.1 *Comparison of the ratings between patients and doctors in patients on neuroleptic medication (II)*

In the first rating, 27 out of 100 patients reported their compliance as 50% or less of the prescribed medication. Doctors estimated 31 of these 100 to be 50% or less compliant. In the reassessment, the corresponding proportions of 50% or fewer compliant patients were 18 out of 53 as assessed by the patients (34%) and 21 out of 53 as estimated by the doctors (40%). The test-retest correlation coefficients of compliance ratings were 0.81 for patients and 0.80 for doctors.

The explanatory variables in the logistic regression model included subjective states and attitudes on the ANT scale; such demographic, treatment and symptom-related factors as age, sex, education, living conditions, neuroleptic dose, diagnostic category, hostility, suspiciousness and the existence of delusions. In the analysis, good ($\geq 75\%$) patient compliance assessment was explained by male gender and high scores in ANT items 3 (length of maintenance treatment), 5 (willingness in taking medication), 6 (reaction to side-effects), and 8 (level of mental problems). The doctors' assessment of patient compliance at a level of 75-100% was explained by patient age and high scores in ANT-items 5 (willingness to take medication), 6 (reaction to side-effects), 9 (need for help), 11 (effect on autonomy) and 13 (importance of neuroleptic medications) as assessed by the doctor. The results of multivariate analyses for patients' and doctors' compliance ratings are presented in Table 6.

4.2.2 *Compliance in first-episode psychosis (III)*

Patient records during 0-3 months showed that 11 (19%) patients were non-compliant with their medications. Ten of them used medication irregularly, and one patient discontinued the medication completely during the follow-up. Four of these patients had predicted their non-compliance in the initial assessment. A further 13 patients assumed to be compliant according to their files in the follow-up had been assigned a prediction of partial or absolute non-compliance at the initial assessment. The p-value of concordance between the patient's prediction of compliance and the observed compliance according to the patient records was 0.54 (chi-square test).

In the logistic regression analyses (Table 7), the following subsets of variables were used prior to the final analyses: 1) insight, 2) psychopathology and level of functioning, 3) side-effects of medication and 4) content of the treatment. Significant variables were then extracted from each subset for the final analysis. In the analyses, observed non-compliance by patient records was determined by variables of several types. Overall harmful side-effects rated by the patient predicted a higher risk of non-compliance. Of the demographic variables, male sex, young age and a lack of social activities were associated with increased risk of non-compliance during the first three months of treatment. Of the

measurements of psychopathology, a high total PANSS score and a low score in the PANSS positive subscale increased the risk of observed non-compliance. In addition, the Pearson correlation between initial positive PANSS scores and the change from 0 to 3 months in respective scores was 0.819 ($p=0.01$).

Variables determining the patient's prediction of non-compliance in initial assessment included items exclusively from the self-rating measures. The overall harmfulness of medication increased the likelihood of the patients' negative prediction. Two of the attitude items, the need for individual appointments and the need for medication determined the predicted compliance. In both items the association was positive, i.e. negative attitudes increased the risk of negative prediction. Finally, if none of the positive symptoms were recognized, the risk of a low compliance prediction was increased.

Table 6. Patients on neuroleptic medication: results of logistic regression analyses for patient and doctor compliance ratings. Seventy-five percent compliance was used as a cut-off point.

Patient compliance rating (75-100%)	OR	95% CI	P
Male gender	3.57	1.05-12.2	0.036
Patient's attitude (ANT item no.):			
-Need for preventive medication (item 3)	1.31 ¹	1.05-1.63	0.015
-Voluntariness in medication taking (item 5)	1.44 ¹	1.02-2.04	0.025
-Reaction to side-effects (item 6)	1.22 ¹	1.00-1.48	0.047
-Insight (item 8)	1.43 ¹	1.12-1.82	0.002
Doctor's rating of patient compliance (75-100%)	OR	95% CI	P
Patient's age/10 years	2.19 ²	0.82-5.8	0.078
Doctor's attitude (ANT item no.):			
-Patient's voluntariness in medication taking (item 5)	1.92 ¹	0.87-4.2	0.080
-Patient's reaction to side-effects (item 6)	3.01 ¹	1.50-6	0.000
-Patient's need for treatment (item 9)	2.92 ¹	1.01-8.5	0.012
-Effect of medication on patient's autonomy (item 11)	3.09 ¹	1.18-8.1	0.007
-Importance of neuroleptics in the treatment of psychosis (item 13)	3.57 ¹	0.86-15	0.045

1 OR for 75-100% compliance rating when VAS score increases by 10 points.

2 OR for 75-100% compliance rating when patient's age increase by 10 years.

Table 7. First episode psychosis: results of logistic regression analysis for patients' prediction of their compliance and observed compliance.

Non-compliance 0-3 months according to patient records	OR	95% CI	P
Experienced harmful side-effects	35.4	1.8-690.2	0.003
Male sex	17.2	1.8-165.5	0.004
Lack of social activities	16.3	1.3-208.5	0.013
PANSS positive symptoms	0.6 ¹	0.4-0.9	0.005
PANSS total score	1.1 ²	1.0-1.2	0.012
Age	0.9 ³	0.8-1.0	0.043
Patient's negative prediction of his/her compliance at the initial assessment	OR	95% CI	P
Experienced harmful side-effects	10.9	1.9-63.0	0.003
Negative attitude towards individual outpatient treatment	5.8	0.9-36.3	0.041
Negative attitude towards medication	4.5	0.7-30.2	0.093
Lack of insight to positive symptoms	3.9	0.7-21.8	0.116

1 A one-point increase in PANSS positive symptoms yielded a lower risk of non-compliance.

2 A one-point increase in PANSS total score yielded a higher risk of non-compliance.

3 An age increase of one year yielded a lower risk of non-compliance

4.3 Factors associated with discrepancies between compliance ratings with patients on neuroleptic medication (sample 1; II)

The Spearman correlation between compliance assessments on a five-point scale made by patients and doctors was 0.50 in the first assessment and 0.54 in the reassessment ($p=0.01$, both assessments). In the first compliance assessment, 12 of the ratings between patient and doctor had an at least 50%-unit positive difference (12%) and 9 had an at least 50%-unit negative difference (9%) (median of difference 0 % units; quartiles 0 and +25% units).

Patient characteristics explaining at least 50%-unit positive difference between the patients' and doctors' compliance ratings included a diagnosis of a manic episode and high neuroleptic dose (Table 8). In the analysis concerning negative difference, female gender, a low level of education and the patient's low scores in ANT items 3 (length of maintenance treatment), 6 (reaction to side-effects), and 8 (level of mental problems) remained as patient-related determinants (for the explanatory variables, see Chapter 4.2.1).

