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Effects of add-on mirtazapine on neurocognition in schizophrenia

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Contents

Abstract

Background. Schizophrenia is a severe, psychiatric illness with neurocognitive deficits as its major component, and affects about 1% of the world population. Improving impaired neurocognitive function is one of the pivotal treatment goals in this patient population. In the treatment of schizophrenia, only a partial treatment response is typically achieved with dopamine antagonists; i.e., "antipsychotics". The antidepressant mirtazapine has a unique mechanism of action with, in theory, an ability to enhance neurocognition and provide added value to antipsychotic treatment. The pharmacological mechanism of action for this neurocognitive enhancing effect of mirtazapine is probably due its receptor- binding profile.

Aims. This study explored whether or not adjunctive mirtazapine has the potential to improve neurocognitive performance and alleviate clinical symptoms in patients with schizophrenia who demonstrated a suboptimal treatment response to first-generation antipsychotics (FGAs).

Study design and Patients. This study was a neurocognitive arm of a single-center, randomized, add-on, double-blinded, placebo-controlled study, which was carried out in the Karelian Republic, Petrozavodsk, Russia. Patients with schizophrenia or a depressive type schizoaffective disorder, according to the Diagnostic and Statistical Manual of Mental and Behavioral Disorders 4th edition (DSM-IV) criteria, who received stable doses of FGA with inadequate treatment response were enrolled into the trial. Twenty patients were assigned to mirtazapine and 21 to placebo. After a one-week single-blind placebo run-in period, the participants were randomized to receive either 30 mg of mirtazapine or the placebo every night at bedtime (QHS) in a double-blind fashion for 6 weeks. Subsequently, those who were eligible to continue entered the following 6-week open-label phase, where they were treated with mirtazapine 30 mg QHS.

Methods. At study weeks 0, 6, and 12, a senior psychologist performed neuropsychological examinations to evaluate neurocognitive functioning. Verbal and visual memory, visuo-spatial and executive functions, verbal fluency and both general mental and psychomotor speeds were assessed by commonly used, validated neuropsychological tests for different neurocognitive domains. Clinical examinations were conducted at week –1 (screening), week 0 (baseline) and after 1, 2, 4, 6, 7, 8, 10, and 12 weeks of treatment. Within group and between group differences were analyzed on Modified Intent-to Treat (MITT) basis with Last Observations Carried Forward (LOCF).

Results. After 6 weeks of treatment, 5/21 neurocognitive parameters (i.e. Wechsler Adult Intelligence Scale Revised (WAIS-R) Block Design, p=0.021; Wechsler Memory Scale (WMS) Logical Memory, p=0.044; WMS Logical Memory Delayed, p=0.044; Stroop Dots, p=0.044; Trail Making Test Part A (TMT-A), p=0.018) were improved with statistical significance in the mirtazapine group. In contrast, only 1 of the 21 parameters changed significantly (WMS

Logical Memory, p=0.039) in the placebo group. Add-on 6-week mirtazapine treatment was superior when compared with placebo in the neuropsychological domains of visuo-spatial ability and general mental speed/attentional control (Block Design mirtazapine group vs. placebo and Stroop dots mirtazapine group vs. placebo, p=0.044 for both comparisons). The enhancing effect on the Block Design-measured visuo-spatial functioning was mediated through changes in positive, depressive symptoms and parkinsonism-like side effects, but not via changes in negative symptoms. Moreover, higher doses of FGAs, longer duration of illness and lower initial Block Design scores predicted this effect. During the 6 weeks extension phase, individuals who continued mirtazapine treatment and those who were switched from placebo to mirtazapine showed significant improvements on several neurocognitive tests. Those who switched from placebo to open label mirtazapine treatment achieved similar results in the 6 following weeks as the mirtazapine group during their first 6 weeks of mirtazapine treatment. From week 0 to week 12, the continuation group demonstrated improvements in 17/21 neurocognitive parameters, while the switch group improved in 8/21 of the measured parameters. Twelve weeks of mirtazapine treatment indicated an advantage over a shorter, 6-week mirtazapine treatment on Stroop Dots time (p=0.035) and Trail Making Test part B (TMT-B), and number of mistakes (p=0.043). During the 6-week open-label phase, significant improvements on several clinical parameters, which included the Positive and Negative Syndrome Scale (PANSS) total score, were observed. In the total population (i.e., pooled switch and continuation groups), the effect size was 0.94 (CI 95%=0.45-1.43) as determined by the PANSS total score.

