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Treatment Response in Psychotic Patients in a Naturalistic Setting

*Classification, Genes, Drugs, Insight and Social
Networks*

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Abstract

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Many patients with psychotic symptoms respond poorly to treatment. Various approaches have been made to classify these patients according to treatment response. However, existing classifications have been criticized for various reasons and a new classification system is needed. Further, no satisfactory explanation of the poor treatment response has been apparent. The general aim of this thesis was therefore to develop and validate a new classification method of functional remission in a naturalistic population of patients with psychosis and to utilize this classification to investigate the population from genetic, drug treatment, insight and social network points of view.

Data for this cross-sectional study of patients (n=123) attending the Psychosis Outpatient Care clinic in the county of Jönköping, Sweden, were obtained from patient interviews, blood samples and information from patient files. The new classification method CANSEPT, which combines the CAN rating scale (CAN), the UKU side effect rating scale (SE) and the patient's previous treatment history (PT), showed validity in discriminating the patients and was accepted well by the patients. CANSEPT was used to group the patients in the other studies in this thesis.

The results indicated that the gene polymorphism ABCB1 3435T, was related to worse significant social and clinical needs for patients on olanzapine, while the polymorphism DRD2 Taq1 A1 was related to a greater risk of significant side effects; especially if male, or taking strong dopamine D2-receptor antagonistic drugs. Drug treatment factors were also related to treatment response; longer duration of untreated prodromal and early psychosis was seen for patients with current significant social and clinical needs and non-adherence to treatment was associated with worse significant side effects. Worse treatment outcomes also appeared to be associated with smaller social network groups, worse insight into illness, poorer knowledge of warning signs and worse coping strategies.

In summary, CANSEPT was shown to be a useful valid, multidimensional tool for classification of treatment response. Gene polymorphisms, duration of untreated illness, non-adherence to treatment, social networks and knowledge should be taken into consideration when investigating inadequate treatment response.

Keywords: Antipsychotic Agents, Drug Resistance, Cross-Sectional Studies, Psychotic Disorders, Naturalistic Setting, Schizophrenia, DRD2, 5-HT2, ABCB1, Cytochrome P-450 CYP2D6, Duration of Untreated Illness (DUI), Duration of Untreated Early Psychosis (DUP), Treatment Outcome, Adherence, Social Support, Health Knowledge, Insight

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To the Patients

Papers Discussed

This thesis is based on the following papers, which will be referred to by their Roman numerals in the text.

- I** **Alenius M**, Hammarlund-Udenaes M, Hartvig P, Sundquist S and Lindström L. Treatment response in psychotic patients classified according to social and clinical needs, drug side effects and previous treatment; a method to identify functional remission. *Comprehensive Psychiatry*. 2009; doi:10.1016/j.comppsy.2008.11.001
- II** **Alenius M**, Wadelius M, Dahl M-D, Hartvig P, Lindström L and Hammarlund-Udenaes M. Gene polymorphism influencing treatment response in psychotic patients in a naturalistic setting. *Journal of Psychiatric Research*. 2008; 42: 884-893.
- III** **Alenius M**, Hartvig P, Lindström L and Hammarlund-Udenaes M. Current and retrospective antipsychotic drug use in relation to treatment response in a naturalistic setting of psychotic patients. *Submitted*.
- IV** **Alenius M**, Hammarlund-Udenaes M, Hartvig P and Lindström L. Social networks, knowledge, insight and treatment response in psychotic patients. *Submitted*.

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Abbreviations

ABCB1	ATP-binding cassette protein B1, transporter protein
APA	American Psychiatric Association
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
CAN	Camberwell Assessment of Need rating scale
CANSEPT	CANSEPT classification method of psychosis patients regarding treatment response
CYP1A2	Liver enzyme Cytochrome P450 (CYP) 1A2
CYP2D6	Liver enzyme Cytochrome P450 (CYP) 2D6
CYP3A4	Liver enzyme Cytochrome P450 (CYP) 3A4
DDD	Defined Daily Dose
DRD2	The dopamine D2 receptor
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition
DUI	Duration of untreated prodromal and early psychotic illness
DUP	Duration of untreated early psychosis
EQ-5D	EuroQol-5D rating scale
FDA	U.S. Food and Drug Administration
FR	Functional Remission
HTR2A	The serotonin 5HT2A receptor
HTR2C	The serotonin 5HT2C receptor
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth revision
LC-MS-MS	Liquid Chromatography- Mass Spectrometry- Mass Spectrometry
NMDA	N-methyl-D-aspartate
Non-FR	Not in Functional Remission
PANSS	Positive And Negative Syndrome Scale
PCR	Polymerase Chain Reaction
PECC	Psychosis Evaluation tool for Common use by Caregivers
SD	Standard Deviation
SPKS	Skattning av Personers Kunskap om Schizofreni
UKU	Udvalg for Kliniske Undersøgelser side effect rating scale
VAS	Visual Analogue Scale
WHO	World Health Organization

Introduction

Mr B was born in 1820 in Middlesex and started at quite a young age to work as a commercial traveller. He got married but, unfortunately, Mrs B died relatively young, leaving no children. When Mr B was 30 years of age he became mentally ill and, with no close next of kin who could take care of him, he was committed 18 months later, in 1852, to the Middlesex County Lunatic Asylum called Colney Hatch. At the asylum he was diagnosed as having dementia (i.e. schizophrenia by the present nomenclature) with the general paralysis of the insane but was also noted to be disposed to jump from windows and to destroy his clothes. During the time at the asylum he gradually succumbed to exhaustion, getting thinner with progressively increasing fatigue and pallor. He was considered to be a hopeless case and he died 14 months after his admission to the asylum (Tyerman 1859).

The outlook for Mr B and many of his fellow patients at asylums in the 1850s was far from hopeful, with more patients than the asylums could handle and no effective treatments. The doctors did all they could under these circumstances and fortunately there were some soothing treatments available for example morphine, chalybeates and porter (Table 1). On the other hand, unfortunately for Mr B, although the whirling chair that was introduced in the 1820s was out of fashion, there were still many treatments that could be utterly harming and painful. For example, patients could be subjected to poisonous conium and tincture of veratria, bloodlettings, the horrific bath of surprise and the very painful counter irritants croton oil and unguentum antimony, used to substitute a real for an imaginary trouble (Table 1) (A 1856; Ajanki 1999; Ranney 1858; Samuelsson 1992; Tuke 1858).

At around the same time as Mr B's stay at the Middlesex County Lunatic Asylum, an Englishman named W.H. Perkin produced an exquisite purple dye called mauve. Because of the dye's commercial value, various compounds with structures similar to mauve were synthesized, resulting in the first phenothiazine derivatives in the 1870s (Shen 1999). Neither Mr Perkin nor Mr B were to see the outcome, but the first step toward a revolution in psychiatric care had occurred.

Almost exactly one hundred years after the death of Mr B, another man, Mr S, was admitted to a psychiatric department, in Winson Green Hospital, Birmingham. He was 46 years old and had been diagnosed with schizophrenia when he was 22 years old. He had spent nine of the 24 years that he had been ill in mental hospitals (Elkes and Elkes 1954). There were more treat-

ment alternatives for patients like Mr S than there were a hundred years earlier when Mr B was admitted. For example, sedatives such as chloral hydrate, diethylbarbiturates and promethazine were available, along with convulsion therapies such as cardiazol injections, insulin coma and electroconvulsive therapy and also surgical remedies including lobotomy (Ajanki 1999; Shulman 1949). Despite these possible treatment alternatives, Mr S was aimlessly overactive, often aggressive and was frequently involved in fights. In conversation he seemed to be reasonably well orientated but disconnected, chattering away irrelevantly. He was domineering and often interfered with other patients and his manner suggested the presence of hallucinations. At one time he had worked on the hospital farm, but had to be removed because of impulsive behaviour (Elkes and Elkes 1954). Nothing seemed to help Mr S and the doctors decided to let him be included in a treatment trial of the new drug chlorpromazine, a phenothiazine derivative, which was to be the first truly antipsychotic drug (Delay, et al. 1952; Delay, et al. 1952). After initiating chlorpromazine therapy, Mr S slowly started to improve and, although he continued to be rather domineering and his manner of speech was unchanged, he became much less aggressive and was involved in no violent incidents after the first three weeks of the trial. He started working on the farm again, and was reported to do very well (Elkes and Elkes 1954). This and a lot of similar stories were reported after trials with the new drug and soon patient after patient was able to return home.

To day, another 50 years later, there are a number of antipsychotic drugs available giving reliefs to many patients. Nonetheless, the outcome of antipsychotic treatment is still far from optimal for all psychotic patients. This has been spurring us to try to find how the patients with inadequate treatment response differ from those doing well with regards to their genetics, drug use, insights and social networks. By developing a deeper understanding of how these patients differ we can make a good platform for further research on treatments and hence contribute to a higher quality of life for those directly or indirectly affected by psychosis.

Table 1. *An example of treatments available in the asylums in the 1850s categorized into four groups (as suggested by M.A.) (A 1856; Ajanki 1999; Ranney 1858; Samuelsson 1992; Tuke 1858).*

Calming treatments	Suitable for mania, general insanity etc	Strengthening treatments	Suitable for dementia and dullness of intellect
Ipecac	Emetic agent. Vomiting probably exhausted the patient causing a calming effect	Meat rich in fat, beer, porter, milk-punch	To supply the brain with proper stimulus by enriching the blood, and thus arousing its dormant excitability
Tartarized antimony	Used as emetic agent	Chalybeates	Iron containing, important for curing anaemia
Morphine	Known calming and pain releasing effect	Cannabis	Was said to stimulate the senses and excite the moral qualities
Opium	Known calming and pain releasing effect	The douche	A stream of cold water which for example could be directed against the crown of the patients head
Quinine	Still used to treat malaria. Was said to prolong the lucid intervals	Moral treatment	Including employment, amusement, establishment of regular habits etc.
Tincture of digitalis	Known antiarrhythmic agent. Probably used because of the calming effect on the heart rate		
Dover's powder	A preparation of ipecac, opium and potash (potassium carbonate)	Diverting treatments	Suitable for delusions, masturbation and suicidal thoughts
Spirit of nitre	A dilute solution of ethyl nitrite in ethanol	Croton oil	Also called oleum tigllii. Caused severe skin irritations when applied externally. Used against masturbation
Conium	Poisonous hemlock. Contains the alkaloid coniin which is similar to curare and can cause paralysis. Highly toxic.	Unguentum antimony	Was placed on the back of the neck and caused inflammation, blisters, rash and ache
Tincture of veratria	Obtained from the root of hellebore and from the sabadillae seeds. Highly toxic.		
Ether	Known sedative		
Taraxacum	Dandelion flower extract		
Calomel	Mercury chloride	Curative treatments	Suitable for insanity etc
Bloodletting	By venesection, cups or leeches Drowsiness was probably achieved from blood loss	Lugol's solution	Potassium iodide. Was said to stimulate the mammae, thus curing the amenorrhoea causing mania in many young women
The shower bath	Cold water showered over the patient while sitting in a bath (sometimes warm)	The bath of surprise	The cold plunge bath. Expressly for the supposed advantages of the shock. A reservoir of water into which the patient, standing on its moveable cover, was suddenly precipitated
The fixed shower bath	If the patient was protesting, he was placed in a sort of upright coffin during the procedure		
The warm bath	Bath in water above 85F (29.5°C)		
Restriction	E.g. the English Cabin, restraining jackets		

Psychosis

Psychotic patients, like Mr B and Mr S can show a number of different symptoms, of which the most salient are the positive symptoms. These include hallucinations (may occur in any sense, although the most common is auditory), delusions (firmly held false belief e.g. delusion of persecution and delusion of grandeur) and thought disorders (distorted or illogical speech). Negative symptoms, which are less obvious to the outside spectator but can be very handicapping for the patient, are also common. These include self neglect, social withdrawal, avolition (loss of motivation and initiative), affective flattening (emotional blunting) and alogia (paucity of speech) (American-Psychiatric-Association 1994; Gelder, et al. 2001; Picchioni and Murray 2007; WHO 1997). Unfortunately many patients also lack insight into their illness (Picchioni and Murray 2007), which hinders them from getting adequate help.

Diagnosis

Patients experiencing psychotic features can have a wide variety of diagnoses, mostly depending on the most prominent symptoms, the order of their appearance and their duration (American-Psychiatric-Association 1994; Gelder, et al. 2001; WHO 1997). The main diagnosis of psychosis is schizophrenia but psychotic features can also exist in many other diagnoses e.g. severe depression, mania, dissociative syndrome and personality disorders (WHO 1997). The two main diagnostic classification systems of (mental) health disorders are to be found in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, (DSM IV) published by the American Psychiatric Association and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, (ICD-10) published by the World Health Organization (WHO). These two systems have many similarities but are not fully concordant regarding the different diagnoses. For example, in DSM IV, schizophrenia is described as being characterized by two or more of the following symptoms (each present for most of the time during a one-month period): delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour and negative symptoms. The symptom requirements are similar in ICD-10 but, in DSM IV, the disturbance must also persist for at least 6 months and this is not required in ICD-10. The organization of the diagnoses also differ to some extent between the two systems (American-Psychiatric-Association 1994; WHO 1997).