Doctor characteristics explaining at least 50%-unit positive difference between patient and doctor ratings included low scores in ANT items 4 (effect on personality), 6 (reaction to side-effects) and 7 (expected effect on present state). High scores by doctors in ANT items 5 and 13 explained the negative difference between their and the patients' ratings.

Table 8. Patients on neuroleptic medication: results of the logistic regression analysis for patients' and doctors' compliance ratings. For the discrepancy between patient's and doctor's ratings, 50 % difference was used as a cut-off point.

Positive rating difference: the patient's rating of compliance is 50-100%-units greater compared with the doctor's rating	OR	95% CI	P
Diagnosis of manic episode	1772 ¹	1.20-2.6E6	0.003
Neuroleptic dose/100 mg	1.63 ²	0.97-2.71	0.047
Doctor's attitude (ANT item no.):			
-Effect of medication on patient's personality (item 4)	0.34 ³	0.13-0.90	0.003
-Patient's reaction to side-effects (item 6)	0.30 ³	0.13-0.71	0.000
-Effect of medication on patient's subjective state (item 7)	0.06 ³	0.006-0.51	0.001
Negative rating difference: the patient's rating of compliance is 50-100%-units less compared with the doctor's rating	OR	95% CI	P
Female gender	8.26	1.17-58.54	0.020
Education	6.17 ⁴	0.64-59.88	0.083
Patient's attitude (ANT item no.):			
-Need for preventive medication (item 3)	0.74 ³	0.52-1.06	0.085
-Reaction to side-effects (item 6)	0.75 ³	0.53-1.06	0.096
-Insight (item 8)	0.66 ³	0.44-0.97	0.020
Doctor's attitude (ANT item no.):			
-Patient's voluntariness in medication taking (item 5)	2.01 ⁵	1.15-3.52	0.004
-Importance of neuroleptics in the treatment of psychosis (item 13)	3.87 ⁵	0.95-15.78	0.025

1 Increased risk of discrepancy in compliance ratings with a diagnosis of manic episode.

2 Increased risk of discrepancy in compliance ratings when neuroleptic dose increases by 100 mg

3 Increased risk of discrepancy in compliance ratings when VAS score decreases by 10 points

4 Low level of education indicates higher risk of discrepancy in compliance ratings

5 Increased risk of discrepancy in compliance ratings when VAS score increases by 10 points

4.4 Clinical and research diagnoses in first psychotic episode (IV)

Among the 80 patients with first-episode psychosis, the overall agreement between the clinical and research diagnoses was 0.55 (kappa) (95% CI 0.44-0.66). In different diagnostic categories, the kappa values were 0.47 for the schizophrenia group, 0.46 for acute and transient psychotic disorder, 0.63 for bipolar disorder and 0.47 for severe depressive episode with psychotic symptoms. The levels of sensitivity and specificity for each group were 0.49 and 0.98 for the schizophrenia group, 0.86 and 0.77 for acute and transient psychotic disorder, 0.55 and 0.99 for bipolar disorder and 0.33 and 1 for severe depressive episode with psychotic symptoms. Comparisons between clinical and research diagnoses are presented in Table 9.

In the multivariate analysis low scores in PANSS negative subscale, low level of education, and a high score (4-7 points) in the PANSS item for delusions predicted a higher risk of discrepancy between the diagnostic categories of clinical and research diagnoses. Acute and transient psychotic disorder as a research diagnosis predicted lower risk of discrepancy. The results are summarised in Table 10.

Table 10. First episode psychosis, total sample: factors explaining the discrepancy between clinical and research diagnoses in logistic regression analysis.

Variable	OR	95% CI	p
Diagnostic group: acute and transient psychotic disorder	0.14	0.03-0.71	<0.01
PANSS negative subscale scores	0.93 ¹	0.86-1.00	0.04
Low level of education	2.83	0.89-8.93	0.07
Moderate to severe (4-7 points) delusions in PANSS item P1	4.02	0.97-16.74	0.04

¹ A one-point increase means lower risk of diagnostic discrepancy.

Table 9. First-episode psychosis: comparison of SCAN-2 and clinical diagnoses.

SCAN-2 diagnosis	Schizophrenia group							Total (SCAN-diagnoses)
	Clinical diagnosis							
	Delusional disorder							
	Acute and transient psychotic disorder							
Schizophrenia group								
	Delusional disorder							
	Acute and transient psychotic disorder							
	Manic episode							
	Severe depressive episode with psychotic symptoms							
	Unspecified psychosis							
	Non-psychotic disorder							
	Total (SCAN-diagnoses)							
Schizophrenia group (F20.x, F25.x, F23.2)	20	9	1	9	3	9	3	42 (52.5%)
Delusional disorder (F22.x)	1	1		3				4 (5.0%)
Acute and transient psychotic disorder (F23.x, F23.2 excluded)	1	12		1				14 (17.5%)
Manic episode (F30.x, F31.x)	1	3	6	1				11 (13.7%)
Severe depressive episode with psychotic symptoms (F32.3)	1	3	3	1	1		1	9 (11.3%)
Total (clinical diagnoses)	21 (26%)	3 (4%)	27 (9%)	7 (9%)	3 (4%)	15 (19%)	4 (5%)	80 (100%)

The multivariate analysis for the group with a schizophrenia research diagnosis produced slightly different results. First of all, psychopathology had no effect on the risk of discrepancy between the diagnostic categories. Patient's age had a positive effect i.e. older age predicted higher risk of diagnostic discrepancy. In addition, social activities outside the home were predictive of higher risk of discrepancy. The results are summarised in Table 11.

In bivariate comparisons with 59 of the patients, observed non-compliance during three months, experienced side-effects of medication, or negative attitudes assessed by self-rating measures were not associated with discrepancies between diagnoses ($p=0.35$, 0.88 , 0.82 respectively; chi-square and Mann-Whitney U-tests).

Table 11. First-episode patients, schizophrenia group: factors explaining the discrepancy between clinical and research diagnoses in the logistic regression analysis.

Variable	OR	95% CI	p
Age	1.11	1.00-1.22	0.03
Lack of social activities	0.12 ¹	0.02-0.64	<0.01

¹ Lack of social activities outside home means lower risk of diagnostic discrepancy.

