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## SCHIZOPHRENIA IN A LONGITUDINAL PERSPECTIVE clinical and neurocognitive aspects

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# SCHIZOPHRENIA IN A LONGITUDINAL PERSPECTIVE

CLINICAL AND NEUROCOGNITIVE ASPECTS

Jonas Eberhard, MD



**LUNDS**  
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## **Akademisk avhandling**

Som med vederbörligt tillstånd av Medicinska Fakulteteten  
vid Lunds Universitet, för avläggande av doktorsexamen i  
medicinsk vetenskap i ämnet psykiatri, kommer att offentligens försvaras i Palaestra Hörsal,  
Universitetsplatsen, Lund  
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Fakultetsopponent:  
Professor Jozef Peuskens  
University of Brussels  
Saint Jozef Hospital, Kortenberg  
Belgium

## Abstract

**Objective:** To explore the long-term course and to study factors of potential relevance for the treatment and rehabilitation process of patients with schizophrenia and schizophrenia-like disorders. Specific issues concerned cognitive reduction, tardive dyskinesia (TD), prolactin-induced side effects, remission and lack of insight.

**Method:** A naturalistic multicenter study of 225 patients, diagnosed with schizophrenia or schizophrenia-related psychotic disorders and treated with risperidone at study entry, of whom 166 participated in a 5 year longitudinal extension of the original study. Patients were assessed annually with respect to relevant background and clinical factors. Specific to the study is the extended use of parallel patient and clinician ratings.

**Results:** The setting of the main study seem to have resulted in an extremely low attrition rate and high objective drug treatment adherence. Patients were much more apt at self-rating symptoms, global illness and side-effects than expected. Having had many previous acute episodes was associated with more pronounced cognitive reduction. TD was not common, associated with an extra magnitude of cognitive slowing and appeared to be only partly drug related. High levels of prolactin could not be linked to any side effects. Remission was not attained by 40% of the patients. Remission reflected clinicians' but not patients' ratings of symptoms and was linked to social outcome but not to cognition. One third of the patients had a clinically significant lack of insight, which was associated with low premorbid IQ and with executive problems.

**Conclusions:** The extended use of parallel ratings by clinicians and patients, and the focus on optimizing drug treatment appear to have fostered an unusual degree of patient involvement in their own treatment and thereby excellent treatment adherence. These features can be implemented in routine clinical management as a "small steps in the right direction" strategy. To attain cure we need a grand break-through in our understanding of the disease.

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Front cover:

Lighthouse, "Sunshine from Darkness poster" 1992, Gift from Patsy & Hal Hollister, La Habra Heights, Los Angeles, founders of National Alliance for Research on Schizophrenia and Depression (NARSAD) artworks

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Till Julius, Emil, Max & Mia

'Where is the wisdom we have lost in knowledge? – Where is the knowledge we have lost  
in information?'  
T.S. Elliot

Where is the information we have lost in our data?



# Contents

|   |    |
|---|----|
| Summary.....  | 7  |
| <i>Introduction</i> .....                                 | 11 |
| <i>General aim of thesis</i> .....                        | 23 |
| Specific aims for the separate reports of the thesis..... | 24 |
| <i>Subjects &amp; Methods</i> .....                       | 27 |
| <i>General Discussion</i> .....                           | 41 |
| <i>Conclusions</i> .....                                  | 49 |
| <i>Acknowledgments</i> .....                              | 51 |
| <i>Populärvetenskaplig sammanfattning</i> .....           | 53 |
| <i>References</i> .....                                   | 57 |
| Paper I:  |    |
| Paper II:   |    |
| Paper III:  |    |
| Paper IV:   |    |
| Paper V:  |    |

# List of papers

## Paper I:

*Eberhard J, Riley F, and Levander S (2003).*

*Premorbid IQ and schizophrenia – "Increasing cognitive reduction by episodes".*

*European Archives of Psychiatry and Clinical Neuroscience 253: 84-88*

## Paper II:

*Eberhard J, Lindström E, and Levander S (2006).*

*Tardive dyskinesia and antipsychotics: a 5-year longitudinal study of frequency, correlates and course.*

*International Clinical Psychopharmacology 21: 35-42*

## Paper III:

*Eberhard J, Lindström E, Holstad M, and Levander S (2007).*

*Prolactin level during five years of risperidone treatment in patients with psychotic disorders.*

*Acta Psychiatr Scand 115: 268-276*

## Paper IV:

*Eberhard J, Levander S, and Lindström E.*

*Remission in schizophrenia: analysis in a naturalistic setting.*

*Manuscript, submitted for publication*

## Paper V:

*Eberhard J, Lindström E, and Levander S.*

*Poor insight in schizophrenia is associated with low premorbid IQ and executive functioning, but not with failure to self-monitor.*

*Manuscript, submitted for publication*

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## Summary

Schizophrenia is a lifelong disabling psychiatric disorder characterized by severe and variable symptoms, and a characteristic temporal pattern of acute episodes sometimes believed to lead to a cognitive deterioration. Residual symptoms and functional deficits are common in the disease. In the treatment of schizophrenia and schizophrenia-like disorders, the bottom line should be to improve functional outcome. Results from current long-term treatment strategies are unsatisfactory. This is unfortunate because there is scientific evidence for effective treatment strategies which are rarely used in 'everyday' practice.

Dopamine antagonist treatment remains the disease management cornerstone, both for the acute episodes and in the residual phase. Acute relapse episodes typically last a few weeks, whereas the residual phase, characterized by negative symptoms, cognitive deterioration, and social dysfunction, usually lasts for many decades. Antipsychotic drugs display their strongest effect on positive symptoms, which are almost obligatory during the acute episodes. The effect on the symptoms of the residual phase is much less impressive. Due to the unpleasant side effects, poor treatment adherence leading to relapse is common and understandable, particularly during the residual phase.

In order to explore the long-term course and to study factors of potential relevance for the treatment and rehabilitation process a 5-year naturalistic multicentre study of 225 patients initially treated with risperidone was started in 1995. 166 patients entered the longitudinal phase of whom 60% could be followed for five years. Patients were assessed by a comprehensive set of clinical methods with respect to relevant background factors, illness severity, symptoms, side effects of drugs, treatment adherence and cognition (for a subset of patients). Specific to the study is the extended use of parallel patient and clinician ratings for many clinical variables. Noteworthy is also the very low attrition rate of 40% over the five years – this is substantially lower than in other longitudinal studies of schizophrenia and schizophrenia-like disorders.

Cognitive reduction in schizophrenia has not been fully recognized as an important symptom domain until the last decade. In previous studies from our research group it appeared that some cognitive measures were much more affected than others among schizophrenia patients, and that the deficit in these measures displayed a stronger association with the number of previous acute episodes than with any other clinical variable. In a separate prestudy of this thesis, these findings were cross-validated on 35 patients with control of premorbid IQ via grades from the 9<sup>th</sup> class (15-16 years of age) of the Swedish school system. In line with the main hypothesis, patients having a history of many relapses were found to be more cognitively impaired, particularly with respect to response readiness. One possibility is that the acute episode is associated with some kind of neurotoxic effect. This is a controversial finding, but is in line with some older observations.



The main part of the thesis concerns topics of importance for the clinical management of patients. Firstly two types of side effects of drug treatment: tardive dyskinesia and prolactin elevation; and secondly two core clinical issues: remission, its definition and correlates, and lack of judgement and insight, which is very common among patients with schizophrenia and affects treatment adherence adversely.

Tardive dyskinesia (TD) is currently viewed as a disabling and possibly irreversible side effect of antipsychotic drug treatment. Our findings challenge this view on certain points: it appears to be more of a dynamic (i.e waxing and waning), rather than an irreversible condition; and not so strongly associated with antipsychotic drug treatment (it may be a motor symptom of schizophrenia as reported in older literature from before the era of antipsychotic drug treatment). Tardive dyskinesia was found to be associated with cognitive impairment, suggesting subcortical involvement, consistent with the hypothesis that TD reflects disturbed basal ganglia processes.

Prolactin secretion elevation induced by dopamine antagonists is assumed to cause sexual side effects, which could not be confirmed, neither could we confirm with certainty any other association with side effects. As reported earlier, risperidone produced a more marked increase of prolactin, with large individual variations. The level tapered off over the years to become normalized for many patients.

We attempted to validate the rather newly coined term of remission in schizophrenia, defined as an improvement of a predefined subset of PANSS rating scale items reflecting important symptoms, which in addition needs to be sustained for at least 6 months. This concept has been introduced after a series of consensus discussions between leading experts in the field. Eight predefined PANSS items have to be rated as ‘mild or better’ (three items on positive symptoms, two on disorganisation and three on negative symptoms). For a patient to be defined as being in *symptomatic remission*, often called *resolution*, it is sufficient that these “severity criteria” are fulfilled and not necessarily the time criterion of stability over 6 months. In our cohort we found 40% of the schizophrenia patients fulfilling the criteria for at least a symptomatic remission already at study entry (there was no information about whether the time criterion of six months duration was fulfilled or not). Thereafter, for practical reasons we used a time criterion of 12 months. The prevalence of remission using that definition stabilised between 55% and 60% after a few years. However, many patients went in and out of remission, which was strongly associated with social outcome as well as global indices of illness, but not with cognition.

Factors that were robustly associated with poor insight (which characterized 60% of the patients at start of the study and 40% after a few years) were poor premorbid IQ and poor executive cognitive functions. The results suggest that poor insight could be addressed by developing better methods of educating and training low IQ patients in coping with and understanding the disease soon after onset. Executive deficits seem to be caused by the disease and are treatment resistant by use of current treatment methods. We need to find methods to circumvent it.

Drug treatment adherence (compliance) was objectively measured via annual blood tests in the majority of the patients (i.e. the group of risperidone treated patients). It was very high every year (~95%). We interpret this finding as a consequence of the trial environment (involved clinicians with an interest in psychopharmacology) and the use of parallel ratings of salient clinical variables. This may have promoted a greater consensus between patients and psychiatrists, and more active and constructive patient involvement in managing/monitoring their own treatment, and possibly even improved insight.

The general conclusion of the studies forming this thesis is that it appears to be important to involve patients in the decision process by teaching them to self-monitor, and this works surprisingly well if the right methods are used. Another conclusion, which reflects the longitudinal approach, is that there are certain and to some extent substantial differences between findings from longitudinal studies and cross-sectional ones. However, a consistent finding is that patients with schizophrenia and schizophrenia-like disorders suffer from a chronic and relatively stable disease, which affects their life adversely in almost all life domains. Awaiting a grand break-through in research on schizophrenia we must take small steps in the right direction concerning treatment, rehabilitation and support. Such steps are defined and validated by research similar to the one of the present thesis, a kind of research that suffers from poor funding and little interest from those who should be concerned.



# Introduction

## Background

Schizophrenia is an aetiologically complex disorder which is believed to arise from the interaction of a range of factors acting at various stages of the life course. Initially recognized as a diagnostic entity around 1840, it can still be debated whether we are really much closer to a significant understanding of the disorder (Malmgren, 2005). Consequently, we do not have any really effective treatment for the disorder. Schizophrenia is a lifelong disabling psychiatric disease that often begins in late adolescence or early adulthood. It is characterized by severe and variable symptoms, including positive and negative symptoms, cognitive deficits and affective symptoms, and has a graded course of illness with acute and residual phases (Figure 1, adapted from Shepherd, 1989). The disease is 50% non-genetic, and as described in a recent review (Read et al, 2005), the possibility of psychogenesis still appears to have some validity. However, we may never be able to fully understand the relationships between the context/environment, the genetic risks and the development over the lifetime of highly complex disorders like schizophrenia.

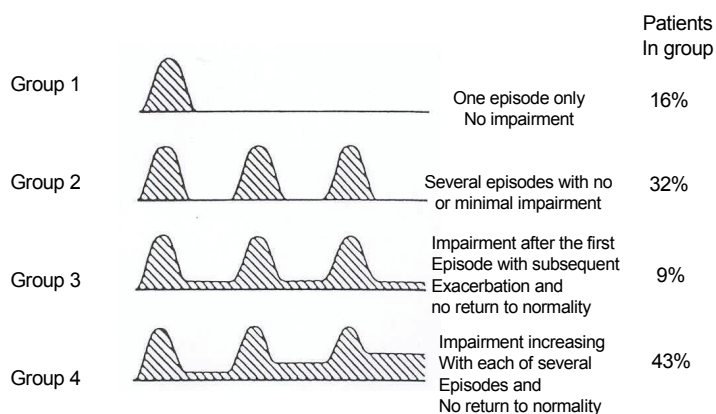


Fig 1. Graded course of illness in schizophrenia patients

## Cognition as a “symptom”

Cognitive impairment was recognized as a key symptom of schizophrenia by the pioneers, Morel, Maignan and Kraepelin, who actually regarded it as a dementia disorder. Bleuler focused on other symptoms, notably productive (positive) ones when he redefined the disease in the early 20<sup>th</sup> Century. A century later cognition was again recognized as a key and core symptom in the groundbreaking meta-analysis by Michael Green (1996). Nowadays almost everyone agrees that the characteristics of schizophrenia involve a range of cognitive and emotional dysfunctions (including perception, inferential thinking, language and communication, behavioural monitoring, fluency and productivity of thought and speech, hedonic capacity, volition, drive, and attention). There is currently an ongoing discussion in the literature whether cognitive impairment should be part of future DSM criteria for schizophrenia. A recent and seemingly prevailing view based on research on the large Israeli conscript database is that psychosis and cognitive impairment could be separate entities, occasionally manifesting in the same individual (Michael Davidson, personal communication, 2007). Whether or not cognitive impairment really is a core symptom, or rather the result of gene-environmental interaction will however, with no doubt, remain a “hot topic” for debate. Davidson and his group have been investigating the subtle cognitive and social impairments that schizophrenia patients have since childhood and adolescence (before the onset of illness), and hypothesized that schizophrenia is a disease in which below-average cognitive abilities and episodic psychosis converge to reduce social and vocational functioning. One observation to support this view is that lower paternal IQ is consistently associated with an increased risk of schizophrenia.

