Lars Helldin

The Importance of Remission in the Treatment of Patients with Schizophrenia Spectrum Syndromes

Clinical Long-term Investigation of Psychosis in Sweden
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To my wife Inga and my daughters, Maria and Malin, who always have been supportive and understanding during long hours for many years.
Abstract

The goal of this thesis was to investigate the hypothesis whether symptomatic remission for patients with schizophrenia spectrum syndrome would provide practical and qualitative benefits for patients and for society.

The first work (Paper I) examines the relationship between cross-sectional remission and the patients' practical resources. The patients' adaptations to society as well as their employments, living situations and social networks were studied. Their activity of daily living resources are described in terms of the extent to which they could pursue various undertakings autonomously. Their need for care was also studied. The results showed that the patient group that had achieved remission scored better on all of the variables studied, had better resources and less need for medical care and sheltered housing.

The second work (Paper II) analysed the relationship between cross-sectional remission and quality of life, burden placed on patients by the illness, and the patients' satisfaction with care received and with their medication, and also their capacity for understanding their symptoms and their illness. Even the results of this study showed that the patients in the remission group had a better quality of life, bore a lesser burden, were more satisfied with their care and had better insight into their illness.

The third work (Paper III) studied the patients' neurocognitive capacity to see if a higher capacity resulted in a higher percentage of patients achieving remission. The results showed unequivocally that the patients
in remission consistently performed better in the cognitive tests. They also showed that they even had a larger vocabulary indicating a higher premorbid capacity.

The fourth work (Paper IV) followed the patients over an average time of 65 months. In this study, the patients’ needs for medical care and for housing were investigated. Patients who were not in cross-sectional remission at baseline had for all the measured variables a higher consumption than those in remission even if the differences were not significant, except for patients who lived in sheltered housing and who had greater need for medical care.

Taking all these findings together, the result of this thesis shows that the attainment of remission provides practical and qualitative advantages to the patients and to society.

Keywords: Schizophrenia spectrum syndrome, functional outcome, quality of life, neurocognitive performance and need of care.
Sammanfattning

och hans/hennes journal har vi valt att definiera de patienter som uppnått remission som cross-sectional.


Det andra arbetet (**Paper II**) analyserade förhållandet mellan cross-sectional remission och livskvalitet, bördan till följd av sjukdomen, patienternas nödighet med sin erhållna vård och medicinering samt slutligen deras förmåga att förstå symptomen och sjukdomen. Resultaten visade även i detta arbete att patienterna i remissionsgruppen uppvisade en bättre livskvalitet, en lägre börda, var nöjdare med vården och hade en bättre sjukdomsinsikt.

Det tredje arbetet (**Paper III**) undersökte patienternas neurokognitiva förmåga och om en högre förmåga medför att dessa patienter i större omfattning uppnått cross-sectional remission. Resultaten visade entydigt att de patienter som var i remission också genomgående presterade bättre i de kognitiva testerna. Dessutom att de även hade ett större ordförråd vilket indikerade en högre premorbid förmåga.

Det fjärde arbetet (**Paper IV**) följde patienterna under en genomsnittlig tid av 65 månader. I denna studie undersöktes patienternas behov av sjukvårds- och boendestödsinsatser. Resultaten var i detta arbete inte lika entydiga. Trots detta så hade i alla mätta variabler de patienter som inte var i cross-sectional remission vid baseline en högre konsumtion. Skillnaden var signifikant för andelen av patienter som hade skyddat boende och totalt antal timmar som de haft behov av vårdinsatser från kommun och sjukvård sedan mätperiodens början.
Sammantaget talar resultaten i avhandlingen för att uppnådd remission medför praktiska och kvalitativa fördelar för patientgruppen och samhället. Vi ser också ett samband mellan förmågan att uppnå remission och patientens kognitiva förmåga. Värdet av att patienter som tidigare inte varit i remission men som till följd av ytterligare insatser kommer att vara det är ännu inte utrett. Likaså kräver sambandet mellan remission och patientens förmåga ytterligare studier då det finns patienter som fungerar dåligt trots att de är i remission. Omvänt finns det en mindre andel patienter som fungerar bra utan att de uppnått remission. Framtida arbeten behöver därför bland annat ta fasta på sambanden mellan patienternas kognitiva förmåga, om de nått fram till remission och deras allmänna funktionsnivå.

Nyckelord: Schizofreniform sjukdom, funktionell förmåga, livskvalitet, neurokognitiv förmåga och behov av sjukvårdsinsatser
The thesis is based on the following four research papers, which will be referred to in the text by their Roman numerals:


IV Helldin L, Kane J. M., Hjärthag F, Karilampi U, Norlander T. The Importance of Cross-sectional Remission in Schizophrenia for long-term outcome; a clinical prospective study. (Submitted)

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1. INTRODUCTION

1.1 Background

Both historically and methodologically there has always been – and there remains today – a strong connection between psychology and psychiatry. Ever since the panorama of schizophrenia spectrum disorder was described by Kraepelin (Kraepelin, 1907; Kraepelin, & Robertson, 1919) as *dementia praecox* and, by Bleuler, as schizophrenia (Bleuler, 1911) research has been characterized by this parallelism. The observations that formed the basis for the hypothesis of *dementia praecox* extended back several decades in time before publication of these articles. The method of classification was typical of this period. By studying the course of the sickness in a large number of patients for whom there was, at the time, no form of treatment, a system for classifying the symptoms was developed that became the basis for a variety of diagnoses. The name for schizophrenia, *dementia praecox*, referred to the chronic course of events with a very poor prognosis and also to the idea that the illness was a dementia-like condition in which the brain regressed back in time from the higher level that had been attained. Even if the research was carried out by physicians, it had much in common with contemporary psychological research, which was also, in reality, carried out largely by physicians. This research may be described as both humanistic (with introspective elements in some cases) and positivistic, which is to say founded on an empirical perceptual view (Miller, 1983). Through the systematisation of the various states of the illness, a foundation was created for a common point of view and for systematic interventions to deal with these conditions.

The treatment of patients took place in mental hospitals and in many cases continued from early adulthood until death (Ottoson, 2003). During the period when the patient was agitated because of his psychotic illness,
a series of measures were taken to moderate these symptoms, measures such as isolation, a warm bath, wrapping the patient in wet sheets and various forms of physical restraint, all of which were of little benefit. Electro-convulsive treatment became part of the arsenal of treatment methods during the 1930s. Lobotomy and insulin-shock therapy were surgical and chemical interventions that were intended to modify the patient’s behaviour either permanently or temporarily. Pharmacologic methods in the form of slow-acting barbiturates and a variety of other drugs were regularly used to deal with anxiety and difficulty in sleeping. All these methods had in common that there was no scientific basis for using them, that the effects were quite limited, and that the illness essentially went on its own way causing greater or lesser psychotic outbreaks.

1.1.1 The introduction of antipsychotic medication

It was not until the 1950s that the first drug, chlorpromazine, appeared that had an effect on the psychotic symptoms (Hibernal, 1954). Even if the mechanism of action of the drug was not clear when Delay and Deniker found the antipsychotic effect in 1953 it later stood clear that chlorpromazine acted on the production of dopamine in the brain, creating a block that over time decreased the occurrence of hallucinations and delusions, the so called positive symptoms. The improvement was, however, not long lasting but was limited to the period during which the drug was being taken. In spite of the fact that treatment did not actually provide a cure, it nevertheless did represent a step towards a scientific paradigm shift of the sort that Kuhn’s concept of paradigm shift represented (Kuhn, 1962). This progress made it possible in part to alleviate the symptoms that were present, and, in addition, to limit their re-occurrence. In contrast with the previously prevailing situation, an effective treatment that radically changed the nature of treatment of schizophrenia now was available. Several psychoactive drugs followed the introduction of chlorpromazine, and, during the 1970s, the first preparation – depot – that acted over a long time interval was introduced. This was administered by injection, with the interval between injections being as much as
four weeks (Quraishi, & David, 2000). The array of available drugs was divided into two groups, high-potency and low-potency neuroleptics respectively (Zavodnick, 1978), and then in the 1980s, an entirely new generation of drugs was introduced, drugs characterized by a broader binding to receptors. Clozapine (Gudelsky, Nash, Berry, & Meltzer, 1989) was the first drug to signal this change. Dopamine had been the primary target for the first drugs; now also serotonin became the target for the new drugs. Serotonin was associated with the social incompetence and lack of energy that appeared when the positive symptoms petered out. It was not until the 1990s that a number of the drugs that now are completely dominant in the treatment of the illness first appeared, drugs that have all been developed to meet the goal of providing for a broader binding to receptors (Creese, 1983; Kapur, & Remington, 2001; Tandon, & Jibson, 2003). In addition to dopamine and serotonin, there is a series of hormone systems with several different subgroups that are attracting the attention of researchers and where especially glutamate may play an important role (Conn, Lindslev, & Jones, 2009; Goff & Wine, 1997) In the field of research on psychoactive drugs, a meeting is taking place between the science dominated by chemical and physiological approaches and the behavioural science that is making evaluations of the utility of the pharmacological interventions that are employed. Since schizophrenia cannot be the subject of objective measurements comparable with x-ray investigations, blood-pressure measurements, or tracing bacteria, one is instead referred to a systematic follow up, using validated instruments to measure predetermined parameters. This mode of operation entails a meeting between the methods of positivistic natural science and those of the humanities.

1.1.2 Treatment issues after the introduction of medication

If the 1950s were marked by the goal of eliminating the patients' psychotic symptoms, the 1960s and 1970s were characterized by the dramatic decrease in the number of mental hospitals and, with that a decrease in the occurrence of life-long hospitalisation. This development was a
direct consequence of the new medications that put some limits to the expression of the most acutely visible symptoms of the illness, and this in turn made it possible to release these patients into society where new types of medical care were being developed. In 1962, the first evaluation scale, the Brief Psychiatric Rating Scale (BPRS) (Overall, & Gorham, 1962) was presented, and this scale made it possible for the first time to follow both the course of the illness and the effects of different methods of treatment. The BPRS especially focused on the positive symptoms such as hallucinations and delusions and to a lesser extent on the negative, i.e. blunted affects and social withdrawal.

In the 1980s, the goal became to limit the number of recurrences of the illness since it had been observed that patients had shown beneficial effects of treatment but that they still experienced repeated relapses when they stopped taking their medicine (Laessle, Pfister, & Wittchen; 1987; Robinson, Woerner, Alvir, Bilder; et al., 1999). There were several reasons why the patients stopped taking their medicine. One reason that the patients had a negative view of these drugs even though the drugs accomplished a visible decrease in symptoms was the occurrence of side effects, particularly when high-potency substances were used, side effects that affected the patient’s motor functions and emotions. The disturbances in motor functions had many similarities with Parkinson’s disease. As concerned emotional side effects, it was as if a glass bowl had been placed over the patient’s head, thus causing severe limitations on the patient’s ability to socially function in society. The side effects were most noticeable when the psychotic symptoms had subsided and then the patient began to feel that the medication did more harm than good.