4.5 Four-year outcome with or without home-based outpatient care in long-term schizophrenia patients (sample 3; V)

4.5.1 Hospitalisation rates

In the group receiving ambulatory outpatient care (AOC), the mean neuroleptic dose did not change significantly during follow-up (neuroleptic dose 0-700mg of chlorpromazine equivalents; mean 322; SD 212 at baseline vs. 50-800 mg; mean 312 mg; SD 196 mg at endpoint; $p=0.958$). During the ambulatory care the patients were hospitalised 0-596 days (median 3 days; quartiles 0 and 118 days) vs. 60-1440 days (median 368 days; quartiles 252 and 633 days) before the AOC ($p=0.001$; Wilcoxon test). Only one AOC patient had more hospital days during the ambulatory treatment than before. Nine of the patients had no hospitalisations at all.

In the non-AOC group, the neuroleptic doses did not change significantly during follow-up (neuroleptic dose 100-800 mg; mean 377; SD 185 at baseline vs. 100-1200 mg; mean 388 mg; SD 229 mg at endpoint; $p=0.897$). During the period January 1992 December 1995 the patients were hospitalised 0-1270 days (median 43 days; quartiles 0 and 293 days) vs. 56-523 days during the period January 1988 December 1991 days (median 324 days; quartiles 113 and 450 days). Eight patients were not hospitalised at all (including three patients who died during follow-up). There was a significant decrease in the numbers of hospital days within the non-AOC group between the periods 1988-91 and 1992-95 ($p=0.009$; Wilcoxon test).

The sum of days hospitalised was 1828 (102 days/patient) in the AOC group during ambulatory care vs. 4606 (200 days/patient) in the non-AOC group during the years 1992-95 ($p=0.26$; Mann-Whitney U-test).

4.5.2 Levels of functioning and survival

There was no change in GAF scores during follow-up in the AOC group (mean 31; SD 6 at baseline vs. mean 33; SD 5 at endpoint). Due to outpatient non-attendance in the non-AOC group levels of functioning could be assessed in only thirteen cases initially and in nine of them at the end of follow-up. There was no change in GAF scores during follow-up (mean 30; SD 5 at baseline vs. mean 30; SD 5 at endpoint).

One of the eighteen patients (6%; 95% CI 0-16%) in the AOC group and five of the twenty-three patients (22%; 95% CI 5-39%) in the non-AOC group died during follow-up. This difference was not statistically significant ($p=0.14$, log rank test). In comparison to the crude mortality rate (CMR), odds ratios were 0.7 (95% CI 0.0-1.9; $p=0.598$) for the AOC group and 2.9 (95% CI 0.7-5.1; $p=0.027$) for the non-AOC group.

5 Discussion

5.1 Patients and methods

The study was based on three different patient populations, all of them presenting a different aspect of clinical problems with non-compliance in the treatment of psychoses. Although the study was performed in an area with mostly urban population, and having a steadily increasing number of inhabitants, the results of the study can be generalised to all patients entering public mental health care in Finland. The study designs were kept as simple as possible to avoid excessive dropouts, and thus several samples were required for a comprehensive overview of the study focus. The 20 patients who declined to participate in sample 1 (patients with neuroleptic medication) did not differ from the final study group regarding age or illness-related characteristics (for details, see paper I).

The assessments for the patients on neuroleptic medication (sample 1) yielded data on a cross-sectional design with an unselected group of patients using anti-psychotic medications. Half of the patients had a diagnosis of schizophrenia, which made separate analyses in this subgroup possible, and extends the possibilities for generalising the results. The focus of the study was on identifying factors associated with both compliance and inaccuracy in compliance reports, and exploring attitudes towards psychopharmacological treatment.

The development of the new ANT scale was an essential part of the process, as attitudes to drugs have been observed to be related to patient compliance, and the results of the ANT items were used in further analyses of compliance assessments. In addition, there was a clear need for a quantitative attitude scale for follow-up purposes, and that would take into account different aspects of treatment compliance during psychopharmacological treatment: attitudes towards drugs, subjective state during medication and insight. The questions in the scale were formulated so that the expectations of drug-naïve patients could also be ascertained. The psychometric properties of the scale were tested with previously medicated patients, as their attitudes and subjective feelings over a short period of time are less likely to change, which gives a better reliability in the test-retest design. The DAI-10 has been used by different investigators in several studies for assessing medication-related attitudes, which was the main reason for choosing it as a reference scale.

The scope of compliance among patients with no earlier treatment for psychosis (sample 2) needed to be examined and the design was constructed to be pragmatic, but comprehensive to take into account as many dimensions of compliance as possible. In this sense, the weight of cognitive functioning did not emerge as an important factor at the time of beginning the study, and it was omitted from the design. There are, however, some recent studies in which cognitive functioning has been related at least to insight on

psychotic symptoms (Cuffel et al. 1996; McEvoy et al. 1996). The study also involved a modern psychosocial intervention that has been proven to reduce relapses, which has been associated with improved compliance.

In sample 2, the SCAN-2 was used as a diagnostic tool. It was designed to make psychiatric diagnoses according to ICD-10 and DSM-IV. It has been reported to have reasonable accuracy in making diagnoses according to DSM-III-R (World Health Organization, 1994; Skodol & Bender, 2000). The symptom assessment and the level of functioning scales used in the study (PANSS, Hamilton Depression Scale, GAF), have also been approved as reliable and valid in their psychometric properties (Bech, 1993; Bech et al. 1993). The self-rating scales used in this sample were based on Likert or dichotomous scales designed to be simple enough for rating to avoid dropouts. These scales were theoretically based on validated investigator-rating scales. The first scale, which was modified from the Brief Psychiatric Rating Scale, focused on recording the symptoms of psychosis the patient is capable of recognising, i.e. insight. The second scale was a modification of the scale of the Committee of Clinical Trials (UKU), and it was designed for self-reports of experienced side-effects of medication. The third scale comprised items on self-assessment of perceived need for treatment as Likert scales.

There was earlier evidence that non-compliance in outpatient treatment may have negative consequences on outcome in schizophrenia. Patients with extreme and continuous non-compliance were selected as one of the study groups (sample 3) to evaluate long-term outcome during the de-institutionalisation process. The effects of two different outpatient treatment models were compared during the four years of follow-up.

5.2 The ANT scale (I)

Though approximately 85% of the patients were suffering from a psychotic disorder, they were quite capable of evaluating the different aspects of their medication. The differences in the answers between clinical diagnostic categories were apparent only in the insight items. As patients with schizophrenia constituted half of the sample, the reliability testing, test-retest analyses and the comparisons with the Drug Attitude Inventory 10 subjective items were made for this subgroup separately. These findings were in concordance with the results in the whole sample.

The statistical analysis of the questionnaire resulted in fair test-retest validity. The patients filled in the questionnaire forms with a 1-2 week interval. The relatively short time interval was chosen to avoid marked changes in the clinical condition of the patients.