The diagnostic systems have also varied over time (Davis, et al. 1980; van Os, et al. 1997; Westermeyer and Harrow 1984). Historically, terms such as dementia (as applied to Mr B), insanity, demencé, dementia praecox (as suggested by Kraepelin), melancholia attonita and demonomania fantastica have been used for different psychotic disorders (Adityanjee, et al. 1999; Bucknill

1856; Menuck 1979). The term schizophrenia was first used in a monograph by Eugen Bleuler in 1911 (Menuck 1979). The terms, and also the meanings of the terms, have changed over the years, creating problems for historical research in psychiatry (Adityanjee, et al. 1999). These problems in finding a coherent term to use are the result of the complexity of mental disorders, the floating boundaries between various disorders and the insufficient knowledge of the causes of these disorders (Moller 2005; van Os, et al. 1997). This complexity results in the difficulties in obtaining a coherent population for scientific investigations involving psychotic disorders. One way to handle this patient selection problem is to study a more naturalistic patient population. In this scenario, every patient with psychotic features at an open ward psychosis clinic would be included in the trial: although this method can result in heterogeneous patient groups, it can also provide a link to clinical reality and yield more robust comparisons between studies and over time.

Epidemiology

Schizophrenia often starts in early adult life and becomes chronic. Estimation of the lifetime risk of developing the illness depends on the criteria for diagnosis and the population surveyed (Gelder, et al. 2001) but the risk is often estimated as 1% (Beiser and Iacono 1990; Picchioni and Murray 2007), occurring a little more often in men than in women (risk ratio 1.4:1)(Picchioni and Murray 2007). The consequences of schizophrenia and other forms of psychotic disorders can be severe: psychotic patients have a 16-fold increased risk of suicide and an increased risk of early death from any cause compared with non-psychotic subjects (Heila, et al. 2005; Limosin, et al. 2007; Osby, et al. 2000).

Disease phases

The clinical picture of the patients varies extensively because of the many ways that the symptoms can be combined and the different phases the patients may be experiencing (Gelder, et al. 2001). Initially, during the prodromal phase, only a few patients present with pronounced psychotic symptoms; instead, the disorder often starts with anxiety, depression, changes in behaviour and social problems which might not immediately point to psychosis (Lieberman, et al. 2001; McGlashan, et al. 2003; McGorry, et al. 1996; Picchioni and Murray 2007).

The disorder can then become more pronounced and the patient may experience an acute phase of the illness during which the psychotic symptoms, especially the positive symptoms, become more obvious, affecting most of the patient's behaviours (Gelder, et al. 2001). After a while, the acute phase might diminish and the patient will experience a more stable/chronic phase which is characterized more by thought disorders and negative symptoms but also some positive symptoms may remain (residual symptoms) (Gelder,

et al. 2001). Even though a patient has become stable, they can experience new acute phases during their life span (Gelder, et al. 2001).

The disease will not necessarily become chronic in every patient; some patients will go into remission and recover. The concept of remission in schizophrenia has attracted increasing interest in recent years, resulting in working groups in Europe and in the United States with the aim to achieve consensus on a definition of response to treatment for patients with this clinical condition. Focus has been directed towards symptomatic remission, i.e. an amelioration of the patient's psychotic symptoms (Andreasen, et al. 2005; van Os, et al. 2006). However, factors other than symptomatology also have a profound impact on the overall outcome of treatment of schizophrenia. Experiences from clinical practice have shown that a patient with schizophrenia may have relatively few overt psychotic symptoms but still not be functioning well in daily life. While symptomatic remission is a good starting point, functional remission is therefore probably at least equally important for the long-term outcome and deserves more attention in clinical studies.

Stress-vulnerability model

There are many theories of the causes of psychosis, one comprehensive is the stress-vulnerability model (Figure 1). According to this model, psychological, biological and social factors can affect the outcome of a disorder (Zubin and Spring 1977; Zubin, et al. 1985) because of interactions between the underlying biology, the effects of stressful events and the patient's social resources such as their social network, cognitive capacity and coping behaviours (Nuechterlein and Dawson 1984).

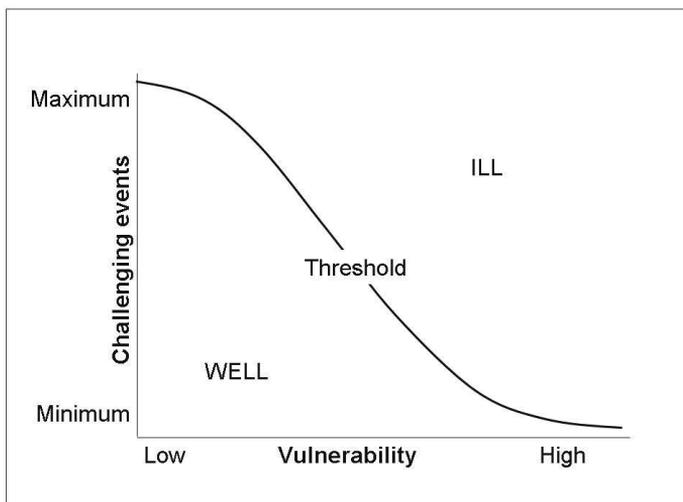


Figure 1. The Stress-Vulnerability Model by Zubin and Spring 1977 (Zubin and Spring 1977), showing the relationship between vulnerability and challenging events.

Psychiatric health care

There are 48 psychosis inpatient care departments and 43 psychosis outpatient care departments in Sweden (sourced from the web pages for each region in autumn 2008). When a patient first comes into contact with psychiatric care resources a thorough case history is taken by a doctor, a diagnosis is made (if possible) and an evaluation of the most appropriate treatment is done. Most of the patients attend an outpatient department. The preferred treatment can include drug therapy but also occupational therapy, physical therapy, home support and various psychological treatments such as cognitive behavioural therapy and psychodynamic therapy. The psychotic patient is often monitored by a contact person at the psychiatric clinic, who will follow the patient's progress and notify the relevant clinician if the patient's health declines. If a patient refuses care but is judged to be a danger to themselves or others, the psychiatric care personnel can take them into custody. If admission is required, however, most patients accept voluntarily (Persson 2008; Vårdguiden 2008).

Drug treatment

The aim of any drug treatment is to cure the patient if possible; if this is not possible, the aim is to ameliorate the symptoms and suffering associated with the illness. Unfortunately there are very few curative drug treatments and most drugs are thus administered with the aim of treating the symptoms, lessening the burden of the disease and helping the patient reach and stay in remission.

Drug treatment of psychotic patients varies considerably, not only as a result of the type and severity of the illness but also because of previous treatment experience and the treatment traditions of the region (Bitter, et al. 2003; Owen, et al. 2003; Xiang, et al. 2007). Several exploratory studies have noted that, of all the available drug treatments, psychotropic drugs (including antipsychotic drugs) are most commonly prescribed for these patients (Acquaviva, et al. 2005; Chakos, et al. 2006; Citrome, et al. 1996).

Antipsychotic drugs

Antipsychotic drugs are the main treatment for psychotic disorders and all of them decrease psychotic symptoms, especially the positive symptoms of psychosis (Stahl 2006). Unfortunately, very few drugs of any description are without side effects, and antipsychotic drugs are not among the exceptions. In various degrees, they have been associated with extrapyramidal symptoms (e.g. distressing restlessness, stiffness and tremor) (Blair and Dauner 1992; Haddad and Sharma 2007), sedation (Haddad and Sharma 2007), sexual

impairment (Ben-Jonathan and Hnasko 2001; Blair and Dauner 1992), anticholinergic effects (e.g. dry mouth, blurred vision, urinary retention and constipation) (Haddad and Sharma 2007), metabolic syndrome (Wirshing 2004), agranulocytosis (Hippius 1989) and cardiovascular problems (Glassman and Bigger 2001; Stahl 2006).

The history of antipsychotic drugs

In 1955, the chlorpromazine revolution of psychiatric care, as mentioned above, reached Sweden with similarly good outcomes for many patients as for Mr S. A large number of new antipsychotic drugs (or neuroleptic drugs as they were called at the time) were introduced in the following years. Not only other phenothiazines arrived but also antipsychotics from other chemical groups such as thioxanthenes and butyrophenones (Awouters and Lewi 2007; Hippius 1989).

At about the same time, the first tricyclic antidepressant drugs were introduced into the market, providing effective treatment also for those patients suffering from depression. In order to evolve the antidepressant treatment further extended research was done with similar chemical structures as those seen effective before, among others resulting in a dibenzapine structure. Some of the dibenzapine compounds had antidepressant properties but three of them seemed to have antipsychotic properties, and one of these substances was clozapine. In 1966, clozapine was described as an effective antipsychotic agent that lacked extrapyramidal side effects, which had previously been thought to be a prerequisite of being a typical neuroleptic drug. Clozapine was therefore described as an “atypical” neuroleptic drug. Some clinics started to use clozapine in the 1970s with excellent results, especially for patients who had been resistant to the positive effects of “typical” antipsychotics or who had bothersome extrapyramidal side effects. However, in 1975, psychiatrists in Finland reported 16 cases of patients receiving clozapine who had developed agranulocytosis (impaired immune system), of whom eight died. This resulted in the withdrawal of clozapine in many countries and it was not until almost 15 years later, in the late 1980s that clozapine reappeared, but now with the notion of close blood monitoring for all patients receiving the drug (Hippius 1989).

Clozapine’s lack of the extrapyramidal side effects commonly seen with typical antipsychotic drugs resulted in an intensive search for other atypical antipsychotic drugs without these effects but also without the problems of agranulocytosis. Eventually, drugs such as risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole and sertindole were introduced and quickly dominated the antipsychotic market (Figure 2) (Apoteket_AB 2008; Gilbody, et al. 2000).

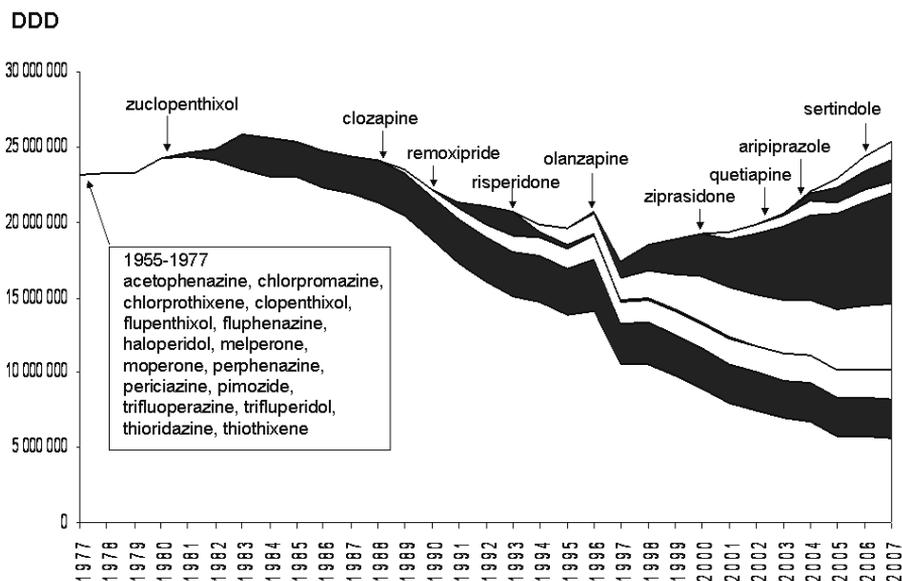


Figure 2. The numbers of DDD (Defined Daily Doses) (WHO 2008) of antipsychotic drugs bought by all the Swedish pharmacies during the years 1977-2007 (data extracted from the purchase statistics from Apoteket AB 2008 (Apoteket_AB 2008)). The numbers of DDD for each drug is described by the area following the drug's introduction in Sweden, as marked by an arrow and the substance name. The numbers of DDD for all drugs introduced before 1977 are fused into one area.

Mechanism of action

All antipsychotic drugs have dopamine D2 receptor antagonistic properties. While a strong association has been seen between dopamine D2 receptor blockade and antipsychotic effect, blockade of this receptor has also been associated with extrapyramidal side effects (Nordstrom, et al. 1993) and increased prolactin levels (resulting in effects such as sexual impairment) (Ben-Jonathan and Hnasko 2001; Hamner 2002). It has been suggested that a receptor blockade of 65-80% is optimal for good effect while avoiding extrapyramidal side effects (Farde and Nordstrom 1993; Kapur and Seeman 2001; Nordstrom, et al. 1993).

Activity at the N-methyl-D-aspartate (NMDA) receptor is thought to affect the activity of dopamine. The atypical antipsychotic drug clozapine has been seen to interact with this receptor which might partly explain clozapine's "atypicality" (Schwieler, et al. 2008).

Some antipsychotic drugs also have serotonin 5HT2 receptor antagonistic properties; while there is some evidence to link this effect with efficacy on negative psychotic symptoms, the results are inconclusive (Kapur and See-

man 2001; Meltzer and Nash 1991). Examples of other receptor systems that can be affected by antipsychotic drugs are the histaminergic system (Stahl 2006) and the cholinergic/muscarinic receptor systems (Stahl 2006).