Toward the end of the 1980s and at the beginning of the 1990s, the negative symptoms became of central interest, both those that were inherent in the illness and those that were caused by taking the various forms of medication. During the 1980s, additional evaluation scales appeared, among them the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, & Olsen, 1982) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) as well as the Positive and
Negative Syndrome Scale (PANSS) (Kay, Fitzbein, & Opler, 1987; Kay, & Opler, 1987; Kay, Opler, & Lindenmayer, 1988; Lindström, Wieselgren, & von Knorring, 1994). These focused on the complexity of the illness and took into account not only the positive and negative symptoms but also the general psychiatric symptoms. These evaluation scales provided the potential for developing a more objective and nuanced view of the illness and its treatment. They represented on the one hand an expression of the changing views of the illness that were appearing within the society and, on the other hand, they contributed to a systematisation that strongly affected the way that the medical system viewed the complexity of the illness and its consequences.

1.1.3 The importance of neurocognition

During the second half of the 1980s, there was an almost explosive development of understanding of neurocognitive restrictions on function that are a part of the illness. Cognitive disturbances among patients with schizophrenia have been demonstrated in a series of studies (Hoff, Sakuma, Wienke, Horon, et al, 1999; O’Leary, Flaum, Kesler, Flashman, et al., 2000; Riley, McGovern, Mockler, Doku, et al., 2000). Many studies have described small patient populations or involved small effect size and/or weak power. In order to deal with these limitations, meta-analyses have been performed that support the strength of these findings (Green, 1996; Green, Kern, Braff, & Mintz, 2000). Above all, four cognitive processes have been emphasized as deserving observation with regard to the development of the disorder: vigilance, working memory, long-term memory and executive functioning (Gold, Randolph, Carpenter, & Goldberg, 1992; Harvey, & Pedley, 1989; Harvey, & Sharma, 2002; McGrath, Scheldt, Welham, & Clair, 1997; Paulsen, Heaton, & Sadek, 1995). Other processes identified as especially important are learning performance (Paulsen, Heaton, & Sadek, 1995), visuomotor speed/efficacy, cognitive flexibility and pre-morbid functioning (Addington, van Mastigrt, & Addington, 2003; Caspi, Reichenberg, Weiser, Rabinowitz, et al, 2003; Fuller, Nopoulos, Arndt, & O’Leary, 2002; Heaton, Gladsjo, Palmer, Kuck, et al., 2001).
These processes are associated with the progress and prognosis of the disorder (Addington, & Addington, 2000; McGurk, Moriarty, Harvey, Parrella, et al., 2000; Weickert, Goldberg, Gold, Bigelow, et al., 2000). Intensive research on cognitive functioning has redirected the clinical focus to paying attention not only to positive and negative symptom profiles, but also to cognitive abilities. In particular, the importance of the implications of positive symptom profiles for prognosis has been reduced, since during the last two decades it is the negative symptom profiles that have come to occupy a central role (Fenton, & McGlashan, 1991; McGlashan, & Fenton, 1992).

In keeping with the recognition of the importance of neurocognitive capacity, a large number of evaluation instruments and tests have been produced. These are not all in agreement with one another, and, in addition, the possibility of different choice of tests have made it difficult to compare results. In an effort to standardize neurocognitive assessments, the National Institute of Mental Health (NIMH) developed the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), the MATRICS Consensus Cognitive Battery (MCCB) (Green, Nuechterlein, Kern, Baade, et al., 2008; Kern, Nuechterlein, Green, Baade, et al., 2008; Nuechterlein, Green, Kern, Baade, et al., 2008).

At the same time, neuroanatomical visualization techniques such as computer assisted tomography and magnetic resonance tomography were developed. These techniques made it possible to demonstrate that the changes in the anatomy of the brain of schizophrenic patients had a broad variation including changes in the brain’s volume (Delisi, 1999; Milev, Ho, Arndt, Nopoulos, et al., 2005) and changes in the structure of white and grey matter (Job, Whalley, Johnstone, & Lawrie, 2005; Mitelman, Shihabuddin, Brickman, Hazlett, et al., 2003; Szeszko, Ardekani, Ashtari, Kumra, et al., 2005) such as regionally localised thinning in the prefrontal and temporal cortex (Kuperberg, Broome, McGuire, David, et al., 2003; Vidal, Rapoport, Hayashi, Geaga, et al., 2006). These changes in the anatomy of the brain are also correlated with different expressions of the illness (Mathalon, Sullivan, Lim, & Pfefferbaum, 2001) and the prog-
nosis of the disorder (Ho, Andreasen, Nopoulos, Arndt, et al., 2003; van Haren, Cahn, Hulshoff Pol, Schnack, et al., 2003). These findings do not correspond with the picture of neuroanatomical changes in dementia. The psychometric research dealing with neurocognitive capacity and the neuroanatomical findings together finally established that schizophrenia was not similar to dementia, as it was originally proposed by Kraepelin (Andreasen, 1997).

1.1.4 Studies of patients in pharmaceutical research and cohorts

A large part of the research that has contributed to the present-day state of knowledge has its roots in the development of psychotropic drugs. As a consequence of this situation, there are several limitations on the selection of patients who could be studied (Hofer, Hummer, Huber, Kurz, et al., 2000; Riedel, Strassing, Müller, Zwich, et al., 2005; Robinson, Woerner, Pollack, & Lerner, 1996). Each study has established criteria that must be met if the patient is to be allowed to participate. There are also a number of exclusion criteria, any one of which if met is sufficient reason for exclusion of the patient. For example, if a woman could be pregnant during the study, an exclusion criterion, she may not be included. Since women as a group are already underrepresented the pregnancy criterion simply adds to this under representation. Another guiding principle is concerned with how well the available patients are functioning before the study is started. It is likely that a physician will not risk worsening the condition of a well functioning patient as a result of a change in medication. Patients who do not take their medication or who fail to appear for checkups cannot be part of drug studies either. There are also restrictions against using patients who are resistant to treatment and continue to display serious symptoms even though they are taking their medication. The result is that women of childbearing age and patients who are either functioning, very well or very badly cannot be part of the foundation on which our knowledge is built. Finally, a large number of patients are needed if conclusions are to be drawn about the utility of a drug being tested. In order to produce a sufficient
number of patients, many elements within the health-care system must participate. A fairly recent example of this is provided by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators (Lieberman, Stroup, McEvoy, Marvin, et al., 2005), a study with more than 1500 patients and also more than 50 different centres that have contributed data. Even if the discoveries that result from drug research are valid, they are based on a limited variation in population of patients and important factors may well have been missed in contrast with the factors that might have been identified if all categories of patients had participated. Drug testing is often restricted to rather short periods of time even though schizophrenia for most people is chronic.

Another type of research that has contributed with important information about the illness comes from patients who have been studied from the very beginning of the appearance of their illness, and who then have been followed for a long time. Nancy Andreasens group in Iowa (Milev, Ho, Arndt, & Andreasen, 2005) and Jean and Donald Addington in Calgary (Addington, et al., 2000; Addington, Saeedi & Addington, 2005) are two examples of research teams that have formed such groups that allow longitudinal studies starting from the first episode of the illness and following its development. In research of this type, the degree to which the group is representative is limited only by the possible unwillingness of patients to participate in follow up studies, assuming there are no other exclusion criteria.
1.2 Theoretical perspectives
– The importance of various factors in determining the prognosis of the illness
In this section, the areas are presented that researchers agree on are important in determining how successful therapy can be, and as a consequence, determine the effect of therapy on the prognosis. These areas are to be seen as mutually complementary and a patient can display problems within several areas and at various levels of difficulty. Some patients display problems restricted to one or another single area, and others in essentially all. The descriptions are not intended to describe a causal relationship but rather to describe the occurrences as separate phenomena even if relationships obviously exist. For example, several of them may be explained by the presence of underlying neurocognitive deficiency.

1.2.1 Symptoms
Every new recurrence worsens the patient’s functioning (Lieberman, Perkins, Belger, Chakos, et al., 2001) (see figure 1). During the first stage of the illness there is lowering in the patient’s level of functioning and after an episode has ended, the patient functions at a lower level than before. This pattern is seen during approximately the first five years of the illness after the occurrence of the first episode. Then, once the patient’s level of functioning has been strongly reduced compared with the level prior to the debut of the illness, a new recurrence only results in a decrease during the actual episode. When the episode tapers down, the patient returns to the prior functional level. As a result, there is a focus on treatment that by various means attempts to break the natural development of the illness by minimizing the number of relapses.
Negative symptoms have been said to have greater importance for the long-term development and prognosis than the positive symptoms (McGlashan, et al, 1992). There is a clear relationship between the negative symptoms and the long-term prognosis for the patient (Fenton, et al, 1991). However, the positive symptoms show no relationship between how extensive or intensive they are during an outbreak and how well the patient functions during a psychosis-free period. In contrast with the positive symptoms, the negative symptoms are essentially stable with the passage of time. As a result, they act to diminish the patient’s ability to function. Finally, the negative symptoms are mildly correlated to the neurocognitive capability in contrast to positive symptoms (Addington, Addington, & Maticka-Tyndale, 1991; Voruganti, Heslegrave, & Awad, 1997), which shows the complexity of the illness.
The more recent antipsychotic drugs have, in addition to targeting the purely psychosis controlling effects, been broadened so that they also are targeted on providing an amelioration of the primary negative symptoms. The extent to which they have been successful in this respect is, however, the subject of discussion. There are a large number of studies (Kane, Leucht, Carpenter, & Docherty, 2003; Leucht, Corves, Arbter, Engel, et al., 2009) that show that the negative symptoms are reduced in comparison with results when the patient is treated only with medication that acts to block dopamine. Some researchers maintain, however, that it is only the secondary negative symptoms, that are those negative symptoms that are a result of existing hallucinations and delusions, that decrease, and those that are not related to the severity of the positive symptoms, are essentially unchanged (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001; Tamminga, Buchanan, Gold, 1998).

1.2.2 Neurocognitive capacity

Neurocognitive capacity is already diminished within a restricted area before the onset of the illness in patients with schizophrenia spectrum disorder (Lussier, & Stip, 2001). It is, however, not possible to identify on this basis alone people who will in the future develop schizophrenia. The dominant view is that after the onset of the illness there is a decrease in neurocognitive capacity, which then remains unchanged until the aging process contributes an addition decrease (Bowie, Reichenberg, Riekmann, Parrella, et al., 2004; Friedman, Harvey, Coleman, Moriarty, et al., 2001). A divergent view is that neurocognitive capacity diminishes continuously during the illness and that many relapses hasten this development (Eberhard, Riley, & Levander, 2005).