Comparison with the DAI-10 confirmed that attitude items of ANT could differentiate the degree of attitudes, especially at the negative end of the scale (Figure 1, page 39). This is particularly useful in the follow-up of patients with high risk of non-compliance.

The questionnaire yielded high internal consistency both for the whole group and the schizophrenia subgroup. It is important to note that the treatment attitudes consist of different dimensions, including subjective state, expectations and general attitudes. The

subjective attitude factor explained one third of the total variance in the single items. The factor analysis of the scale supported previous findings that insight works as an independent factor in compliance behaviour (Fenton, Blyler & Heinssen, 1997), although the insight component explained only 10% of the variance in the present study.

The results of the ANT scale were also compared with both patients' and their treating doctors' assessments of patient compliance. These findings demonstrated significant differences in almost every VAS item between compliant and non-compliant patients assessed both by the patients themselves and their treating doctors. Minor difficulties in discriminating between the compliant and non-compliant patients in some items (effect on personality (4), effect on autonomy (11), effect on ability to do things (12)) concerning the subjective state could describe the difficulty for some individuals to analyse their subjective state, since this has been shown to be an important factor in predicting compliance in previous studies (Adams & Howe, 1993; Awad, 1993). It should be noted, however, that no pill counts or serum level tests were made, but compliance reports were used, and they always include the risk of invalid reports.

Previous rating-scales, including the DAI-10, have concentrated on the attitudes and subjective effects of medication, need for treatment, or recognizing the symptoms of the psychosis. The ANT questionnaire's 12 Visual Analogue Scales take into account three different dimensions important for compliance. The VAS structure makes rating of the items quick and easy, but it should be properly introduced to the patient. By doing so in this study, there appeared no particular difficulties for the patients to understand the VAS structure. Single items are presented in numerical form and thus can be compared from test to test. Hence, the scale is tailored for long-term follow-up purposes and the change in separate items can be observed, which is an advantage compared with the DAI-10. The disadvantage in using it during short-term follow-up is the risk of high variance in single items between test situations due to the nature of the VAS.

5.3 Self-rating scales for assessing insight, side-effects and need for treatment (III)

The inter-item reliability in all three self-rating scales was on a moderate level at least, and the findings in the comparison between patients' and doctors' ratings of insight concurred with previous findings in the literature (for a detailed discussion see paper III). The highly concordant results in the item dealing with elevation of mood were exceptional in this sense, as most studies have confirmed that manic patients lack insight on their symptoms (Peralta & Cuesta, 1998). The main purpose in assessing insight was only to ascertain whether or not the patients recognised any of the symptoms. A more detailed view of insight would have required using specific insight scales such as that developed by David et al. (1990) or the Scale to Assess Unawareness of Mental Disorder (Amador et al. 1993). Similarly, the existence of perceived side-effects was also regarded as more important than their actual quality, and thus no objective screening of side-effects was included. The

importance of subjective state in relation to compliance has been pointed out in previous studies by Hogan et al. (1983) and Awad et al. (1996) or Van Putten (1979).

5.4 Compliance with patients on neuroleptic medication (sample 1; II)

In the multivariate analysis concerning the first assessments, the finding that male gender was associated with better compliance was contradictory to previous compliance studies, which have most often found no gender differences (Buchanan, 1992; Draine & Solomon, 1994; Razali & Yahya, 1995). The other determinants of good (at least 75%) patient compliance ratings included high scores in ANT items concerning general attitudes to medication (length of maintenance treatment (3), willingness in taking medication (5), and reaction to side-effects (6)) and insight (item 8). Previous studies on the issue have likewise concluded that positive attitudes play a crucial role in patient compliance (Awad et al. 1996; Gallhofer et al. 1996).

The doctors' view of good patient compliance was determined by their opinion of the patient's attitudes towards medication (willingness in taking medication (5), reaction to side-effects (6), and effect on autonomy (11)), perceived need for treatment (item 9), and the patient's age. Most of the compliance studies dealing with psychotic patient samples did not find any association between age and compliance (Fenton, Blyler & Heinssen, 1997), but in a study by Hoffmann (1994) higher age was associated with good compliance.

5.5 Compliance in first psychotic episode (sample 2; III)

The aim was to examine the weight of different patient and treatment-related factors of compliance in a natural setting. The standard treatment programme comprised family psycho-education for all first-onset psychosis patients in areas obtaining trained therapists. During the study, the implementation of the model was in its early stages at the area, which should be considered when interpreting the results. According to the Buckingham model (Falloon & Fadden, 1993), two therapists work with the patient's family and appointments take place at home. Half of the sample lived in areas where this treatment was available during the study. The patient selection for family psycho-education included no bias, as it was done according to the patients' current home address. The initial interview was made using semi-structured standardised diagnostic interview and structured rating of symptoms.

No drug-level measurements or pill counts were undertaken in the compliance assessments, which includes sources of error. The patients' prediction of their compliance and information from the patient records were used in completing the assessment. This approach was chosen to avoid possible dropouts, especially in the non-compliant patient group.

It is possible that the information collected from patient records reveals only the most extreme cases of non-compliance and that some of the partially non-compliant patients were assigned to the compliant group, as the relationship between predicted and observed compliance appeared to be random.

Variables explaining the observed compliance in this sample of first-episode psychotic patients concur with the findings of previous studies of psychotic populations. Self-rated side-effects were predictive of compliance, as in a study by Hogan and co-authors (1983). Male sex has been associated with non-compliance in some previous trials with schizophrenia patients, but gender differences have not been found in the majority of studies (Fenton, Blyler & Heinssen, 1997). Similarly to the finding even in this sample, Hoffmann (1994) reported increased compliance with age. A lack of social activities was also shown to be a risk factor for non-compliance in our sample. Draine and Solomon found a connection between positive attitudes to medication and social activities (Draine & Solomon, 1994). In the present sample, an association between psychotic symptom severity and observed compliance was of interest. A high total PANSS score has been associated with poor compliance in the majority of previous studies (Fenton, Blyler & Heinssen, 1997). In our study, the severity of positive symptoms predicted good compliance. This contradictory finding could be related to a good treatment response, as there was a strong correlation between the severity of initial positive symptoms and improvement during the first three months measured using the same scale. The duration of untreated psychosis was not associated with compliance, as has also been reported by Buchanan (1992).

A negative prediction of compliance was determined solely by self-rated measures. As with observed compliance, overall experience of side-effects was important. The three other determinants were connected with insight. Insight has been an important contributing factor of compliance in several previous studies. In this sample of first-episode patients a poor recognition of both the need for treatment and positive psychotic symptoms were associated with a negative prediction of compliance.