Conclusions. Adjunctive mirtazapine treatment might offer added value as a neurocognitive enhancer, and may augment the antipsychotic effect in FGA-treated schizophrenia patients with inadequate treatment response. The ability to generalize these results for a larger population may be limited by the small sample size of the present study.

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List of original publications

This dissertation is based on the following original publications, which are referred to in the text by Roman numerals I to IV:

I. Stenberg JH, Terevnikov V, Joffe M, Tiihonen J, Tchoukhine E, Burkin M, Joffe G. Effects of add-on mirtazapine on neurocognition in schizophrenia: a double-blind, randomized, placebo-controlled study. Int J Neuropsychopharmacol 2010;13:433-41.

II. Stenberg JH, Terevnikov V, Joffe M, Tiihonen J, Chukhin E, Burkin M, Joffe G. Predictors and mediators of add-on mirtazapine-induced cognitive enhancement in schizophrenia--a path model investigation. Neuropharmacology 2013;64:248-53.

III. Stenberg JH, Terevnikov V, Joffe M, Tiihonen J, Tchoukhine E, Burkin M, Joffe G. More evidence on proneurocognitive effects of add-on mirtazapine in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:1080-6.

IV. Terevnikov V, Stenberg JH, Joffe M, Tiihonen J, Burkin M, Tchoukhine E, Joffe G. More evidence on additive antipsychotic effect of adjunctive mirtazapine in schizophrenia: an extension phase of a randomized controlled trial. Hum Psychopharmacol. 2010;25:431-8.

Abbreviations

APA, American Psychiatric Association
BDNF, Brain-Derived Neurotrophic Factor
CATIE, The Clinical Antipsychotic Trials of Intervention Effectiveness study
CGI, Clinical Global Impression Scale
CDSS, Calgary Depression Scale for Schizophrenia
DSM-IV, The Diagnostic and Statistical Manual of Mental and Behavioral Disorders 4th edition
DSM-5, The Diagnostic and Statistical Manual of Mental and Behavioral Disorders 5th edition
ECT, Electroconvulsive Therapy
FDR, False Discovery Rate
FGA, First-Generation Antipsychotic
GABA, *Gamma*-aminobutyric Acid
GCP, Good Clinical Practice
LOCF, Last Observations Carried Forward
MATRICS CCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery
MITT, Modified Intent-to Treat
MLR, Robust Maximum Likelihood
NICE, National Institute for Health and Care Excellence
NMDA, *N*-Methyl-D-aspartic acid
PANSS, Positive and Negative Syndrome Scale
PGI, Patient Global Impression Scale
PFC, Prefrontal Cortex
QHS, *Quaque hora somni* (L.) Every night at bedtime
RCT, Randomized Controlled Trial
SAS, Simson-Angus Scale for Extrapyramidal Side Effects
SGA, Second-Generation Antipsychotic
TMT-A, Trail Making Test, part A
TMT-B, Trail Making Test, part B
WAIS-R, Wechsler Adult Intelligence Scale - Revised
WCST, Wisconsin Card Sorting Test
WMS, Wechsler Adult Memory Scale

Introduction

About 24 million people suffer from schizophrenia worldwide, yet less than 50% of this population receives appropriate care (World Health Organization 2001). Even those who are privileged, with access to the best treatment, still suffer from severe social and functional deficits that are largely based on neurocognitive deficits. Thus, developing more effective treatments for neurocognitive deficits is an important goal.

History of schizophrenia concept

Mental disorders have been described since the history of medical records began. It was the German psychiatrist Emil Kraepelin (1856–1926), who first classified mental illness as an actual disease, with a specific onset, course and outcome. As part of this classification, Kraepelin described the condition of 'dementia praecox', to identify early mental decline. Dementia praecox was later renamed schizophrenia, after a symptom-oriented study of this disorder by Swiss psychiatrist Eugen Bleuler (1857–1939) (McGlashan 2011). The term schizophrenia (from the Greek: schizo = split, phrenos = mind) was selected to reflect the poor connection between thought processes and other functions of mind such as emotional, behavioral, or volitional (motivational) components.