The collective IQ of the patient group has been found in various studies to lie between 95 and 100 (Leeson, Barnes, Hutton, Ron, et al., 2009). However, central functions are reduced as much as two standard deviations below the norm, in spite of the normal or just under normal IQ. The reduction in functioning within key areas causes the patient to
function overall far worse than what would normally be expected of an individual with a global capacity of 95 in IQ (Green, 2006). The most important functional deficiencies are found in working memory (McGurk, Coleman, Harvey, Reichenberg, et al., 2004 and Forbes, Carrick, McIntosh, & Lawrie, 2008), learning capacity (Karilampi, Helldin, Hjärthag, Norlander, et al., 2006), memory (Twamley, Woods, Zurhellen, Vertinski, et al., 2008) and executive function (Velligan et al., 2000; Rempfer et al., 2003). All these areas can be scored with validated evaluation scales where MATRICS is an expression of the goal of standardizing the neurocognitive assessments (Green, Kern, & Heaton, 2004; Green, et al, 2008; Kern, et al., 2008; Nuechterlein, et al., 2008).

Working memory is important in order to be able to remember information that is important for a brief moment, for example remembering a telephone number that is to be called or other information that concerns various tasks to be carried out. Executive function describes an individual's ability to be able to plan and to carry out various tasks. Another area that is affected is social cognition, the ability to interpret and evaluate social interactions in different situations (Brüne, 2005). In contrast with the other areas, there is no agreement here between the various measurement instruments, but it is recognized that this phenomenon is difficult to measure fairly (Bozikas, Kosmidis, Giannakou, Anezoulaki, et al., 2007; Brüne, Abdel-Hamid, Sonntag, Lehmkämper, et al., 2009; Corcoran, Cahill, & Frith, 1997; Green, Olivieri, Crawley, Penn, et al., 2005). At the same time there are differences in levels of cognitive performance between patients, and those who display a lower level also have the worst prognoses (Addington, et al., 2000; McGurk, et al., 2000; Weickert, et al., 2000). Just recently, a relationship between the patients IQ capacity and their prognosis of the illness was presented (Carlsson, Nyman, Ganse, & Cullberg, 2006; Leeson, et al., 2009).

The level of neurocognitive functioning can be improved, but which intervention that offers the greatest positive effect is the subject of discussion. In principle, there are two psychopharmacological ways to affect neurocognitive functioning. The first is the ability of the medication to
1.2.3 Adherence

The degree of adherence, or compliance, to prescribed treatment is a strong contributing factor to both short-term treatment results and the long-term consequences. (Donohoe, Owens, O'Donnell, Burke, et al., 2001). The risk for relapse increase with a factor of five for both patients after their first or later-on episode of the illness if their adherence are low (Robinson, et al., 1999). Given the complexity of the symptoms inherent in the illness, it is difficult for the patient to evaluate the situation in a realistic manner. The extent of this lack of insight into the individual’s illness varies across individuals and over time for any one specific individual. Some patients may display a strong experience of the symptoms but lack the resources to understand the causes lying behind them. Others have insights into both the symptoms and the illness but these insights become most evident when the patient’s illness has been treated well and tapers down at the same time that the patient experiences a new episode. Patients with low or strongly varying insight about their illness show a low degree of compliance (Hull, Goodman, Hedayat-Harris, Willson, et al., 1999).

Neurocognitive capacity affects the patient’s possibilities to follow an established treatment plan. Diminished cognitive functioning with lowered
executive capacity can result in the patient experiencing difficulty on his own in finding routines for remembering to take his medicine. A patient who is positive towards treatment can, as a consequence, still experience relapses as a result of failure to consistently take his medicine. This phenomenon is summarized by the concept partial compliance (Smith, Hull, Goodman, Hedayat-Harris, et al., 1999; Jeste, Patterson, Palmer, Dolder, et al., 2003). Published results show that a patient only needs to miss taking the medication a small number of times to cause a decrease in the essential antipsychotic effects (Weiden, Kozma, Grogg, & Locklear, 2004).

The side effects of treatment also cause the patient’s motivation to take the prescribed medicine to be low (Loffler, Kilian, Touni, & Angermeyer, 2003). This was particularly common with the older high-potency neuroleptics, which among other things have an abundance of extrapyramidal side effects (Lambert, Conus, Eide, Mass, et al., 2004). Other side effects that can affect adherence are fatigue, weight gain, and sexual malfunction (Perkins, 2002).

In summary, there is support for the position that careful control of symptoms, satisfaction with patient care, and a small number of side effects result in higher adherence (Chue, 2006).

And finally, there is the possibility of training the patients’ potential for being able to take their medication or the desire to follow the prescribed course (O’Donnell, Donohoe, Sharkey, Owens, et al., 2003).

1.2.4 The choice of medication

All antipsychotic drugs have a documented effect on the positive symptoms of the illness. The first-generation antipsychotic drugs were completely targeted on blocking dopamine. The second generation has a more complicated pattern of receptor affinity where several different receptors are the targets of treatment. It is essentially still dopamine that is the target but with the addition of serotonin to which the drug can bind. At the same time, the broader attack on receptors is complemented by pharmacological interactions other than antagonism such as partial
agonism (Shapiro, Renock, Arrington, Chiodo, et. al., 2003). The reciprocal importance of the different types of binding has not been well established for the atypical drugs, and this is best exemplified by clozapine (Gudelsky, et. al., 1989; Wahlbeck, Cheine, Essali, & Adams, 1999) for which there is no clear understanding of the substance complexity. However, in the case of clozapine the different mechanism may be explained by agonism to the dopamine D1-receptor (Salmi & Ahlenius, 1996) that is not present in conventional neuroleptics where the D2-receptors are blocked.

In addition to the purely pharmacological effects, there is also the pharmokinetic importance of the character of the drug to be considered. The various forms of the drugs make possible treatment alternatives ranging from taking one pill twice a day to having an injection once every four weeks. Some oral medications also require that they need to be taken together with meal to give the maximum effect. Studies show that medication given by injection is more effective than the same substance administered orally. This affiliation is reported for both the older generation’s depot-neuroleptics (Barnes, & Curson, 1994) and for Risperdal Consta (Fleischhacker, Eerdekens, Karcher, Remington, et al., 2003).

There are a large number of scientific studies that show the effects of various drugs including head to head comparisons. The results are not unambiguous, which reflects in part the use of differing protocols, populations, and follow-up time. The overall view is, however, that the effect of the new generation of drugs on positive symptoms is at least as satisfactory as the old. There is also support for the view that the new drugs, in contrast with the older, have an alleviating effect on the negative symptoms and neurocognitive ability (Leucht, et al., 2009).

What have only been discussed to a lesser extent are the side-effect profiles of the different drugs (Voruganti, Cortese, Oewumi, Cernovsky, et al., 2000). The first generation of high-potency neuroleptic drugs displays primarily extrapyramidal side effects such as parkinsonism, motor restlessness (akathisia) and tardive dyskinesia whereas the low-potency group is characterized primarily by causing cardiovascular and autonomic
effects, fatigue. The patients report for both groups the creation of emotional distance between them and their surroundings parallel with neurocognitive inhibition. The atypical drugs constitute a more heterogeneous group than the older. The extrapyramidal side effects are found, if at all, to a lesser degree for some of them, while others are accompanied by above all metabolic syndrome. Especially to be addressed are weight gain, elevated blood pressure and risk for diabetes. Substances from all groups may cause elevated prolactin with sexual secondary side effects (Stahl, 2006).

The choice of drug is influenced by the patient’s situation and support as well as by the characteristics of the different drugs. A patient who as a result of diminished executive function has difficulty in regularly taking the medication should not be using a drug that must be taken several times a day at the same time that something must be eaten.

1.3 The absence of a common goal for treatment of patients with schizophrenia spectrum syndrome

In the preceding section the intent has been primarily to illuminate the great breadth of research within the field of schizophrenia. This research engages many different researchers within widely separated research areas using equally different scientific methodologies that embrace everything from bioscience research on the genome, receptors and cells to other kinds of research on behaviour, societal issues, and health-care economics. Even so, we are forced to admit that more than fifty years after the introduction of the first antipsychotic medication there is still no qualitative goal for the treatment of schizophrenia spectrum disorder in contrast with a number of somatic illnesses for which there are quantitative goals for treatment. For diabetes and hypertension there are exact values for the specified intervals of blood sugar and blood pressure that are to be target for the treatment, and for cancer the measure is five-year survival or remission (Lister, & Armitage, 2000). Even for chronic illnesses
such as multiple sclerosis (Miller, 2000), and rheumatism (Prevoo, Van Gestel, Van’T Hof, Van Rijswijk, et al., 1996) the goal of remission has been expressed as the highest acceptable level of activity of the illness. In the field of psychiatry there are goals for the treatment of depression (Frank, Prien, Jarrett, Keller, et al., 1991), anxiety disorder (Doyle, & Pollack, 2003), panic anxiety disorder (Ballenger, Davidson, Lecrubier, Nutt, et al., 1998) and eating disorders (Kordy, Kramer, Palmer, Papezova, et al., 2002) where remission as well as recovery are defined.

1.3.1. Recommended goals for the treatment of schizophrenia

Weiden (Weiden, Aquila, & Standard, 1996) defined three stages in the treatment of patients with schizophrenia spectrum disorder. The first stage was “Maintaining stability” which means that a level of stability has been attained through control of the symptoms as a foundation for continued treatment and normalization. The second stage was “Improving Quality of Life” which indicated that quality of life was a secondary effect of stability. The third and final stage “Recovering Functioning” described a level of functional and social autonomy. The model has a hierarchical structure where each successive stage is based on fulfilment of the preceding stage (figure 2). In the development of a concept for defining symptomatic remission the Weiden model was modified to “Response” as the basic fundament, “Remission” as the second level and “Recovery” as the third and final level.
Figure: 2. Recovery from a psychotic episode based on Peter Weiden’s description, on the left part of the pyramid, from 1996 and the adaptation to Symptomatic Remission on the right part. The first stage is to reach stability “Maintaining Stability or Response”, and only after that does it become possible to regain a good quality of life, “Quality of Life or Remission”, and finally, a patient may completely get back his or her functional capacity, “Recovering Functioning or Recovery”.

Liberman (Liberman, Kopelowicz, Venture, & Gutkind, 2002) suggested criteria for determining that the patient has reached Recovery. The model includes all the essential social aspects and the patient’s condition must have been stable for at least two years. The relationship to the observation of symptoms is not absolute but rather it is the level of functioning that is the core of the diagnosis. A criticism that has arisen against this recommendation is that only a small percentage of the total group of patients will be included given this definition so that the utility of this is limited. The model has therefore a very limited application (Leucht, & Lasser, 2008).