Minimizing the side-effects of medication during the early stages of treatment can prevent problems of non-compliance in first-episode psychosis patients. A high-risk patient for early non-compliance is most likely to be a young man with social isolation and a high level of overall psychopathology with limited positive psychotic symptoms.

5.6 Factors associated with discrepancies between compliance ratings (II)

The aims were to identifying and explaining the sources of discrepancy in compliance assessment between patients receiving neuroleptic treatment and their doctors (sample 1), with methods available in the clinical treatment setting. The compliance assessments made by patients and their treating doctors were mostly congruent. Seventy-nine percent of the ratings revealed a discrepancy within the limits of ± 25 percent units and the patients'

reports were markedly more positive than the doctors' estimations in only 1/10 of cases. It is likely that the doctors overestimated patient compliance in the remaining 1/10 of cases.

When determining variables possibly explaining the differences in compliance ratings between patients and their doctors, the focus was separately on positive and negative discordant ratings between patients and doctors. To this end a 25% tolerance was allowed to connect only the most significant discrepancies in the regression model. The positive difference in the ratings by patients was assumed to be clinically more important, whereas the negative difference represents an overestimation of patient compliance by the doctors.

The manic patients showed a constant tendency to positive compliance assessment compared to that of their doctors. Due to the small number of these patients, no analyses on the background of this finding could be done. It is, however, likely that insight is connected with the capability to determine the level of compliance and insight in most cases is distorted during manic episodes (Peralta & Cuesta, 1998).

The high neuroleptic dosage determining a more marked discrepancy in the compliance assessment may reflect the severity of the patients' psychopathology, or the uncertainty doctors feel about patient compliance when higher doses of neuroleptics are prescribed.

The doctors' estimation of subjective medication effects (effect on personality (4) and expected effect on present state (7)) or patient's reaction to side-effects (item 6) as indicators of positive rating difference link together expected beneficial drug effects and patient's general attitudes to medication with the doctors' negative view of patient compliance.

The doctors having a more positive rating than the patients was associated with a low level of education and female gender. As discussed earlier, women had a lower compliance rate in our sample. Furthermore, both the patients' and the doctors' ratings on attitude items reflected the negative difference between compliance ratings.

Compliance ratings made by patients during neuroleptic treatment seem to be mostly concordant with the estimates made by their doctors. It is possible to identify the factors associated with discrepancies between assessments and they seem mostly to be connected with the attitudes of both patients and doctors. Certain psychopathology, like manic episode or high-dose treatment may also preclude reliable compliance assessment.

5.7 Diagnosis in first psychotic episode (IV)

Results on the diagnostic discrepancy between clinical and research diagnoses were similar to other Finnish studies using DSM-III-R or DSM-IV criteria (Isohanni et al. 1997; Taiminen et al. 2001). There was marked diversity in overall diagnostic agreement and schizophrenia was under-diagnosed among clinicians compared with the researchers' view. At the time of this study, the implementation of the ICD-10 criteria was quite recent, which made diagnostics even more challenging for the clinicians. Diagnostic agreement was equal between the diagnostic groups except in the bipolar disorder group, where it was higher than in the other groups. The other diagnostic groups had quite low or moderate

sensitivity and very high specificity, but the group F23.x acute and transient psychotic disorders (F23.2 excluded) had the highest sensitivity, but the lowest specificity of the diagnostic groups. This indicates that the clinicians tended to use diagnoses of this group even though the criteria of some other diagnostic group were fulfilled.

The primary aim was to examine the patient-related reasons for diagnostic discrepancies both in the total sample and schizophrenia group alone. With multivariate analysis for the total sample acute and transient psychotic disorder (F23.x, F23.2 excluded) as a research diagnosis was connected with high diagnostic agreement. This group of diagnoses is probably the least stigmatising of the psychotic disorders and may thus be easier for the clinicians to use. Negative symptoms assessed with the PANSS scale predicted diagnostic discrepancy. It is likely that this finding is connected with a higher level of negative symptoms in the schizophrenia group. Moderate to severe delusions resulted in higher risk of diagnostic discrepancy. This finding could be related to the doctor-patient relationship, which may be disrupted in delusional states (David, 1990). On the other hand, no relationships between self-rated attitudes, perceived side-effects, or treatment compliance were found. However, this group of variables was analysed only with bivariate testing due to the small number of cases with accurate self-rating measures.

Lower level of education was associated with higher discrepancy in diagnoses. This finding is contradictory to the study by Fennig et al. (1994), which showed no relationship between patient's education and diagnostic agreement between clinical and research diagnoses. This result may reflect educated patients' better capability in both reporting about their psychic state and reflecting on the doctors' communication compared with non-educated patients.

In the schizophrenia group older patients had a higher risk of diagnostic discrepancy. This is contradictory to previous findings, where age has not been associated (Fennig et al. 1994; Taiminen et al. 2001). In cases of first-episode psychosis, the clinicians may be more uncertain about giving a schizophrenia diagnosis to older patients. Patients with no social activities outside the home had a lower risk of diagnostic discrepancy in this group. In practice this means that socially isolated patients may be more easily detected to have schizophrenia in a clinical situation. Psychopathology did not explain diagnostic discrepancy in the schizophrenia group. This finding may be related to the complex nature of the schizophrenic syndrome, which does not only concern certain symptoms, but also the duration and course of the psychotic illness.

In conclusion, the diagnosis of schizophrenia is likely to be delayed in clinical practice, even if negative symptoms are present. Young patients and those with no social activities are more likely to get this diagnosis at an earlier stage of illness. Marked delusions may contribute on misdiagnosis in first-episode psychosis. The connection with this finding and disrupted doctor-patient relationship needs further study.

5.8 Outcome during ambulatory outpatient care (V)

The aim was to explore outcome during de-institutionalisation in a non-compliant group of schizophrenia patients with a relapsing course of illness. These patients often drop out of treatment and have a poor prognosis without extra support. The effectiveness of a specific treatment practice focused on this group was evaluated by means of outcome.

The results indicate that non-attendance at injection appointments is likely to produce an elevated risk for relapse in conventional outpatient treatment. In home-based treatment (AOC) the nurse has a better chance to ensure continuity both in collaboration and medication.

The proportion of males was 80% in the AOC group compared with 60% in the non-AOC group. Previous studies have found no marked differences in compliance rates between men and women (Fenton, Blyler & Heinssen, 1997). It is likely that there is a selection bias in favour of men in the group chosen for the ambulatory treatment. The number of psychiatric hospital beds in Finland was constantly reduced during the period 1986-1995, resulting in a decreasing total number of inpatient days in schizophrenia patients (Kaltiala-Heino, Laippala & Joukamaa, 2001). This change was seen even in the non-AOC group as reduced numbers of hospital days during follow-up.