However, cognitive deficits in patients with schizophrenia are closely associated with functional outcome and furthermore it has been shown that adolescents with early onset schizophrenia have more global IQ deficits than other psychosis patients (Fagerlund et al, 2006).

The cognitive impairment almost certainly covers more than what is measured by traditional psychometric tests (IQ) and modern neuropsychological batteries, i.e. components such as **coping** and communicative ability (**social cognition**) (Lögberg, et al, 1999), and **opportunity to practice** cognitive skills. Thus, a wider conception of intelligence, like that suggested by Howard Gardner, might be more suitable in order to better understand the actual cognitive problems that patients have. Each of the abovementioned components can be assumed to contribute more or less to the resulting clinical picture, which is that around 75% of patients have impaired cognition as measured with neuropsychological test batteries. However, there is an enormous variation in cognitive reduction, including those 25% who appear to be more or less intact cognitively, sometimes nicknamed “superphrenics” (MacCabe, 2002).

## Antipsychotic treatment

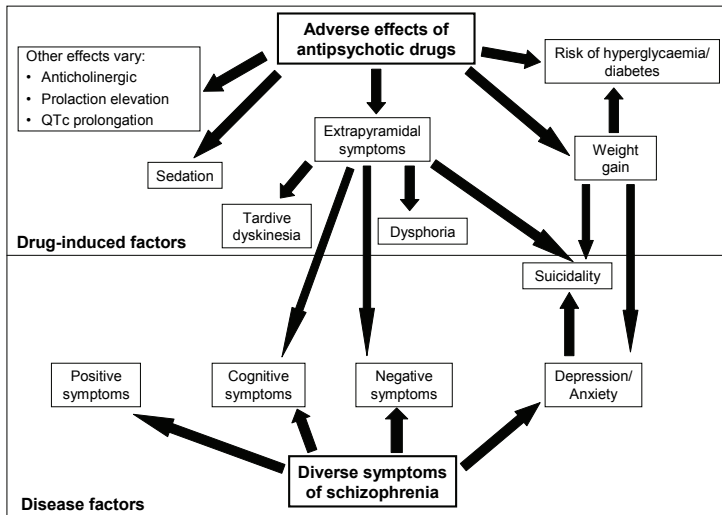
Early detection of the disease is commonly seen as best practice. It still remains to be proven that early interventions can delay or even prevent a new episode/exacerbation, but the idea to treat a disease before it has had time to cause damage appeals to common sense.

Dopamine antagonist treatment remains the disease management cornerstone, but due to the unpleasant side effects, poor treatment adherence leading to relapse is common and understandable. Acute relapse episodes typically last a few weeks, whereas the residual phase, characterized by negative symptoms, cognitive deterioration, and social dysfunction, usually lasts for many decades.

Although typical antipsychotics were proven to be consistently effective in the treatment of patients with schizophrenia, their widespread use has revealed many limitations (Lublin et al. 2005). Atypical antipsychotics were developed to overcome some of the limitations associated with typical antipsychotic medications, and to address unmet clinical needs. While EPS symptoms have become less problematic for patients on atypical antipsychotics (Tamminga and Lathi, 1996; Kane et al, 1998; Gerlach, 2002; Meltzer, 2004), other side-effects, such as weight gain, new onset diabetes and sedation, take on increased importance (Figure 2, reproduced with the publishers permission from Lublin et al).

There are reasons to be dissatisfied with what has so far been achieved by drug treatment of the cognitive impairment, and the above mentioned unmet needs (Hegarty et al., 1994). One important issue is whether newer compounds offer any real advantages in this respect compared to traditional typical antipsychotic drugs. A milestone in this ongoing discussion is the meta-analysis of cognitive deficits published by Green (1996), which suggests that indices of cognitive deficits are much better predictors of functional outcome than indices from any other symptom domain. Awareness of this previously neglected symptom domain of schizophrenia has now increased. In drug studies, as well as in clinical practice, cognition was only rarely assessed by comprehensive neurocognitive test batteries before the millennium shift.

**Figure 2.** Inter-relationship between disease factors and drug-induced adverse factors in the burden of schizophrenia (from Lublin et al, 2005)



Currently, comparisons among the antipsychotic compounds in terms of efficacy must address this core issue, in addition to the traditionally assessed effects on positive, negative, and affective symptoms, and the pattern of side-effects. Treatment has to be life-long in most cases. Therefore, side-effects must be few and manageable to ensure that patients are comfortable with their long-term treatment, in spite of failing insight and treatment motivation, which is characteristic of the disease.

## Treatment strategies

During the last three decades, knowledge in this field has grown substantially from three sources: Randomised Clinical Trials (RCTs), Phase IV trials and the experience which cumulates through routine clinical work. From this knowledge strategies have been developed for the treatment and rehabilitation of patients with schizophrenia that have been shown to markedly reduce the clinical, social and career morbidity and improve the efficiency of mental health resources. Several reviews of clinical trial literature have concluded that every person with a schizophrenic disorder should be provided with a combination of: a) an optimal dose of antipsychotics; b) psycho-education for patients and caregivers; and c) assertive outreach management. Yet, despite strong scientific support for the routine implementation of these ‘evidence-based’ strategies, few services provide more than the pharmacotherapy component, and even for this component knowledge generated from RCTs is not necessarily applied.

## Costs of treatment

Schizophrenia afflicts slightly less than 1% of the population (Saha et al, 2005), but indirectly it affects many more. Psychotic disorders are considered to be the most expensive mental illnesses in terms of costs of care per patient, accounting for 1.5% (UK), 2% (the Netherlands, France) or 2.5% (USA) of the total national healthcare budget during the 1990s (Lindström et al, 2006; Rössler, 2005). The Swedish figures are of a similar magnitude (i.e. two to three times more than the average population costs) according to the National psychiatric Services Coordination (Wieselgren & Milton, 2006).

In the 1990s, patients with schizophrenia occupied 25% of all hospital beds, and constituted 10% of the American population suffering a permanent and full disability (Rupp & Keith, 1993). The early onset and chronic nature of schizophrenia result in major cumulative direct costs from medication, hospitalization and sheltered living, and from the day society decided to build separate facilities (mental asylums and hospitals) for these patients, it has probably been one of the most costly diseases (Lindström et al, 2007a). How patients fared before that era is harrowing to contemplate. Actually, patients in the mental hospitals in Sweden from the mid 19<sup>th</sup> Century probably had a higher standard of living than the average citizen. Industrialization led to a rapid increase in the standard of living for the general population from the late 19<sup>th</sup> Century and onwards but society could not afford to match this increase for patients in the hospitals. In 1950, 35% of the Swedish Health Care budget was directed to such hospitals, where around half of the in-patients suffered from schizophrenia. In spite of that, the quality of life was poor compared to the general population. It could not go on for two reasons: money was needed elsewhere, and the criticism of the system grew rapidly until it was decided that mental hospitals should be closed – beginning in Italy in the late 1970s. Now the entire psychiatric field has to be satisfied with 10% of the Health Care Budget and the large mental hospitals are a thing of the past. Instead, people with schizophrenia comprise up to 14% of the homeless population in some large urban areas, and the indirect costs are huge (Rupp & Keith, 1993; (Lindström et al, 2007a) (Table 1). This represents a good reason to require that such patients should receive the best evidence-based treatment, including monitoring of metabolic risk factors and physical health. Such services are not provided, and it is not known how much there is to gain, either financially or in terms of quality of life, by adding effective treatment components to “treatment as usual”.



**Table 1.** Costs of schizophrenia (adapted from Lindström, 1996)

| Cost category    | Specification | Items   |
|------------------|---------------|---|
| Direct costs     | Medical       | Hospital days, out-patient care, residential institutions, sheltered accommodations<br>Medical professional, nursing and other health professional services<br>Drugs, appliances, other treatment<br>Rehabilitation |
|                  | Non-medical   | Capital costs<br>Public expenditures (crime, social welfare etc.)<br>Legal costs of carers  |
| Indirect costs   | Patient       | Loss of productivity: increased sick leave, disability pension (part/full), death before retirement age   |
|                  | Family        | Loss of productivity by time spent caring   |
| Intangible costs |               | Personal suffering (patient, family, relatives)<br>Premature death<br>Social isolation<br>Emotional distress<br>Depression  |

## Adherence to medication

Clearly “drugs don’t work in patients who don’t take them”, a statement valid in medicine and in general clinical practice, was recently depicted by Osterberg & Blaschke, (2005) and by Cramer & Rosenheck (1998). It is very reasonable to assume that adherence is still much poorer in chronic conditions, particularly if there is no immediate subjective gain of the therapy. Keith & Kane (2003) did a comparison of the degrees of difficulty to obtain sufficient adherence between different conditions. To obtain treatment adherence in schizophrenia proved to be almost as difficult as making obese patients participate in weight reduction programmes and equally difficult as making people exercise more. Discontinuation of medication, more common in patients with poorer premorbid cognitive functioning (Robinson et al, 2002), is the most powerful predictor of relapse. The risk of relapse when not taking medication has been shown to be up to 5 times greater than when taking it (Robinson et al, 1999).

Discontinuing medication is indeed very common in schizophrenia. During the first year after discharge the average rate of non-adherence is approximately 50% (Zygmunt et al. 2002). The overall postdischarge nonadherence rate has been estimated to be 7.6% per month, which is a major contributing factor to the annual cost of hospital admissions for relapsing schizophrenia (Weiden & Olfson, 1995).

## Remission

An operational definition of remission in schizophrenia was recently proposed by Andreasen and coworkers (Andreasen et al, 2005). It was defined as a stable reduction of a number of characteristic symptoms. The definition was not based on any specific study or set of data, nor validated against any external criteria, but reflected the vast clinical as well as research experience of the group. The US expert group focused on three dimensions of psychopathology that have been identified within the schizophrenic syndrome: positive symptoms; negative symptoms; and disorganised symptoms. These dimensions have been identified by factor-analytic studies of the PANSS and cover five symptom domains in DSM-IV and ICD-10 (American Psychiatric Association (APA), 1994; World Health Organisation (WHO), 1993; van Os et al, 2006). To be in remission a patient must have eight PANSS items rated as ‘mild or better’ (three items on positive symptoms, two on disorganisation and three on negative symptoms), and remain stable over six months. To be in symptomatic remission, often called “resolution”, the time criterion does not need to be fulfilled. There are several other factors, which have been shown to be salient in the recovery process, for example insight; cognitive deficits; and social functioning, that have not been included in the remission concept. Investigating to what extent those factors contribute in the remission/”recovery” process should be next step in this line of research.

According to a recent survey among carers for people with schizophrenia performed by EUFAMI (2007), 81 % of the carers felt that the chances of achieving remission improve if appropriate treatment is instigated shortly after diagnosis, and in order to stay in remission adherence to treatment was identified as the most important factor.

## How to improve treatment strategies

### 1) Shared decision making

Rational clinical decisions concerning treatment choices are crucial for treatment outcome in all medical fields. Such decisions should normally involve clinicians and patients. This is underlined in modern conceptions of the interactive process, aiming at consensus between patients and clinicians. However, when one party, the patient, suffers from reduced autonomy, this process becomes less self-evident. Ideally these patients should also be involved – and thereby *empowered* – in contrast to the previous paternalistic model. In other medical fields, “shared decision-making” (a strategy for including patients in therapeutic decision processes) has been extensively studied. In contrast such studies are rare in psychiatry (Hamann et al, 2003), but badly needed, simply due to patient

characteristics which are widespread in a major psychiatric illness such as schizophrenia: poor insight, cognitive impairment, and reduced autonomy. Clinical decision-making processes relevant to study in this context are (i) how clinicians prescribe antipsychotic drugs in relation to national or professional guidelines, (ii) how patient characteristics influence the prescription patterns, and (iii) how shared decision-making is implemented and how it can be improved. A literature search using the following key-words combined: schizophrenia; self-ratings; and symptoms, resulted in only a handful salient hits, underlining the conclusion that the application of shared decision-making to psychiatry is still in its infancy (Hamann et al, 2003).