Recently an American (Andreasen, Carpenter, Kane, Lasser, et al., 2005) and a European (Van Os, Burns, Cavallaro, Leucht, et al., 2006) expert group presented common criteria for symptomatic remission during treatment of schizophrenia. The model has three dimensions: symptoms, severity, and time. The symptoms that were selected represent all the core-symptoms that are required for the diagnosis of schizophrenia to
be made according to the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (1994). These symptoms are delusions, conceptual disorganisation, hallucinatory behaviour, unusual thought content, mannerism and posturing, blunted affect, social withdrawal and lack of spontaneity/flow of conversation. A certain degree of symptomatic activity may be present within these areas for a patient in remission but these must not affect the patient’s ability to live a normal life. In order for a patient to be in symptomatic remission, no symptoms within any of these eight areas may occur to such an extent that daily functioning is affected. There is therefore no total value that must not be reached or exceeded to decide if the patient is to be in remission. However, if any single symptom affects the patient to such an extent that he or she cannot carry out normal daily activities then the patient is not in remission. The final criterion is that the patient’s condition must have been stable during a period of at least six months. If the occurrence of symptoms is limited within allowed levels but the time criterion has not been met, then the condition is described as cross-sectional remission. In order to determine that the patient is in remission (Andreasen, et al, 2005) the patient must be evaluated by using either PANSS, SAPS and SANS or BPRS. BPRS is the least suited scale because this illustrates the negative symptom panorama less well than the others. Eight items are taken from PANSS for the assessment of remission (figure 3) and if the SAPS and SANS scales are used, ten items are needed. The instrument that has been used most regularly is PANSS. For every item in PANSS there are seven alternatives: absent, minimal, mild, moderate, moderate severe, severe and extreme which leads to a seven step scale with between 1 and 7 possible points per item. In order for a patient to be in remission none of these must exceed 3 points.
Remission in Schizophrenia
Patient achieves intensity level...

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**...ON ALL 8 SYMPTOM ITEMS**
- P1 Delusions
- P2 Conceptual disorganization
- P3 Hallucinatory behavior
- G9 Unusual thought content
- G5 Stereotyped behavior
- N1 Blunted affect
- N4 Social withdrawal
- N6 Lack of spontaneity/flow of conversation

**...PANSS SCALE LEVEL OF MILD OR LESS**
1. Absent
2. Minimal
3. Mild
4. Moderate
5. Moderate severe
6. Severe
7. Extreme

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**...OF AT LEAST 6 MONTHS**

Figure: 3. Remission criteria based on the Positive And Negative Syndrome Scale (PANSS).

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1.3.2. Limitations in the structure of the models

Weidens model of the hierarchical relationship between the different effects that are reached during treatment as well as definitions of recovery and remission are based on psychological empiricism. Perception is the foundation of the models, which actually only constitute hypotheses that have been formulated that are not scientifically falsifiable. The concept of remission has certainly been based on meta-analyses of medical studies, but the choice of symptoms and the aspect of time that was agreed upon are based on consensus reached in discussions in the two expert groups (Andreasen, et al, 2005; Van Os, et al, 2006).
2. THE PRESENT INVESTIGATION

2.1 Introduction

2.1.1 The Clinical Long-term Investigation of Psychosis in Sweden

In 1998 work was begun at the Psychiatric Clinic at NU-Health Hospital in western Sweden on what would later be developed as “the Clinical Long-term Investigation of Psychosis in Sweden” (CLIPS). The goal was from the very beginning to include as many patients as possible with the diagnoses schizophrenia, schizoaffective and delusional disorders in a long term follow up study of outpatients. The choice of patients was based on the view that schizophrenia is a heterogeneous condition with a marked overlap of different diagnoses. There are large variations in symptom severity and between the degree of difficulty and presentation of symptoms by different individuals (Tsuang, Woolson, Winokur, & Crowe, 1981; Hollis, 2000; Chen, Swann, & Johnson, 1998; Romney, 1987).

The study has several different dimensions. The patient’s social situation including civil status, housing, type and extent of employment, social network and the degree to which the patient can function independently all are registered. The activity level of symptoms together with the occurrence of side effects resulting from pharmacological treatment are evaluated. The patient’s satisfaction with the care provided and medication given was registered as well as quality of life and the burdens caused by the illness. The patient’s neurocognitive capacity including verbal learning and memory, vigilance, visuomotor speed, simultaneous capacity, working memory, pre-morbid intelligence and executive functions were studied. In addition, a study of family burden was made on family members, considering the presence of a family member who has a chronic psychotic illness. Each patient needed to complete an agreement of Informed consent before he/she could be included in the study. The study was approved by the Ethical Research Committee of the University of Gothenburg.
The first patient was admitted in the fall of 2000. During the period from November 2000 to June 2004, every patient was examined on one occasion. Over and above the criterion that the patient not had any other parallel illness had to be fulfilled. It was also required that the patient was in what was for him/her a stable condition. A condition that was for each individual the best as concerned both symptoms and functional level given each patient’s experience with the illness up to that time. Therefore the patient could not be affected by positive symptoms more serious than what was for each individual the absolutely lowest level experienced to date. The goal of the study was to describe each patient’s illness, functional capacity, and living situation during a period that was not temporarily affected by an episode of the illness. Our intent was to be able to describe, in a fair manner, each patient’s situation and even report results that had previously not been presented. The study of each patient together with the retrieval of data from the journals and from case managers took as many as four working days. At least two people, one of whom was a psychologist, took part in the study of each patient. During the four years, five people were part of the team, a psychologist, three nurses, and a psychiatrist. Before the first patient was recruited, all the members of the team had gone through training in the use of the instruments selected for the study and had engaged in evaluation training sessions. After evaluations were carried out, where each took place independent of the others, the results were compared as a means of ensuring the future quality of the data. From 2005 onward, every patient was followed up annually and those patients who were studied during the period 2000 till 2004 continued in the study parallel with the recruitment of new patients. The patients are examined once a year, in addition to the ordinary treatment, and will continue to be so over a period of 12 years. At the time of setting the baseline and then every four years after, a broader examination is made while in each of the three intervening years a smaller examination is carried out.

The study, which is planned to continue until at least 2016, has now been expanded to include all of the outpatient sites. Selected nurses at
these locations have been trained and are undergoing evaluation practice sessions before the first patients are admitted in this phase of the study. A resource team consisting of seven people, a psychologist, a Ph.D. student in psychology, three nurses, an occupational therapist and a psychiatrist, has been created with task of supporting and monitoring the nine centres in Trollhättan, Uddevalla, Vänersborg, Dalsland, Munkedal, Lilla Edet, Orust, Strömstad and Åmål. Nurses, a psychologist, an occupational therapist and a psychiatrist will carry out the study at these units. The protocol for the first phase of the study between 2000 and 2004 was developed in collaboration with Professor Michael F Green, University of California Los Angeles, UCLA, and Professor Philip Harvey, Emory University School of Medicine, Atlanta, who above all contributed to the choice of neurocognitive tests that came to be a part of the research. From 2001 on, research were connected to the Institute of Psychology at Karlstad University under the scientific guidance of Professor Torsten Norlander. Professor John M Kane of the Zucker Hillside Hospital and the Albert Einstein College of Medicine, New York, and his work with symptomatic remission as a quantitative goal in the treatment of schizophrenia is included in the research project from 2003 onward.

2.1.2 The purpose of the current thesis

When the collection of data during the first phase happened to coincide with the development of the proposal on remission, a possibility was created for being able to describe the importance of the introduction of such a qualitative goal of treatment. The scientific support for the concept of remissions was carried over from studies of drugs that had been carried out in the past.

The hypothesis that is tested in the thesis is that patients who have reached a stable level corresponding to remission as an outcome of their treatment function better, have a better life situation and a better prognosis than those who have not reached this state. The hypothesis was given a form that made it possible for Poppers demand of falsification to
be met (Miller, 1983). The first study (Paper I) was designed to see if patients in remission had a higher functional capacity with respect to daily activities, a better adaptation to society as concerned education, working, social network and civil status and did not need the level of medical care that others needed. The second study (Paper II) examined the relationship between remission and quality of life, burden placed on the patient by the illness, satisfaction with the medical care and pharmacological treatment provided, as well as the extent of the patient's symptoms and insights about the illness. In order for the hypothesis to be met, the majority of the variables studied would have to show results superior for those in remission and also the opposite result that only a small number of significant differences or results in favour of those not in remission would appear.

The follow-up studies examined the relationship between remission and neurocognitive capacity and also if the patient who is in remission is less in need of outpatient and inpatient care. The first of these two studies (Paper III) examined the hypothesis that a higher neurocognitive capacity increases the probability of remission. Vigilance, psychomotoric capacity, cognitive flexibility, working memory, learning capacity, short-term memory, executive capacity, pre-illness cognitive capacity were studied, and as a means of falsification, all of these were to be superior in the patients in remission for the hypothesis to be fulfilled. Finally, the fourth study (Paper IV) examined the hypothesis that patients in a stable condition, who at the very least met the requirement of cross-sectional remission of symptoms would need less care activities. The extent of this care experienced as outpatient visits, number of hospitalisations and the number of days hospitalised as well as the need for sheltered living were studied to document the differences between groups.

The first three studies were carried out at the Department of Psychiatry, NU Health Care, during the period November 2000 to June 2004. The fourth study was based on long-term data on the same population collected up to 2008. Patients were recruited by their case manager at the outpatient settings at which they received their treatment. All participation
was on a voluntary basis and could be terminated whenever the patient wished and without having to provide any rationale. Patients agreeing to participate in the investigation underwent tests and interviews that were not normally a part of their treatment interviews. Patients meeting the inclusion criteria were examined over two days and patients with serious cognitive disturbances sometimes required examination during an extra day. The patients were interviewed and their medical records were examined to complement the already-existing information. Each patient needed to sign an “Informed consent” form before he/she could be included in the study. The study was approved by the Ethical Research Committee at the University of Göteborg and carried out in accordance with the latest version of the Helsinki Declaration.

2.2 Paper I.
Remission in Prognosis of Functional Outcome:
A New Dimension in the Treatment of Patients with Psychotic Disorder

2.2.1 Aim
The question posed in this study was to ask if the attainment of cross-sectional symptomatic remission is coupled with an improved functional capacity expressed as the ability to manage the activities of daily life and the individual’s place in society. Areas that were studied were the degree of autonomy with which patients managed to function out in society, their ability to work, and their educational level, civil status, housing situation and the extent to which they consumed in-patient facilities. In order for that achieved remission should be judged to be in favour for the patient, the large number of the parameters studied had to show superior function for patients in remission and only in exceptional cases could it be seen that those patients not in remission managed as well or better.
2.2.2 Design

In this study 243 patients (140 male and 103 female) with schizophrenia, schizoaffective disorder or delusional disorder were examined with the PANSS instrument in order to establish the degree of symptomatic remission. The patients were evaluated only once, and it was therefore only possible to specify the occurrence of cross-sectional remission. However, the inclusion criterion required that at the time of evaluation the patients would not be experiencing a psychotic episode and would not be suffering from the after effects of such an event but rather that their condition had been stable for a relatively long time and would be representative of the best level of control of their symptoms and their best level of functional performance. We assumed that the effect of the missing time criterion would be counterbalanced by this inclusion criterion. The dependent variables were measures from several different instruments, including ADL (Activity of Daily Living) ability and the extent of health care service utilization. A distinction is made between ADL ability, which explicitly is based only on each single individual’s ability, and the social position in society, which is measured by considering the individual’s capability and needs in relationship to others. For example, an individual may have a good ability to work but because of widespread unemployment may not have a job. Additionally, an individual may have such a low level of functioning that he/she requires an institutional level of care, but since funding is not provided is not receiving that care. In order to exclude the possibility that the observed differences in function might better be explained by differences in diagnosis, i.e. schizophrenia, schizoaffective disorder and delusional disorder, the influence of diagnosis was also explored.