The levels of functioning showed no change in the AOC group during follow-up. It was not possible to obtain representative data of levels of functioning in the non-AOC group. In a previous Australian study an Assertive Community Treatment (ACT) programme reduced the need for hospitalisation to less than half among seriously ill patients (Hambridge & Rosen, 1994). A Cochrane meta-analysis of the effectiveness between ACT and conventional individual outpatient treatment by Marshall and Lockwood resulted in better continuity and fewer days of hospitalisation in favour of ACT, whereas levels of psychopathology or social functioning remained equal between groups (Marshall & Lockwood, 2001). ACT and AOC focus on ensuring continuity in outpatient treatment, but there are also some essential dissimilarities. ACT is based on multi-disciplinary teamwork, and includes the option to have contact both day and night. AOC functions with much more limited resources and appointments take place exclusively during office hours.

The mortality rate in the AOC group was on the same level as the mortality of schizophrenia patients in general (Brown, 1997), whereas the non-AOC group showed a trend to excess mortality. Although the number of cases is small, the finding could be related to the poorer continuity of treatment in the non-AOC group. Testing this hypothesis requires a larger sample size, which would also make it justifiable to examine the causes of death. Previous epidemiological surveys in Finland regarding patients with schizophrenia alone or including cases with delusional disorder have shown the mortality rates as 6.4% in three years (Honkonen, Saarinen & Salokangas, 1999), and between 12-16% in four years (Sohlman & Lehtinen, 1999). A Finnish epidemiological study with 99 cases of schizophrenia showed an excess mortality from respiratory disease in both genders and from suicide in males (Joukamaa et al. 2001).

Among the non-compliant and relapsing subgroup of schizophrenia patients the risk of insufficient treatment may increase if no assertive outpatient treatment practices are

applied to compensate for the smaller number of hospital beds. The need for hospitalisation in this selected population decreased by almost 80% during AOC, whereas a more limited change was seen during conventional outpatient treatment. AOC can be implemented with limited resources. It should focus on patients incapable of maintaining regular oral medication and having recurrent relapses due to non-compliance. Showing the effectiveness of AOC on survival in schizophrenia patients needs further studies. The high mortality rate in the non-AOC group is an alarming result, and its background needs to be investigated in future research.

6 Conclusions and implications for further studies

The results of the present study indicate the following conclusions:

1. Non-compliance in the treatment of psychoses can be detected precisely enough with simple self-rating measures.
2. Medication related attitudes, which are closely related with patient compliance, can be accurately assessed quantitatively even in follow-up.
3. In first-episode psychoses, the patients at high risk for non-compliance can be identified during early stages of the treatment process.

All these findings give rise to better chances to recognise and prevent non-compliance in the treatment of psychoses.

4. There are marked discrepancies between clinical and research diagnoses in first-episode psychosis.
5. The diagnoses in psychotic mood disorders and schizophrenia may have high specificity, but these disorders tend to be under-diagnosed, and unspecified or transient psychosis diagnoses are used instead.

This kind of clinical practice may be interpreted as means of avoiding patient stigmatisation. On the other hand, it may preclude appropriate maintenance treatment and accelerate the risk of relapse. Delusional patients especially may have difficulties in adequately describing their symptoms, which may give rise to a diagnostic error.

6. In long-term schizophrenia, ambulatory treatment may be helpful in managing non-compliant patients with schizophrenia after de-institutionalisation, although the effect of the treatment model on fewer hospitalisations remained unclear.
7. Despite earlier non-compliance and frequent relapses, it is possible to maintain treatment collaboration with the majority of patients during ambulatory treatment.

8. Ambulatory treatment may prevent mortality among non-compliant schizophrenia patients.

Clinical implications and recommendations for future research:

1. Non-compliance in psychoses, and particularly in the long-term treatment of such disorders as schizophrenia or bipolar disorder should be systematically screened both during acute exacerbation of symptoms and in follow-up. The screening involves at least exploring the general attitudes of the patient and the relatives towards medication and other treatment.
2. It is important to detect the possible side-effects of medication and provide information on these for the patient and near relatives. In cases of continuous or recurrent non-compliance, both the side-effects and symptom response to previous medications need to be carefully evaluated.
3. Subjective state during medication was associated with patient compliance in the present study. There is evidence showing that the new, atypical anti-psychotic agents are favourable in this sense. However, their effect on patient compliance needs to be verified in long-term follow-up studies.
4. In the study, the effectiveness of two different psychosocial treatment models was examined. According to some recent findings, psychosocial treatment programmes in psychotic disorders should include cognitive-behavioural interventions to influence attitudes towards treatment. In selected groups of patients with schizophrenia and bipolar disorder assertive treatment programmes may result in better outcome due to better adherence and continuity in treatment.

7 Summary

The aims of the study were 1) to develop a reliable quantitative measuring instrument for attitudes towards neuroleptic medication, 2) to examine attitudes towards drugs among patients with anti-psychotic medication, 3) to observe the concordance between patients' and doctors' compliance assessments, 4) to examine the weight of different compliance-related factors in the treatment of first-episode psychoses, 5) to define patient-related factors leading to diagnostic discrepancy in first-episode psychoses, and 6) to evaluate outcome among long-term schizophrenia patients.

In 106 patients using neuroleptic medication, a self-rating scale based on 12 Visual Analogue Scale (VAS) items measuring patient's attitudes towards medication was tested. This rating-scale, named Attitudes towards Neuroleptic Treatment (ANT), showed good reliability and validity in repeated measures. In comparison with a previously published attitude scale with dichotomous questions, the Drug Attitude Inventory 10 (DAI-10), the results of the ANT items were in concordance with the results of the DAI-10.

Twenty-seven percent of the patients reported their compliance as 50% or less of the prescribed medication. In 79 percent of cases the difference between the patient's and the doctor's compliance assessment was at most ± 25 % units. In multivariate analysis high reported compliance was explained by male gender, positive attitudes towards medication taking and subjective experience of the medication, and insight on need for treatment. The factors explaining the doctors' lower compliance assessments compared with the patients' assessments (positive difference) included a manic episode, high neuroleptic dose and the doctors' attitudes of negative effects of medication on the patient. A negative difference (lower patient compliance assessments compared with the doctors' assessments) was explained by female gender, low level of education, and both the patients' and the doctors' attitudes towards medication.