Schizophrenic disorders

Schizophrenia, schizophreniform disorder, and schizoaffective disorder are often conceptualized as a group of schizophrenic disorders. In addition, as with schizotypal personality disorder and schizoid personality disorder, schizophrenia, schizophreniform disorder and schizoaffective disorder all belong to the so-called schizophrenia spectrum disorders, as this illness typically presents a variety of symptoms with each patient, rather than a single psychopathology.

General description and etiology

Schizophrenia is a serious mental illness that is characterized by severe psychotic symptoms, such as auditory hallucinations. The Diagnostic and Statistical Manual of Mental and Behavioral Disorders 4th edition, (DSM-IV) diagnostic criteria for schizophrenia (American Psychiatric Association 1994) are presented in Table 1.

Multiple impairments in the regulation of affect, perception, cognition and social functioning are common. Schizophrenia is usually associated with chronic disability and poor outcome in most areas of life. Due to the chronicity and pervasive functional impairments, this illness often requires intensive, long-term treatment.

Schizophrenia is a lifelong disease, where the lifetime prevalence has been estimated to be around 1% of the population. About 22 per 100 000 people present new cases of schizophrenia every year (Tsuang and Faraone 1997). This gives an incidence rate of about 0.02%. The incidence rate is lower than the abovementioned prevalence rate, because schizophrenia is a predominantly chronic disorder. Thus, the presence in the population is cumulative.

The onset of schizophrenia can range between a sudden psychosis or a gradual deterioration, usually between the yearly ages of 15 to 35. It has been proposed that the age at onset of schizophrenia is associated to its severity, where an earlier onset age has been associated with more severe clinical and behavioral symptoms (Lieberman et al. 1996). Schizophrenia affects all cultures and is equally prevalent in men and women, while the onset of illness is usually earlier in males (Mueser and McGurk 2004).

Some questions concerning the unity of schizophrenia as a syndrome have recently emerged, as schizophrenia is often discussed as if it was a single disease with a common etiology. However, the clinical heterogeneity of schizophrenia has raised some doubts on this perspective, as symptoms may represent disease groups of common phenotypic expressions, but of diverse underlying etiopathologies (Buckley et al. 2009). Current knowledge might also support a hypothesis for a diagnosis of schizophrenia according to distinct disorders, though with similar psychological or behavioral symptoms and clinical presentations. Several attempts to determine subtypes of schizophrenia by phenotype, genotype and treatment response have been made, but no sustainable results have been achieved thus far. There is still a discussion on whether or not to define schizophrenia as a neurodegenerative or neurodevelopmental disorder (Rund 2009). General cerebral atrophy, lateral ventricle enlargement and a lack of gliosis represent the variety of pathological findings in the central nervous system of patients with schizophrenia (Frith and Johnstone 2003; Rund 2009).

While the central cause of schizophrenia is not known, many studies point towards a combination of genetic and environmental factors that influence brain function (Niwa et al. 2011). Despite the research and consideration that has been invested in an effort to understand the etiology of schizophrenia, none of the factors seem to be especially significant in the genesis of schizophrenia. Instead, multiple factors seem to be involved, which results in multiple disorders of varied pathologies behind the schizophrenia phenotype. The search to uncover a specific etiology of schizophrenia has identified some of genetic markers that match with explanatory models, which may incorporate identified risk factors in the common environment.

The importance of genetic factors has been demonstrated in twin studies. Concordance rates of monozygotic twins are approximately 41 – 65 %, and heritability estimations approximate 80 – 85 % of cases (Cardno et al. 1999; Cardno & Gottesman 2000). On the

other hand, twin studies have shown that the development of schizophrenia is not solely explained by genetic inheritance. In those cases where only one identical twin developed schizophrenia, the other identical twin developed schizophrenia in approximately 50% of cases. The epigenetic conclusion of this finding is that genes play an important role in determining whether or not an individual will develop schizophrenia, but that other factors must also play a significant role. Subsequent research has found that environmental factors have a substantial role in the etiology of schizophrenia, and contribute to approximately 30 to 50 % of the cases (Sadock et al. 2005).