2.2.3 Instruments

2.2.3.1 Positive and Negative Syndrome Scale – PANSS

Subjects were interviewed using an adapted Swedish translation of the Structured Clinical Interview – Positive and Negative Syndrome Scale
(SCI-PANSS) (Kay, et al., 1987; Kay et al., 1987; Kay, et al., 1988; Lindström, et al., 1994), in order to determine which patients had attained the condition of symptomatic remission.

2.2.3.2 Camberwell Assessment of Need – CAN

The instrument was developed by the Health Services Research Department at the Institute of Psychiatry in London (Phelan, Slade, Thornicroft, Dunn, et. Al., 1995), and the Swedish version was validated (Hansson, Björkman, & Svensson, 1995; Ericson, Hansson, & Teike, 1997; Slade, Thornicroft, Loftus, Phelan, et al., 1999). In the current study, the Swedish translation of the research version of the adult Camberwell Assessment of Need (CAN-R) was used. It assesses the needs and help provided during the preceding month in five health and social domains: basic functions, health, social functions, general functions, service and the total number of needs. The members of the research team performed the assessments with support from the patient’s case manager.

2.2.3.3 Strauss-Carpenter (extended version)

This scale (Strauss, & Carpenter, 1972) with a total of five items includes domains for living conditions, social contacts, working ability, number of days for sheltered living and hospital admission in the past 12 months. The first three questions each offer four response alternatives whereas responses to the final two questions require that the answers present the exact number of days spent in sheltered living and in psychiatric wards in the clinic. The reports are extracted directly from patient interviews, patient medical records and reports from relatives and caregivers.

2.2.3.4 Educational and civil status

In order to elucidate these factors, two parameters were constructed as a complement to the Strauss-Carpenter. Answers to each question can provide from 1 to 3 points. Education is categorized as the level of edu-
cation that the patient had reached. Those patients that had undergone the basic school level were awarded 1 point although they had not necessarily achieved a complete attendance; those patients who had completed high-school were awarded 2 points; and those patients who had completed university-level education were awarded 3 points. Civil status is described in the following manner: those patients who had never experienced an established partner relationship were awarded 1 point; those patients who had experienced a partner relationship but which, at time of testing, was terminated were awarded 2 points; and those patients who, at time of testing, were involved in a permanent relationship were awarded 3 points. Widows and widowers were awarded 2 points.

2.2.4 Statistics
Differences in social status and remission were analysed with the Mann-Whitney test (5% level). For diagnoses differences between the three groups were analysed with the Kruskal-Wallis test and then with the Mann-Whitney test (5% level) for a head to head comparison of the different diagnoses. Ability in daily life situations was analysed with the Pillais' MANOVA and for diagnoses with One-way ANOVA and Bonferroni Post Hoc Test. Finally, differences in hospitalisation, numbers of occasions and total time, and need for sheltered living were analysed with One-way ANOVA.

2.2.5 Results
With the eight items from the PANSS instrument as a starting point, it was established that 93 patients (38%) had achieved remission severity criteria whereas 150 patients (62%) failed to fulfil the criteria for remission. No gender differences regarding remission were observed (Fisher's Exact Test, \( p > 0.05 \)). The cut-off% shows that three items are of particular importance for indicating that a patient is not in remission: ‘N4 Passive/apathetic and social withdrawal’, 44.6%, ‘P1 Delusions’, 36.5% and ‘P3 Hallucinatory behaviour’ 31.8% of the patients did not achieve remission.
The present findings indicated that those patients who fulfilled the severity criteria for cross-sectional remission showed a significantly superior outcome with regard to activity in daily life, social functioning in society and consumption of health care. Remission patients functioned more adequately in social contexts than did non-remission patients. They had superior education, more often had an occupation, possessed more established social networks and were more likely to live under family-like conditions. They exhibited a lower need for support in order to fulfil their everyday activities. Finally, the remission patients made much less use of health care resources, both in the form of psychiatric treatment and community habitation support, than did non-remission. The postulated differences in functioning could not be explained as a result of different diagnoses within the schizophrenia syndrome spectrum.

2.3. Paper II.
Experience of Quality of Life and Attitude to Care and Treatment in Patients with Schizophrenia: Role of Cross-sectional Remission.

2.3.1 Aim

The aim of this study was to determine if achieved cross-sectional remission would result in improved quality of life compared to non-remission. To explore this, the patients’ quality of life was assessed from a practical point of view by determining how satisfied they are with different aspects of life, and also to determine their level of insight about their illness and their degree of satisfaction with care. Our hypothesis is that patients in cross-sectional remission will have a superior quality of life, face a lower level of burden secondary to the illness, have a better understanding of their condition and, finally, be more satisfied with their treatment.
2.3.2 Design

The patients were examined with the PANSS instrument in order to evaluate their remission. The data were then analysed according to an independent variable termed Remission group (Non-remission, Remission). The dependent variables were derived using several different instruments. Quality of life was estimated with the MOS 36-Item Short Form Health Survey (SF-36) (Russo, Trujillo, Wingerson, Decker, et al., 1998). The patients’ perception of the burden of the disorder was estimated with the Rosser Index (Rosser, & Kind, 1978 och Kind, & Rosser, 1988), assessing disability and distress. The patients’ insight into their symptoms and the disorder was estimated by using two questions from the Psychosis Evaluation Tool for Common Use by Caregivers (PECC) (De Hert, Wampers, Thys, Wieselgren, et al., 2002). The patients’ appreciation of their care and pharmacological treatment was examined using the two self-rating instruments Consumers Satisfaction (ConSat) and Drug Attitude Inventory (DAI) (Hogan, Awad, & Eastwood, 1983). To indicate the patients’ medical status, GAF scores were analysed for symptoms and social functioning.

The mean age of the patients was 47.7 years (SD=12.0). Mean age at first consultation was 27.6 years (SD=9.8), and at the first admission to psychiatric hospital 30.0 years (SD=11.28). One-way ANOVA with remission as the independent variable (Non-remission versus Remission) revealed no significant group effects for age at testing, age at first consultation, or age at first registration (p>0.05).

2.3.3 Instruments

2.3.3.1 Positive and Negative Syndrome Scale – PANSS.

Subjects were interviewed using an adapted Swedish translation of the Structured Clinical Interview – Positive and Negative Syndrome Scale (SCI-PANSS) (Kay, et al., 1987; Kay et al., 1987; Kay, et al., 1988; Lindström, et al., 1994).
2.3.3.2 The MOS 36-Item Short Form Health Survey (SF-36)
This instrument is a shortened version of a battery of 149 health status questions developed to monitor patient outcomes. Recall period is the past month. The SF-36 uses eight scales to measure three aspects of health: (1) Functional status (physical functioning, social functioning, and role limitations attributable to physical problems and role limitations attributable to emotional problems), (2) Well-being (mental health, energy and fatigue, and pain) and (3) Overall evaluation of health (general health perception) (Russo, et al., 1998).

2.3.3.3 Rosser Index.
The patients’ disability (level of handicap) and distress were assessed using the Rosser Index. Disability is an index divided into eight degrees assessing the severity of disability during the preceding two weeks with respect to activities of daily living and social life. Distress assesses the patients' experience of the burden of the disorder. Distress consists of a question with four response alternatives: “Not at all”, “A little bit”, “Quite a lot”, and “Heavy” (Rosser, et al., 1978; Kind., et al, 1988).

2.3.3.4 Psychosis Evaluation Tool for Common use by Caregivers – PECC
This instrument is a diagnostic tool developed for the assessment of psychotic patients (De Hert, et al., 2002), and can be applied by all health care workers, including nurses.

2.3.3.5 The Consumer Satisfaction rating scale – UKU/ConSat
This scale measures the subject’s satisfaction with the care provided. The scale is administrated as a semi-structured interview and consists of 13 items in total (Ahlfors, Lewander, Lindström, Malt, et al., 2001).
2.3.3.6 Drug Attitude Inventory – DAI
The DAI is a brief, self-administered 10-item scale to assess the subject’s satisfaction with antipsychotic drug therapy (Hogan, Awad, & Eastwood, 1983).

2.3.3.7 Global Assessment of Functioning – GAF
In this study, GAF is presented as a total score that is also separated into two sub-scores. One sub-score represents symptom severity and the other functional level. Total GAF score for each patient is the lowest value of the two sub-scores (Diagnostic and Statistical Manual of Mental Disorder, Forth Edition, (1994), American Psychiatric Association).

2.3.4 Statistics
Differences in the rate of remission between male and female patients were calculated with the Fisher’s Exact Test ($p<0.05$ level). Differences between patients’ mean age when tested, mean age at first consultation and mean age at the first admission to psychiatric hospital were decided with the One-way ANOVA with remission as the independent variable (Non-remission versus Remission), ($p<0.05$). Differences in patients’ quality of life, SF-36 ten different dimensions, were investigated with the Pillai’s MANOVA ($p<0.05$) with remission as the independent variable (Non-remission versus Remission). Patients’ distress, handicap and insight were analysed with the Mann-Whitney Test ($p<0.05$). Patients’ attitudes towards care and pharmaceutical treatment were assessed with the One-way ANOVA ($p<0.05$) with remission as the independent variable (Non-remission versus Remission). Finally, patients’ symptom severity and functional level expressed as GAF scores as well as the total GAF score were analysed with Independent Samples T-Test ($p<0.05$) with remission as the independent variable (Non-remission versus Remission).
2.3.5 Results

Applying the cross-sectional criteria for remission, 93 patients (38%) were in remission, whereas 150 patients (62%) were not in remission. There was no difference in the rate of remission between male and female patients (Fisher's Exact Test, \( p > 0.05 \)).