Developing a template for shared decision-making can become the basis for effective monitoring and improved treatment compliance for people with chronic conditions. This is also likely to improve the relationship and collaboration between the clinicians and service users, and could also be of value for monitoring the fidelity to the intervention model. The concept includes involving a social network of caregivers in the implementation of strategies that might enhance adherence and outcomes. Shared decision-making for the monitoring of medication and accompanying non-pharmacological interventions represents a promising template in such a context.

In an RCT trial by Malm et al (2003) it was shown that the integration of shared decision-making was valuable for reaching better 2-year patient outcomes in the areas of social function and service user satisfaction, and the effect was still present after five years (Ulf Malm, personal communication, 2007). Furthermore, perhaps shared decision-making resulting from using both structured clinician and patient rating scales for monitoring the treatment and life-style of educated service users might improve not only compliance, but also the overall outcome and quality of community based treatment programs.

For non-psychiatric diagnoses that have generally attracted more clinical/treatment research funding than psychiatry, there is ample evidence that by developing "treatment as usual" into more effective evidence-based clinical practices there is a large potential for saving money on "indirect" costs, such as not being able to work, and needing support, in addition to saving on hospitalization costs.

Even if the cognitive abilities of schizophrenia patients could be improved by pharmacological means it is not certain that this would yield an improved social and occupational function, "unless accompanied by vigorous non-pharmacological interventions that specifically target these outcome areas" (Green, 2007). One relevant and basic intervention could be to promote more active patient involvement using both structured rating scales and cognitive dysfunction analyses for monitoring the treatment. Still it is not known for sure whether training of cognitive basic functions (like response readiness) and executive functions (like error checking) is possible among patients with schizophrenia, or if aids like handheld computers can improve overall functioning. This testifies to the enormous amount of clinical research that remains to be done in the area and raises the question why it has not been done already.

## **2) Follow-up on routine care**

Patients will be more likely to receive cost-effective treatment once clinicians regularly measure and analyze outcomes and costs in routine care. It is to some extent a question of knowledge climate and mind set. Academics who do research are the key people in this context, they are supposed to be role models for those who do routine clinical work. Unfortunately, many factors have made such persons almost extinct in Swedish psychiatry, more than in other comparable countries including our Nordic neighbours. Psychiatry, internationally as well as in Sweden, suffered badly during the “antipsychiatric campaign” beginning in the mid 1960s and abated only recently. One message was that “research is unnecessary; we know what we need to know already” (Rosenberg, 2005). Obviously, psychiatry, as a profession, knows much less about our most important diagnoses than our non-psychiatric colleagues know about theirs, partly because the brain is the most complex structure in the universe, and partly because we have not been encouraged and financed to research salient issues to any degree comparable with our colleagues in other fields of medicine.

Improving treatment processes and monitoring of these processes, for example, by encouraging psychiatrists to adhere to guidelines and treatment algorithms is likely to result in fewer schizophrenia patients being hospitalized and isolated, and more of them employed, perhaps realistically in special settings. While the financial reward may be small (though this has yet to be proven), it is certainly worthwhile for the improvement in quality of life.

## **Limitations in research**

### **1) Lack of long-term studies**

Although a five-year outcome can be viewed as the minimal time period for evaluating modifications in the natural course of major disorders by effective treatment, very few field trials of psychiatric treatment strategies have evaluated prospectively the benefits and risks of treatment for more than one year. One might compare this with the abundance of decade-long large-scale outcome studies of hypertension, coronary heart disease, diabetes, hyperlipidemia and an array of less common and important (from a national health perspective) physical disorders.

Five-year clinical practice evaluations of patient populations suffering from Serious Mental Illness (SMI) with low drop-out rates are rare. The main study of this thesis is a real life “near-naturalistic” study of every-day practice, treatment and outcomes for patients with schizophrenia and schizophrenia like disorders.

## **2) Bridging practical/naturalistic and RCT research**

The vast majority of clinical research dealing with the treatment of schizophrenia are short-term double blind RCTs required for the registration of new drugs. Several researchers (among them many involved with the Cochrane library in the UK) have called for longer term trials and more naturalistic “effectiveness” trials with pragmatic designs to complement the traditional RCTs. This is far from being implemented; we appear to prioritize reliability by rigorous RCT designs rather than generalizability in soft designs. Obviously, a bridge is lacking between practical/naturalistic and RCT trials, and this study provides an illustration of an attempt to link these two research areas.

While RCTs and Phase IV studies are extremely important, the results can only truly be evaluated by their practical use in routine care. Thus, RCTs, Phase IV studies and knowledge that cumulate during routine clinical work are all needed to improve real life practice. The trial design of the main study of the present thesis, with its measurement of every-day practice over time, is an example of the kind of bridge between RCTs and every-day clinical practice that Sir Isaac Marks sought for in an editorial (*British Journal of Psychiatry*) in 1998.

## **3) Collaboration between independent researchers, universities and industry**

Current schizophrenia research enables us to take small steps in the right direction but it is a long time since we saw any really significant break-throughs. For many reasons, practical as well as political, it is difficult to implement and incorporate research aimed towards making treatment more effective in the clinical ‘everyday’ practice. It is particularly difficult if the research concerns treatment strategies, which for political or ideological reasons are unwanted. Consequently there are many unmet needs in the treatment of schizophrenia and treatment is usually not evidence based, using a reasonably strict definition of the word. To move forward it is essential to define the small steps needed to best monitor rehabilitation, and to improve and optimize treatment of these patients. Such steps have to be defined and validated by research. This is the type of research that suffers from poor funding, but where the pharmaceutical industry traditionally has acquired much more skill than the practicing clinicians. It is encouraging to note that many clusters are currently being formed where Biotech & Pharma industry work together with universities and clinics to gather enough resources, power, and a critical mass to be successful. We are currently trying to build and develop an active collaboration between the main regional academic groups and private companies/institutions on both the Swedish and Danish sides of Øresund.

#### **4) Looking beyond medication**

Most other long-term studies are mainly concerned with the pharmacological component, but in this study we aspired to look beyond medication. Actually, the trial protocol served as a sort of monitoring guideline, which may have had a beneficial effect on outcome and treatment adherence. As was explored by Wayne Fenton in an *Acta Psychiatrica Scandinavica* editorial in 2003, an acute intervention conception of the disease must be complemented by the recognition of schizophrenia as a chronic and often life-long disorder. This has led to a shift of goals of the medical care from cure to disease management, and monitoring.



# General aim of thesis

The main aim of the studies upon which this thesis is based was to follow different aspects of outcome in a clinically representative group of patients with schizophrenia and related disorders over a long time span. At the time of inclusion the patients were adults, the majority of whom were out-patients. The study started at the time when the first atypical antipsychotics (except clozapine) were introduced to Swedish clinicians, and concurrently Sweden implemented a new model for the care of patients with Serious Mental Illness (SMI).

One focus is the problem of treatment adherence and specifically its links with one of the most common and problematic symptoms of psychotic disorders namely lack of insight. In a provocative way the problem can be formulated in the following way – “Clinicians whose patients disagree with their judgement denote such patients as lacking in insight”. Regardless of whether it is true, a reasonable issue then is in *which respects* do they differ and *how much* do they differ. One strategy of the main study was to perform parallel ratings by both the clinician and the patient (as often as possible), including the daring project of psychotic patients rating their own psychotic symptoms. Was this possible? Did it make clinicians and patients more interested in making good ratings? Did it increase cooperation and improve treatment alliance?

Another focus is cognition, recognized only during the last ten to fifteen years as perhaps the most important symptom domain in schizophrenia, at least with respect to functional outcome. This theme will be developed further in forthcoming publications. In this context cognition is studied as a correlate of other significant clinical variables and investigated cross-sectionally as well as in the very long term perspective.

A third focus is the issue of variability/stability of the psychotic disorders and its manifestations. Studies of larger populations of psychotic patients being assessed annually over five years are extremely rare. In addition, as will be evident to the reader, we were lucky to be able to keep a large majority of the patients in the study over six years. At the same period of time, new drugs were introduced and Sweden changed its strategies with respect to the target group of citizens with SMI problems. The fact that stability was upheld during such changes also helped verify that these were stable “chronic” patients. One aspect of “stability is whether patients reach treatment mile-stones (in this context “remission”), and if they then remain remitted over the following years.



## Specific aims for the separate reports of the thesis

### Pre-Study

- I. The main aim was to replicate a previous finding of episode-related deterioration of response readiness, with control over premorbid IQ, in a group of DSM-IV-schizophrenia outpatients with a relatively late onset of illness. The patients came from a university town and were expected to have a higher level of premorbid functioning and therefore possibly less pronounced cognitive deficits than the average schizophrenia patient has. The pseudo-experimental design provided us with a theoretical possibility for a retrospective analysis of the course of cognitive decline over 25 years (from 15 to on average 40 years of age).

### Main Study (II-IV)

- II. The aim was to investigate the nature of TD in a population of subjects who had long-term treatment for a psychotic disorder. Patients were treated either with risperidone only, risperidone plus another medication, or other antipsychotic drugs (typical as well as atypical). Apart from the association between TD, type of medication and dose, we also evaluated other potential correlates to TD. The relationship between TD and cognitive functions was investigated, with particular focus impaired response readiness. The pathology of TD, like Parkinson's and Wilson's disease, originates in the basal ganglia, i.e. the same area that is implicated for our ability to respond quickly and coherently, by forming a logistic scheme (for the timing and synchronization of muscle activity) to an intention to move (physical work). In analogy, problem-solving processing ("thought work") may need establishment of a logistic scheme of the cognitive processes in response to an intention to solve a problem.
- III. The aim was to investigate the effects of risperidone, its metabolite 9-OH-risperidone, and other antipsychotic compounds on prolactin levels. Furthermore the associations between prolactin level, symptoms, and certain side effects assumed to be prolactin-related (sexual dysfunction, mental side effects, and weight gain) were examined. Other pharmacokinetic and pharmacodynamic effects of risperidone were also investigated.

IV. This study had four aims:

1. To assess the frequency of remission in a naturalistic sample of patients with schizophrenia or schizophrenia-like disorders, representative of the patients who are treated in every-day psychiatric services, and how remission frequency changed over a five-year follow-up period.
2. To try to identify causal factors that changed a patient's remission status, for instance changes in medication.
3. To validate the definition remission versus global assessments of degree of illness, paying special interest to the additional predictive value of PANSS item G12 (lack of insight and judgment).
4. To investigate the association between remission and cognitive and social functioning.

V. The aim of this study was to analyse indices of insight and related concepts (awareness of illness and self-monitoring capacity) and relate them to clinical characteristics and cognitive functions. Of particular interest was the extent to which patients were able to judge their own condition within different domains (symptoms, side effects, and cognitive performance), and if poor insight is uni-dimensional or reflects different processes and aptitudes, for instance premorbid IQ, attention, memory and executive functions.



# Subjects & Methods

This thesis is based on three published studies and two submitted manuscripts. The first study (paper I) [A] was performed on a partly separate patient population, and aimed at replicating findings from three previous studies by our research group suggesting that some of the decline in certain cognitive domains was more strongly associated with the number of previous acute episodes than with any other disease characteristic. The other four articles (paper II-V) [B] of the present thesis are based on compiled data from a large naturalistic 5-year longitudinal patient material, where I was one among many investigators, and contributed with approximately one tenth of all patients. Our research group has published seven other articles based on this material, most recently together with Ulf Malm (as a guest editor), an *Acta Psychiatrica Scandinavica* 2007 Supplementum (S435): “Schizophrenia in a longitudinal perspective: optimizing patient management through active monitoring”. The focus of the thesis is put on the articles that are included, but there will by necessity be many references, particularly for more general issues, to the Supplementum articles.

To be included in this research project, patients had to give an informed consent, be above age 18, and suffer from schizophrenia or a related disorder, at least partially responding to antipsychotic treatment (Table 2). Patients on risperidone treatment could enter the large 5-year longitudinal naturalistic follow-up study, which was a national multicentre Phase IV observational study named RIS-SWE-14, initiated by Eva Lindström with support from the Swedish Janssen-Cilag affiliate.

**Table 2.** Inclusion and exclusion criteria for all studies

| Inclusion criteria  | Exclusion criteria   |
|---|--|
| Informed consent  | Refused participation, other serious illness or not able to give informed consent. |
| Diagnosed with schizophrenia or a related disorder according to DSM-IV (30) | Non-responder to antipsychotic drugs.  |
| Males and females >18 years of age.   |  |
| In- and outpatients.  |  |
| Responder or partial responder to antipsychotic drugs                       |  |

## A. Pre-study (Paper I):

Of the 72 consecutive patients, below 60 years of age with a registered diagnosis of schizophrenia (coded as 295 in the ICD-9 system) (WHO, 1977) I saw while serving in the out-patient units of the psychiatric clinics in Ystad and Lund University hospital during 1995-1998, 60 consented to participate in this research.