Classifying antipsychotic drugs

A common method of discriminating between the various antipsychotic drugs is to classify them as typical or atypical. All drugs introduced after 1990 claim atypical qualities, and are most often referred to as atypical antipsychotic drugs. There is, however, some disagreement about which drugs should be classified as atypical and why they should be classified as atypical.

Discrimination according to effect

Clozapine, as described before, differed from the other antipsychotic drugs when it arrived since clozapine did not induce extrapyramidal symptoms as the typical drugs did. This has been one of the cornerstones of the definition of atypicality. However, although the incidence of extrapyramidal symptoms is lower with the newer atypical antipsychotic drugs than with the older typical antipsychotics, most can still cause extrapyramidal symptoms in higher doses (Kapur and Seeman 2001). Thus, according to this definition, clozapine is the only truly atypical antipsychotic drug.

Another effect said to be related to atypical antipsychotic drugs are their effect on negative symptoms. The results regarding the advantage of atypical antipsychotics as compared to the typical antipsychotics are though inconclusive (Leucht, et al. 1999).

Discrimination according to mechanism of action

While all antipsychotic drugs are antagonistic at the dopamine D2 receptor, the affinities to this receptor differ (Kapur and Seeman 2001; Seeger, et al. 1995; Seeman 2002; Seeman, et al. 1997). The dissociation constants from the dopamine D2 receptor are lower (i.e. have higher affinity to the receptor) for the older antipsychotic drugs and the newer drug risperidone than for dopamine itself (Seeman 2002). These drugs can be defined as drugs with strong dopamine D2 receptor antagonistic properties and also as typical antipsychotic drugs.

It has been suggested that differences in the relative affinities for the serotonin 5HT₂ receptor and dopamine D2 receptor can differentiate between atypical and typical antipsychotic drugs (Kapur and Seeman 2001; Meltzer, et al. 1989). The term atypical can hence be said to be indicative for a greater focus on the serotonin system and not only the dopamine system of the brain (Ichikawa and Meltzer 1999; Seeman 2002).

Discrimination according to date of introduction

Because of the debate regarding typical and atypical antipsychotic drugs and because extrapyramidal side effects are also caused by atypical drugs, the

terms first and second generation antipsychotic drugs are sometimes used. First generation antipsychotic drugs are those who came early (as the name indicates) and consists of the phenothiazines, thioxanthenes and butyrophenones. Second generation antipsychotic drugs were, in general, introduced later than the first generation and include, among others, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole and ziprasidone (Ichikawa and Meltzer 1999; Stahl 2006).

Haloperidol equivalents

The effective doses of antipsychotic drugs can be compared using haloperidol equivalents i.e. converting the effective dose of a specific drug into the dose of haloperidol producing an equivalent effect. The problem with this technique is that it is difficult to find the correct equivalent dose for each antipsychotic drug; there are dangers associated with not comparing “apples with apples” when comparing drugs with different mechanisms of action. In the study that formed the basis for the thesis, we used American (where available) and Swedish consensus guidelines to find haloperidol equivalents (Table 2) (APA 1997; Eriksson and Pelling 2005; Kane, et al. 2003).

Table 2. *Haloperidol equivalents expressed as the daily dose of antipsychotic drug corresponding to 1 mg haloperidol a day.*

Antipsychotic drug	Haloperidol equivalent
Chlorpromazine	50 mg
Chlorprothixene	50 mg
Clozapine	50 mg
Flupenthixol	1 mg
Fluphenazine	2 mg
Haloperidol	1 mg
Melperone	40 mg
Olanzapine	3 mg
Perphenazine	4 mg
Risperidone	1 mg
Thioridazine	50 mg
Ziprasidone	40 mg
Zuclopenthixol	5 mg

Adherence

Although the prescription of several concomitant drugs is common, many patients do not take all their drugs as prescribed (Cramer and Rosenheck 1998; Lacro, et al. 2002). Non-adherence to therapy can be the result of an inability to follow the therapeutic plan, or patient choice based on an aversion to the drug or indirectly due to self monitoring of the drug effects and side effects.

Treatment outcome

The outcome of antipsychotic treatment is still far from optimal for all psychotic patients. In one study, approximately 60% of schizophrenic patients had persistent impairment after treatment and 28% had a persistently poor outcome. Only about 20-30% had a good outcome after 5-7.5 years' follow-up (Harrow, et al. 1997; Wieselgren and Lindstrom 1996), with similar results reported in other studies (Ciompi 1980; Harding, et al. 1987, 1987; Huber, et al. 1980; Modestin, et al. 2003).

The outcome of treatment can be influenced by biological, psychological and social factors as suggested in the vulnerability-stress model (Zubin and Spring 1977; Zubin, et al. 1985); for example, genetic factors, treatment factors (e.g. choice of drug treatment, adherence) and psychological/social factors (e.g. stress, support, attitudes) can all influence the outcome.

Definitions of inadequate treatment response

When the atypical antipsychotic drug clozapine entered or re-entered the market in many countries in 1989, the U.S. Food and Drug Administration (FDA) recommended that it be reserved for patients with an inadequate response to previous therapy (FDA 2006). Because it was felt that this indication required a clearer definition (Meltzer 1990), various approaches to classify the characteristics of psychotic patients falling into this category were made and terms such as treatment resistant, treatment refractory and suboptimal treatment response were introduced (APA 1997; Brenner, et al. 1990; Harrow, et al. 1997; Kane, et al. 1988; Meltzer 1990; Volavka, et al. 2002) (Table 3). In the recent years, attempts have also been made to define the term remission, the other side of treatment response (Andreasen, et al. 2005; van Os, et al. 2006).

Criticism of the definition by Kane et al. (Kane, et al. 1988) involved its focus on the positive symptoms of psychosis and the lack of consideration of the impact of drug side effects on the patient's overall situation (Peuskens 1999). The definitions of Volavka et al., Brenner et al. and Harrow et al. also ignored the impact of side effects (Brenner, et al. 1990; Harrow, et al. 1997; Volavka, et al. 2002). The definitions of Meltzer and the American Psychiatric Association (APA) are more open to individual interpretation, which could result in problems in reproducing the results of clinical studies (APA 1997; Brenner, et al. 1990; Meltzer 1990). In the definition of remission by Andreasen et al. and van Os et al., only symptomatic remission has been discussed (Andreasen, et al. 2005; van Os, et al. 2006). Experience from clinical practice indicates that a patient with schizophrenia may have relatively few overt psychotic symptoms but still not function well in daily life. This dimension must therefore be included when developing a comprehensive classification system to differentiate remission from inadequate treatment response (the latter including both side effects and lack of effect).

Table 3. Various definitions of inadequate treatment response.

Published by	Number of treatment periods	Retrospective period	No. of different chemical drug classes	CHZ dosage equivalents	Duration of treatment	Symptoms/ Problems	Rating scales
Kane et al. 1988	≥ 3	Preceding 5 years	≥ 2	≥ 1000mg/ day	≥ 6 weeks	·Positive symptoms ·Total psychotic symptoms	BPRS CGI
Bremner et al. 1990	≥ 3	Preceding 2 years	≥ 3	≥ 1000mg/ day	≥ 6 weeks	·Total psychotic symptoms ·Functional deficits ·Behavioural excesses	BPRS CGI Living skills survey
Meltzer 1990	Not defined	Not defined	Not defined	Not defined	Not defined	·Total psychotic symptoms ·Positive symptoms ·Negative symptoms ·Social deficits	Suggests use of QLSH
APA 1997 (refers to Brenner et al 1990)	≥ 1	Unlimited	≥ 1	Not defined	Not defined	·Positive symptoms ·Negative symptoms ·Social deficits ·Severe EPS	Not defined
Harrow et al. 1997	Not defined	Not defined	Not defined	Not defined	Not defined	· Overall functioning	LKP scale
Volavka et al. 2002	≥ 1	Unlimited	≥ 1	≥ 600 mg/ day	≥ 6 weeks	·Total psychotic symptoms ·Vocational situation ·Social relations	PANSS

BPRS= Brief Psychiatric Rating Scale

CGI = Clinical Global Impressions Scale

CHZ = chlorpromazine

EPS = Extrapyramidal symptoms

LKP = Levenstein, Klein and Pollack Scale

QLSH= Quality of Life Scale of Heinrichs et al. 1984

PANSS= Positive and Negative Syndrome Scale

Genetic factors

The role of genetic factors in determining the response to antipsychotic treatment has been investigated to some extent (Malhotra, et al. 2004). Theoretically, genes that code for proteins involved in a drug's pharmacodynamics and pharmacokinetics could affect the therapeutic response. The exact gene polymorphisms affecting the treatment response and the consequences of this have not, however, been fully determined.

The primary candidates for affecting the pharmacodynamics of a drug are genes coding for the drug's site of action. Blockade of the dopamine D2 receptor in the brain is the principal mechanism of action of most antipsychotic drugs. Several polymorphisms of the dopamine D2 receptor gene (*DRD2*) that theoretically could influence the antipsychotic effect are known; these include Ser311Cys, Taq1 A and -141C Ins/Del (Kaiser, et al. 2002). Antagonism of serotonin receptors could also contribute to the effect of some antipsychotic drugs (Meltzer and Nash 1991; Nordstrom, et al. 1993; Schotte, et al. 1995). There is some evidence that the 102C allele of the serotonin 2A receptor gene (*HTR2A*) might be correlated with both the therapeutic response and the development of tardive dyskinesia, although the results are inconclusive (Arranz, et al. 1995; Joobar, et al. 1999; Lin, et al. 1999; Malhotra, et al. 1996; Masellis, et al. 1998; Nothen, et al. 1995; Segman, et al. 2001; Tan, et al. 2001; Williams, et al. 1996). Polymorphisms of *HTR2C*, which encode the serotonin 2C receptor have also been associated with tardive dyskinesia as well (Malhotra, et al. 1996; Segman, et al. 2000).

One of the main metabolic paths for antipsychotic drugs involves the CYP2D6 enzyme, the activity of which varies from complete lack (in poor metabolizers) to extremely high activity (in ultra rapid metabolizers) (Dahl 2002; Dahl, et al. 1995; Heim and Meyer 1990; Steen, et al. 1995). A large number of studies have explored the importance of the *CYP2D6* genotype on the pharmacokinetics and treatment outcome of antipsychotic drugs (Dahl 2002).

One way for a drug to cross biological membranes in the body (such as the blood-brain barrier) is by the superfamily of ATP-binding cassette proteins (ABC proteins). The most extensively studied of these is P-glycoprotein, which is encoded by the *ABCB1* gene (also called *MDR1*). The relationship between the *ABCB1* 3435C>T polymorphism and the transport of drugs, including some antipsychotic drugs, has been widely studied, although with inconsistent results (Siddiqui, et al. 2003; Sills, et al. 2005; Yasui-Furukori, et al. 2004).

Treatment factors

The antipsychotic drugs on the market differ to some degree regarding mechanism of action and side effect profiles (Stahl 2006). The choice of drug treatment may therefore affect the outcome for specific patients, depending

on the suitability of the drug of choice for that particular patient. Refusal by the patient to use the drug prescribed would of course also affect the response to the drug. Thus, non-adherence with drug regimens has been associated with worse treatment outcomes (Helgason 1990; Weiden, et al. 2004).

Studies have shown that beginning antipsychotic drug treatment soon after the appearance of the first psychotic symptoms, i.e. shorten the duration of untreated early psychosis (DUP), might enhance the treatment outcome (Lieberman, et al. 2001; Marshall and Rathbone 2006). Drug treatment during the prodromal phase, however, has not been associated with the same good result on treatment outcome. This is partly due to the mild, diffuse symptoms during this phase resulting in low predictive validity as individual markers of psychosis (Lieberman, et al. 2001; McGlashan, et al. 2003; McGorry, et al. 1996). More studies are therefore needed to investigate the effect of the duration of untreated psychotic illness (DUI) in regard to long-term treatment outcome of antipsychotic drugs.

Psychological/social factors

The patient's attitudes, such as their belief in a positive effect of the drug, are a prerequisite to placebo response. A placebo response can enhance the effect of the drug and hence improve the treatment response (Johansen, et al. 2003; Link, et al. 2006). The patient's insight into their illness can also affect the treatment outcome. A lack of insight to the illness has been correlated with a worse clinical outcome for patients with psychosis (Drake, et al. 2007; Saeedi, et al. 2007).

Social support can be important for treatment outcomes as well. For example, a meta-analysis of trials found that the schizophrenia relapse rate decreased by 20% when the relatives of the patient were included in the treatment plan (Pitschel-Walz, et al. 2001). Specifically, social relationships such as having a life partner or being part of a working environment positively affect the well-being of patients with psychosis (Eklund and Hansson 2007; Erickson, et al. 1989; Nordt, et al. 2007; Peralta, et al. 2005; Rymaszewska, et al. 2007). Becker et al. have demonstrated that a social network of 10 to 12 people is optimal for maximizing the psychotic patient's quality of life, with poorer results for smaller or larger social networks (Becker, et al. 1998).

Rating scales

In many somatic disorders, the diagnosis, severity of the illness and treatment response are decided by assessing at the patient's symptoms and various biological markers (e.g. blood sugar measurements in diabetes). In psychiatric disorders, the patient's symptoms are also important but, since there are no reliable biological assessment tools available, various rating scales are often used instead. Some of these rating scales are presented in more detail below.