Some evidence suggests that the environmental risk for schizophrenia appears to begin already in the first and second trimesters of pregnancy, as maternal exposure to influenza has been associated with an increased risk of later developing schizophrenia (Mednick et al. 1988; Brown et al. 2004). Other environmental factors include maternal rubella, some other maternal viral infections, obstetric complications, low socio-economic status, maternal deprivation and lack of proper nutrition, natural catastrophes or war, birth in late winter/early spring and even urban birth (Dohrenwend et al. 1992; Lewis and Murray 1987; Marcelis et al. 1999; Susser et al.1996; Torrey et al.1997). Tienari et al. (2004) reported an increased prevalence of schizophrenia in adopted children of mothers having schizophrenia or schizophrenic spectrum disorder. Additional reports have process a neurodevelopmental hypothesis, which explains this disease as a result of multi-etiologically altered factors in neuronal cell birth, cell differentiation, cell migration, formation of synapses between neurons (synaptogenesis), programmed cell death and the malformation of neuronal circuitry, which later present as cognitive dysfunctions (Bunney and Bunney 1999; Eastwood and Harrison 2003).

In summation, no single causative factor has been identified so far. The strongest evidence to date supports a hypothesis that identifies schizophrenia as an inherited/familial disorder, which is exacerbated by environmental stress.

Table 1

Diagnostic criteria for schizophrenia (DSM-IV, American Psychiatric Association 1994)

A. Characteristic symptoms: Two or more of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
1. Delusions
2. Hallucinations
3. Disorganized speech
4. Grossly disorganized or catatonic behavior
5. Negative symptoms

Only one of these five symptoms is required if delusions are bizarre, or if the hallucinations consist of a voice that keeps up a running commentary on the person's behavior or thoughts, or with two or more voices conversing with each other.

B. Social/occupational dysfunction: for a significant portion of the time, after the onset of symptoms, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to onset (or a failure to achieve an expected level of achievement, when the onset occurs in childhood or adolescence).

C. Duration: Continuous signs of the disturbance persist for at least 6 months, of which at least one month should have symptoms that meet Criterion A. This 6 months may also include periods of prodromal and residual symptoms.

D. Schizoaffective and mood disorder exclusion: Schizoaffective disorder and mood disorder with psychotic features have been ruled out, due to the absence of major depressive, manic, or mixed episodes that have occurred concurrently with the active-phase symptoms. If such mood episodes have occurred during active-phase symptoms, then their total duration is brief, relative to the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance or another medical condition.

F. Relationship to a pervasive developmental disorder: if there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Symptom domains in schizophrenia

Since the concept of schizophrenia began over a century ago, the heterogeneity within this concept has been ontologically explained in terms of distinct clinical subtypes; i.e., disorganized (previously hebephrenic), catatonic, paranoid, and undifferentiated symptomologies. Although these subtypes are generally recognized to have poor reliability, low stability over time, and insignificant prognostic value, they were included in the DSM-IV. The fifth edition of the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was recently published, thus superseding the DSM-IV (American Psychiatric Association 2013). In the DSM-5, all aforementioned subtypes of schizophrenia are omitted. However, the use of psychopathological dimensions in the DSM-5 may improve its ability to describe the heterogeneity of schizophrenia (Tandon et al. 2013).

The importance of psychopathological dimensions was accepted in the field of schizophrenia research long before a formal discussion of diagnostic criteria began. After Kay et al. (1987) clustered symptoms of schizophrenia into positive, negative, and general symptoms, this concept became widely accepted in both scientific research and clinical work. This development mostly occurred after Kay et al. devised the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) as a standardized diagnostic tool of measure, to improve the validity of schizophrenia research.

Prodromal symptomatology

Schizophrenia and its symptoms tend to gradually progress over months or years, and so-called prodromal symptoms often precede the active phase of the disorder. Sometimes the symptoms emerge suddenly, which can be multiple and may include anxiety, purposelessness, eccentric thinking, milder forms of psychotic symptoms, and withdrawal from social contacts, loss of interest in previously pleasant activities, or spending most of the time in bed (American Psychiatric Association 1994).