Four of these patients were too ill to be tested, and seven were excluded because of concomitant alcohol or drug abuse. In nine cases we were not able to obtain the school records necessary for the evaluation, primarily because they had been going to school abroad. Of the remaining 40 patients, one died before the study was completed. In four further cases, the original diagnosis was changed after more clinical information accumulated and thus they were excluded from the analysis. All of the remaining 35 patients with complete data sets (age 22–59) had a schizophrenia diagnosis according to DSM-IV (APA, 1994; for details see Paper I, Eberhard et al, 2003)

The remaining patients were allocated to three subgroups on the basis of the number of previous acute episodes: those having had 1; 2 or 3; or more than 3 previous acute episodes. Such episodes were defined as a distinct increase in symptoms, that required a substantial change in the treatment of the patients, either a change in status (from out- to inpatient), or a non-trivial change of medication (cf. Tuninger, 1997). A new episode was not tallied unless 6 months had passed since the previous one. The distribution of the patients into these three subgroups was fairly even.

### **Data on Medication**

Of the 34 medicated patients all except one received antipsychotics. Compounds were classified as typical or atypical (risperidone, clozapine, olanzapine or remoxipride). Sixteen patients were treated with atypicals alone (in a few cases in combination with each other). The remaining patients were treated with typical antipsychotics, in some cases in combinations with atypicals. Doses of the drugs were converted to an equivalent dose of oral chlorpromazine (CPZ) as described by Tuninger (1997).

### **Procedure**

In addition to asking for permission to obtain school records cognitive testing was performed. The test session takes approximately 90 minutes for a healthy subject and typically a much longer time for a patient with schizophrenia. In order to avoid exhaustion and keep motivation high almost all patients who completed all tests had to attend the test session at least twice to complete the battery. Cognitive testing was performed in line with recommendations from the Swedish Psychiatric Association.

## B. Main Study (Paper II-V):

Of the 60 schizophrenia patients that had consented to participate in this research, 13 individuals were medicated with risperidone, and were therefore invited to continue in the longitudinal prospective study. Initially this was a large naturalistic cross-sectional multicentre study concerning effects of risperidone treatment on schizophrenia or schizophrenia related psychotic disorders according to DSM-IV criteria (APA, 1994). Altogether 225 patients, initially treated with risperidone, were included. This Phase IV observational study initially had two overall primary objectives:

- 1) To identify the sub-groups of patients that benefited most from receiving risperidone, which at this time was a newly registered atypical antipsychotic
- 2) To define the optimal dose and plasma concentration interval with maximum efficacy and a minimum of adverse events.

After the first year the multicentre study was extended to a 5-year longitudinal study. The aim was to explore the long-term course of schizophrenia and schizophrenia related psychotic disorders, and to study factors of potential relevance for the rehabilitation process. It was amended as described in **Appendix 1**, whereby a number of additional assessments were included. In total 59 patients never entered the longitudinal phase (as described in further detail in Lindström et al, 2007b). All patients were treated according to good clinical practice with a combination of medication and psychosocial interventions throughout the study. At inclusion (Year 0) all patients were treated with risperidone. Some of the patients had additional psychotropic medication, i.e., other antipsychotics, benzodiazepines, lithium, anticholinergics or antidepressants. At inclusion and at every annual assessment (Year 1 to Year 5), information was collected according to the comprehensive study protocol.

## Scales and instruments

Patients were followed prospectively for five years with respect to changes in medication, symptoms, side effects, cognition, social outcome and a set of other variables (Table 3). A unique feature of the study design was that self-ratings corresponding to the ratings conducted by the investigators were collected from the patients whenever possible, in order to identify areas of disagreement between clinician and patient. Assessments utilized in analyses for each study are shown in Table 4.

**Table 3.** List of assessments, with numbers of participating patients, carried out during the study. Ratings carried out in parallel by both patients and clinicians are indicated in bold.

|   | Year 0   | Year 1   | Year 2   | Year 3   | Year 4   | Year 5   |
|---|----------|----------|----------|----------|----------|----------|
| Number of patients  | 225      | 150      | 122      | 112      | 96       | 101      |
| Background variables <sup>1</sup>   | X        | X        | X        | X        | X        | X        |
| <b>PANSS<sup>2</sup> (symptoms)</b>   | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> |
| 4S <sup>3</sup> (symptoms)*   | X        | X        |          |          |          |          |
| <b>CGI<sup>4</sup> (disease severity)</b>   | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> |
| <b>GAF<sup>5</sup> (symptoms &amp; functional capacity)</b>                       | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> |
| <b>UKU-SERS<sup>6</sup> (side effects)</b>  | <b>X</b> | <b>X</b> | <b>X</b> |          |          |          |
| ESRS <sup>7</sup> (side effects)  | X        | X        | X        | X        | X        | X        |
| AIMS <sup>8</sup> (side effects)  | X        | X        | X        | X        | X        | X        |
| Strauss-Carpenter test <sup>9</sup> (living circumstances)                        | X        | X        | X        | X        | X        | X        |
| <b>EuroCog<sup>10</sup> (cognitive functioning)</b>                               | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> | <b>X</b> |
| Plasma concentration of risperidone, 9-OH-risperidone and prolactin <sup>11</sup> | X        | X        | X        | X        | X        | X        |
| DIP-Q <sup>12</sup> (personality)   |          | X        | X        |          |          |          |
| SSP <sup>13</sup> (personality)   |          |          |          |          | X        |          |
| DAI-10 <sup>14</sup> (drug attitude)  |          | X        | X        |          |          |          |

\* 4S rated by patients only

**Table 4.** List of assessments utilized in analyses for each study.

|   | Focus areas in the studies of this thesis |                     |                    |                 |
|---|---|---------------------|--------------------|-----------------|
|   | TD Study II                               | Prolactin Study III | Remission Study IV | Insight Study V |
| Number of patients  | 166                                       | 218                 | 162                | 151             |
| Background variables <sup>1</sup>   | X   | X                   | X                  | X               |
| PANSS <sup>2</sup> (symptoms)   | X   | X                   | X                  | X               |
| 4S <sup>3</sup> (symptoms)  |   |                     |                    | X               |
| <b>CGI<sup>4</sup> (disease severity)</b>   |   |                     | X                  | X               |
| <b>GAF<sup>5</sup> (symptoms &amp; functional capacity)</b>                       |   |                     | X                  | X               |
| UKU-SERS <sup>6</sup> (side effects)  |   | X                   | X                  | X               |
| ESRS <sup>7</sup> (side effects)  |   |                     |                    | X               |
| AIMS <sup>8</sup> (side effects)  | X   |                     |                    | X               |
| Strauss-Carpenter test <sup>9</sup> (living circumstances)                        |   |                     | X                  | X               |
| EuroCog <sup>10</sup> (cognitive functioning)                                     | X   |                     | X                  | X               |
| Plasma concentration of risperidone, 9-OH-risperidone and prolactin <sup>11</sup> |   | X                   |                    | X               |

- 1) Background variables: sex, age, age at onset (Lindström et al, 2007b), nicotine (smoking and chewing tobacco /"snuff") (Levander et al, 2007a)
- 2) The Positive and Negative syndrome Scale for Schizophrenia (**PANSS**) measuring symptoms. The 30-item PANSS rating scale has been translated into Swedish and the construct validity and interrater reliability has been validated (von Knorring et al, 1992). The original PANSS version is divided into three sub-scales: 7-item scales for positive and negative symptoms and a 16-item scale covering general psychopathological items (G1-G16). The participating clinicians were trained to assess symptoms using PANSS.

**Remission:** We attempted to validate the concept of remission in schizophrenia. The criteria specify that a patient in remission does not score more than 3 on any of the following PANSS items: 1. Delusions; 2. Unusual thought content; 3. Hallucinatory behaviour; 4. Conceptual disorganization; 5. Mannerism/posturing; 6. Blunted affect; 7. Passive apathetic social withdrawal; 8. Lack of spontaneity and flow of conversation. In addition the symptomatic remission must be stable for six months.

- 3) The Symptom Self-rating Scale for Schizophrenia (**4S**) is a scale constructed in the mid 1990s by our group (Jedenius & Lindström, 1999; Lindström et al, submitted). Items are modelled according to a subset of PANSS items, selected and modified to be possible to use for self-ratings by patients with schizophrenia. The instrument comprises six symptom subscales and in addition it has two side effects scales: extra-pyramidal, 9 items and autonomic, 4 items. The response format is Yes/No and some items are reversed.
- 4) Clinical Global Impression and Improvement Scales (**CGI**) (Guy, 1976). This scale for severity of illness refers to the clinician's global impression of the patient. Scoring is done in relation to the clinician's clinical experience with the syndrome under assessment. Scores range from 0 to 7. The CGI refers to the clinical distance between the patient's current condition and that prior to treatment. The 7-point scoring system of the version used in this study ranges from -2 (much worse), -1 (moderately worse), 0 (unchanged) to 4 (greatly improved). CGI ratings were performed by the clinician (expert ratings) as well as by the patient (self-ratings) at each annual visit.
- 5) Global Assessment of Functioning (**GAF**) (APA 1994). DSM-IV defines Axis 5 refers to the assessment of the overall impression of a patient's symptoms and functional capacity. In that way the GAF score reflects the current need for treatment and care of a patient. The participating clinicians were trained to assess GAF scores at the start (Year 0) and at Year 1. A self-rating version of the original GAF scale was also used, in order to compare clinicians' and patients' assessments. A similar self-rating GAF scale is included in the DIP-Q instrument (Bodlund et al, 1998). Such data were collected in Year 1 and Year 2.
- 6) **UKU-SERS Clinician** (Linggaerde et al, 1987). This rating scale is a comprehensive side effect rating scale with well-defined items and scale steps, developed for usage in clinical drug trials and in routine clinical practice. It comprises ratings (0-3) of 48 single



items, a global assessment of the influence of the reported side effects on daily performance, and a statement whether an adverse event should result in discontinuation of the medication. The items are clustered into four sub-groups: Mental, Neurological, Autonomic and Other side effects.

**UKU-SERS Patient** (Lindström et al, 2001). This rating scale comprises the same 48 symptom questions re-phrased for self-ratings. Items are clustered into the same four subgroups as the parent scale (UKU-SERS Clin). The main difference between the two scales is that the sexual side effect items are constructed differently. The items physical dependence and psychological dependence in the UKU-SERS Clin were not considered suitable for self-ratings and are not part of the UKU-SERS Pat.

- 7) Extrapyramidal Symptom Rating Scale (**ESRS**) (Chouinard, 1980). This scale is a comprehensive rating scale for the assessment of neurological side effects occurring during treatment with antipsychotic drugs. The scale includes both subjective and objective information, and is structured into four subscales: subjective assessment of extrapyramidal symptoms and objective evaluation of Parkinsonism, dystonia and dyskinesia, and two global subscales of dyskinesia and Parkinsonism.
- 8) Tardive dyskinesia was assessed by the Abnormal Involuntary Movement Scale (**AIMS**) (Guy, 1976). An AIMS rating is made on the basis of the highest level of severity observed and refers to facial and oral movements, extremity movements, trunk movement and global judgement. Item 11 and 12 refer to teeth status.
- 9) The **Strauss-Carpenter** Scale (Strauss & Carpenter 1972) was used to assess living circumstances. The original scale is an outcome scale with four items to evaluate the following domains: need for hospitalization, frequency of social contacts, employment status and symptom load. Each item is scored on a five-point scale from 1 (very poor), to 5 (very good). In the present study social outcome was rated according to a modified version of the scale (Lindström et al, 1995). Each patient's living arrangements (ranging from patient admitted to hospital to patient living independently), employment status (from patient unemployed to patient working or studying fulltime), and social life (from patient never meeting friends and relatives to patient meeting friends and relatives more than once weekly), were rated on a four-point scale to give a Global Social Functioning score ranging from 3 to 12.
- 10) Cognitive functioning, (following recommendations from the Swedish Psychiatric Association) was assessed at some centres for a subgroup of 90 patients by a comprehensive computerized cognitive test battery, the **EuroCog**. The test session takes approximately 90 minutes for a healthy subject and often longer for patients with schizophrenia. Clinicians at some centres thought that this was too time-consuming or lacked suitable facilities to perform the tests. Some patients did not participate at all six test sessions and some refused to be tested at all.  
The neuropsychological battery includes tests selected from the computerized neuropsychological **EuroCog system** (previously APT, Automated Psychological Test, Levander, 1987; Jensen et al, 1999, Eberhard et al 2003 [Paper I]), which is considered "State of the art" in computerized testing by Kane (1999). Tasks and instructions are

presented on a computer screen in front of the subject, who responds to stimuli and tasks by pressing keys on a custom-designed ergonomic keyboard. In order to reduce the vast number of variables that can be output from the system, a standardized set of meta-analysis variables, expressed as T-scores for healthy male controls aged 20-50 years (N>1000), were entered into the statistical calculations. The specific tests are listed below.