The findings in the present study indicate that cross-sectional remission is related to a better outcome in all the areas evaluated. Quality of life is improved, experience of burden and handicap is reduced and satisfaction with care and pharmacological treatment are enhanced for patients who meet the cross-sectional criteria for remission. Patients in cross-sectional remission also demonstrated a better understanding of their symptoms and a higher level of insight into the disorder. On all the SF-36 subscales, except General health, patients in cross-sectional remission gave higher quality of life ratings than did patients not in remission. The burden that patients experienced secondary to the disorder (Disability and Distress as measured by the Rosser Index) was significantly lower among patients in cross-sectional remission than those who were not in remission. Patients who achieved cross-sectional remission were more capable of assessing their disorder, both with regard to their recognition of symptoms and their understanding of the relationship between the symptoms and the disease state that causes them, than were patients not in remission. Attitudes to care and antipsychotic medications were improved among patients in cross-sectional remission, according to both the Consumers’ Satisfaction instrument and the Drug Attitude Inventory. Finally, patients in cross-sectional remission are rated by their caregivers to have fewer symptoms and a higher level of function, according to GAF scores, resulting in a higher total GAF-score.
2.4 Paper III.
Remission and cognitive ability in a cohort of patients with schizophrenia.

2.4.1 Aim
This study explores the relationship between the patients’ cognitive functioning and remission status. A major purpose was to examine whether or not those patients who had achieved remission possessed a superior cognitive performance profile. Since none of the patients was the object of any explicitly directed intervention aimed at achievement of remission, the present analysis may unearth the importance of cognitive ability as a factor that could explain why only 76 patients (i.e. 36%) out of the 211 patients included attained remission. Thus, the present population of patients was given a comprehensive battery of cognitive tests designed to study vigilance, working memory, learning performance, long-term memory, executive functioning, visuomotor speed/efficacy, cognitive flexibility and pre-morbid functioning.

2.4.2 Design
Two hundred eleven patients (127 male and 84 female) completed all aspects of the investigation. Of these, nine individuals were diagnosed with disorganized schizophrenia, one with catatonic schizophrenia, 79 with paranoid schizophrenia, 14 with residual schizophrenia, 50 with schizoaffective disorder and finally 58 individuals with undifferentiated schizophrenia. In this study patients with delusional disorder were excluded. The reason for this was that there were no earlier studies performed that indicated if the cognitive ability were comparable for schizophrenia, schizoaffective disorder and delusional disorder. As a consequence of this we decided to be conservative in the choice of the study population. A decision that also reduced the population with 32 patients.

Applying the severity component, but not the time component of the remission criteria proposed by Andreasen et al, it was established that 76 patients (36%) had achieved remission whereas 135 (64%) had not.
No gender differences regarding remission were observed (Fisher's Exact Test, \( p > 0.05 \)). The average age of the patients was 46.3 years (\( SD = 11.57 \)). At the first consultation, the average age was 25.7 years (\( SD = 7.75 \)), and at the first psychiatric hospital admission, 27.7 years (\( SD = 9.18 \)). One-way ANOVA with Remission group (i.e. Non-remission, Remission) as independent variable indicated no significant effects for age at testing, age at first consultation, age at first registration or duration of illness (\( ps > 0.05 \)). There was, however, a significant difference regarding GAF at testing between groups (\( p < 0.01 \)), in which the non-remission group obtained lower scores on GAF (\( M = 45, SD = 8.6 \)) as compared with the group in remission (\( M = 52, SD = 7.4 \)). The GAF score indicates that remission, apart from being a result of lower PANSS scores, is also followed by less impairment in daily life.

### 2.4.3 Instruments

#### 2.4.3.1 Positive and Negative Syndrome Scale – PANSS


#### 2.4.3.2 Rey Auditory Verbal Learning Test – RAVLT

The RAVLT (Rey, 1964; Schmidt, 1996) consists of a 15-item word list that is presented five times, always in the same order, with an assessment of recall immediately after each presentation. Thereafter an interference list is presented, followed by a request to recall the original list without further presentation of the original list words. Finally, a delayed recall test is presented after 20 minutes.

In this study, the number of words correctly recalled in the RAVLT Trial I was used for assessing immediate memory, the number of words correctly recalled in the RAVLT Trial V and the total of recalled words in
the RAVLT Trial I to V was used for learning and the number of words correctly recalled in the RAVLT Trial VII was used for long-term memory.

2.4.3.3 Continuous Performance Test – Identical Pairs – 450 trials – CPT-IP-450
The CPT-IP is a computerized vigilance test measured as d’prime 1, 2 and 3 (Rosvold, Mirsky, Sarason, Bransome, et al., 1956; Cornblatt, Risch, Faris, Friedman, et al., 1988) that assesses the subjects’ ability to respond to a target stimulus, namely the second of a pair of identical stimuli (a four-digit number). Stimuli are flashed on the computer screen at a constant rate of one per second, with a stimulus “on” time of 50 ms. Responses are made as fast as possible by lifting a finger from a mouse button.

The test is constructed in three equal-sized sequences, each with 150 trials, given in one session.

2.4.3.4 Trail Making Test Part A and Part B – TMT-A and TMT-B
The Trail Making Test is one of the most widely used and most sensitive brief examinations to evaluate the level of brain impairment (Reitan, 1958). Subjects are required to join consecutive numbers (Part A) and to alternate between two sets, connecting numbers and letters (Part B), all under the pressure of doing the task as rapidly as possible.

In this study, the performance time for Part A was used as a measure of visuomotor speed/efficacy, and the performance time for Part B as a measure of cognitive flexibility.

2.4.3.5 Letter Number Sequencing – LNS
The LNS, now a supplementary subtest in the WAIS-III, is often used for assessment of auditory working memory performance (Gold, Carpenter, Carpenter, & Goldberg, 1997; Wechsler, 1997). It requires the subjects to sort out letters from numbers within a row of alternating letters and
numbers that are read to them, and to separately recall the letters and numbers in successive order. The numbers of correct recalls in 21 trials of increasing difficulty are calculated and used in this study as a measure of working memory.

2.4.3.6 Vocabulary subtest from Wechsler Adult Intelligence Scale – Revised

This test estimates pre-morbid intelligence, and has been identified as the single best measure of both verbal and general mental abilities (Wechsler, 1981 & Lezak, 1995).

The subject is asked the meaning of 40 words, arranged in order of difficulty. The test score is used in this study as a measure of vocabulary.

2.4.3.7 Wisconsin Card Sorting Test – WCST

The WCST has increasingly been employed as a clinical neuropsychological instrument and can be considered a measure of executive function (Heaton, Chelune, Talley, Kay et al., 1993). It consists of four stimulus cards and 128 response cards that depict figures, colours, and numbers. The subject is instructed to match each consecutive card from the deck with one of the stimulus cards by pressing a computer key. A message on the screen tells the subject whether each response is right or wrong. Once the subject has made a specified number of consecutive correct matches to the initial sorting principle, the sorting principle is changed without warning. The WCST proceeds in this manner through a number of shifts in sorting principle among the three possible sorting categories. The computer program calculates the test scores. In this study, the number of completed categories was used as a measure of executive functioning.
2.4.4 Statistics

Remission and non-remission respectively are presented on items level as mean values and standard deviations. Cut-off levels are given in percentages, indicating the percentage of patients who score lower than 4 on each given item. Gender differences as regards groups were calculated using the Fisher’s Exact Test. Age at day of assessment, age at onset, illness duration, illness activity according to GAF and cognitive ability comparing patients with schizophrenia and schizoaffective disorder, were tested by One-way ANOVAs. Vigilance, working memory, immediate memory, learning, long-term memory, executive functioning, visuomotor speed/efficacy. Cognitive flexibility and pre-morbid functioning were finally assessed by One-way ANOVAs comparing the groups (remission and non-remission). A p-value <0.05 was considered significant. In comparison of cognitive level of functioning between the two groups, results are also presented as values of effect size (Eta²) and power, given with the F-values.

2.4.5 Results

The present study revealed marked differences in cognitive ability between those patients who were in remission and those who did not meet the remission criteria. Across every aspect of cognition there were significant differences between the two groups of patients. There are differences in vigilance, working memory, long-term memory and executive functioning in favour of those in remission. The difference between the groups has implications, e.g. the CPT-IP assessments of vigilance indicate that patients in the remission group in all three assessments performed at a higher level. Furthermore, a possible trend indicates that the patients in the remission group may be able to increase their performance and maintain it over time while the other patients fall back to their original level in the third part of the test, after an initial improvement.
2.5 Paper IV
– The Importance of Cross-sectional Remission in Schizophrenia for long-term outcome, a clinical prospective study

2.5.1 Aim

This paper is based on long-term outcome data for a group of patients that have been followed since 2000. The goal was to determine if patients who were tested during a calm period of their illness that was representative of the highest level of symptom-control and performance and who had gone into cross-sectional remission would have a better long-term prognosis measured in terms of lesser need for care. The number of visits to a psychiatrist or another member of the specialist psychiatric team, the number of hospitalisations, and the time spent in hospital or nursing-homes were calculated for a period of average length six and a half years for both groups. The hypothesis was that patients who reach a stable level corresponding with remission would have a better outcome as measured by the need for care.

2.5.2 Design

Information was sought about the patients, who have been followed from the time they entered the study, concerning contact with the psychiatric specialist outpatient treatment, admission to psychiatric outpatient care, and housing in “nursing homes”. The visits to a doctor or other care-giving staff (especially nurses) at outpatient wards were registered as the number of visits, institutional-care consumption as the number of hospitalisations and number of care days, and sheltered living days were also counted in the total number of days. The total consumption of care and treatment was measured in terms of hours. Each visit in outpatient care has been recalculated to the number of hours, where each visit is assumed to take on the average one hour and where the number of care days and number of days in sheltered living also were recalculated to the number of hours. The number of hospitalisations has also been recalculated to a corresponding number of hours where the time spent
with the doctor who made the decision to hospitalise the patient is included in the statistic “hours of hospitalisation”. In other words, that meeting is not treated as a free-standing event recorded as part of the pre-hospitalisation statistic. It is likely that one hour per doctor’s appointment in connection with an acute phase and the establishment of a hospitalisation journal is an underestimate but in order to not overestimate this activity the number of hours has been chosen conservatively.

2.5.3 Instruments

2.5.3.1 Positive and Negative Syndrome Scale – PANSS

Subjects were interviewed using an adapted Swedish translation of the Structured Clinical Interview – Positive and Negative Syndrome Scale (SCI-PANSS) (Kay, et al., 1987; Kay et al., 1987; Kay, et al., 1988; Lindström, et al., 1994).

2.5.3.2 Strauss-Carpenter (extended version)

This scale (Strauss, et al., 1972) with a total of five items includes domains for living conditions, social contacts, working ability, number of days for sheltered living and hospital admission in the past 12 months. The first three questions each offer four response-alternatives whereas responses to the final two questions require stating the exact number of days spent in sheltered living and in psychiatric wards in the clinic, respectively. The reports are extracted directly from patient interviews, patient medical records and reports from relatives and caregivers.

2.5.4 Statistics

The composition of the population was examined on the basis of the differences between patients who at first evaluation were in remission and those who were not. As concerns the degree to which the sample’s were representative, for gender distribution we used Fischer’s Exact Test,
for average age at the time of inclusion an Independent Samples T-Test, and for the time of participation in the study Pearson Chi-Square Test. The occurrence of differences between groups with respect to effort put into care in the form of doctor’s appointments and appointments with other care-providers in the specialized psychiatric outpatient ward, the number of hospitalisations to psychiatric care wards as well as the number of care days, the number of sheltered living days and the total consumption of care was analysed using an Independent Samples T-Test.