As the illness progresses, more pronounced problems occur with thinking, cognition, emotions, and behavior, which disrupts the process of making rational decisions. These underlying pathogenic processes produce symptoms that are variable, but typically include hallucinations, delusions, apathy, blunt emotional affect, odd behavior, poor personal care, and social withdrawal. Early prodromal signs of this illness are often identified as warning signs, and they can be spotted before the primary symptoms of schizophrenia occur.

Because schizophrenia involves dysfunction in major areas of mentation, people in the initial phase of illness usually begin to have trouble in everyday life, such as problems in relations

or in achieving goals (Couture et al. 2006). In addition, diffuse problems with anxiety, depression, and suicidal thoughts or behavior are common, in addition to problems with substance misuse.

Positive, disorganized, negative, affective and cognitive symptoms

Currently, the symptoms of schizophrenia are considered to fall into five broad categories; i.e., positive symptoms, disorganized symptoms, negative symptoms, affective symptoms and cognitive symptoms (Fuller et al. 2003; Tamminga and Holcomb 2005).

Positive symptoms

Positive symptoms include explicitly psychotic phenomena and behaviors, and people with positive symptoms seem to "lose touch" with reality. These symptoms can fluctuate and occasionally they are severe. Other times these symptoms may be hardly noticeable, depending on the individual and the treatment received. Positive symptoms may include hallucinations, delusions and formal thought disorders (Fuller et al. 2003; Tamminga and Holcomb 2005).

Hallucinations are false auditory, visual, olfactory or tactual perceptions that have no relationship to reality, and which are not explained by any exterior stimuli. Auditory hallucinations, often referred to as "voices", are the most common type of hallucination in schizophrenia (Waters et al. 2012). These voices may talk to the person about his or her behavior, order things to be done, or warn about dangers that otherwise do not exist. Sometimes there may be multiple voices, which can talk to each other. People suffering from schizophrenia may hear voices for a long time before others notice the significance of this symptom. Visual hallucinations are actually rare in schizophrenia, as are, olfactory and tactile hallucinations. Regardless, the affected person cannot readily separate these hallucinations from real perceptions.

Delusions are long-lasting false beliefs or fears that are not real and not part of the person's culture (Blackwood et al. 2001). Affected individuals may believe in such delusions even after other people (e.g., family members, friends or medical staff) have explained that such beliefs are not true or even logical. People suffering from schizophrenia can have delusions that seem bizarre, such as believing that someone else can control their thoughts, feelings or behavior by remote control, or that people on television are directing special messages to them. Sometimes one can even believe that they are somebody else, such as a famous historical figure. As a case vignette, a well-known Finnish patient with schizophrenia “Kellokosken prinsessa” (Anna Lappalainen, 1896–1988) thought that she was a real princess, although she had no known connection to royalty (Raitasuo and Siltala 2010).

Persons with such delusions may have paranoid beliefs that someone is trying to harm them; e.g., by cheating, harassing, poisoning, spying, or plotting against them or people they care about. Such beliefs are referred to as delusions of persecution. Delusions can sometimes cause serious harm or even danger to others, as the affected person may try to defend him/herself against the imaginary threat.

Disorganized symptoms

Thought disorders are uncommon, dysfunctional and usually illogical ways of thinking (Fuller et al. 2003). One may, for example, have difficulties in organizing thoughts or logically connecting them to emotions. This sort of disturbance is called "disorganized thinking", which is one form of thought disorder. One may talk in a muddled way that is hard to comprehend, and illogical reasons may substitute for rational explanations. One may, for example, stop speaking unexpectedly in the middle of an idea. When asked why the explanation has stopping, the affected person may say that the thought had been taken away, or that the thought is hiding in “the mountains of the brain”. Perhaps the most disturbed type of formal thought disorder may result in meaningless words or neologisms. Neologisms are newly created words, terms or phrases, which are used independently of their common meaning; i.e., the words only have meaning to the person who uses them. The basic idea of thought disorders is that concepts from different contexts are mingled together in a way that is against normative logic.

Some individuals with schizophrenia also have movement disorders, such as agitated body movements (Walther and Strik 2012). A person with a movement disorder may compulsively repeat certain motions while some may become catatonic. This may include motor hyperactivity, odd body and limb positions or even a state of neurogenic motor immobility (stupor). Non-medicated catatonia is nowadays infrequent, but it was more common before modern psychopharmacological treatments for schizophrenia.