The **Associative learning test** modelled on the Digit Symbol Substitution Test uses letters instead of symbols. A translation table between 10 letters and digits is continuously present at the top of the screen. Letters are presented one by one in the centre of the screen. The subject responds by entering the corresponding digit and at the same time tries to learn the link between the letters and digits.

The **Long-term Memory test** is given 20 minutes after the Associative Learning test. The task is the same but without access to the translation table between digits and letters.

In the **Digit Span test**, digits are presented visually one after the other with process control of the length of the digit sequence. The task is to reproduce the presented sequence, first forwards for 13 sequences, and then in the reverse order for 11 sequences.

In the **Finger tapping test** five subtasks are presented: Tapping with the index finger and Alternation between the index and middle finger, for both hands, and Alternation between the right and left index finger.

In the K-test of **Selective Attention**, the task is to decide, as fast as possible, whether the letter k is present in a set of 10 characters presented in random positions on the screen. The test is administered in two versions, with either uniform squares or randomly selected letters as distracters. Rational subjects use a global strategy in the first and a sequential strategy in the second task.

In Elithorn's **Perceptual Maze test**, the task is to select a pathway through a triangular maze pattern that passes as many target dots as possible. Again, two versions are presented one version that encourages a sequential strategy (with target information) and one for which a global intuitive strategy is best suited (no target information).

The **Reaction time** module comprises four versions (simple auditory, simple visual, two-choice visual, and two-choice visual with auditory response inhibition (Go-NoGo).

The **Word recognition** test is a lexicon decision task in which subjects decide whether a combination of letters presented on the screen is a word or is nonsensical. After training on 32 three-letter stimuli, 80 4-letter stimuli are presented, of which 20 are commonly used words, 20 are less commonly used words, 20 are pronounceable non-words and 20 are non-pronounceable non-words. From the test an index of vocabulary and an index of word decoding speed is calculated.

**Meta-indices of Cognitive Strategies** are extracted from several tests, e.g., the Speed-vs-Accuracy, the Impulsiveness-vs-Reflectivity, and the K-test Flexibility indices (Wirsén Meurling, 1999).

- 11) **Plasma concentration** of risperidone, 9-OH-risperidone and prolactin. A blood sample was drawn between 7:00 and 9:00 A.M. before the first dose of the day, approximately 12 hours after the last dose. The blood samples were transported to the laboratory and stored frozen until analysed. The serum concentration of risperidone and 9-OH-risperidone was determined using high pressure liquid chromatography (HPLC).

The serum concentration of prolactin was routinely assayed by a radio immuno-chemical method (Djursing, 1987). The individual prolactin value was related to an upper normal reference value of 300 nmol/l for men and 500 nmol/l for women.

- 12) Aspects of personality disorders were examined using the DSM-IV and ICD-10 Personality Interview Questionnaire (**DIP-Q**; Ottosson et al, 1999).
- 13) Personality traits were examined using the self-report inventory Stockholm Scales of Personality (**SSP**; Gustavsson et al, 2000).
- 14) Patients' attitude to drugs was examined using the Drug Attitude Inventory (**DAI**; Hogan et al, 1983; Hogan & Awad, 1992).

## Statistics

The results of the psychometric tests are presented as T-scores ( $M=50$ ,  $SD=10$ ) of the EuroCog meta-analysis variables. The statistical analyses are based on these scores. Various standard statistical methods were used, as implemented in the SPSS 10.0 package, when analysing clinical, educational, drug and neuropsychological test results in the different patient groups.

# Results and comments

This five-year follow-up study differs from the few similar studies that have been performed elsewhere in the world in a number of respects: (i) inclusion criteria were deliberately broad; (ii) the attrition rate was very low and (iii) parallel ratings were performed both by patient and clinician

At baseline there were 132 men and 93 women included in the study, of mean age  $38 \pm 11.7$  years (range 18-79), age at disease onset  $26 \pm 8.3$  years (range 6-54) (Lindström et al, 2007b), mean weight 79kg (Neovius et al, 2007) and there were 63% nicotine users (Levander et al, 2007a).

A main finding of the study was that the very low drop-out rate (from Year 1 to Year 2 it was 19% [Year 1,  $n = 150$ ; Year 2,  $n = 122$ ], and then a further 14% dropped out between Year 2 and Year 5 [Year 5,  $n = 101$ ]). Furthermore much of the drop-out from Year 1-2 was due to the withdrawal of an investigator from the study. This is exceptionally low in comparison to other longitudinal studies over such a long time period with comparable patient populations.

As previously pointed out, another unique feature of the study is that patient self-ratings corresponding to the ratings conducted by the investigators have been obtained whenever possible, in order to identify areas of disagreement between clinicians and patients. GAF and CGI ratings performed by the clinician (expert ratings) as well as by the patient (self-ratings) at each annual visit, showed relatively high correlations within and between expert and patient ratings. The results are shown in Table 5 (Lindström et al, 2007b). Clinician GAF scores were 55–61, but overall, patients rated their symptom load / functioning (GAF scores) significantly higher ( $p < 0.05$ ), whereas clinicians and patients agreed well on the CGI scores. The intra-class correlation ( $r_{icc}$ ) for the six expert CGI ratings was 0.88 (single measures 0.55), the corresponding coefficients for patients were 0.86 (0.51) respectively. The median Pearson correlation between clinician and patient ratings was 0.53 (range 0.47–0.64). Thus, the CGI ratings were stable over time (no worsening and no improvement) and patients were well able to perform the task of self-rating their CGI. The  $r_{icc}$  for the six expert GAF ratings was 0.90 (0.60 for single items). The task of GAF ratings appear to have been more problematic for some of the patients as illustrated by a substantially lower consistency over time:  $r_{icc} = 0.79$  (0.39 for single items).

Inspection of the data suggested that some patients produced obviously inadequate GAF ratings (for instance clinician rated 35, patient rated 100). Using a cut-off of 1.65 SD difference in GAF rating (5%, one-tailed) singled out 33% of the patients as poor GAF raters. Re-analyzing clinician and patient scores without these patients resulted in much higher  $r_{icc}$  values approaching the clinician and non-significance of the difference in GAF scores between clinicians and patients. The most likely hypothesis concerning the poor GAF raters is lack of judgment and insight, which is assessed by the PANSS item G12. A comparison between competent and poor GAF raters showed that the poor ones had 0.61 higher G12 rating scores, a difference that is highly significant ( $p < 0.001$ ). The stability of symptoms and side effects was noted.

**Table 5.** GAF and CGI mean scores ( $\pm$  SD) assessed by clinicians and patients over five years

| Year |     | Clinician     | Patient       | Difference Clin/Pat |
|------|-----|---------------|---------------|---------------------|
| 0†   | GAF | 55 $\pm$ 14   | 67 $\pm$ 20   | 12*                 |
|      | CGI | 2.4 $\pm$ 1.2 | 2.5 $\pm$ 1.5 | ns                  |
| 1    | GAF | 58 $\pm$ 15   | 72 $\pm$ 18   | 14*                 |
|      | CGI | 2.1 $\pm$ 1.4 | 2.3 $\pm$ 1.5 | ns                  |
| 2    | GAF | 61 $\pm$ 15   | 72 $\pm$ 18   | 11*                 |
|      | CGI | 2.0 $\pm$ 1.4 | 2.3 $\pm$ 1.4 | ns                  |
| 3    | GAF | 61 $\pm$ 15   | 73 $\pm$ 16   | 12*                 |
|      | CGI | 2.1 $\pm$ 1.3 | 2.1 $\pm$ 1.5 | ns                  |
| 4    | GAF | 61 $\pm$ 15   | 73 $\pm$ 17   | 12*                 |
|      | CGI | 2.1 $\pm$ 1.3 | 2.2 $\pm$ 1.5 | ns                  |
| 5    | GAF | 60 $\pm$ 16   | 74 $\pm$ 16   | 14*                 |
|      | CGI | 2.2 $\pm$ 1.4 | 2.0 $\pm$ 1.4 | ns                  |

\*  $p < 0.05$

† At the start of the study, GAF scores were obtained for only a subset of patients ( $n = 76$ )

Furthermore, we had a compliance rate of 93% for the risperidone treated patients (initially 100% were treated with risperidone, dropping to approximately 60% at Year 5). For such patients, drug compliance could be verified by plasma samples. This adds to the validity of the study. For the other patients (no drug or other drugs) we cannot estimate drug compliance, but there is a reasonable assumption that it would not differ much. Patients with no medication (approximately 10%) participated in the study and were thereby, by definition, compliant.

## Results of separate papers

### Paper I

In a pseudo-experimental design the hypothesis of an episode dependent cognitive deterioration was tested, utilizing the calculation of a premorbid cognitive score based on school grades, validated by comparison with academic career and current cognitive performance ( $r=0.56$ ). Of the patient population investigated, half had college level studies or higher, and the overall school grades for the group were above average. The average Sum PANSS was 59 and GAF 59. The average level of antipsychotic medication was 230 CPZ-units, which suggested a moderate illness severity level. Two patients had no drugs, 16 had atypical and 17 had typical antipsychotics. Vocabulary was intact, but on average patients had lost 1 standard deviation (SD) in most cognitive tests. However, increase in response time amounted to 3.5 SD. There were no differences in cognition between drug types and no correlation with CPZ-levels. The number of previous episodes was positively correlated with reaction time prolongation and negatively correlated with short-term verbal memory, consistent with previous studies from our research group, suggesting that acute episodes cause specific cognitive reduction.

### Paper II

At study entry, 14% of the patients had TD according to a criterion index, and half of them were aware of it, but few reported distress. The occurrence of TD correlated neither with age nor with sex, but it was more common among patients with schizophrenia or bipolar disorder in comparison with the patients who had schizo-affective or schizophreniform disorders. The presence and intensity of TD correlated with all Positive and Negative Syndrome Scale for Schizophrenia symptom dimensions except the affective factor, but not with type of medication or chlorpromazine-equivalent levels. Tardive dyskinesia patients were cognitively impaired in tests reflecting mental speed, but not in other cognitive modalities. Over the 453 patient years of exposure, five patients developed TD and 14 became free of it. Our findings support the view that TD: (i) is a dynamic phenomenon; (ii) is only partly drug-induced; (iii) has a mild course during treatment with modern antipsychotics; and (iv) appears to have some correlation with mental slowness, similar to another basal ganglia disorder, Wilson's disease (Portala et al 2001).

### Paper III

At study entry the patients, who were all treated with risperidone, displayed levels of prolactin that were fivefold the norm in women, and threefold in men. When adjustment for sex, current age, and age at onset of psychosis was applied, prolactin levels did not correlate with diagnosis, symptom scores (measured by total-PANSS & subscales) or side effects. Drugs other than risperidone were not associated with high prolactin levels. For

patients on continuous risperidone monotherapy there was a marked linear reduction of prolactin level over all 5 years, so that several patients had normal levels at the end of the study (Table 6, from Eberhard et al, paper III).

**Table 6.** Prolactin level (nmol/l) for 59 subjects over five years, and concurrent sum of CPZ equivalent doses for all antipsychotic drugs and for risperidone separately.

| Year      | 0         | 1         | 2         | 3         | 4         | 5         |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Nmol/l    | 1192      | 730       | 533       | 543       | 369       | 412       |
| CPZ total | 264 ± 134 | 239 ± 137 | 263 ± 196 | 303 ± 231 | 273 ± 180 | 268 ± 216 |
| CPZ risp  | 232 ± 131 | 142 ± 140 | 131 ± 158 | 137 ± 161 | 130 ± 159 | 119 ± 159 |

## Paper IV

At study entry 40% of the schizophrenia patients were in symptomatic remission, stabilizing between 55% and 60% after a few years. The need for hospitalisation became less frequent over time; initially 31%, dropping to 7% Year 4 and 5. Many patients went in and out of remission. Remission was strongly associated with global indices of illness and with social outcome (except work/studies) but not with cognition. It appears that the current definition of remission is primarily a symptomatic measure, covering a subset of symptoms, some of which are not schizophrenia-specific. One conclusion from this attempt at a naturalistic validation of the current definition of remission in schizophrenia is that the connotation of the word, “remission” perhaps makes it sound better than it is. Our findings indicate that this milestone is in fact not reached for a large proportion of the patients (40%) (Table 7, from Eberhard et al paper IV). Remission is still just a step on the way to recovery. More studies are needed before we are able to conclude that remission as defined here is a clinically really useful concept

**Table 7.** Frequency of schizophrenia patients in symptomatic remission, (subdivided into patients with and without hospitalisation), and non-remitted patients

| Year | Remission       |                    | Unremitted | Total |
|------|-----------------|--------------------|------------|-------|
|      | Hospitalization | No Hospitalization |            |       |
| 1    | 17 (17%)        | 37 (37%)           | 46 (46%)   | 100   |
| 2    | 14 (16%)        | 39 (46%)           | 32 (38%)   | 85    |
| 3    | 8 (11%)         | 37 (53%)           | 25 (36%)   | 70    |
| 4    | 2 (3%)          | 35 (56%)           | 26 (41%)   | 63    |
| 5    | 3 (4%)          | 34 (51%)           | 30 (45%)   | 67    |

## Paper V

One in 3 patients displayed a relevant lack of insight (defined as a score of  $\geq 3$  on the PANSS item G12), which was associated with clinicians' ratings of symptoms and global illness but not with patients' ratings of illness severity. Some of the discrepancy scores between the parallel ratings performed by both clinicians and patients also correlated with lack of judgement and insight as measured by the PANSS item G12, and others did not (such associations appear to be domain-specific). G12 correlated strongly with clinicians' ratings of a set of PANSS symptoms, and with two global indices of illness severity, but not with patient ratings of illness severity. G12 scores were also associated with several non-executive indices of cognitive problems reflecting poor premorbid IQ. However, in addition, poor insight (and clinicians' global rating of illness) was linearly associated with a set of core executive problems, which were not mediated by poor premorbid IQ. In conclusion poor insight was associated with poor premorbid IQ and with illness-related core cognitive-executive problems.