2.5.5 Results

There was no difference between those in remission and those not in terms of subsequent study refusal. Seventy two of the remaining study population were female and 119 were male. Fisher’s Exact Test found no differences regarding gender between the remission and the non-remission groups, ($p=0.21$). The mean age at baseline for patients in remission was 46.9 years ($SD=11.6$) and was 47.6 years for the other patients ($SD=12.6$). Independent Samples T-Test was not significant, ($p=0.70$).

During the more than five and a half years of the follow-up process, 25 (35%) of the patients who attained remission have been hospitalised one or several times while the corresponding number for the other patients was 46 (39%). On the average, patients in the first group have been hospitalised 0.8 times compared with 1.4 times for patients in the other group. None of these differences were significant, however.

Contact with the specialized psychiatric outpatient care and the extent of inpatient care were as follows with values for patients in remission first followed by patients in non-remission. Visit to doctor mean 7.5 ($SD=3.9$) vs. 8.7 ($SD=6.1$), other visits 114.8 ($SD=122.6$) vs. 139.8 ($SD=185.7$), number of admissions 0.78 ($SD=1.6$) and day at hospital 42.4 ($SD=102.8$) vs. 51.2 ($SD=121.3$).

For all the variables, the number of care contacts are greater and the time of stay longer for the group not in remission (Independent Samples T-Test ns, $p>0.05$).
Ten patients (14%) from the remission group have needed or need sheltered living during the follow-up period compared to 34 (29%) in the non-remission group (Pearson Chi-Square Test p=0.02). The average care time for patients in the remission group 91.5 days (SD=322.0) compared to 184.9 (SD=392.9) for the patients not in the remission group (Independent Samples T-Test ns, p=0.09).

The total consumption of the different care efforts, doctors visits, visits to other caregivers in outpatient care, the number of hospitalisations, the number of care days and the number of days at a nursing home, where the two latter categories have been translated to hours, is, on the average during the follow-up period for remission patients, 3709.8 (SD=9007.2) equivalent to 55.2 hours per month. For the patients who did not go into remission, the average consumption was 8425.9 (SD=13872.1) hours or expressed per month 122.6 hours. (Independent Samples T-Test, p=0.012).
3. General discussion

3.1 The findings support the Remission concept

The hypothesis tested in this dissertation states that a patient who has reached a stable level corresponding to cross-sectional remission is functioning better, has a better life situation and a better prognosis than patients who have not achieved remission. In order for this hypothesis to be confirmed, the majority of the variables studied should indicate a superior outcome for those in remission and, stated as the converse, only a minority should show no difference between groups or should show a better outcome for those not in remission.

The first study (Paper I) was designed to determine if a patient in remission displayed a higher functional capacity as concerned daily activities, better adaptation to society in such areas as education, employment, social network and civil status, and needed relatively less inpatient and outpatient care. In all the areas studied, the patients in remission had a significantly higher functional capacity and less need for in- and outpatient care than those not in remission. These findings has been replicated in a study based on six of the eight items of remission (De Hert, van Winkel, Wampers, Kane, et al., 2007) and in a five years follow-up study on first episode patients (Bodén, Sundström, Lindström & Lindström, 2009).

The second study (Paper II) was an investigation of the relationship between cross-sectional remission and quality of life, the burden placed on the patient by the illness, satisfaction with the care and medication provided and also of the breadth of insight shown by the patients concerning their symptoms and their illness. Even in this respect, patients who had attained remission uniformly displayed a better life situation, were more satisfied with the care given, and had a better understanding without being affected by secondary depressive effects.
Results from the long-term follow up study of the patients’ need for inpatient and outpatient care that was subsequently carried out (Paper IV) gave the same results as the first study. Patients who have attained a stable level corresponding to remission require sheltered living situations to a lesser extent than the comparison group and also require less in- and outpatient care than those not in remission. The picture here is, however, more complex. With respect to those same measures, those who were not in remission at the time of baseline had a greater number of visits, were more often inpatients, and needed a greater number of hours of care than those in remission, but they did not differ significantly from the remission group as concerns the percentage needing protected housing and their total consumption of care. It is possible that these differences would have been significant if those with the greatest need for medical care had not been provided with communal group living opportunities, which resulted in a decreased need for care in clinics and hospitals. Paper IV also provides additional support for the benefits of achieving remission even if this is not as strong as the earlier papers (Papers I and II) were able to show. What is important to note is that none of the comparisons made in this study or the two earlier studies indicate any advantages for the group that did not achieve remission. A balanced judgment must be that patients who responded to treatment in a stable manner and achieved remission more successfully established themselves in society, experiences a better living situation, and were able to live a more autonomous life including a lesser need for repeated interventions from medical care providers.

The third study (Paper III) addressed the question concerning who has the greatest potential for achieving remission. The hypothesis, based on earlier research, was that patients with a higher level of neurocognitive functioning would have better chances for achieving remission. The study showed that this was indeed the case. In all the areas measured: capacity to observe, vigilance, visuomotoric speed, neurocognitive flexibility, working memory including immediate memory, learning capacity, short-term memory and executive capacity, the results indicated that those
who had achieved cross-sectional remission had a higher neurocognitive capacity. Parallel with this finding, we found that patients in remission had a larger vocabulary, which is an indication that these people already had a higher neurocognitive capacity before they became ill with schizophrenia. Several important conclusions may be drawn from these results. Perhaps the most important is that although all the patients in our study were all offered the same basic kinds of medical care, it was only those patients with the best neurocognitive functioning who have been able to profit from the treatment to such an extent that they achieved remission. Two secondary conclusions can lead to treatment practice that incorporates a systematic study of the neurocognitive capacity of all patients in order to identify at an early stage those patients with good and poor performance. At the same time design treatment in such a way that a greater percentage of patients can enjoy a better prognosis than otherwise might have been possible. Previously it has been maintained for example that errorless learning can improve the cognitive capacity of patients (Kern, et al, 2005; Bell, et al, 2001; Kern, et al, 2002; Twamley, et al, 2003). Even other methods have been shown to be effective in raising patients' functional level such as community oriented treatment programs with case management models (Malla, Norman, Manchanda, McLean, et al., 2002) and psychoeducational training, including activity-stimulating checklists, offering greater possibilities for patients as well as close relatives to attain successful care (Medalia, Revheim, & Casey, 2002; Liberman, et al., 2002; McFarlane, Link, Dushay, Marchal, et al., 1995).

3.2 Secondary benefits of evaluation of the patient’s remission status

The importance of neurocognition has already been discussed in section 1.2.2 as has its influence on the prognosis of the illness. An additional aspect of the phenomenon is that the prognosis can be worsened if caregivers receive inadequate information from the patient because of the character of treatment provided. A secondary positive effect of studies designed to determine if the patient is in remission is that the investigation becomes formalized and is carried out on the basis of a
semi-structured interview procedure. This procedure is advantageous in comparison with a procedure where the patient’s status is evaluated by posing open questions, where a considerable responsibility is thus placed on the patient to spontaneously provide information. It may be especially difficult for patients with schizophrenia and a diminished cognitive capacity in the form of decreased memory and executive capacity to provide a balanced history of their illness. Regular use of remission evaluation offers, in addition to the determination of the patient’s remission status, essentially better information on which to base treatment.

3.3 The findings in correlation with postulated theories

Above and beyond the importance of neurocognitive capacity referred to in section 1.2 Theoretical perspectives even the negative symptoms, adherence and choice of medication affect the prognosis of the illness. Paper III illustrates the importance of good neurocognitive capacity for a good prognosis. In an analysis to determine which symptoms are most important in preventing the attainment of remission it became evident that three items had the greatest importance. Item 4 of the Negative symptoms in PANSS, ‘Passive/apathetic and social withdrawal’ contributed 44.6% to not being in remission. The next most important were delusions, PANSS item 1 of the Positive symptoms, ‘Delusions’ where 36.5% were not in remission and in third place was item 3 of the Positive symptoms, ‘Hallucinatory behaviour’ 31.5%. Compared with current theory, it is to be expected that a negative symptom is the most common cause for not achieving remission (McGlashan, et al, 1992; Fenton, et al, 1991). This finding was as postulated, however the most common item to inhibit remission was followed by two positive symptoms. Both of these are responsible for a third of all patients not reaching the remission severity criteria. In addition it may be argued that a passive/apathetic behaviour and social withdrawal can be an expected consequence of the occurrence of delusions and hallucinations. It is possible to draw the conclusion that the negative symptoms have the greatest importance for the long-term prognosis given that the patient’s positive symptoms are
successfully treated. If, as in our study, patients still are suffering from positive symptoms this may limit the patients’ chances to live an autonomous life, which could be misunderstood as secondary to negative symptoms. Our results indicate that negative as well as positive symptoms prevent the occurrence of remission in all situations, which requires therefore that a more nuanced view than the view that only negative symptoms are of importance for the prognosis needs to be developed (Heinrich, Ammari, Miles, McDermid, et al., 2009).

Adherence is shown to be important for the illness development and a high level of adherence reduces the risk of new episodes. Patients who are more satisfied with their treatment and who have, in addition, greater insight into their illness have been found to have better compliance. A positive attitude leads to an increase in motivation to follow the prescribed treatment. Parallel with this, a patient who already has a good neurocognitive capacity finds it easier to take his or her medication. Taken all together, results from the second study show that patients in remission are more satisfied with their treatment and have better insight as well. These findings connected to the result in the third study that shows the relationship between remission and having a better neurocognitive capacity. There is therefore nothing in our research that speaks against the relationships already presented but, on the contrary, our findings simply strengthen earlier observations.

In our study the patients’ choice of medication has not been guided by any consideration other than the physician’s choice and the patient’s own wishes. Patients with good adherence and a low risk of only partial compliance as a consequence of good neurocognitive capacity obviously have better preconditions for profiting from the pharmacological treatment. When the results from the first four years were compiled 38 percent had achieved at least cross-sectional remission. Since the beginning of 2005 the goal for the treatment of patients with schizophrenia spectrum syndrome in the NU-Health Hospital has been remission. By the end of 2008, just over 50% had achieved remission. This increase is based more on the awareness among the care providers of remission as
the goal for treatment than on a conscious pharmacological methodology to achieve this. Even if the group of physicians responsible for care knows very well that patients taking depot medication or medication that acts over a long time experience a better effect (Barnes, et al., 1994; o Fleischhacker, et al., 2003) if they try to motivate the patient to accept this form of treatment, it is nevertheless true that in the end it is the patient who makes the decision about his or her intake of medication. The advantages of medicines given by injection are obvious to the caregivers. The form taken makes clear exactly how much medication a patient consumes and when an interruption takes place it will then lead automatically to a motivational intervention from the caregiver so that treatment can be started again. Our research does not contribute anything additional in this area, an assumption that is however in line with existing research that an increased usage of long acting antipsychotic medications probably will increase the occurrence of remission for those who are basically positive towards treatment but do not manage to take their medication according to the treatment plan.