Negative symptoms

The negative symptoms of schizophrenia include problems with motivation, social withdrawal, diminished affective responsiveness, speech, and movement (Fuller et al. 2003; Tamminga and Holcomb 2005). "Flat affect", meaning a lack of common emotional gestures, or monotonous talk with a face that does not move, is a common example of this category. Negative symptoms may be harder to recognize, and they can be mistaken for depression or amotivational conditions like unwillingness or laziness. Research suggests that negative

symptoms influence poor functional outcomes and quality of life for individuals with schizophrenia than do positive symptoms (Velligan et al. 1997; Norman et al. 2000; Lysaker et al. 2004; Lysaker and Davis 2005; Milev et al. 2005; Kirckpatrick et al. 2006). Negative symptoms tend to live on longer than positive symptoms, and are usually more difficult to treat (Kirkpatrick et al. 2006; Alphs 2006). Moreover, negative symptoms are associated with impaired functional outcomes such as diminished independent living skills or reduced social functioning (Leeuwenkamp et al. 2007).

Affective symptoms

In addition to the previously described positive, disorganized or negative symptoms, patients with schizophrenia often exhibit affective symptoms, such as depression and anxiety. Affective symptoms are common in schizophrenia and can be particularly disturbing, even to the point of increasing the risk of suicide (Hor and Taylor 2010) and diminishing both the quality of life and life span of these individuals. For this reason it is important that affective symptoms are properly diagnosed and treated accordingly. The majority of patients with schizophrenia who commit suicide do so while experiencing depressive symptoms (Hawton et al. 2005). Depressive symptoms are reported in up to 80% of the patients with schizophrenia, while symptoms of mania are reported in about 20% of these cases (Kasckow et al. 2010). Moreover, only part of the patients with schizophrenia meet the established criteria for major depression, while even more experience subclinical depressive symptoms (Kasckow et al. 2010). Schizoaffective disorder is another condition, where the individual experiences a combination of schizophrenic symptoms and affective symptoms, such as mania or depression.

Neurocognitive symptoms

In addition to positive symptoms (delusions and hallucinations), negative symptoms (like reduced poverty of speech and blunted affect), and affective symptoms (depression, mania and anxiety), schizophrenia is also associated with changes in cognitive symptoms. Cognitive symptoms typically include problems with attention (shorter), memory (diminished) and declined executive functioning (i.e, the ability to understand information and use it to make decisions). Declinations in cognitive symptoms typically reflect dysfunctions in the central nervous system. These are often referred to as neurocognitive functions, and are distinct from the mental processes of formulating inner meanings or inspecting connections between thoughts, emotions and behavior. Therefore, the term neurocognitive symptoms is used in this research to describe brain dysfunctions that are related to the cognitive process.

The presence of neurocognitive symptoms is independent of positive symptoms, but cognitive symptoms are associated with both disorganized symptoms and negative symptoms (O'Leary et al. 2000). It has been argued that neurocognitive deficits may present as a trait-like component of schizophrenia by comparing it to a neurodevelopmental disease (Kristensen and Myatt 2011). Although neurocognitive symptoms are currently recognized as a core feature of schizophrenia, they are commonly understated in clinical settings. In contrast to negative symptoms, neurocognitive symptoms are often difficult to recognize and they are mostly identified after psychological testing.

Neurocognitive impairment and dysfunctions in schizophrenia

Although neurocognitive deficits are a trait-like component of schizophrenia, there is currently no specific neurocognitive profile for schizophrenia (Mohamed et al. 1999; Bilder et al. 2000). While no particular type of neurocognitive deficit is unique to schizophrenia, tasks that require active retrieval of verbal material from long-term memory, visuo-motor processing, attention, vigilance or integrity of executive functions seem to be difficult for most of these patients (Blanchard and Neale 1994; Heinrichs and Zakzanis 1998; Nopoulos et al. 1994; Raine et al. 1992; Saykin et al. 1994; Sullivan et al. 1994). The neurocognitive performance of patients with schizophrenia is generally one to two standard deviations below the scores of healthy controls. Compared with other severe mental disorders, like major depression or bipolar disorder, patients with schizophrenia present a wider range of neurocognitive domains and to a more severe degree (Buchanan et al. 2005).