# General Discussion

The main aim of this research was to investigate the association between clinical parameters and different aspects of outcome over a long period of time in a clinically representative patient population. The study was performed in a naturalistic setting addressing a broadly defined clinical population diagnosed with schizophrenia and schizophrenia-like disorders. In that respect, our findings can be generalized to the clinical reality facing clinicians in their daily work (Tansella et al, 2006). The result from the pre-study (Paper I) on episode-related cognitive deterioration confirms a previous finding by Levander et al (2001), but these findings have yet to be cross-validated by independent research groups. An explanation why this finding has not been identified before now may be because the EuroCog assessments used by our research group are special by the consistent focus on speed and accuracy as the building blocks of performance, by the high accuracy of the response time measurements, and by adaptive testing (the level of difficulty varies continuously with the performance of the proband – no floor or ceiling effects). Another reason why this has not been investigated extensively may be because the gradual deterioration process in schizophrenia has been part of general “text book knowledge” for many years, and is perceived by many psychiatrists as obvious and intuitive knowledge (the Kaplan textbook; Phil Harvey, personal communication, 2004). Nevertheless there are some recent and ongoing studies at other clinics aiming to replicate our findings; one of those is the Gotland study, which has been analysed and reported (in a preliminary form) in Levander et al, 2006. In this cross-sectional study, primary school grades are being collected for an analysis similar to that in Paper I. A strength of the Gotland study is that it includes all testable people with a diagnosis of schizophrenia and known to the psychiatric services of the island. Another strength is that the schizophrenia patients can be compared to many other diagnostic groups including bipolar patients, substance abuse patients, and patients with neuropsychiatric and personality disorders in a low migration, geographically stable rural population.

The main part of this thesis refers to the 5-year outcome study, which so far has resulted in nine publications (of which two are part of the thesis) and three submitted manuscripts (of which another two are part of the thesis). In the following discussion the papers and manuscript, which are not part of the thesis will also be referred to.

## Broad applicability of findings from this thesis

At the start of the study risperidone had just been introduced on the market. Results from clinical trials indicated a superior effect, and a more beneficial side effect profile in comparison to the first generation antipsychotics (Leysen et al, 1993; Fleischhacker, 1994; Kane, 1994; Marder & Meibach, 1994; Ayd, 1995; Cardoni, 1995; Carman et al, 1995; Kee et al, 1998; Tomasi et al, 2006). However, inclusion criteria for participating in clinical trials are narrow, for example, a defined age interval, no cardiac or neurological disorders, no abuse, not pregnant or nursing, on safe contraceptives. When the drug is introduced on the market it will be prescribed to quite a different population than the one studied in clinical trials. As clinicians do not change medication if a patient's symptoms are well controlled and there are few side effects, the target population for new drugs can be assumed to comprise of a higher ratio of problem patients with e.g., treatment resistant symptoms, troublesome side effects, elderly patients and patients with complicating somatic disorders, teenagers with vague psychotic symptoms and patients with comorbid disorders (Weinmann et al, 2005; Haro & Salvador-Carulla, 2006; Carnahan et al, 2006).

In the present main study the age span was wide (up to 76 years of age at inclusion), both sexes are represented and patients with various additional medication, co-morbidity with axis II and different somatic disorders were included. Most of the patients had a chronic disorder with a long history of antipsychotic treatment. The duration of pre-study antipsychotic treatment was for most patients more than ten years and even longer in the subgroup with core schizophrenia. Doses of risperidone and other psychotropic drugs were adjusted to optimize clinical response before inclusion, and at study start all patients were in a maintenance phase of treatment. All included patients were treated according to good clinical practice with a combination of antipsychotic medication and psychosocial treatment methods, but treatment programs differed between sites. During the five years a sub-group of patients discontinued antipsychotic drugs for varying periods of time.

## Parallel ratings by clinicians and patients

A unique feature of the 5-year study was the extensive use of expert clinical rating scales for symptoms, global illness/functioning and side effects, and corresponding scales for use by patients. We have found patients suffering from schizophrenia to be relatively better at evaluating their condition, including symptoms and degree of illness compared to what has been shown in earlier studies (Levander et al, 2007; Bowie et al 2006), provided that they are trained to perform these ratings. To use such instruments more than is commonly done could be a way to increase trust and improve the collaboration between patients, clinicians and carers, and an easy and realistic way to improve the poor prognosis via an improved treatment adherence. Not unlike any other disease, medication discontinuation rates are very high in patients with schizophrenia. Although side effects

can be very difficult to differentiate from some of the disease manifestations, which make them even more difficult to assess, we were surprised at how small the discrepancy was between the patients' and clinicians' ratings. This relative agreement between patients' and clinicians' assessments also helps explain the very low discontinuation rate seen over the five year study duration. Consequently we want to argue strongly in favour of including similar ratings as part of current "state of the art" practice guidelines. The rationale for parallel ratings was that shared structured assessments could be one way to increase the patients' participation in planning and implementing their own treatment. However, we had not expected that the two parties would agree to the extent they did. Much of our data also suggests that patient participation was indeed high. Patients were generally well aware of their illness and able to sort out symptoms from drug side effects. This opens for more active involvement of patients in monitoring their own treatment.

## Symptom ratings

The total PANSS score at inclusion was rather low in comparison with earlier studies measuring symptoms during maintenance treatment with risperidone (score was 59), also reflected in the fairly high mean GAF ratings (just under 60). However, there was a very large variation in total PANSS score among patients. One weakness of the present study is that we had no information on symptom scores before the switch to risperidone. There were only small differences between mean PANSS ratings for adjacent years and between study entry and Year 5. Thus, symptoms were stable year after year despite changes in both type and dose of antipsychotic medication, and co-medication. This finding is in line with previous studies. Efficacy does not vary much between different antipsychotic compounds, maybe with one exception, clozapine in refractory patients (Lieberman & Safferman 1992; Kurihara et al, 2005; Williams et al, 2006).

According to our diagnostic systems, DSM IV and ICD-10, schizophrenia is diagnosed by grouping individuals together according to certain symptom characteristics, i.e., a categorical hypothesis. However, many individuals with schizophrenia might not share any symptoms at all. Another approach is to identify symptoms that are statistically correlated with one another, and use that to group patients. This is a multi-dimensional model, based on the hypothesis that psychoses constitute a distribution of symptoms (profiles) rather than dichotomous categories. Most factor analyses of symptoms assume orthogonality among the factors. Earlier studies from the 1980s reported three symptom-groups or syndromes in schizophrenia, the positive-, the negative-, and the disorganized syndrome. During the last decade both four- and five-factor models have been presented. Common to all models is the identification of a positive and a negative factor, which overlap strongly with the conceptually defined Positive and Negative scales. Most studies also present an affective factor and a manic/excitatory factor. The fifth factor varies most between studies and is sometimes identified as a cognitive factor, sometimes as reflecting disorganization, and sometimes as a catatonic factor. Our analyses did not presuppose orthogonality and initially specified six factors for each of the years. Combining the six separate analyses (Year 0 to 5) yielded a consistent pattern of four almost identical factors

over the years, explaining 70% of the total variance. These four factors are the same as the ones identified by a majority of factor analytic studies of PANSS data: disorganization, negative, positive and affective factors. It is noteworthy that item G12 (lack of judgement and insight) was allocated to the positive factor as well as some other cognitive items (Rund et al, 2006; Huges et al, 2005). Overall the factor analyses support the validity of the PANSS ratings of the present study.

The data for the patient symptom ratings (the 4S scale) are reported separately (Lindström, Jedenius & Levander, 2007). For obvious reasons PANSS items cannot be adapted for self-ratings by patients – it is much too complex, neither does the factor structure apply. This creates difficulties when trying to compute indices of agreement between clinician and patient ratings. For the current discussion it suffices to say that the shared variance for symptom groups was larger than 50% - in line with the agreement for the other ratings of the 5-year study. The psychometric characteristics of the 4S scale are good enough for the scale to be used in clinical routine work.

## Severity and functioning ratings

In the present study, patients generally rated themselves higher on GAF than did the clinicians. The discrepancies between patient and clinician ratings were larger with GAF than with any other ratings. In contrast the correlation between clinician and patient CGI ratings were substantial and patients seem to be able to grade their global illness relative to other patients. Concerning the discrepancies a part of the problem could be poor insight, but there are many other possible explanations: e.g., denial, cognitive impairment, wish to please, and schizoid traits (Lauber et al, 2006; Cooke et al, 2005). Unlike schizophrenia patients it has previously been shown that patients with other psychiatric disorders tend to score themselves lower than the clinician, particularly patients with depressive symptoms and mood disorders (Bodlund et al, 1994).

## Remission

Remington and Kapur (2005) cautioned that the selection of the word, remission, without further qualification, is over-inclusive and confers unrealistic hopes. Citing these authors, “a schizophrenic patient in remission is likely to remain cognitively impaired, socially isolated, unemployed, and marginalized”. Obvious misuse of a similar word, *recovery*, has recently been criticised for the same reason (Harrow, 2005; Remington, 2005). It is probably wise to be careful when communicating words connected with so much hope. If we respect our patients we should provide balanced information about the likely prognosis of their illness. Similarly for carers, according to the recent large EUFAMI survey, the concepts of remission and recovery are usually not being discussed (EUFAMI, 2007). The prognosis for return to premorbid functioning in schizophrenia is

poor, and it is not fair to conceal this. There has been progress with respect to treatment of schizophrenia, better drugs as well as psychotherapeutic and psychosocial interventions, but we are far from the goal of finding a cure. Further resources should be directed towards making use of the knowledge we have acquired so far, so that the appropriate steps are taken in the right direction. But even if we reach the milestone of remission there is a long way to recovery. More studies are needed before we are able to conclude that remission as defined here is a clinically really useful concept.

## Living circumstances

Re-integration into society is the bottom line with respect to goals for treatment/rehabilitation. In many respects our findings are disappointing with respect to independent living, meaningful activities and social contacts. The study period coincided with a period of rather marked changes in the way the social and health care systems handled people with psychotic illness: the “Swedish Psychiatric Reform” which was launched in 1995. The social system got more responsibilities and the psychiatric system could not maintain the previous number of in-patient beds because of financial limitations (beds were reduced by 27% during the study period). The reform is likely to have contributed to the reduction of inpatient days and the increase of days in sheltered accommodations over the years of the study. However, the reduction of the number of hospital days over the 5-year period for the study patients was substantially larger (76%) than the national number. One possible explanation is that the participating patients got “better than standard” monitoring and treatment with respect to choice and dose of drugs, agreement between clinicians and patients, and psychosocial interventions. Better support and more social contacts in sheltered living compared with living alone in a flat, and other factors are also likely to have contributed. Even so, a substantial proportion of the patients had social contacts only with health care staff, and a large majority lacked meaningful daily activities (Lindström et al, 2007b). A detailed analysis of the Strauss-Carpenter data using a health economic approach has been published separately (Lindström et al, 2007a).

## Cognitive assessments

Neurocognitive impairment may be a common underlying factor for many of the problems in schizophrenia, for example, negative symptoms, self-monitoring problems, and lack of insight (Jensen, 2004).