In 80 patients with first-episode psychosis, a highly structured interview including self-report scales on symptoms and side-effects recognition, and on need for treatment, was performed in the acute phase of the treatment. In addition, information about medication compliance and clinical diagnoses was obtained from medical records and the hospital register. Half of the patients were offered outpatient treatment according to a psycho-educational model. Eleven (19 %) of the 59 patients at three-month follow-up showed non-compliance with medications. Seventeen (29 %) of the patients predicted themselves as non-compliers in the early assessment. Harmful side-effects of medication, male gender, young age, and lack of social activities explained the observed non-compliance. Exclusively self-rating items, including harmfulness of medication, and negative attitudes towards different treatment modalities, explained the predicted non-compliance.

The research diagnoses in the first-episode psychosis population obtained according to the SCAN-2 interview were compared with the clinical diagnoses during the first three months of treatment. The overall agreement level between the two diagnoses was 0.55. The agreement levels in different diagnostic categories varied between 0.46-0.63, being highest in bipolar disorder and equal between the other groups. In the total sample, low scores in PANSS negative subscale, low level of education, and high delusion scores predicted diagnostic discrepancy. In the schizophrenia group older age and existing social activities were predictive of diagnostic discrepancy.

Outcome measures among patients with long-term schizophrenia with relapsing course of illness, repeated hospitalisations and persistent non-compliance were examined in four-year follow-up (n=41). During this period, nearly half of the patients (n=18) received home-based ambulatory outpatient care (AOC). The rest of the sample (n=23) received conventional outpatient care (non-AOC). Both groups had significantly lower rates of hospitalisations during follow-up than before it, but between groups there were no differences in hospitalisation rates. In the AOC group the hospitalisation rate was less than one-third of the pre-baseline period. No changes were seen in the levels of functioning (GAF). The mortality rate compared with an aggregate analysis of mortality in schizophrenia was on the same level in the AOC group, whereas the non-AOC group showed a tendency to excess mortality.

8 References

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Appendix 1

The Attitudes towards Neuroleptic Treatment (ANT) questionnaire

This questionnaire is to measure your opinions about psychiatric medications. Please mark a line across the vertical line next to the statement (or between two statements) that best describes your current opinion on every question.

1. Estimate the importance of medication in psychiatric treatment:

100	It is not possible to get better without medication.
90	Medication is the most important in getting better.
80	Medication is very important in getting better.
70	Medication is important in getting better.
60	Medication is somewhat important in getting better.
50	Medication is partly important/partly unimportant
40	Medication is somewhat unimportant in getting better.
30	Medication is unimportant in getting better.
20	Medication is very unimportant in getting better.
10	Medication is totally unimportant in getting better.
0	Medication has no effect on getting better.

2. Compare the importance of medication and psychosocial treatment (individual and group discussions, family meetings):

100	Medication is the only proper treatment and psychosocial treatment has no meaning.
90	Medication is most important and psychosocial treatment supports it very little indeed.
80	Medication is very important and psychosocial treatment supports it very little.
70	Medication is important and psychosocial treatment supports it a little.
60	Medication is somewhat important and psychosocial treatment supports it to some extent.
50	Medication and psychosocial treatment are equally important treatments.
40	Psychosocial treatment is somewhat important and medication supports it to some extent.
30	Psychosocial treatment is important and medication supports it a little.
20	Psychosocial treatment is very important and medication supports it very little.
10	Psychosocial treatment is most important and medication supports it very little indeed.
0	Psychosocial treatment is the only proper treatment and medication has no meaning.

3. Estimate for how long it is necessary to continue the medication after the symptoms have disappeared:

100	It is necessary to continue the medication for the rest of one's life.
90	It is necessary to continue the medication for an extremely long time (8 years).
80	It is necessary to continue the medication for a very long time (4 years).
70	It is necessary to continue the medication for a long time (2 years).
60	It is necessary to continue the medication for quite a long time (1 year).
50	It is necessary to continue the medication for a while (6 months).
40	The medication can be stopped quite soon (4 months).
30	The medication can be stopped soon (2 months).
20	The medication can be stopped very soon (1 month).
10	The medication can be stopped extremely soon (2 weeks).
0	The medication can be stopped immediately; it is used only when the symptoms appear.

Appendix 1

The Attitudes towards Neuroleptic Treatment (ANT) questionnaire

This questionnaire is to measure your opinions about psychiatric medications. Please mark a line across the vertical line next to the statement (or between two statements) that best describes your current opinion on every question.

4. Estimate how the medication will influence your personality:

100	The medication will not influence my personality.
90	The medication will influence my personality extremely little.
80	The medication will influence my personality very little.
70	The medication will influence my personality a little.
60	The medication will slightly influence my personality.
50	The medication will influence my personality to some extent.
40	The medication will influence my personality quite a lot.
30	The medication will influence my personality a lot.
20	The medication will influence my personality very much.
10	The medication will influence my personality extremely much.
0	The medication will totally change my personality into an unfamiliar one.

5. Estimate how ready you are to take your medication:

100	I take my medication completely of my own will and I think it is extremely important for me.
90	I take my medication of my own will and I think it is most important for me.
80	I take my medication of my own will and I think it is very important for me.
70	I take my medication of my own will and I think it is important for me.
60	I take my medication of my own will and I think it is to some extent good for me.
50	I take my medication readily.
40	I take my medication against my own will and I don't think it is good for me.
30	I take my medication against my own will and I think it is useless to me
20	I take my medication against my own will and I think it might be harmful to me.
10	I take my medication against my own will and I think it is mostly harmful to me.
0	I take my medication against my own will and I think it is only harmful to me.

6. Estimate how you will deal with possible side-effects of medication:

100	I will continue my regular dose in spite of side-effects.
90	I will continue my regular dose, but will tell my doctor about the side-effects.
80	I will continue my regular dose, but I hope it will be decreased.
70	I will continue my regular dose, but I want it to be decreased.
60	I will continue my regular dose, but I will insist it is decreased.
50	I will continue my regular dose, but I will protest against the dosage.
40	I will decrease the dose a little.
30	I will decrease the dose to some extent.
20	I will decrease the dose a bit.
10	I will decrease the dose a lot.
0	I will completely stop taking my medication due to side-effects.

Appendix 1

The Attitudes towards Neuroleptic Treatment (ANT) questionnaire

This questionnaire is to measure your opinions about psychiatric medications. Please mark a line across the vertical line next to the statement (or between two statements) that best describes your current opinion on every question.