Neurocognition in psychotic illness

While there is no single causative etiology for the neurocognitive deficits in schizophrenia, a current hypothesis considers schizophrenia to be a neuropsychiatric disorder with neurocognitive deficits as a major trait component (Keefe and Fenton 2007). Moreover, neurocognitive problems can lead to an increased risk for both illness and a more severe symptomatology.

A stress vulnerability model was originally proposed by Zubin and Spring (1977). This approach suggests that an individual has biological, psychological and environmental (or social) components, which all contain strengths and vulnerabilities for coping with stressors. Vulnerability in this context is a variable that results in a failure to cope with stress, which may then cause an increased risk for information processing problems, and this becomes part of a process that leads to psychotic symptoms. In conjunction with vulnerability factors, environmental factors can influence both the onset and course of such symptoms. Living in a

stressful environment, with seemingly insurmountable conflicts or criticism, may contribute to more stress than the individual can successfully cope with. Also, the misuse of drugs such as amphetamine or sometimes even cannabis may contribute to the development of psychotic symptoms in vulnerable individuals. According to the stress-vulnerability model (Zubin and Spring 1977), symptoms or psychoses emerge when stress exceeds an individual's vulnerability threshold. The model is obviously simplistic and it has since been revised in more sophisticated models, such as that of Nuechterlein and Dawson (1984).

According to the stress-vulnerability model (and thus accepting the predisposed biological vulnerability factors), schizophrenia is widely accepted as a brain disease with affections on brain function and even brain structure (Harrison 1999). Numerous studies have tried to find biological markers for this vulnerability in (mainly first-degree) relatives of patients with schizophrenia. Prefrontal cortex dysfunctions (Allen et al. 2011) have been consistently reported in schizophrenia studies, and this phenomenon has frequently been identified as one of the major causes of the executive function deficits seen in schizophrenia (Minzenberg et al. 2009). Among prefrontal cortex dysfunctions, general cortical thickness and degradation (Kuperberg et al. 2003; Harris et al. 2004; Puri 2010), ventricular enlargement (Gaser et al. 2004), reduction in brain volume and weight (Lawrie and Abukmeil 1998; Harrison et al. 2003), abnormalities in gray and white matter (Cannon et al. 2002; Job et al. 2002; Puri 2010), altered hippocampal shape and volume (Suddath et al. 1989; Gur et al. 2000; Wiegand et al. 2004) have all been observed in both never medicated first-episode patients and patients with longer durations of illness.

With functional magnetic resonance imaging, abnormal brain activity and a lack of neuronal connectivity have been identified in the mechanisms of distributed circuits that involve the prefrontal cortex of patients with schizophrenia (Ragland et al. 2004). This is in addition to significantly reduced activation, predominantly in the right hemisphere, also in the dorsolateral frontal and temporal regions, and in the inferior parietal areas and sub-cortically in the thalamus (Shenton et al. 2002; Salgado-Pineda et al. 2004, Ragland et al. 2007; Tseng et al. 2009).

It seems clear that disturbed neurocognition and brain dysfunctions are a major part of schizophrenia. Moreover, acute psychosis itself can be somehow seen as a decompensation mechanism of general information processing. In stressful situations, for example, an underlying vulnerability affects the individual's capacity to consider the world in a rational or normological way, which is identified by impaired reality testing.

Schizophrenia is a neurocognitive psychosis

Neurocognitive impairment is regarded as a core component of schizophrenia, and is increasingly under investigation as a potential target for treatment modalities. On average, cognitive impairment in schizophrenia is severe to moderately severe when compared to healthy controls, and almost all patients demonstrate neurocognitive impairments. Similarly, when comparing patients with severe affective disorders (i.e., major depression or mania), cognitive impairment in schizophrenia emerges earlier, is more severe, and tends to be independent of clinical symptoms. To this effect, a growing body of evidence suggests that the neurocognitive deficits observed in patients with schizophrenia are both primary and a core domain of the illness. Thus, schizophrenia is a neuropsychiatric disorder with neurocognitive deficits as a major component (Keefe and Fenton 2007).