BPRS

The Brief Psychiatric Rating Scale (BPRS) is a symptom rating scale which initially comprised 16 items but which, on the addition of two more items (Overall 1974; Overall and Gorham 1962) included: somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behaviour, motor retardation, uncooperativeness, unusual thought content, blunted affect, excitement and disorganisation (Overall 1974). The BPRS was later expanded to 24 items with the addition of the items bizarre behaviour, suicidality, self-neglect, elevated mood, distractibility and motor hyperactivity (Ventura, et al. 2000).

PANSS

The Positive And Negative Syndrome Scale (PANSS) is a symptom-rating scale that has adapted the 18 items from the BPRS and another 12 items from the Psychopathology Rating Schedule (Kay, et al. 1987; Kay, et al. 1988, 1989). The PANSS thus includes 30 items each assessed by 1-7 points, where 1 indicates absence of symptoms and 7 indicates extreme symptoms. The positive symptom items are: delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness and hostility. The negative symptom items are: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The general psychopathology items are: somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgement and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance (Kay, et al. 1987).

PECC rating scale

The Psychosis Evaluation tool for Common use by Caregivers (PECC) rating scale (de Hert, et al. 2002; Lindström, et al. 1997) evaluates the severity of psychotic symptoms using a visual analogue scale (VAS) of 60 millimetres per symptom, where higher scores indicate more severe symptoms (de Hert, et al. 2002; Lindström, et al. 1997). The PECC rating scale contains 20 of the 30 symptom items in the PANSS rating scale, although these are grouped somewhat differently under the headings positive, negative, depressive, excitatory and cognitive symptoms. Each symptom group contains four psychotic symptoms. Positive symptoms include delusions, grandiosity, hallucinatory behaviour and unusual thought content. Negative symptoms include motor and speech disturbances, blunted affect, blunted emotional relationships and passive/apathetic withdrawal. Depressive symptoms include anxiety, depression, guilt feelings and somatic concern. Excitatory

symptoms include excitement, impulsivity, hostility and uncooperativeness. Cognitive symptoms include difficulty in abstract thinking, spatial disorientation, conceptual disorientation and poor attention. The values for each symptom on the VAS scales can be added together for each overall symptom group, resulting in a maximum of 240 mm per group.

CAN rating scale

The Camberwell Assessment of Need (CAN) rating scale (Arvidsson 2003; Hansson, et al. 1995; Phelan, et al. 1995) evaluates the clinical and social needs of patients with severe mental illness. It consists of 22 items, covering accommodation, food preparation, household skills, self-care, occupation, physical health, psychotic symptoms, information about illness and treatment, psychological distress, safety to self, safety to others, use of alcohol and drugs, company of others, intimate relationships, sexual expression, child care, basic education, telephone access, use of transport, economic situation and welfare benefits. Each item can be assessed from 0 points (no problems) to 2 points (severe problems) (Arvidsson 2003; Hansson, et al. 1995; Phelan, et al. 1995).

EQ-5D rating scale

The EuroQol-5D (EQ-5D) rating scale (Brooks 1996; Prieto, et al. 2004) evaluates health-related quality of life. The rating scale is divided into two parts; part one contains five health-related multi-choice questions regarding mobility, hygiene, occupation, pain and anxiety. Part two consists of a visual analogue rating scale (VAS) where the patient rates his/her quality of life, with 100 being the best imaginable state of life and 0 being the worst (Brooks 1996; Prieto, et al. 2004).

UKU rating scale

The Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale evaluates side effects experienced by patients receiving psychotropic drug treatments (Lingjaerde, et al. 1987). The scale exists as observer-rated and self-rated versions. The 48 items include; concentration difficulties, asthenia, sleepiness, failing memory, depression, tension, increased duration of sleep, reduced duration of sleep, increased dream activity, decreased dream activity, emotional indifference, dystonia, rigidity, hypokinesia, hyperkinesia, tremor, akathisia, epileptic seizures, paraesthesias, accommodation disturbances, increased salivation, reduced salivation, nausea, diarrhoea, constipation, micturition disturbances, polyuria, orthostatic dizziness, palpitations, increased sweating, rash, pruritus, photosensitivity, increased pigmentation, weight gain, weight loss, menorrhagia, amenorrhoea, galactorrhoea, gynecomastia, increased sexual desire, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, orgasmic dysfunction, dry vagina, headache, physical dependence and psychic dependence. Each question is graded in four steps: 0

is normal i.e. side effects are not or probably not present, 1 indicates mild symptoms, 2 indicates that symptoms of side effects are present to a moderate degree and 3 indicates that symptoms of side effects are severe.

SPKS

The rating scale measuring the patient's knowledge of schizophrenia ("Skattning av personers kunskap om schizofreni", SPKS) (Borell, et al. 1995; Falloon, et al. 1997; Falloon 1988) includes the following questions (translated from Swedish), SPKS 1: Describe your problems; SPKS 2: What is the current diagnosis for your problems? SPKS 3: Why do you think your problems were diagnosed thus? SPKS 4: Have you heard voices and, if so, why do you think you heard them? SPKS 5: Have you had thoughts which others regard as incorrect (delusions)? SPKS 6: What are the warning signs for your illness? SPKS 7: What do you do when the warning signs appear? SPKS 8: What makes your symptoms worse? SPKS 9: What makes you better? SPKS 10: What are your residual symptoms? SPKS 11: How do you manage the residual symptoms? SPKS 12: What medicines are you taking and what are the doses for each? SPKS 13: What are the positive effects of taking the drugs? SPKS 14: What are the negative effects of taking the drugs? SPKS 15: How do you expect your life to be in five years?

If required, the patient can be given further information to clarify the questions. The answers are recorded by hand during the interview in as much detail as possible and scores ranging from one to five (low to high accuracy/knowledge/insight) using the SPKS coding procedure, including a transformer key, are then allocated (Borell, et al. 1995; Falloon, et al. 1997; Falloon 1988). A similar questionnaire answered by the patient's contact person can be used along with information from the patient's files during the scoring procedure to clarify the actual situation if this is not obvious from the patient's answers.

Sociogram

A sociogram can be used for assessing the patient's social network. This tool can vary in appearance (Rapoport and Horvath 1961; Rich 1978). The sociogram used in this study was a figure of a dot surrounded by a circle. The patient is asked to record the names of, or a code for, all the people they are in contact with; the closer to the dot they record the person, the closer the relationship. The contacts are then rated according to whether they are important to the patient, supportive, a nice person, someone they want to see more often, annoying, or someone they want to see less often; the members of the patient's health care team can also be identified. Each person listed in the sociogram can be registered under more than one descriptor.

Aims of the Thesis

The general aim of this thesis was to develop a classification method for treatment response in a naturalistic patient population with psychosis and to utilize this classification when investigating if and how patients with different treatment response discriminate regarding genetic, drug treatment, insight and social network aspects.

The specific aims were:

- I To develop and evaluate a new classification method, the CANSEPT method, as a means of classifying psychotic patients in a naturalistic setting according to treatment response; i.e. differentiating between functional remission and inadequate treatment response.
- II To investigate whether targeted genetic polymorphisms could be indicators of treatment response to antipsychotic drugs in psychotic patients.
- III To examine the early initiation of, current use of, and adherence to, antipsychotic treatment in relation to treatment response, as defined by the CANSEPT classification, in psychotic patients.
- IV To examine social networks, insight into and knowledge of illness, coping strategies, drugs and expectations for the future in a cohort of patients with psychosis in relation to treatment response.

Materials and Methods

Data collection

A naturalistic, cross-sectional and retrospective cohort study was performed at the Psychosis Outpatient Care clinic in Jönköping, Sweden. Patients were enrolled from November 1st 2001 to June 4th 2004. Each patient was interviewed on one occasion, while in a relatively stable state of psychotic illness. One person conducted all the interviews (M.A.). The interview included use of rating scales and patient-specific questions. After the interview, the interviewer read the patient files, and the patient's contact person filled in the CAN rating scale for contact persons and a version of the SPKS for contact persons. Information on drug treatment, disorders, hospitalizations and the patient's social situation was extracted from the patient files. All patients were also weighed, their height was measured and blood samples were collected. The collected data was analyzed and used for the four papers in this thesis (Figure 3).

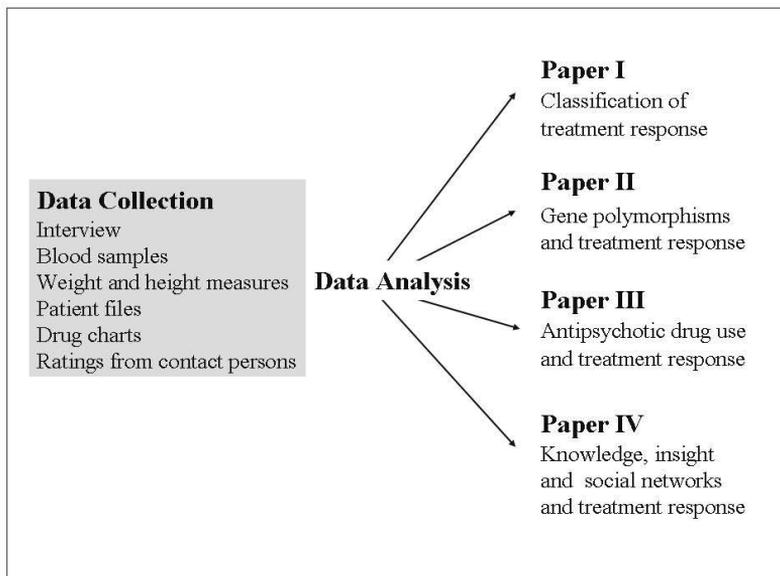


Figure 3. Schematic diagram of the methods used for this thesis.

Rating scales

The interview comprised application of the rating scales needed for the CANSEPT classification; the Camberwell Assessment of Need (CAN) rating scale (Arvidsson 2003; Hansson, et al. 1995; Phelan, et al. 1995), the Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale (Lingjaerde, et al. 1987), together with the EuroQol-5D (EQ-5D) rating scale (Brooks 1996; Prieto, et al. 2004), the Psychosis Evaluation tool for Common use by Caregivers (PECC) rating scale (de Hert, et al. 2002; Lindström, et al. 1997) the “Skattning av personers kunskap om schizofreni” (SPKS) (the patient’s personal knowledge of schizophrenia) rating scale (Borell, et al. 1995; Falloon, et al. 1997; Falloon 1988), and a sociogram for assessment of the patient’s social network (Rapoport and Horvath 1961; Rich 1978)

Patient-specific questions

Patient-specific questions concerning children, partners, daily living, social life, job situation and parents’ ethnicity were asked together with questions about the patient’s drug treatments, drug intake, psychiatric contacts and disorders. Data concerning these questions were also collected from patient files (where the patient answers did not correspond to their file data, the data in the files was used).

Blood sample analyses

Blood samples were taken from the patients after the interview. The serum samples, and the full blood sample for genotyping, were stored at -70°C until analysis.

Prolactin

Blood for serum prolactin analyses was collected in BD Vacutainer plastic tubes containing Clot Activator and gel for serum separation. Serum prolactin was analysed at the Clinical Chemistry department of Jönköping residential hospital, Sweden, by the immune fluorimetric method Autodelfia (Prolactin-Kit, Wallace) with a working range of 0.25 to 250 $\mu\text{g/L}$.

Genotype analysis

All genotypes were checked for deviation from Hardy-Weinberg equilibrium. The blood samples for genotyping were collected in plastic tubes containing liquid EDTA and the analyses were performed at the Clinical Pharmacology department of Uppsala University Hospital, Sweden. DNA was

isolated from whole blood using the QIAamp® DNA Blood Mini Kit (QIAGEN Ltd). Genotyping of the coding *DRD2* polymorphism Ser311Cys (dbSNP rs1801028) was performed by polymerase chain reaction (PCR) with an automated thermal cycler (MJ Research, USA), followed by digestion with restriction enzymes and electrophoresis on an agarose gel (Arinami, et al. 1994). The polymorphism denoted -141C Ins/Del (dbSNP rs1799732), was genotyped using the same technique (Arinami, et al. 1997; Breen, et al. 1999; Kaiser, et al. 2002). The Taq1A restriction site polymorphism (dbSNP rs1800497) was genotyped using a similar method (Grandy, et al. 1993; Thompson, et al. 1997). The synonymous coding *HTR2A* polymorphism, which is commonly referred to as 102T/C (dbSNP rs6313), and the Cys23Ser polymorphism (dbSNP rs6318) of the *HTR2C* gene were also analyzed by PCR with restriction enzyme digestion and agarose electrophoresis (Lappalainen, et al. 1995; Tot, et al. 2003; Warren, et al. 1993).