7. Estimate how the medication will influence how you feel:

100		The medication will cure me completely.
90		The medication will have an extremely positive effect on my state.
80		The medication will be very good for my state of mind.
70		The medication will be good for my state of mind.
60		The medication will be quite good for my state of mind..
50		The medication will have no effect on my state of mind.
40		The medication will have quite a bad effect on my state of mind.
30		The medication will have a bad effect on my state of mind.
20		The medication will have a very bad effect on my state of mind.
10		The medication will have an extremely bad effect on my state of mind.
0		The medication will completely ruin my health.

8. Estimate the extent of your current mental problems:

100		I have terribly many mental problems.
90		I have very many mental problems.
80		I have plenty of mental problems.
70		I have quite a lot of mental problems.
60		I have fairly many mental problems.
50		I have mental problems to some extent.
40		I have a few mental problems.
30		I have few mental problems.
20		I have very few mental problems.
10		I have very, very few mental problems.
0		I have no mental problems at all.

9. Estimate your current need for help:

100		I need all the help I can get.
90		I need very much help.
80		I need a lot of help.
70		I need quite a lot of help.
60		I need fairly much help.
50		I need help to some extent.
40		I need a little help.
30		I need quite little help.
20		I need help really very little.
10		I need very, very little help.
0		I need no help at all.

Appendix 1

The Attitudes towards Neuroleptic Treatment (ANT) questionnaire

This questionnaire is to measure your opinions about psychiatric medications. Please mark a line across the vertical line next to the statement (or between two statements) that best describes your current opinion on every question.

10. Estimate how the medication will influence your thinking ability:

- | | | |
|-----|--|---|
| 100 | | Due to effects of the medication I will be able to think completely normally and my thoughts will be clear. |
| 90 | | The medication will improve my thinking ability to a great extent and make my thoughts much more clear. |
| 80 | | The medication will improve my thinking ability very much and make my thoughts quite a lot of clearer. |
| 70 | | The medication will much improve my thinking ability and make my thoughts clearer. |
| 60 | | The medication will improve my thinking ability fairly much and make my thoughts somewhat clearer. |
| 50 | | The medication will not influence my thinking ability or the clarity of my thoughts. |
| 40 | | The medication will worsen my thinking fairly much and make my thoughts somewhat confused. |
| 30 | | The medication will much worsen my thinking ability and make my thoughts quite a lot of confused. |
| 20 | | The medication will worsen my thinking ability very much and make my thoughts more confused. |
| 10 | | The medication will worsen my thinking ability very, very much and make my thoughts much more confused. |
| 0 | | The medication will ruin my thinking ability and my thoughts will become completely confused. |

11. Estimate how the medication will influence your autonomy (=self-control, independence):

- | | | |
|-----|--|---|
| 100 | | The medication will increase my autonomy very, very much. |
| 90 | | The medication will increase my autonomy very much. |
| 80 | | The medication will increase my autonomy a lot. |
| 70 | | The medication will increase my autonomy quite a lot. |
| 60 | | The medication will increase my autonomy to some extent. |
| 50 | | The medication will not influence my autonomy |
| 40 | | The medication will cut down my autonomy to some extent. |
| 30 | | The medication will cut down my autonomy quite a lot. |
| 20 | | The medication will cut down my autonomy a lot. |
| 10 | | The medication will cut down my autonomy very much. |
| 0 | | The medication will cut down my autonomy very, very much. |

12. Estimate how the medication will influence your ability to do things in the future:

- | | | |
|-----|--|---|
| 0 | | The medication will destroy my ability to do things completely and I will not be able to manage without others' help. |
| 10 | | The medication will worsen my ability to do things in the future very much. |
| 20 | | The medication will worsen my ability to do things in the future a lot. |
| 30 | | The medication will worsen my ability to do things in the future quite a lot. |
| 40 | | The medication will worsen my ability to do things in the future to some extent. |
| 50 | | The medication will not influence my ability to do things in the future. |
| 60 | | The medication will improve my ability to do things in the future to some extent. |
| 70 | | The medication will improve my ability to do things in the future quite a lot. |
| 80 | | The medication will improve my ability to do things in the future a lot. |
| 90 | | The medication will improve my ability to do things in the future very much. |
| 100 | | Due to the effects of medication I will be able to manage completely independently in the future. |

Appendix 2

The self-rating scale used for assessing insight (question 1), perceived side-effects (question 2), overall harmfulness of medication (question 3) and need for treatment (questions (4-7)

In questions 1-2 circle numbers in all alternatives describing your current state:

1. Symptoms that have led to the current medication:

1. visual or auditory hallucinations
2. agitated or aggressive behavior
3. delusions or bizarre thoughts
4. incoherence of speech or thoughts
5. unusual elevation of mood
6. apathy or aloofness in relation to the environment
7. depressive mood
8. anxiety
9. tension
10. abnormal movements or posture
11. slowness or lack of movements
12. preoccupation with physical health
13. sleep problems

2. Perceived side-effects of the current medication:

1. excessive fatigue or sluggishness
2. dizziness
3. heart pounding
4. dry mouth
5. excessive salivation
6. coordination problems in the muscles (e.g. muscular cramps in the tongue, face or neck)
7. stiffness in the movements or speech problems
8. physical restlessness or urgency to keep moving
9. nausea
10. constipation
11. urination problems

Appendix 2

The self-rating scale used for assessing insight (question 1), perceived side-effects (question 2), overall harmfulness of medication (question 3) and need for treatment (questions (4-7)

In questions 3-7 circle a number in one alternative in each question that best describes your current situation:

3. Harmfulness of the current medication due to side-effects:

1. No harm at all
2. Some harm that has no effect on my use of medication in the future
3. Moderate harm that may affect my use of medication in the future
4. A lot of harm, due to which I will not use the medication

4. The need for my current medication:

1. The medication is absolutely essential.
2. The medication is necessary.
3. The medication is partly necessary, partly unnecessary.
4. The medication is harmful.
5. The medication is extremely harmful.

5. The need for family appointments:

1. The family appointments are absolutely essential.
2. The family appointments are necessary.
3. The family appointments are partly necessary, partly unnecessary.
4. The family appointments are harmful.
5. The family appointments are extremely harmful.

6. The need for regular, individual appointments (at least once a week):

1. The individual appointments are absolutely essential.
2. The individual appointments are necessary.
3. The individual appointments are partly necessary, partly unnecessary.
4. The individual appointments are harmful.
5. The individual appointments are extremely harmful.

7. The need for hospital treatment:

1. Hospital treatment is absolutely essential.
2. Hospital treatment is necessary.
3. Hospital treatment is partly necessary, partly unnecessary.
4. Hospital treatment is harmful.
5. Hospital treatment is extremely harmful.