3.4 Restrictions in the concept of remission

Remission is defined on the basis of a review of symptoms during a specific time interval. None of the scores for the eight symptoms may be over 3 points on the PANSS and for remission to be fulfilled this state must have been stable during a period of at least six months (Andreasen, et al., 2005). The problem is, however, that an evaluation using PANSS only concerns the previous week. To guarantee that the patient is in stable remission the patient must be examined using PANSS each and every week. If this is already a very demanding task to be carried out during a trial of medications, where extra staff resources are provided, it is an almost impossible task for caregivers providing routine medical care. A consequence of this statement is that the definition of remission needs to be modified to be usable in a clinical context. One possibility is to only apply the symptom criteria that define cross-sectional remission in clinical practice. The weakness with such a solution is that it does not
provide any information on how stable the patient’s condition is over
time.

Certainly repeated examinations over a period of years provide valuable
information about a patient's state of health. Patients who reach a stable
state, either in remission or not-remission as well as patients who move
between these two states provide meaningful information for the case
manager and the physician who has responsibility, information that can
provide the basis for plans for future care and treatment program. It is
plausible that one would receive more extensive knowledge of a patient's
illness if one combines cross-sectional remission with information from
the journal that covers the time between evaluations. If the patient has
not needed an adjustment in dose or even new medicine and has not
had unplanned doctor's visits or hospitalisations then there is a strong
support for believing that the patient has been stable between the two
consecutive evaluations. Information can furthermore be collected from
close relatives or municipal caregivers as complement to the collected
knowledge within hospital care from staff and journals.

An assumption that partially underlies the structure of the concept of
remission is Weiden’s model for Response, Remission and Recovery
(Weiden et al., 1996). The idea is that the first step is the basis for the
next. In the same way we could state in our work that the patients in
remission had a higher functioning level in all areas than those that did
not attain it. In this respect the study lends support to the hypothesis.
However, if we look at the distribution within both groups there are
interesting deviations.

The variable “level of function” was constructed by assessing the total
number of needs, both met and unmet, according to the Camberwell
Assessment of Need (CAN). Then the participants were assigned to three
groups (cut-off points=27.60%, 63.00%): Good Function (GF) (33 male
patients and 34 female patients), Intermediate Function (IF) (47 male
patients and 39 female patients), and Poor Function (PF) (60 male
patients and 30 female patients). Participants described as GF had a
mean of 2.12 needs ($SD=0.86$), those described as IF 4.91 needs ($SD=0.83$)
and those described as PF 8.73 needs ($SD=1.70$). Further analysis (Chi-Square, Goodness-of-fit, 5% level) indicated that the three groups were randomly distributed with regard to diagnosis.

![Remission vs Function](image)

**Figure 4.** Relationship between the patients’ function level according to the Camberwell Assessment of Need scale (CAN) and their remission status.

In the Remission group slightly less than 20% of the patients have a low functioning level, compared to about 15% of those who are not in remission but in spite of that belong to the group that is functioning best (figure 4). The same picture is obtained even when the patients are examined using UCSD Performance-Based Skills Assessment – Brief version (UPSA-B) (Patterson, Goldman, McKibbin, Hughs, et al., 2001; Mausbach, Harvey, Goldman, Jeste, et al., 2007). The nuanced image is obtained when not only the groups’ average scores are compared but when each individual’s ability is compared head to head. Our reflections based on the results obtained are that Weiden’s model needs to be developed further. It is not enough to simply examine the prevalence of symptoms to create an understanding of the patient’s functioning level. In order for the definition to be accurate, the evaluation of symptoms
must be separated from the evaluation of the ability to function. Neurocognitive ability must also play a vital part in the model as neurocognition is important for both the possibility of attaining remission and the level at which the patient can function. Parallel with this, there are patients who function at a low level even though they are in remission as a consequence of poor cognitive performance, and the reverse is also seen. To create an accurate picture of the patient’s situation, neurocognitive ability, symptom control and functioning ability must each be systematically examined (figure 5). Another way to describe the relationship is to discriminate between symptomatic and functional remission (Bowie, Reichenberg, Patterson, Heaton, et al., 2006; Carlsson, et al., 2006; Kopelowicz, Liberman, Ventura, Zarate, et. al., 2005; Paper III).

Figure 5. Our research indicates that both remission as well as level of functioning are affected by the patient’s cognitive ability. Parallel with this there is a strong relationship between having attained remission and having a better functioning level.
3.5 Future research

Research relating to symptomatic and functional remission is still in its infancy. Several parallel tracks need to be followed-up. Knowledge on an individual level concerning the importance of remission needs to be investigated further and to be put in a long-term-perspective. The significance of an increasing number of patients attaining remission as a product of goal-oriented treatment programs must also be examined. A central question is if patients whose symptom level is reduced in order to achieve remission, at the same time develop a higher level of functioning. It is possible that a certain amount of time in remission is needed before it is possible to detect an improved level of functioning. Another central question is if treatment directed towards increasing the prevalence of remission, could improve the life-curve described by Lieberman in cases of schizophrenia, both individually and collectively?

At the same time there is a need for further development of the techniques for evaluating functional level. The differences between the social politics in different countries results in varying levels of living alone and of early retirement (Harvey, Helldin, Bowie, Heaton, et al., in press). An uneven balance between resources and needs lead to false positive and negative results respectively. The results that are found also depend on the method of investigation that is chosen. The CAN-scale indirectly describes an individual’s ability to function by registering the number of areas in which the individual cannot manage to perform on his or her own without help. The scale is not influenced by external factors but is based only on the individual’s functional level. The Strauss-Carpenter scale, by contrast, is affected by external factors. An individual can have a potential capacity to work, but because of widespread unemployment still cannot find a position and instead quite simply becomes a candidate for early retirement. The patient then comes to appear as less capable than his or her true capacity might indicate. The reverse may also be true, if, for example, a patient needs sheltered living but is not provided with such because of a commonly occurring shortage of such facilities and thus, paradoxically, is seen as better functioning than is actually the
case. UPSA-B is based on a test situation and therefore describes primarily the patient’s innate capacity in the absence of influences from the societal setting or the existing political situation. UPSA-B is one of many available techniques that we believe is well suited to illuminating functional remission.

Additional areas that are essential to an understanding of the importance of remission are the situation of family members and the medico-economic aspects of the results of various kinds of treatment.
4. Conclusions

In this dissertation we have examined the utility of introducing a qualitative goal for the treatment of patients with schizophrenia spectrum syndrome. In this study, patients with schizophrenia, schizoaffective disorder and delusional disorder have been studied with respect to the importance of symptomatic remission as this concept was presented in 2005 by an American expert group and in 2006 by a European expert group (Andreasen, et al., 2005; Van Os, et al, 2006). The patients have been studied at several times during the period 2000 to 2008. The hypothesis proposed was that patients who have attained a stable level corresponding to remission would show superior outcome in almost all respects in the investigations that were carried out. The patients' functional level, the degree to which they were established in society, their need for medical care, quality of life, burden placed by the illness, satisfaction with the care received and their understanding of the illness were all studied and in all respects it was found that patients in remission displayed better results and a more positive attitude toward their situation than did those not in remission. The results were unequivocal and the converse was not found for even a single parameter. The conclusion is that remission ensures a better life situation for the patient.

The study shows at the same time that it is more or less impossible to meet the time criteria demands of symptomatic remission. This as a consequence of the inherent methodology in PANSS which demands that the patient must be evaluated every week. A modified form for use in clinical practice is to determine with the help of information from patient journals, care givers, and relatives that the time between two patient examinations does not depart from the results of these examinations. Another, probably safer method, is to only determine the occurrence of cross-sectional remission and complement this finding with data about the incidence of hospitalisation or other reliable signs of periods of deterioration in the intervening period between evaluations.
Approximately one fifth of the patients in remission have a low functional capacity at the same time that the reverse is true for about 15% of the patients not in remission who do have a functional capacity comparable with that shown by the best functioning in the remission group. To be in remission implies that conditions for a good functional level exist, but does not exclude the opposite. In order to clarify the patient’s capacity it is necessary to divide remission into two parallel dimensions, symptomatic and functional. An objective formulation of an individual’s functional capacity is complicated because this capacity is affected several kinds of environmental factors. UPSA-B is the method that in our research has shown itself to be most promising since it is not affected by local external conditions or by differences between two countries.

In addition to complementing symptomatic remission with a functional dimension in the future, our group plans to follow up by examining the importance from both an individual and a societal perspective of more patients achieving remission. Our research methodology will then be complemented by following individual patients over time in contrast with our work to date, which has been based on patient groups that have achieved or have not achieved remission. A central question to be addressed is if patients being switched from non remission to remission will improve their functional ability and if so, how long time it will require before they perform on the same level as patients who were in remission from the very beginning. This project will be carried out at the NU-Health Hospital up to 2016 by a multidisciplinary research group consisting of researchers from psychiatry, psychology and occupational therapy.
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The Importance of Remission in the Treatment of Patients with Schizophrenia Spectrum Syndromes

The goal of this thesis was to investigate the hypothesis whether symptomatic remission for patients with schizophrenia spectrum syndrome would provide practical and qualitative benefits for patients and for society.

The first work (Paper I) examines the relationship between cross-sectional remission and the patients' practical resources. The patients' adaptation to society as well as their employment, living situations and social networks were studied. Their activity of daily living resources are described in terms of the extent to which they could pursue various undertakings autonomously. Their need for care was also studied. The results showed that the patient group that had achieved remission scored better on all of the variables studied, had better resources and less need for medical care and sheltered housing.

The second work (Paper II) analysed the relationship between cross-sectional remission and quality of life, burden placed on patients by the illness, and the patients' satisfaction with care received and with their medication, and also their capacity for understanding their symptoms and their illness. Even the results of this study showed that the patients in the remission group had a better quality of life, bore a lesser burden, were more satisfied with their care and had better insight into their illness.

The third work (Paper III) studied the patients' neurocognitive capacity to see if a higher capacity resulted in a higher percentage of patients achieving remission. The results showed unequivocally that the patients in remission consistently performed better in the cognitive tests. They also showed that they even had a larger vocabulary indicating a higher premorbid capacity.

The fourth work (Paper IV) followed the patients over an average time of 65 months. In this study, the patients' needs for medical care and for housing were investigated. Patients who were not in cross-sectional remission at baseline had for all the measured variables a higher consumption than those in remission even if the differences were not significant, except for patients who lived in sheltered housing and who had greater need for medical care.

Taking all these findings together, the result of this thesis shows that the attainment of remission provides practical and qualitative advantages to the patients and to society.