The deletion of A at genomic position 2549 in *CYP2D6* (dbSNP rs35742686), which is diagnostic for *3, and the g.1846G>A exchange (dbSNP rs3892097), which is diagnostic for *4, were analyzed by PCR with restriction enzyme digestion and polyacrylamide electrophoresis (Gough, et al. 1990; Smith, et al. 1992; Wolf, et al. 1990). The *CYP2D6**5 allele (total deletion of the gene) was detected by long PCR followed by 1% agarose gel electrophoresis (Hersberger, et al. 2000). The *CYP2D6* gene duplication, which usually confers ultra rapid metabolism, was detected using long PCR as described by Steijns and Van Der Weide (Steijns and Van Der Weide 1998). The *CYP2D6* alleles *6 (dbSNP rs5030655; g.1707delT), *7 (dbSNP rs5030867; g.2935A>C) and *8 (dbSNP rs5030865; g.1758G>T) were analyzed using TaqMan® Pre-Developed Assay Reagents for allelic discrimination (primers, probes, positive controls: part numbers 4312556, 4312557, and 4312558) and the ABI PRISM 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA). When neither the *CYP2D6* variants *3, *4, *5, *6, *7, *8 nor the duplication was detected, the allele was classified as wild type *CYP2D6**1.

Genotyping of three *ABCB1* polymorphisms was performed using the ABI PRISM 7000 Sequence Detection System. Genotyping of *ABCB1* 2677G>T/A (dbSNP rs2032582), was performed according to Saito *et al* 2003 with the addition of 40µg/ml bovine serum albumin to optimize PCR (Saito, et al. 2003). Allelic discrimination of the synonymous *ABCB1* polymorphisms g.1236C>T (dbSNP rs1128503) and g.3435C>T (dbSNP rs1045642) was performed using TaqMan® SNP Genotyping Assay kits containing primers and probes (C__7586662_10 and C__7586657_1, Applied Biosystems, CA, USA).

Drug concentrations

Most of the antipsychotic drug serum concentrations were analyzed using the standard procedures of the Department of Clinical Pharmacology, Lund University Hospital, Sweden. LC-MS-MS was used to analyze the serum concentrations of olanzapine, N-demethylated olanzapine, risperidone, 9-OH risperidone, haloperidol, clozapine and N-demethylated clozapine, while HPLC followed by UV detection was used to analyze serum concentrations of flupenthixol, fluphenazine, perphenazine, chlorpromazine, levomepromazine, zuclopenthixol and thioridazine. Serum concentrations of chlorprothixene were analyzed by LC-MS-MS at the Forensic chemistry department at the University of Linköping, Sweden.

A concentration below 50% of the minimum therapeutic drug serum concentration was considered to be an indicator of non-adherence to therapy (Department-of-Clinical-pharmacology 1993; Freeman and Oyewumi 1997; Hiemke, et al. 2004; Kistrup, et al. 1991; Kjolbye, et al. 1994; Schulz and Schmoldt 1994; Ulrich, et al. 1998).

Classification Method (CANSEPT)

The CANSEPT method was designed to address the various aspects of treatment response such as functional remission and inadequate treatment response. It comprises assessment of clinical and social needs using the CAN rating scale (CAN), side effects (SE) using the UKU rating scale, and previous treatment (PT), with thresholds set for each dimension.

Thresholds

Patients were able to be considered having an inadequate treatment response if they had tried a minimum of two antipsychotic drugs from different chemical classes since treatment first started (APA 1997). They also had to have been treated for a minimum of six weeks with each drug (Kane, et al. 1988; Peuskens 1999).

The threshold for significant clinical/social needs according to CANSEPT was defined as 10 points or higher from a possible 44 points on the CAN rating scale.

The significant side effects threshold for the UKU rating scale was defined as one or more items with severe symptoms (the item maximum score of 3 points) and/or four or more items with symptoms present to a moderate degree (2 points).

Definition of patient groups

The patients were divided into five groups (Groups 1-4 plus a residual group) using the thresholds for the CAN and UKU rating scales and previous treatment assessment (Table 4). The groups were assigned as follows: Group 1: patients in functional remission (FR); Group 2: patients with significant side effects but no significant clinical/social needs; Group 3: patients with no significant side effects but with significant clinical/social needs; Group 4: patients with significant side effects and significant needs; Residual group: patients with significant clinical/social needs and/or significant side effects who had not previously received enough different antipsychotic drugs to be classified as having an inadequate treatment response. In Group 1+2 (the combination group of Group 1 and Group 2) all patients were without significant social and clinical needs (CAN <10p) while in Group 3+4, all patients had significant needs (CAN ≥10p). Similarly, the patients in Group 1+3 were all without significant side effects (UKU < 4 items with 2p and no item with 3p) while the patients in Group 2+4 all had significant side effects (UKU ≥ 4 items with 2p and/or 1 item with 3p). The Group 2+3+4 comprised patients with a significant treatment-related problem (CAN ≥10p and/or UKU ≥ 4 items with 2p and/or 1 item with 3p) and were hence not in functional remission (non-FR).

Table 4. *The CANSEPT classification method.*

Component of CANSEPT	Thresholds	Group 1 (In functional remission)	Group 2 (Significant side effects)	Group 3 (Significant needs)	Group 4 (Significant side effect and needs)
Clinical/ social needs (CAN)	≥ 10 points from CAN-patient and/or CAN-contact person	No	No	Yes	Yes
Side Effects (SE)	≥ 1 item with 3 points from UKU and/or ≥ 4 items with 2 points from UKU	No	Yes	No	Yes
Previous Treatment (PT)	≥ 2 antipsychotic drugs from different chemical classes for ≥ 6 weeks of treatment	Yes/No	Yes	Yes	Yes

Validation method

CANSEPT was evaluated using a reference standard concept based on another set of data. The other data set consisted of the answers to the validation tools used in the study, i.e. the patient-specific questions, the patient files, blood samples, the EQ-5D rating scale and the PECC rating scale. For CANSEPT to show validity, patients in functional remission according to CANSEPT (Group 1) were required to have statistically significantly better well-being [i.e. fewer hospitalizations over the previous two years, higher rates of full or part-time work and a better quality of life (EQ-5D)] than those not in functional remission (Group 2+3+4).

There was also a desire for the group of patients without significant social and clinical needs (Group 1+2) to have less severe psychotic symptoms (PECC rating scale) than those with significant needs (Group 3+4).

The patients without significant side effects (Group 1+3) were also to have fewer unwanted side effect markers than those with significant side effects (Group 2+4). The side effects chosen for validation of the CANSEPT method included extreme obesity, severe hyperprolactinaemia, diabetes, severe extrapyramidal symptoms and cardiovascular problems. The height and weight of all patients were measured with the same scales and ruler; the body mass index (BMI) of each patient was calculated by dividing their weight (kg) by the square of their height (m²). The cut-off for extreme obesity (obesity class III) was a BMI of 40 kg/m² or higher (National-Institute-of-Health 1998). The cut-off for severe hyperprolactinaemia was 60 µg/L or higher (Friesen, et al. 1977; Movin-Osswald and Hammarlund-Udenaes 1995; Movin-Osswald, et al. 1995; Movin-Osswald, et al. 1994). The presence of severe diabetes, severe extrapyramidal symptoms or cardiovascular problems was indicated by the use of anti-diabetic drugs (systemic insulin and/or oral drugs), the anticholinergic drugs biperiden or orfenadine and antiplatelet therapy with low dose aspirin respectively (data obtained from patient drug files). It was expected that extreme obesity, severe hyperprolactinaemia, and use of anticholinergic drugs, antidiabetic drugs and antiplatelet drugs would occur less often in patients without significant side effects (Group 1+3) than in those with significant side effects (Group 2+4).

Inclusion and exclusion criteria

Patients enrolled in the trial included those who, on the 22nd of September 2001, were registered with the Psychosis Outpatient Care clinic in Jönköping, Sweden, had active contact with the Patient Care staff (i.e. had a contact person at the clinic) and required antipsychotic drugs (regardless of whether or not they complied with the drug regimen). Patients were excluded if they were too ill to participate as judged by their contact person

(for example patients who never spoke), needed an interpreter, or did not require antipsychotic drugs.

Ethics Committee

The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2000, and was approved by the Ethics Committee of the Medical Faculty at Linköping University, Sweden. The participating patients signed a written informed consent form after the procedures had been fully explained.

Statistics

The data were coded and entered into the statistical software package system SPSS 14.0 for analysis. Pearson Chi-square analyses were used for categorical variables and the Kruskal Wallis test was used for continuous variables. Analyses were two tailed and p-values of <0.05 were considered indicative of a statistically significant difference between the compared groups. Results are given as mean values (SD) in the text.

Results and Discussion

The research for this thesis focused on the definition of functional remission in psychotic patients and the associated relationship with genetics, drug treatment, and patient knowledge, insight and social networks. The results are based mainly on long-term outcomes since the patients had been in contact with psychiatric care for an average of twenty years (range 1-45 years; 96% had been in contact with care for 5 years or more).

Study population

One hundred and twenty-four patients were enrolled from the Psychosis Outpatient Care Clinic in Jönköping, Sweden (Figure 4). One patient was excluded because of protocol violation, leaving 123 in the study. The mean age of the included patients was 43.8 years (range 23-79 years); 58% of the patients were males and 42% were females. Ninety-nine of the participating patients had Swedish ethnicity; the ethnicity of the other patients was other European (n=19), Middle East (n=2) and Far East Asian (n=3), as defined by the origin/ethnicity of their parents. Thus, 18% had non-Swedish ethnicity. This was somewhat higher than the mean occurrence of foreign ethnicity in the county of Jönköping (11% in the year 2004), and in the total population of Sweden (12% in 2004), according to Statistics Sweden (StatisticsSweden 2006).

All patients at the Psychosis Out Patient Care Clinic of Jönköping were included if they had had symptoms of psychosis and still needed antipsychotic drugs, regardless of diagnosis, in order to keep the study as naturalistic as possible. Seventy-seven percent of the included patients in this population had a schizophrenic or delusional disorder diagnosis (ICD10 F20-F29), while the other patients had affective disorders (8%), anxiety disorders (2%), personality disorders (6%) or other psychiatric disorders (7%). This means that 22% of the patients had diagnoses other than schizophrenic or delusional disorders. These patients were, however, evenly distributed across the CAN-SEPT groups, resulting in similar results in the total population as to those in the subgroup of schizophrenic or delusional patients.

All the participating patients attended a psychosis open ward clinic. As a result of this approach, patients who had fully recovered from their psychosis and had no ongoing pharmacological treatment were not included, since these patients were no longer in contact with psychiatric caregivers. Thus Group 1 (patients in functional remission) included patients with no or little interfer-

ence from their illness or medication but did not include fully recovered patients. This should not interfere with interpretation of the data, since the aim was to differentiate between patients in functional remission and those with an inadequate treatment response, and not to study patients in full recovery.

One hundred and five patients from the same clinic declined participation, mostly without giving any reason for their refusal (Figure 4). The mean age of the patients who declined participation was 47.7 years (range 21-77 years); 55% were males and 45% females, and 81% had a schizophrenic or delusional disorder diagnosis. The participating patients and the patients who declined to participate did not differ significantly according to any characteristic except mean age ($p=0.023$).

When the patients were grouped according to the CANSEPT classification, six of the 123 enrolled patients ended up in the residual group. This occurred because, although they were not in functional remission (i.e. they had significant clinical and social needs and/or side effects), they could not be classified as having inadequate treatment response either since they had not yet tried enough alternative antipsychotic drugs. These six patients were not included in further analyses.

The 117 remaining patients were divided, according to the CANSEPT criteria (Table 4), into four groups. Thirty-two percent of the patients fulfilled the criteria for Group 1, 17% for Group 2, 23% for Group 3 and 27% for Group 4. The groups did not differ statistically significantly according to age, sex, ethnicity, diagnosis, or years since first in contact with psychiatric care.

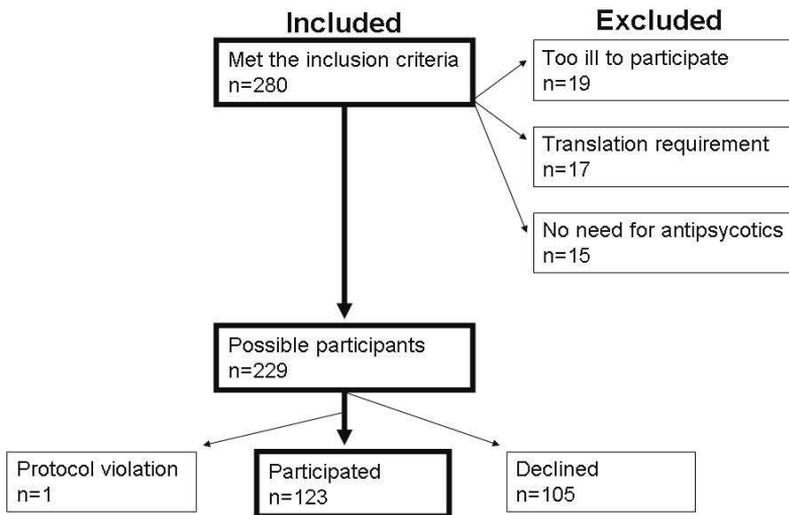


Figure 4. Schematic diagram of patient enrolment.

The CANSEPT classification method (Paper I)

In this study, a new method was developed and used to classify patients with psychosis according to treatment response; the CANSEPT classification method was also validated. The functionality of psychotic patients is a product of the total practical and social burden of the residual psychotic illness together with the side effect burden of the drugs and the subsequent handicapping effects on the patient. For functional remission, therefore, the patient should not only have a low level of psychotic symptoms but also have minimal practical and social burdens and no handicapping side effects. Our intention was therefore to create a classification method which would take the above factors into account when classifying remission and treatment outcome. To this end, the CAN rating scale, which measures the social and clinical needs of the patient, and the side effect rating scale UKU were chosen (Arvidsson 2003; Lingjaerde, et al. 1987). This created a multifaceted, user-friendly and clinically valuable method of classifying functional remission, which was confirmed by the global outcome results during validation.