The pre-study indicated that it is in particular the processing speed/response readiness that deteriorates over time, as a function of the number of acute episodes the patients suffer over the course of illness. These preliminary results encouraged us to explore the possibilities of improving response readiness through training. We have already done a

small pilot study involving 15 patients and found a clear effect of focused training of response readiness, using computers, where they receive an automated and immediate feed-back. We could also verify a positive effect on verbal working memory of the response readiness training, suggesting that the training effect could generalise to other cognitive functions. Previous studies of healthy controls have been unable to demonstrate training effects on response readiness, even after 15 sessions, but in patients with schizophrenia a significant effect was seen already after 5 sessions (CV Hellberg, unpublished manuscript). This is much in line with recent findings, confirming that these kind of computerized training devices could be a useful way to increase individual performance and motivation (Hasmann et al, 2004) in parallel with optimized pharmacotherapy. One might note the much larger extent to which development of aids and the effects of training have been investigated for other disorders characterized by cognitive problems, for instance brain lesions and dementia (Brun, 2007).

## Observed vs. self-rated side effects

Side effects of drugs may impair patients' acceptance of drug treatment and adherence. In the treatment of schizophrenia and related psychotic disorders this represents a major problem, since poor compliance reduces the effectiveness of treatment and the prognosis of these serious disorders. The observer UKU side effect rating scale is comprehensive and therefore time-consuming. For this reason a self-rating version of the UKU Side Effect Rating Scale has been developed. Most intercorrelations between clinician and patient scores for single, corresponding items, subscores of Mental, Neurological, Autonomic and Other side effects, as well as the Total score were rather high and statistically significant. The results support the validity of the SERS-Pat. Previous findings suggest that patient rated side effects may provide important clinical information not detected by clinicians (Lindström et al, 2001). Thus, the self-report side effect rating scale may be useful both as a stand-alone instrument and as a complementary measure to clinicians' ratings in clinical practice.

## Medication attitudes and compliance

Attitude to drugs is an important factor determining drug treatment adherence. Such attitudes were assessed by the DAI-10 instrument (Hogan et al, 1983). A large majority of the patients had a positive attitude to drug treatment possibly because the patients were involved to such an extent in rating symptoms and side effects of various kinds. It is also reasonable to assume that patients were informed more thoroughly about antipsychotic drugs than the average schizophrenia patient by being participants in a longitudinal drug study in which almost half of the patients experienced a switch to other drugs (or to no medication). One conclusion is that it is worthwhile to inform patients in a rational way

about advantages and disadvantages of antipsychotic drugs, and that a majority of the patients are able to comprehend such information. This has also been shown by Wolfgang Fleischhacker's group (Hofer & Fleischhacker, 2006).

What actually determines clinicians' and patients' choice of medication and other treatments? Formal methods like treatment algorithms are likely to be perceived as cumbersome, and to be unwieldy to be met with broad acceptance by clinicians working in a complex world. On an overall level clinicians probably prefer to base their decision on heuristics and intuition (Chris Hawley, personal communication, 2007). Is it perhaps the packaging of information that matters more than the information also in this field? Can skillful marketing compensate for product inferiority? These questions have been elaborated by Stefan Leucht who points out the importance (and relevance) of "marketing based medicine", without any negative connotations (personal communication, Waldemar Greil via Stefan Leucht, 2007). One of the *Acta Psychiatrica Scandinavica Supplementum* studies analysed similar issues. We could not identify any robust association between symptoms, side effects or any other relevant variable and a decision to change dose or drug (Levander et al, 2007b).

The design of the present study made it possible to assess compliance in an objective way for risperidone-treated patients. The compliance among those patients was very high (95%) compared to all other studies that the author is aware of (Lindström et al, 2007b), probably due to increased patient participation through the parallel ratings. Most other studies rely on indirect methods to assess compliance. A representative study, the Pan-European study (SOHO), reported a discontinuation rate of 22% due to lack of compliance over a 24 month period, along with another 25% partial non-compliance (Haro, 2005).

## Insight

Lack of judgement and insight is perhaps the most prominent and relevant problem when treating psychotic patients because it adversely affects treatment adherence. A comprehensive clinical data set was analysed by Rettenbacher et al (2004) in relation to compliance data. They found that 53% were fully compliant, 40% were partly compliant and 8% noncompliant. No doubt, poor insight is a major contributor to the high frequency of non-compliance. One way to handle poor compliance is through compulsory measures, which should be avoided as much as possible. An even less constructive way to handle the problem is to blame the patient for lack of motivation or an unwarranted negative attitude. To see insight as still another symptom, which a patient needs help to cope with, and having its roots in cognitive problems may be both a more fair and a more productive way to conceptualize the problem and find remedies.

Part of the solution of the problem lies in meeting the patient where s/he stands, which implies that the subjective attitudes and concerns of patients should be taken seriously.



One way is to offer patients tools that allow them to assess themselves better than they do intuitively using common language; in a way to teach them to become experts on self-monitoring. A similar route was taken 20 years ago by Liberman and coworkers in social skills training (Liberman et al, 1986), later followed by others (Nilsson et al, 1998; McGurk et al, 2007). This can be viewed as training of higher cognitive functions, close to real life, in contrast to the basic cognitive functions like response readiness, attention and the efficient use of the working memory systems. If it is possible to train patients to self-monitor more accurately, they can really be included in the treatment decision process (Hamann et al, 2003).

Involvement of patients in treatment decision processes, combined with the possibility of predicting whether patients will respond to treatment, creates the possibility of tailor-made treatment solutions. This should be seen as an immediate necessity in schizophrenia treatment as indicated by a recent survey from five European countries (UK, France, Germany, Spain and Italy), where it was found that more than 80% of patients with schizophrenia do not achieve satisfactory effectiveness with their initial antipsychotic therapy. Furthermore psychiatrists require 12-18months to determine this (Perry & Locklear, 2007).

Ultimately, in the future we may be able to predict the disease through pathophysiological measurements, and pre-empt the onset through personalized treatment. Such are the hopes of the current head of NIMH, Tom Insel, (Schizophrenia Research Forum, 2007), and then we would actually be able to intervene and stop the onset of psychotic episodes, and thereby make a real impact on the health of patients suffering from schizophrenia.

# Conclusions

The findings in this thesis should give the reader food for thought about schizophrenia patient care. On the positive side, patients seem to be able to participate much more actively in their own treatment than commonly believed, provided that they are equipped with proper methods and instructed in their use. The results of the recent EUFAMI survey (2007) certainly supports this view concluding that the most common reasons why people with schizophrenia do not adhere to their medication are treatment side effects and lack of education both regarding the condition and the possible benefits of staying on treatment. If we invite patients to really participate, rather than pretend they are, the outcome of the process can be denoted as “true empowerment”. If so, patients appear to develop a positive attitude to treatment, including drug treatment, and continue to have contact with the care-givers. By good treatment adherence, particularly with respect to drugs, there will be fewer relapses and less potential further damage to the patients’ cognitive machinery.

The sad message is that schizophrenia again presents as a chronic and severe illness carrying with it a range of problems within different domains, and interfering with participation in normal social life. As stated by Remington and Kapur (2005) “a schizophrenia patient (even) in remission is likely to remain cognitively impaired, socially isolated, unemployed, and marginalized”.

The present thesis is an example of a fruitful collaboration between independent clinical psychiatrists, clinical researchers representing different psychiatric research frontiers, universities (each with little funding) and a pharmaceutical industry, willing to recognize the needs of the patient as a common denominator. In this case, the synergic effect of the interaction of one clinician and two industry representatives produced research, which hopefully will ultimately benefit the patient.

The broad and comprehensive outcome measurements, including effectiveness rating scales, patient attitudes to treatment, and a cost-effectiveness analysis could serve as a good example of the kind of monitoring that ought to be mandatory for the continuous quality assurance and evaluation of mental health services.

A final take home message of this study and thesis is that one of the most profitable societal investments should be increased funding for treatment research in the field of serious mental illness, and subsequently to make use of the research findings by launching evidence based treatment programs. Such a development has started, having its epicentre in the British Isles, and slowly spreading via the Netherlands, to the rest of Europe. It is however a part of human nature that we are much more likely to adopt something which has been developed by ourselves or at least comes from our own country or culture. This

thesis is based on a Swedish multicentre investigation performed in a large number of primarily out-patient units, all across the nation, therefore it is reasonable to assume that the conclusions can be generalized at least to the Swedish situation. In this context it can be seen as a golden opportunity that extra resources are now becoming available for the development of Swedish psychiatry, as suggested by a national committee (an accident investigation advisory group) appointed by the government after the killing of the Swedish minister of foreign affairs, and some other high profile violent crimes committed by citizens with serious mental illness.

If the results and summaries of this study will be of some value and guidance to help politicians catch up, and re-establish Swedish psychiatry and health care to an appropriate Western European standard it would be very encouraging, and make all the years spent with this project worthwhile.

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To Sophia, my dear wife, I would like to say that I really hope that you can still remember me in other situations than sitting in front of the computer. Our four wonderful children Julius, Emil, Max and Mia, all born during the work with this thesis, have made me become less restless as a person, and much more enduring when it comes to remaining in one place. But, understating it slightly...., sitting down is not always adequate with three

small boys running around, and consequently, Sophia - I suppose it is your turn now, after having had to rush around so much over the last 10 years!

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I know I have forgotten many of you, but neither have time nor energy left to reconsider (after again having been sitting all night working with this). Thanks to Jonas Palm at Media Tryck. You have surely extended the deadline several times now 😊

# Populärvetenskaplig sammanfattning

## (Summary in Swedish)

Schizofreni är en kronisk och handikappande sjukdom som karakteriseras av allvarliga men fluktuerande symtom, med återkommande akuta episoder. Sjukdomen är förknippad med reducerad kognitiv och social funktionsförmåga. Patienterna vilka i regel insjuknar i unga år, bibehåller vanligtvis kvarstående restsymtom och därmed associerade stigma fram till ålderdomen.

Det övergripande målet för behandlingen av schizofreni och schizofreni-liknande sjukdomstillstånd bör vara att försöka förbättra den sociala och den kognitiva funktionen, och därvid sträva efter att patienten kan fungera i arbete eller annan meningsfull sysselsättning och upprätthålla sociala kontakter. Med nuvarande standardbehandling är behandlingsresultaten tyvärr nedslående, vilket är tragiskt då det finns vetenskaplig evidens för effektiv behandling som avsevärt förbättrar behandlingsutfallet.

Behandling med dopaminhämmande läkemedel är den självklara hörnstenen i terapin av denna svåra sjukdom, under såväl akuta som mer stillsamma skeden i sjukdomsförloppet. Akuta återfallsepisoder varar som regel bara några veckor, men andra symtom och sjukdomstecken kvarstår oftast i åtskilliga decennier. Framförallt gäller detta de s.k. ”negativa symtomen” som främst manifesterar sig som tillbakadragenhet, passivitet och känslomässig avtrubning med åtföljande bristande social funktionsförmåga, samt den nedsatta kognitiva förmågan. Läkemedelsbehandling har vanligtvis god effekt på de s.k. ”positiva symtomen” (tankestörningar, hallucinationer, vanföreställningar) som är framträdande främst under de akuta faserna och som typiskt förknippas med psykosjukdomar. Den gängse behandlingen med antipsykotika är emellertid betydligt mindre effektiv mot de negativa och kognitiva symtom som dominerar under de ”icke-akuta” ibland decennielånga perioderna mellan de akuta episoderna. Icke desto mindre finns det massivt vetenskapligt stöd för att en fortsatt antipsykotisk behandling behövs även under dessa perioder för att undvika återfall och i någon mån påverka kvarstående symtom. Eftersom dessa läkemedel har många biverkningar, både oangenäma och ibland plågsamma, så är behandlingsföljsamheten förstärkt nog dålig och återfall mer regel än undantag. I patientens perspektiv är motståndet mot att ta läkemedel naturligt under de faserna då symtomen är mer ”vilande” och särskilt i ljuset av att behandlingsfokus traditionellt är riktat mot de symtom som karakteriserar det akuta skedet, vilka ju också är tydliga och ibland mycket störande för andra människor.

Med syftet att undersöka långtidsförloppet av schizofreni och liknande psykosjukdomar och lära mer om vilka faktorer som kan tänkas vara relevanta för behandlingen och rehabiliteringen så startade vi en 5-årig uppföljningsstudie av 166 patienter som initialt alla var behandlade med risperidon, ett av de allra första bland de som ibland kallas den nya generationen antipsykosläkemedel. Av dessa patienter kunde hela två tredjedelar följas under hela 5-årsperioden vilket är exceptionellt många i vetenskapliga studier av patienter med denna typ av sjukdomar. Patienterna undersöktes och skattades avseende relevanta bakgrundsfaktorer, sjukdomsgrad, symtom, läkemedelsbiverkningar & behandlingsföljsamhet och två av tre patienter genomgick en omfattande datoriserad kognitiv testning minst en gång. Vad som också är specifikt för denna studie är det konsekventa användandet av ”parallella” skattningsinstrument (utförda av både behandlande kliniker och patienten) för bedömning av viktiga kliniska variabler. Detta gör det möjligt att utvärdera i vilken grad deras uppfattningar skiljer sig åt men är också ett sätt att göra patienten mer delaktig i behandlingsplaneringen.