The CANSEPT method was designed for use in both a naturalistic setting in clinical psychiatric care and in a research scenario by using a combined cross-sectional and retrospective approach. The method was based on the understanding that psychotic patients have problems not only as a result of positive symptoms, but also from residual symptoms and treatment side effects, as well as considerable social problems, as described above. The method also takes into account the fact that it is necessary to capture the relevant information using stringent methodology from the perspective of both the patient and the mental health care givers (Peuskens 1999). It should be pointed out that the study was not designed to follow changes in outcome over time for each individual. The three dimensions chosen (clinical and social needs, side effects from ongoing treatments, and the number of previous treatments) were considered important aspects of daily-life functioning for patients with psychosis.

The classification method and its thresholds were chosen after consideration of definitions and discussions in the literature (APA 1997; Brenner, et al. 1990; Harrow, et al. 1997; Hegarty, et al. 1994; Kane, et al. 1988; Meltzer 1990; Peuskens 1999; Volavka, et al. 2002). The patient's previous treatments, residual symptoms, treatment side effects, and clinical/social needs and perspectives, and the views of their mental health caregivers, were considered to be the core items for classifying treatment response when designing CANSEPT. The method was also designed to use as few elements as possible while still obtaining adequate answers, in order to keep it simple and make it as user-friendly as possible.

The CANSEPT interview schedule was well accepted by the patients, with only one patient withdrawing during the interview. The method was easy to utilise; each interview session lasted for approximately 45 minutes

and could be in general completed in the course of one visit. The grouping method can be used to compare each individual group with the others, or to compare the patients with functional remission (FR; Group 1) with those not in functional remission (non-FR; Group 2+3+4). It can also be used to compare the groups with significant side effects (Group 2+4) with those that do not have significant side effects (Group 1+3) or the groups with significant clinical/social needs with those without significant needs (Group 1+2 versus Group 3+4). This diversity is an advantage when using CANSEPT in both clinical care and treatment-response research scenarios.

The nature of functional remission and inadequate treatment response is not, however, as dichotomous as CANSEPT might suggest. While the applied thresholds resulted in generalizations that allowed the patients to be grouped, these generalizations may not have fitted each individual perfectly. Nonetheless, bearing in mind that discrimination is necessary in clinical research, optimal methods should be used.

Validation of CANSEPT

CANSEPT was validated from three perspectives: global outcome, effectiveness (with respect to the presence of significant social and clinical needs), and side effects. During the validation procedure, the observed results from this study were compared with the expected rankings between the groups for each parameter.

Global outcome

CANSEPT showed validity in classifying patients according to global outcome. Patients in functional remission (Group 1) were compared with those not in functional remission (Group 2+3+4) regarding parameters related to the patient's well-being (number of hospitalizations in the last two years, full or part-time work, and quality of life as measured by the EQ-5D quality-of-life rating scale). For the classification method to be successful, the observed results of these parameters should differ in the same directions as the expected rankings, for patients in functional remission as compared to patients not in functional remission. These conditions were fulfilled by CANSEPT, as seen in Table 5, indicating better global outcomes for patients in functional remission than for those not in functional remission, as would be expected.

Table 5. *The validation of CANSEPT according to global outcome.*

Evaluation parameters	Expected result	Observed result		
Global outcome	In functional remission vs Not in functional remission	Group 1 result(SD)	Group 2+3+4 result(SD)	P value^a
No. of hospitalizations in the last 2 years (numbers)	Group 1 < Group 2+3+4	0.3 (0.6)	1.4 (2.4)	P=0.010
Full or part-time work (%)	Group 1 > Group 2+3+4	24.3%	5.1%	P=0.002
EQ-5D questions (points)	Group 1 < Group 2+3+4	6.3 (1.0)	7.5 (2.0)	P<0.001
EQ-5D VAS (mm)	Group 1 > Group 2+3+4	71.4 (14.4)	62.1 (20.2)	P=0.027

^a The p values were calculated for continuous variables using the Mann Whitney U test and for categorical variables using Pearson Chi-square test.

Effectiveness/ Significant social and clinical needs

The PECC symptom rating scale was used to validate the CANSEPT method from the perspective of effectiveness of treatment with respect to significant needs. The PECC scale was chosen because it measures not only the positive symptoms of psychosis but also the negative, depressive, excitatory and cognitive symptoms, as described before (de Hert, et al. 2002). All these symptoms contribute to the development of significant social and clinical needs. Patients classified as having no significant social and clinical needs (Group 1+2) would be expected to have less severe symptoms than those classified as having significant needs (Group 3+4). Although the results indicated that this was not the case for depressive and excitatory symptoms, the core symptoms of psychosis (positive, negative and cognitive symptoms (van Os, et al. 2006)) were less severe in patients classified as having no significant social and clinical needs (Table 6). Thus, CANSEPT is considered to be a valid method of classifying patients with respect to effectiveness/significant needs.

Table 6. *The validation of CANSEPT according to effectiveness/ significant needs.*

Evaluation parameters	Expected result	Observed result		
Significant social and clinical needs/ effectiveness	No significant needs vs Significant needs	Group 1+2 mm (SD)	Group 3+4 mm (SD)	P value^a
Positive symptoms ^b	Group1+2 < Group3+4	30.6 (36.1)	47.8 (42.7)	P=0.014
Negative symptoms ^b	Group1+2 < Group3+4	21.3 (15.1)	39.1 (32.1)	P=0.007
Depressive symptoms ^b	Group1+2 < Group3+4	26.3 (19.8)	38.8 (33.2)	P=0.121
Excitatory symptoms ^b	Group1+2 < Group3+4	10.0 (10.8)	16.3 (17.6)	P=0.103
Cognitive symptoms ^b	Group1+2 < Group3+4	18.2 (18.0)	27.9 (19.0)	P=0.012

^a The p values were calculated for continuous variables using the Mann Whitney U test.

^b PECC ratings. Only available for the 80 most recently interviewed patients.

Side effects

The significant side effect perspective of CANSEPT was evaluated by comparing the group classified as being without significant side effects (Group 1+3) with those classified as having significant side effects (Group 2+4) in relation to objective parameters regarding antipsychotic side effects. For this, physical measurement of the patients and perusal of their drug files were used, with specific attention to extreme obesity, diabetes, severe prolactin disturbances, severe extrapyramidal symptoms and cardiovascular problems.

Obesity

Obesity induced by antipsychotic drugs is a problem that has recently attracted more attention because it is so commonly reported and because of the risk of developing metabolic syndrome (Baptista 1999; Schwartz, et al. 2004; Wirshing 2004; Wirshing, et al. 1999). Obesity (class I) is defined as having a BMI of 30 kg/m² or higher, but a strong association between obesity and risk of death occurs first at class III obesity, with a BMI of 40 kg/m² or higher (Calle, et al. 1999; National-Institute-of-Health 1998). As this validation was specifically investigating the perspective of significant side effects, the frequency of patients with a BMI of 40 kg/m² or higher was chosen as the threshold for the side effect obesity.

Diabetes

Diabetes can also be caused by antipsychotic drug treatment, through antipsychotic-induced obesity but also through effects such as increased insulin resistance (Scheen and De Hert 2007). The use of any antidiabetic drug (oral or by injections) was chosen as an indicator of diabetes in this study.

Prolactin disturbances

Antipsychotic drugs can increase the secretion of prolactin, probably because of their dopamine receptor antagonistic properties (Ben-Jonathan and Hnasko 2001; Hamner 2002). This can lead to decreased libido, erectile dysfunction, amenorrhoea and galactorrhoea (Kinon, et al. 2003; Pollock and McLaren 1998). The levels of circulating prolactin change diurnally, with as many as 5-15 secretory episodes a day (Weitzman 1976). A cut-off point above the normal daily fluctuations in prolactin level was chosen. Because the cut-off was to be correlated with significant side effects, a level of 60ng/ml or above was chosen; which is above the normal expected changes due to an antipsychotic drug dose (Movin-Osswald and Hammarlund-Udenaes 1995; Movin-Osswald, et al. 1995; Movin-Osswald, et al. 1994), and is the level at which amenorrhoea often starts to develop (Friesen, et al. 1977).

Extrapyramidal symptoms

Extrapyramidal symptoms such as dystonia, akathisia and parkinsonism are well known side effects of antipsychotic drugs, probably also caused by their dopamine receptor antagonistic properties of these drugs (Blair and Dauner

1992; Burgyone, et al. 2004; Gerlach, et al. 1996; Ossowska 2002; Pierre 2005). Antiparkinsonian drugs (i.e. anticholinergic drugs) are used to treat these side effects (Burgyone, et al. 2004). Since the use of these drugs indicates severe extrapyramidal symptoms, the use of biperiden or orfenadine (drugs used in this context in Sweden) was chosen as an indicator of significant extrapyramidal side effects.

Cardiovascular disorders

Antipsychotic drugs have also been associated with increased QTc interval, Torsade de Pointes and cardiac arrest (Glassman and Bigger 2001). Antiplatelet therapy is often used by patients with a moderate to high risk of cardiovascular events (Antithrombotic-Trialists-Collaboration 2002; Bartolucci and Howard 2006; Patrono, et al. 2005). The administration of these drugs can therefore be used as an indication of cardiovascular disorders, especially since documentation of cardiovascular disorders may not appear in psychiatric patient files. The use of antiplatelet therapy (low-dose aspirin) was therefore chosen as a marker for cardiovascular disorders.

Expected vs observed results

For CANSEPT to be valid, patients without significant side effects (Group 1+3) should have lower rates of extreme obesity, antidiabetic drug use, severe hyperprolactinaemia, anticholinergic drug use and antiplatelet therapy use than those with significant side effects (Group 2+4). A statistically significantly higher rate of severe hyperprolactinaemia was seen in Group 2+4 than in Group 1+3. For extreme obesity, the use of antidiabetic drugs and the use of antiplatelet therapy, the differences between the groups were not statistically significant, although there was a clear trend for a higher rate (at least twice as high) in patients with significant side effects than in those without. The use of anticholinergic drugs was almost the same in the two groups. The lack of a significant difference between the groups in this respect could have been due to masking of the extrapyramidal symptoms by the anticholinergic drugs during the rating or due to patients continuing to use anticholinergic drugs despite no longer needing them. This latter explanation was also indicated by the duration of use of anticholinergic drugs, a mean of 9.0 (7.8 SD) years; 60% of the patients had used them for more than five years. The clear trend for lower rates of extreme obesity, use of antidiabetic drugs and use of antiplatelet therapy in patients without versus those with significant side effects suggests a difference between the groups that was unable to be statistically captured because of the low power of the study (Table 7). This indicates that CANSEPT could be valid in classifying patients regarding significant side effects, but the power of this study was too low to prove it.

Table 7. The validation of CANSEPT according to side effects.

Evaluation parameters	Expected result	Observed result		P value ^a
	No significant side effects vs. Significant side effects	Group 1+3 % of pts	Group 2+4 % of pts	
Extreme obesity ^b	Group1+3 < Group2+4	3.1%	7.7%	P=0.261
Severe hyperprolactinaemia ^c	Group1+3 < Group2+4	0%	11.8%	P=0.016
Anticholinergic drugs	Group1+3 < Group2+4	18.5%	21.2%	P=0.716
Antidiabetic drugs	Group1+3 < Group2+4	4.6%	11.5%	P=0.163
Antiplatelet therapy ^d	Group1+3 < Group2+4	3.1%	11.5%	P=0.072

^aThe p-values were calculated for categorical variables using Pearson Chi-square.

^bBMI \geq 40 kgm⁻² (obesity class III)

^cProlactin \geq 60 μ g/L. N=81

^dLow-dose aspirin

Gene polymorphisms (Paper II)

Our naturalistic cross-sectional study suggested that the response to antipsychotic drugs is actually modulated by genetic polymorphisms. Patients with one or two *DRD2* Taq1 A1 alleles appeared to have a greater risk of significant side effects, especially if they were males, Caucasian (i.e. from Europe or the Middle East), had schizophrenic or delusional disorders or were prescribed antipsychotic drugs with strong dopamine D2 receptor antagonistic properties. For males using drugs with strong D2 antagonistic properties, these results were consistent even after correction for multiple testing. On the other hand, patients on olanzapine who were homozygous for *ABCB1* 3435T tended to have more significant social and clinical needs than patients with one or two wild type alleles, even after correction for multiple testing.

Pharmacodynamic gene polymorphisms

Overall, there were indications in this naturalistic group of psychotic patients that antipsychotic drug outcome could be significantly influenced by some of the studied polymorphisms.

The Taq1 A1 allele of the *DRD2* gene was more frequent in patients with significant side effects than in those without. The rate was even higher in Caucasians, males and patients treated with drugs with strong dopamine D2 receptor antagonistic properties ($p < 0.05$; Table 8). No relationships were discerned between any *DRD2* polymorphisms and significant social and clinical needs in psychotic patients. These findings imply that genetic variations in the dopamine D2 receptor gene do not determine the therapeutic effect of the antipsychotic drug, but may influence the risk of developing significant side effects. To have impact on the side effects of a psychotropic drug but not on the therapeutic effectiveness is not a new scenario (Murphy, et al. 2004). The greater

incidence of significant side effects in patients, especially males, with the A1 allele could be explained by the dopamine D2 receptor density.

The Taq1 A1 polymorphism of the dopamine D2 receptor gene seems to be associated with alterations in dopamine D2 receptor density in the striatum (Arinami, et al. 1997; Jonsson, et al. 1999; Noble, et al. 1991; Thompson, et al. 1997). This effect appeared to be more marked in males than in females (Thompson, et al. 1997). The impact of drugs binding strongly to the dopamine D2 receptor could theoretically be greater in individuals with a lower density of dopamine D2 receptors in the striatum. Thus, theoretically, patients, especially men, with the Taq1 A1 allele would be more vulnerable to the effects of dopamine D2 antagonistic drugs, especially drugs with strong dopamine D2 receptor antagonistic properties. The lower dopamine D2 receptor density caused by the Taq1 A1 allele could result in greater vulnerability to dopamine blockade and, hence, an increased incidence of significant side effects, as seen in the present study. This is in agreement with the results of Young *et al* who showed that patients with an A1 allele who were receiving antipsychotic drugs had higher prolactin levels than patients without an A1 allele (Young, et al. 2004). If our results are confirmed, it could be recommended that patients with an A1 allele receive antipsychotic drugs with a low dopamine D2 blocking profile, e.g. clozapine and olanzapine, so as to avoid significant side effects.

Table 8. Presentation of results regarding the Taq1 A1 polymorphism of the dopamine D2 receptor gene. The results are for the groups without significant side effects (Group 1+3) and the groups with significant side effects (Group 2+4). The frequencies are presented for the total study population and for selected populations.

	n	Group 1+3 Without significant side effects (%)	Group 2+4 With significant side effects (%)	P value
Total population	116	28	45	0.052
Caucasians	113	24	45	0.019
Diagnosis (ICD-10 F20-29) ¹	90	26	47	0.038
Females	48	38	38	1
Males	68	22	52	0.011
Using strong DRD2 drugs	71	25	58	0.005
Females using strong DRD2 drugs	32	38	50	0.476
Males using strong DRD2 drugs	39	17	67	0.002

¹Schizophrenia and delusional disorders.

Studies have also indicated that Ins/Ins homozygous subjects may have lower dopamine D2 receptor density in the striatum than those with one or two Del alleles, although the results were not conclusive (Jonsson, et al. 1999; Pohjalainen, et al. 1999). Our study did not indicate any relationship between the Ins/Del polymorphism and treatment outcome except for the subgroup comprising males using strong dopamine D2 receptor binding drugs, which showed higher rates of the Ins/Ins genotype in patients with significant side effects (93% in Group 2+4) compared to those without (63% in Group 1+3; $p=0.032$). Results from other clinical studies concerning the impact of the Ins/Del polymorphism on psychotic symptoms and side effects have been inconclusive (Arranz, et al. 1998; Himei, et al. 2002; Hori, et al. 2001; Mihara, et al. 2002; Ohara, et al. 1998; Suzuki, et al. 2001). More studies are required to clarify the impact of the Ins/Del polymorphism on antipsychotic treatment response.

In our study, there were too few (only three) mutations of the *DRD2* polymorphism Ser311Cys to investigate a possible difference between patients with the Cys311 and Ser311 alleles. Earlier studies, however, have indicated that patients with the Cys311 allele have significantly fewer positive and negative symptoms (Himei, et al. 2002), require shorter lengths of stay in hospital (Arinami, et al. 1994) and are less likely to be resistant to typical antipsychotic drugs than patients without the Cys311 allele (Shaikh, et al. 1994). Studies with patient samples larger than ours are required to assess a possible correlation between the Ser311Cys polymorphism and treatment response.

Our study did not find any association between the patient groups and the polymorphisms *HTR2A* 102T/C or *HTR2C* Cys23Ser with respect to either therapeutic effectiveness or side effects. A significant association between failure to respond to clozapine and presence of the 102C allele of the *HTR2A* gene was reported in 1995 in patients with chronic schizophrenia (Arranz, et al. 1995; Williams, et al. 1996). These results have not been replicated by other studies, including ours (Lin, et al. 1999; Malhotra, et al. 1996; Masetlis, et al. 1998; Nothen, et al. 1995). The 102C/C genotype did, however, tend to be more frequent in male non-responders than in male responders in one study (Joober, et al. 1999). The 102C allele has also been associated with the incidence of tardive dyskinesia following use of antipsychotic drugs (Segman, et al. 2001; Tan, et al. 2001). These results were not repeated in our analysis of side effects, although tardive dyskinesia was not studied as a separate symptom. The Ser allele of the serotonin receptor *HTR2C* polymorphism Cys23Ser has also been associated with an increased frequency of tardive dyskinesia (Malhotra, et al. 1996; Segman, et al. 2000).

Pharmacokinetic gene polymorphisms

A large number of studies have investigated associations between *CYP2D6* polymorphisms and the steady-state serum concentrations, effects and side effects of various antipsychotic drugs. The contribution of *CYP2D6* to the pharmacokinetics of different antipsychotic drugs varies, and the studies with outcome data give variable results (Armstrong, et al. 1997; Dahl 2002; Kapitan, et al. 1998; Scordo, et al. 1999; Yasui-Furukori, et al. 2002). In our study, the only related association was the tentative association between extensive metabolizers and therapeutic effectiveness. Patients without significant social and clinical needs were more often extensive metabolizers (67%) than those with significant needs (46%; $p=0.023$). One reason for the low correlation between the *CYP2D6* phenotype and the treatment outcome seen in this study might be the nominally significant correlation between the phenotype and the mean antipsychotic drug dose. This showed that poor metabolizers had only received approximately half the mean dose (2.4mg mean haloperidol equivalent dose) of that given to the intermediate, fast or ultra rapid metabolizers (4.5-5.8mg mean dose; $p=0.012$). This may have been due to the doctor monitoring the effects and side effects and compensating for the slower metabolism in poor metabolizers by giving them a lower mean dose.

Transporter gene polymorphisms

The 3435C>T polymorphism in exon 26 of the *ABCB1* gene seems to be related with alterations of the substrate specificity, which has for example been shown for digoxin (Hoffmeyer, et al. 2000). No associations between drug response and the *ABCB1* 1236C>T and 26677G>T/A polymorphisms were discerned in our study. The association between drug response and the 3435C>T polymorphism in patients on olanzapine was significant, but was not seen in patients on other antipsychotic drugs. Patients on olanzapine who were homozygous for 3435T occurred more often in the groups with significant needs (71%) compared to those without significant needs (14%; $p=0.002$). This suggests that the transport of olanzapine involves P-glycoprotein ABCB1. However, in vitro studies have shown that olanzapine only has an intermediate affinity to P-glycoprotein compared with for example risperidone, which is a relatively good P-glycoprotein substrate (Boulton, et al. 2002; Wang, et al. 2006). Further studies are needed to further investigate the in vivo correlation between olanzapine pharmacokinetics and *ABCB1* genotype.

Antipsychotic drug treatment (Paper III)

This study analyzed the antipsychotic drug treatment of psychotic patients in a naturalistic setting in Sweden, focusing on the patients' current treatment outcomes. One of the main results of this study indicates that the initial duration of untreated prodromal and early psychotic illness (DUI) in a patient can affect the outcome even after 20 years.

Retrospective drug use

The time between first contact with psychiatric care and the first prescription of an antipsychotic drug was more than twice as long for patients with significant social and clinical needs [3.8 (4.8) years] as for those without significant needs [1.6 (2.3); $p=0.006$]. The time delay was 2.6 (4.0) years for the patients with schizophrenic or delusional disorder and 2.6 (4.0) years for those with other diagnoses (n.s.), which indicates that the difference in outcome was not attributable to differences in diagnosis. For the subgroup of patients who had been receiving antipsychotic medication for ≥ 20 years, the delay in treatment initiation was more than four times as long for those with significant needs [4.9 (5.5) years; $n=34$] as for those without significant needs [1.2 (2.0) year; $n=23$; $p=0.003$]. Thus, long term treatment outcomes can be adversely affected by the DUI not only when the DUI is decades long, as reported in earlier studies (Scully, et al. 1997; Waddington, et al. 1995), but also when it is relatively short, as seen with the 3-year DUI for the total study population in this study.

The DUI was not correlated with the total duration of antipsychotic drug treatment or the current appearance of negative, positive, depressive or excitatory symptoms (as measured by the PECC rating scale; each parameter $R^2 < 0.05$; $p > 0.05$). There was, however, a positive correlation between DUI and the appearance of current cognitive symptoms (according to the PECC rating scale; $R^2 = 0.069$; $p = 0.019$), with more severe cognitive deficits in patients with longer DUI. This trend remained after analysis of the subgroups with schizophrenia or delusional disorders. The corresponding results from related shorter studies have varied from impairment of most aspects of the patients' lives to no correlation at all (Barnes, et al. 2000; Clarke, et al. 2006; Edwards, et al. 1998; Haas, et al. 1998; Larsen, et al. 1998; Lieberman, et al. 2001; Loebel, et al. 1992). There have been two studies investigating long term treatment outcomes in patients with an extensive period of untreated psychosis (due to onset of illness before the first market authorisation of antipsychotic drugs). Both these studies showed a correlation between the duration of untreated psychosis and negative and cognitive but not positive symptoms (Scully, et al. 1997; Waddington, et al. 1995). This, along with the results of our study, indicates that cognitive impairment can be apparent decades after a longer initial duration of untreated illness. The decline in

cognitive function often seen in psychotic patients has been shown predominantly to occur in the early phases of the illness, followed by a more stabilized phase with less deterioration (Lieberman, et al. 2001). It has been suggested that antipsychotic drug treatment diminish the deterioration of psychotic patients (Lieberman, et al. 1997; Wyatt 1991). Thus, early treatment with antipsychotic drugs might lessen cognitive decline during the crucial initial years when most of the deterioration usually occurs. Early initiation of treatment could in turn result in less severe cognitive deficits even after 20 years of illness, as seen in this study. All opportunities to diminish the deterioration of psychotic patients should, of course, be encouraged. There is thus a need for a better and more precise way of establishing people at risk of developing psychosis, so that antipsychotic treatment can be started in the very early stages so as to improve the future prospects of these patients.

Current psychotropic drug use

Patients with significant social and clinical needs took higher mean antipsychotic drug doses [5.7 (3.9) mg haloperidol equivalents] than those without significant needs [3.4 (2.3) mg haloperidol equivalents; $p < 0.001$]. This result was not surprising, since the patients with significant needs, by definition, were more severely hampered by their illnesses and therefore required more support and treatment. The average dosage for the total study population [4.6 (3.4) mg haloperidol equivalents; Table 9] was similar to dosages reported in previous studies in Sweden (Bingefors, et al. 2003; Cullberg, et al. 2006; Kiivet, et al. 1995; Lindstrom, et al. 1996).

The comparative proportions of first and second generation antipsychotic drugs in the whole study population, 39% and 63% respectively (the figures do not add up to 100% because some patients were receiving both first and second generation drugs), were similar to those in earlier studies (Hanssens, et al. 2006; Luo, et al. 2002). Patients without significant social or clinical needs used first generation antipsychotic drugs less often (24%) and the second generation antipsychotic drug risperidone more often (35%) than those with significant needs (53% and 10% respectively; $p < 0.01$). Interpretation of these results is difficult. The higher use of first generation antipsychotic drugs in the group with significant needs could be interpreted as a sign of failure of treatment effect, but could also be interpreted as indicative of the empiric superiority of these drugs, resulting in their choice for patients in whom previous treatment had failed. The cross-sectional approach of this study does not allow inference of a causal relationship.

The use of depot antipsychotic drugs in the whole study population (27%) was also similar to that in an earlier study (Citrome, et al. 1996). The use of antiparkinsonian drugs (21% in this study) differs widely among studies, with a range of 5-67% (Acquaviva, et al. 2005; Buchanan, et al. 2002; Haro and Salvador-Carulla 2006; Kiivet, et al. 1995). The lower requirement for

antiparkinsonian drugs in Sweden may be the result of the relatively low doses of antipsychotic drugs used in this country.

Table 9. Current use of antipsychotic drugs in the CANSEPT groups and the total study sample.