Att schizofrenipatienter är kognitivt försämrade noterades av Kraepelin vid förra sekelskiftet, men har sedan förbisetts under största delen av 1900-talet och inte ansetts viktigt förrän på 1990-talet. I tidigare studier som vår forskargrupp har genomfört har vi noterat att vissa kognitiva domäner påverkas mer än andra hos patienter med schizofreni och att graden av försämring tycks ha mer att göra med hur många akuta sjukdomsepisoder patienten haft än med någon annan klinisk variabel. För att undersöka detta närmare utförde vi den förstudie som är redovisad i Artikel I i denna avhandling. I den studien ingick 35 av de patienter som genomgick en komplett kognitiv testning. Vi använde oss av skolbetygen från grundskolan för att få ett mått på patienternas kognitiva förmåga innan de blev sjuka. Därefter gick vi igenom deras sjukhistoria och registrerade hur många sjukdomsepisoder de hade haft sedan de insjuknade första gången. Vi jämförde deras nuvarande test-prestation med den beräknade premorbida nivån för att få ett mått på graden av kognitiv försämring, och fann i linje med vår hypotes att patienterna som haft många akuta episoder var de som hade försämrats mest jämfört med sina utgångsvärden. Detta syntes tydligast i tester där det är viktigt att ha en hög beredskap att svara på stimuli, bl.a. olika reaktionstidstester. Tänkbart är att de akuta episoderna vid en psykosjukdom har någon form av toxisk effekt på nervsystemet. Allmänt kan sägas att detta är ett kontroversiellt fynd, om än i linje med vad många inom den psykiatriska vården tycker sig ha observerat, och med vad som har skrivits i psykiatriläroböcker, utan att för den skull ha några referenser till vetenskapliga studier.

Avhandlingens huvuddel handlar om faktorer av vikt för det kliniska patient-omhändertagandet: två typer av läkemedelsbiverkningar: (tardiv dyskinesi och förhöjd nivå av könshormonet prolaktin), remission som delmål för behandlingsarbetet och den brist på insikt som är ett vanligt fenomen vid psykosjukdomar och som ofta leder till dålig behandlingsföljsamhet?

Tardiv dyskinesi (TD) brukar ses som en fruktad och handikappande biverkan till behandling med antipsykotiska läkemedel som eventuellt är irreversibel. Men orsakerna är

fortfarande oklara, och det rapporteras att TD existerade även innan de antipsykotiska läkemedlen kom på 1950-talet. Den långa uppföljningstiden i vår studie har erbjudit en unik möjlighet att studera förekomsten av dessa ofrivilliga rörelser över tid och vår analys ifrågasätter den gängse bilden så tillvida att förloppet är betydligt mer fluktuerande snarare än irreversibelt, och ej så tydligt kopplat till läkemedel som man har antagit. TD kan ibland vara ett motoriskt symptom som ingår i schizofrenisjukdomen. Dessutom fann vi TD vara kopplat till nedsatta kognitiva prestationer av samma slag som vi iakttog hos de patienter som haft många akuta psykosepisoder (subkortikal demens). Detta är i linje med hypotesen att TD beror på läkemedelsbetingade eller sjukdomsutlösta skador på dopaminsystemet i hjärnans basala ganglier.

Någon korrelation mellan en förhöjd serumnivå av Prolaktin (inducerad av dopaminhämmande läkemedel) och sexuella eller andra biverkningar kunde vi inte finna i denna patientkohort trots att plasmanivåerna vid studiestart var mångfalt över normvärdena hos både män och kvinnor. Efter några års behandling tenderade nivåerna att minska ner mot normalområdet.

Remission är ett begrepp som utvecklats inom somatisk medicin. Avsikten är att specificera att ett delmål i behandlingen uppnåtts, vilket är en förutsättning för planeringen av den fortsatta behandlingen. Inom psykiatri har detta begrepp definierats helt nyligen av en internationell expertgrupp. Det finns därför anledning att undersöka hur denna definition fungerar under långtidsbehandling. Definitionen omfattar ett symptomkriterium (förbättring så att man inte har högre symptomnivå än "lindrig", skalvärde 3, på åtta av delskalorna i skattningsskattningen PANSS) och ett förloppskriterium (förbättringen är stabil under minst sex månader). Av de åtta delskalorna avser tre av dem positiva symptom, två avser desorganisationssymptom och tre avser negativa symptom. Symtomatisk remission, som inte väger in tidskriteriet, kallas i engelsk text ofta *resolution*.

Vi fann att 40% av schizofrenipatienterna befann sig i resolution vid ingång i studien och att denna andel ökade till 60% under de tre sista åren av uppföljningen, inklusive stabilitet i den symptomatiska remissionen under 12 månader. Den genomsnittliga sjukdomstiden före ingång i studien var drygt tio år – omhändertagandet under studiens gång, inklusive användningen av atypiska antipsykosläkemedel, tycks alltså ha ökat andelen patienter i remission. Dock var det åtskilliga patienter som hade ett flukterande förlopp, ömsom i remission, ömsom med ökad symptomnivå mätt med de åtta PANSS-subskalorna. Även i ett patientmaterial med i huvudsak kroniska sjukdomsbilder fluktuerar sjukdomen – man kan inte slå sig till ro med att ha uppnått ett delmål för behandlingen. Patienterna behöver långa uppföljningstider och så täta kontakter att försämringar kan identifieras tidigt och åtgärder vidtas.

Bristande sjukdomsinsikt karakteriserade 60% av patienterna med typisk schizofreni vid ingång i studien. Bristande sjukdomsinsikt var mindre vanlig bland patienter med schizofreniliknande syndrom. Under studiens gång ökade andelen schizofrena patienter



med tillfredsställande insikt till 60%, i linje med att många andra mått på behandlingsutfall förbättrades (t.ex. remission) och trots att symtomnivå och allmän funktionsförmåga var konstant. Patienter med bristande insikt hade också större svårigheter att bedöma sig själva och sitt eget tillstånd i vissa men inte alla avseenden. Detta skulle man kunna använda för att objektivisera bedömningar av bristande insikt och därmed nedsatt autonomi (alternativet är annars att acceptera en klinisk global bedömning av insikt så som detta operationaliseras i PANSS-skalan). En ökad säkerhet i bedömningen av nedsatt autonomi är önskvärd för att motivera tvångsåtgärder av det slag som definieras i den kommande lagen om öppenvård med särskilda villkor.

Vi fann att bristande insikt var kopplad dels med en premorbid riskfaktor, låg allmänbegåvning, och dels med sjukdomsframkallade specifika kognitiva svårigheter (exekutiva problem). För patienter med låg premorbid IQ bör problemet med bristande insikt kunna reduceras genom bättre pedagogik i förhållande till patient och nätverk i samband med sjukdomsdebuten. De exekutiva problemen kan vi inte behandla direkt men det finns metoder utvecklade inom hjärnskaderehabilitering och barnhabilitering, såväl som ADHD-behandling som fungerar. Det är på många sätt märkligt att sådana metoder inte alls används i behandlingen av patienter med schizofreni.

Behandlingsfölsamheten till läkemedlet risperidon kunde mätas i vår studie genom årliga blodprover, en mycket säkrare metod än de indirekta metoder som vanligen används. Fölsamheten var extremt hög under alla år, klart över 90%. Vi tolkar detta som en konsekvens av studiens allmänna uppläggning (som man kan se som i många avseenden bättre än ”standardbehandling”, bl.a. genom att deltagande kliniker var engagerade (annars hade de inte deltagit) och kunniga i psykofarmakologi (samma argument), och att patienterna på ett tydligt sätt inbjöds att delta i bedömningarna a sitt eget tillstånd, bl.a. symtom och biverkningar. Detta bör ha ökat känslan av faktisk delaktighet i behandlingsplaneringen och kanske är en delförklaring till den förbättring i insikt som vi kunde registrera under studiens gång.

En allmän sammanfattande slutsats av detta projekt är att alltmedan vi väntar på en vetenskapligt genombrott i paritet med när Arvid Carlsson upptäckte dopaminet, så finns det många små steg vi kan ta i riktning mot att förbättra möjligheterna för människor med psykossjukdomar att få ett bättre liv. Det handlar om fortsatt klinisk forskning, men lika viktigt är att i större utsträckning tillämpa de relativt enkla metoder som sannolikt skulle förbättra behandlingsresultaten avsevärt, om de bara hade använts...

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## Appendix 1: Protokoll amendment

|  |  |
|--|--|
| Punktprevalensstudie Risperdal® (RIS-SWE-14)   |  |
| RIS-SWE-14   |  |
|  | 1995-01-09   |
| Studiedesign:  | Multicenterstudie  |
| Amendment datum:   | 1996-05-29   |
|  | Janssen-Cilag AB<br>Box 5052, 426 05 Västra Frölunda   |
| Eva Lindström, M.D.  | Inst för psykiatri, University Hospital, 785 53 Uppsala<br>Tfn: 018/66 30 00   |
|  | Rolf Axelsson, M.D.<br>Inst för psykiatri, Sahlgrenska Hospital, 413 45 Göteborg<br>Tfn: 031/60 10 00  |
|  | Bo Eriksson, klinisk gruppchef<br>Erik Jedenius, produktgruppchef<br>Janssen-Cilag AB, Box 5052<br>426 05 Västra Frölunda<br>Tfn 031/69 59 00<br>Fax: 031/69 07 62 |
| Protokollet innehåller konfidentiell information endast avsedd för de i prövningen ansvariga personerna och får ej föras vidare. |  |

Sidan 2: **Syfte** *Tidigare text:* Syftet med punktprevalensstudien är att:

- studera bakgrundsvariabler såsom diagnos, ålder, duration, dos och övrig medicinering
- titta på aktuell symptomatologi med hjälp av PANSS (skattningsskala för positiva och negativa syndrom vid schizofreni)
- studera möjliga biverkningar med hjälp av UKUs biverkningsskala (manual för registrering av oönskade effekter, s k "biverkningar" vid psykofarmakabehandling) samt ESRS (Extrapyramidal Side-Effect Rating Scale)
- studera plasmanivåer och relatera dessa till läkemedelsdos och effekt (mätt med PANSS) samt biverkningar (mätt med UKU och ESRS)

Den övergripande målsättningen är dels att finna den grupp av patienter som har störst nytta av preparatet och dels att hitta den dos och det plasmakoncentrationsintervall där patienten har största möjliga symptomlindring med minsta möjliga biverkningsrisk.

*Ändra till:* Syftet med punktprevalensstudien är att:

- studera bakgrundsvariabler såsom diagnos, ålder, duration, dos och övrig medicinering samt en gång om året i 5 år:
- titta på aktuell symptomatologi med hjälp av PANSS (skattningsskala för positiva och negativa syndrom vid schizofreni)
- studera möjliga akuta biverkningar och långtidsbiverkningar med hjälp av UKUs biverkningsskala (manual för registrering av oönskade effekter, s k "biverkningar" vid psykofarmakabehandling) samt ESRS (Extrapyramidal Side-Effect Rating Scale) och AIMS test (skattningsskala för att bedöma tardiva dyskinesier)
- studera plasmanivåer och relatera dessa till läkemedelsdos och effekt (mätt med PANSS) samt biverkningar (mätt med UKU, ESRS och AIMS) (endast för de patienter som fortfarande behandlas med Risperdal)
- studera kognitiv funktionsförmåga med hjälp av APT - ett datoriserat testbatteri
- studera social funktionsnivå (Strauss-Carpenter-skalan)

Den övergripande målsättningen är dels att finna den grupp av patienter som har störst nytta av preparatet och dels att hitta den dos och det plasmakoncentrationsintervall där patienten har största möjliga symptomlindring med minsta möjliga biverkningsrisk samt studera långtidseffekter av Risperdal, speciellt kognitiva effekter och eventuell TD.

**Prövningens Tidigare genomförande**

Vid ett enda tillfälle skattas patienter enligt följande:

*text:*

1. Bakgrundsvariabler
2. Symptombedömning, PANSS
3. Biverkningsbedömning, UKU och ESRS

*Ändra till:* En gång om året i 5 år skattas patienter enligt följande:

1. Bakgrundsvariabler
2. Symptombedömning, PANSS
3. Biverkningsbedömning, UKU, ESRS och AIMS
4. Kognitiv förmåga, APT
5. Social funktionsnivå, Strauss-Carpenter

*Tidigare text:* Vid samma tillfälle tas också ett blodprov för laboratoriekontroll och risperidonbestämning

*Ändra till:* Vid dessa tillfällen tas också ett blodprov för laboratoriekontroll (samtliga patienter) och risperidonbestämning (endast för de patienter som fortfarande behandlas med Risperdal).

**Tidsplan** *Tidigare text:* Studien kommer att genomföras under perioden 30 januari-11 mars 1995.

*Ändra till:* Studien kommer att genomföras under perioden 15 februari 1995 till 30 juni 2001.

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