	Group 1 (functional remission) (n=38) [result (SD)]	Group 2 (significant side effects) (n=20) [result (SD)]	Group 3 (significant social/clinical needs) (n=27) [result (SD)]	Group 4 (significant side effects and needs) (n=32) [result (SD)]	Total study sample (n=117) [result (SD)]	P value^a
1 st generation AP (%)	28.9	15.0	55.6	50.0	38.5	P=0.011
2 nd generation AP (%)	63.2	85.0	55.6	56.3	63.2	P=0.143
Clozapine (%)	7.9	15.0	14.8	18.8	13.7	P=0.608
Risperidone (%)	28.9	45.0	11.1	9.4	22.2	P=0.007
Olanzapine (%)	26.3	25.0	25.9	21.9	24.8	P=0.976
Ziprasidone (%)	2.6	0.0	3.7	6.3	3.4	P=0.668
Depot AP (%)	18.4	25.0	25.9	40.6	27.4	P=0.217
Patients taking 2 AP (%)	5.3	5.0	18.5	12.5	10.3	P=0.283
Haloperidol equivalents (mg)	3.5 (2.5)	3.3 (2.2)	5.9 (3.9)	5.4 (3.9)	4.6 (3.4)	P=0.002
Self-stated non-adherence >once a month (%)	15.8	20.0	25.9	19.4	19.8	P=0.795
<50% of minimal therapeutic serum levels (%)	14.7	38.9	8.0	20.7	18.9	P=0.069

AP= Antipsychotic drugs

^a The p values were calculated for continuous variables using the Mann Whitney U test for continuous variables and the Pearson Chi-square test for categorical variables

Antipsychotic drug intake/adherence

Twenty percent of the study population reported being non-adherent to their drug regimen more than once a month (Table 9) and 16% were non-adherent at least once a week with no differences between the CANSEPT groups. This was in the lower range of the non-adherence seen in earlier studies (Cramer and Rosenheck 1998; Lacro, et al. 2002; Weiden, et al. 2004). The method of self-reporting non-adherence to treatment used in this study appears to correlate relatively well with true adherence according to other studies (Boczkowski, et al. 1985; Rickels and Briscoe 1970).

Of the patients in the group without significant side effects, Group 1+3, 12% had less than half the minimum therapeutic serum concentration of their antipsychotic drug. In the group with significant side effects, Group 2+4, more than twice this number, 28%, had less than half the minimum therapeutic

tic serum concentration ($p=0.039$). It is intriguing that the patients with current significant side effects were also least adherent to their treatment regimens, as indicated from the serum drug concentration results. It is suggested that the two-fold higher occurrence of non-adherence in this group could have been due to intermittent non-adherence as a result of an aversion to the drugs because of their disabling side effects. Intermittent non-adherence could lead to low drug concentrations while still resulting in significant levels of side effects.

Knowledge, Insight and Social Networks (Paper IV)

In this study, the associations between social networks, insight into and knowledge of illness, drugs and extent of coping were analyzed according to functional remission for psychotic patients in a naturalistic setting in Sweden.

Social networks

The patients in functional remission (FR; Group 1) generally had more positive relationships in their social sphere than those not in functional remission (non-FR; Group 2+3+4). The FR group had, compared to the non-FR group, more acquaintances classified as important [5.3 (3.4) people vs 3.6 (3.1) people in the respective groups; $p=0.002$], supportive [3.6 (3.2) vs 2.6 (2.8); $p=0.047$] or nice [5.9 (3.4) vs 3.9 (3.1); $p<0.001$; Figure 5]. A significant difference was also seen between the groups in the total number of positive personal relationships, defined as relationships with people not from the psychiatric care unit who were seen as important, supportive or nice; 6.0 (3.7) in the FR group vs 4.1 (3.2) in the non-FR group ($p=0.002$). The higher incidence of positive relationships for those in functional remission could be either a causal effect of their superior level of social ability or the converse, i.e. because of greater support from their social networks, as indicated from earlier studies (Eklund and Hansson 2007; Erickson, et al. 1989; Nordt, et al. 2007; Peralta, et al. 2005; Pitschel-Walz, et al. 2001; Rymaszewska, et al. 2007). The causality has been difficult to investigate in other studies as well as in this one, but there seems to be a dynamic influence from two directions with regard to social interactions (Eklund and Hansson 2007).

The patients in the non-FR group not only had fewer positive relationships than those in the FR group but also tended to label more people in their social network as annoying [0.2 (0.4) in the FR group vs 0.4 (0.7) in the non-FR; n.s.] or as someone they would like to see less of [0.1 (0.3) vs 0.2 (0.5); n.s.]. The difference between the groups with respect to people labeled as annoying was statistically significant for women patients (0.1 (0.3) vs 0.6 (1.0); $p=0.048$). This difference was not seen for men; 0.2 (0.4) people were

classified by men as annoying in both groups. The trend for a higher rate of negative relationships in the non-FR group could be due to their inability to handle negative relationships or to their suspicious/paranoid view of other people. Further, negative psychotic symptoms themselves have the potential for decreasing the social skill levels and hence affecting social networks (Hamilton, et al. 1989; Macdonald, et al. 1998). Repeated relapses in a chronic illness could also strain relationships in the patient's social sphere and vocational network (Halper 2007). Becker et al. have demonstrated that a social network of 10 to 12 people is optimal for maximizing the psychotic patient's quality of life, with poorer results for smaller or larger social networks (Becker, et al. 1998). The overall mean number of people in each patient's social network was 5.9 (3.3). This value was higher in the FR group than in the non-FR group (7.1 (3.5) vs 5.3 (3.1); $p=0.005$). The mean size of the social networks of patients in our study is smaller than the optimal number, indicating a need for social support interventions for this patient group, especially for the non-FR group, as demonstrated by Hogan et al. (Hogan, et al. 2002).

This study found no relationship between the size of the social network and the diagnosis ($p=0.983$) but did find a relationship between the size of the social network and the incidence of functional remission ($p=0.005$). This is in line with a recent study which demonstrated a link between social functioning and the severity of psychopathological symptoms but not the diagnosis of a mental disorder per se (Rymaszewska, et al. 2007).

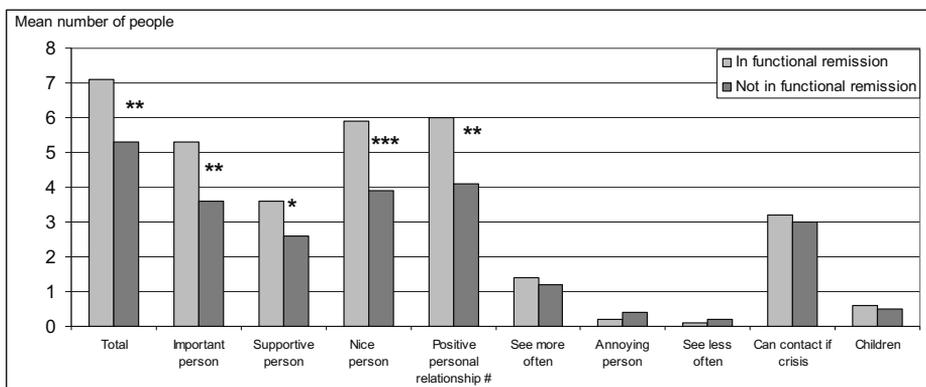


Figure 5. The number of members in the social networks of psychotic patients in functional remission or not in functional remission. Members of the patient's social network could be considered for more than one role.

Positive personal relationships: people the patient regarded as important, supportive and/or nice, who were not part of the patient's care team.

* <0.05

** <0.01

*** <0.001

Knowledge and insight

Sixty-six percent of the patients in our study knew what their symptoms were, 68% knew they were regarded as having psychotic features but only 19% saw a correlation between their symptoms and their diagnosis. This shows that their knowledge of their individual symptoms was deeper than their insight into the relationship between their symptoms and the diagnosis. The proportion of patients with this insight was also much lower than the 60-83% with insight of illness reported in an earlier study (Saeedi, et al. 2007). This lower rate could have been due to the high proportion of chronically psychotic patients in our study, while the earlier study investigated psychotic patients at first admission. The definition of insight can also differ widely. Nonetheless, the incidence of insight was much higher in the FR group (37%) than in the non-FR group (10%; $p=0.001$). A better outcome for patients with good insight into their illness has also been noted in other studies (Drake, et al. 2007; Saeedi, et al. 2007). The better outcomes could have resulted in improved cognitive capacity or may have been due to a greater awareness of the illness and subsequently more positive acceptance of any kind of treatment.

About half as many patients in the non-FR group (26%) as in the FR group (50%) were able to recognise their warning signs, and about three times as many had no plan of action when these warning signs occurred (23% in the non-FR group vs 8% in the FR group; $p=0.046$). A similar, but not statistically significant, trend was seen for residual symptoms; fewer patients in the non-FR than in the FR group knew about their residual symptoms and how to handle them. This indicates that coping strategies could be correlated with outcomes. While Carter and co-workers failed to show a relationship between coping strategies and outcomes (Carter, et al. 1996), there were differences between the studies that were of potential relevance. The Psychosis Outpatient Care Clinic in Jönköping had been attempting to teach patients to seek help in response to the appearance of warning signs, while the coping strategies in the study by Carter et al. were made up by the patients themselves. A theory to explain the difference between the groups in the present study is that unawareness of a coping strategy could lead to greater worsening at time for relapse and hence give worse treatment outcomes. The proportion of patients with a realistic/optimistic view of the future was almost twice as high in the FR group (47%) as in the non-FR group (28%; $p=0.042$). This was probably due to their better current quality of life but may also have been related to their level of state optimism, since optimism as a personal trait has been associated with positive outcomes (Nes and Segerstrom 2006).

Fifty-five percent of the patients in this study did not know the name or the dosage of their drugs; previous studies have reported similar results (56-72%) (Clary, et al. 1992; Geller 1982; Macpherson, et al. 1993). The propor-

tion of patients who knew the names of their drugs was higher in the FR group (95%) than in the non-FR group (72%; $p=0.004$). More patients in this group also knew the advantages of taking their prescribed drugs (61% vs 37%; $p=0.018$), possibly because they had experienced more positive effects from their medication. An understanding of the advantages of a drug are probably a prerequisite for a placebo response, so patients in the FR group might have experienced a greater placebo response (and thus a better outcome) as a result of a wider knowledge of their drugs. A number of studies have demonstrated a clinical effect due to placebo (Johansen, et al. 2003; Link, et al. 2006). However, although there was no statistically significant difference between the groups in an understanding of potential side effects (29% vs 14%; $p=0.056$), there was a trend indicating that the FR group was also better informed in this respect. Thus, the higher proportion of patients who were aware of both the positive and negative effects of their drugs in the FR group suggests more that there may have been a difference in cognitive ability between the groups than that the difference in outcome was due to attitudes influencing the placebo/nocebo effect.

Conclusion

CANSEPT is a useful, valid, multidimensional tool for classification of treatment response. Gene polymorphisms, duration of untreated illness, non-adherence to treatment, extent of social networks and relevant knowledge are related to treatment outcomes.

- I The investigation of CANSEPT showed that this is a valid method for classifying psychotic patients in a naturalistic setting according to treatment response expressed as functional remission. The method could therefore be a useful tool for classifying patients with regard to treatment response both in clinical care and in research.
- II Prescription of olanzapine or clozapine, rather than strong dopamine D2 receptor antagonists, to Taq1 A1 allele carriers seems wise, in order to decrease the risk of significant side effects. Furthermore, it is suggested that patients carrying the *ABCB1* 3435T/T genotype should avoid olanzapine. If our results are confirmed, clinical antipsychotic guidelines may need to be updated with pharmacogenetic-based recommendations.
- III A longer duration of untreated prodromal and early psychotic illness is related to worse long-term outcomes, especially with respect to cognitive impairment. This emphasizes the need for good guidelines for the identification of at-risk patients followed by fast initial antipsychotic treatment. Significant side effects could be related to non-adherence to antipsychotic drug treatment regimens, stressing the need to monitor for the lowest effective dose for each individual to minimize significant side effects and hence increase adherence to treatment.
- IV Patients with psychosis, especially those not in functional remission, often have a smaller number of people in their social networks than required for well-being. Other parameters which seem to be associated with not reaching functional remission include a poorer insight into the illness, a poorer knowledge of warning signs, lack of a coping strategy when symptoms recur and a less realistic/positive view of the future. Patients not in functional remission also seem to know the names, doses and advantages of their antipsychotic drugs to a lesser extent than those in functional remission.

Future perspectives

In the future, it is hoped that we will see a greater proportion of psychotic patients in functional remission. This will probably not be achieved by one single solution, but could come about as a result of a number of contributing events. Examples of these include:

- The drug industries will focus more on functional remission during their clinical trials, e.g. by using the CANSEPT method.
- Most psychotic patients will be genotyped for different polymorphisms related to treatment response, e.g. *DRD2* Taq1 A and *ABCB1* 3435C>T, and treated in concordance with their genotype.
- An effective discrimination tool will be developed that will assist the providers of psychiatric care to recognize and react to the prodromal symptoms of psychosis, resulting in earlier drug treatments.
- New drugs, especially those aiming to reduce side effects and the cognitive deficits, will be developed for patients with psychosis, e.g.:
 - NMDA agonists and glycine agonists could be of interest, since a dysfunction in glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptors appears to be associated with psychiatric diseases (Banerjee, et al. 1995; Hashimoto 2006; Wood 2005).
 - Partial serotonin 5HT 1A receptor agonists could be developed as a result of recent evidence linking 5HT1A receptors with the cognitive deficits of schizophrenia (Meltzer and Sumiyoshi 2008; Millan 2000).
 - Balanced partial dopamine and serotonin agonists could result in less extrapyramidal symptoms, prolactin increase, metabolic symptoms and heart problems (Ben-Jonathan and Hnasko 2001; Blair and Dauner 1992; Calle, et al. 1999; Glassman and Bigger 2001; Scheen and De Hert 2007).
- More rehabilitating health care measures with focus on enhancing the cognitive capacity and insight of the patient and to increase their social interactions.

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