Neurocognition and Neuropsychology

Neuropsychology and neuropsychological examination

Neuropsychology is a scientific explanation of psychology, which combines different aspects of brain structure and function, in relation to their putative behavioral and psychological processes. This approach combines clinical and experimental methods of psychology that aim to study, assess, explain and treat such processes as thinking, feeling and behavior as they directly relate to brain function. Neuropsychology shares the same view of mental information processing as cognitive psychology, and the same terms are used in both fields of study.

In clinical settings, when examining patients with schizophrenia, neuropsychology employs psychological, neurological and physiological methods to evaluate neurocognitive processes. This includes cognitive, emotional and behavioral domains, and relates relevant findings of the examination to normal and abnormal functions of the central nervous system.

The main method in neuropsychology is neuropsychological testing. The tasks of different tests have been designed to link the performance on the task with one or more neurocognitive processes. These tests are typically standardized, meaning that they have been administered in general population to obtain normative values.

Typical examples of neuropsychological tests include the Wechsler Adult Intelligence Scale (WAIS, Wechsler 1981; Lezak 1995), the Wechsler Adult Memory Scale (WMS, Wechsler 1945), the Wisconsin Card Sorting Test (WCST, Monchi et al. 2001), the Stroop Colored Word

Test (Jensen and Rohwer 1966; Reitan and Wolfson 1985; Lezak 1995) and the Trail Making Test (TMT, Reitan and Wolfson 1985; Lezak 1995).

Major Neurocognitive functions and their schizophrenia related deficits

There are various important aspects to evaluate in human neurocognition and its impairment. The precise terms may vary, depending on the specific approach, and no rigorous taxonomy exists. However, attention, verbal (or language) skills, visual (or perceptional) skills, motor skills, memory, and executive functions are commonly accepted as the main terms that are used to describe the major neurocognitive domains. Also, the concept of measurable intelligence must be mentioned as an important dimension of cognition. However, the concept of intelligence encompasses a general collection of cognitive functions, abilities and cultural values, so the best choice is to examine patterns of deficits in specific domains, even though a global decline in intellect is a common feature in schizophrenia (Blanchard and Neale 1994; Bilder et al. 2000).

While there is some localization in different neurocognitive functions of the brain, these cannot be completely localized to any specific brain area. In other words, different areas in the brain are more specialized for some neurocognitive processes than others, and the central nervous system also integrates and connects the information produced in these regions.

Attention

Attention is a multifactorial construct, which includes the ability to maintain an alert state (for a specific amount of time), to orient to new stimuli, to filter information and to distinguish stimuli over some duration of time. Attention is a cognitive process of selectively concentrating on some feature(s) in the environment while ignoring others. Thus, attention refers to processes where the individual becomes alert to internal or external stimuli (Lezak et al. 2004). The critical elements of attention are focusing, selectivity, exclusiveness, and vigilance (Lezak et al. 2004). To choose from a flow of stimuli and sustain attention are the fundamental requirements for all cognitive functioning. A close relationship between attention, working memory and vigilance is close and in they are somehow part of the same process. A neural correlate of attention is the enhanced firing of neurons. It has been shown that receptive fields and thus response properties of sensory-cortical neurons are stimulus-specifically modulated during selective attention to filter task-relevant stimulus features from amongst irrelevant ones (see Jääskeläinen et al. 2011)

While individuals who suffer from schizophrenia demonstrate a wide variety of attention deficits, these deficits seem to be independent of both the clinical state and medication, and are present at the earliest stages of the disease (Saykin et al. 1991; Cornblatt and Keilp 1994; Heinrichs and Zakzanis 1998; Cornblatt et al. 1997; Albus et al. 2006).

Verbal skills

Verbal skills are a part of general verbal intelligence, which means the ability to analyze information and solve problems using language-based reasoning. Verbal skills include the ability to listen and recall spoken information, understand the meaning of spoken or written information, solve language-based problems, understand the relationships between language concepts and perform language comparisons or analogies, and to perform multipart language-based analyses. In society, verbal reasoning is important to most aspects of everyday life, such as attending school or working.

When testing patients in research on schizophrenia, basic verbal reasoning is typically evaluated through brief tests. According to a large meta-analysis by Heinrichs and Zakzanis (1998), basic verbal skill impairments were apparent with standard deviations between 0.5 and 0.8, depending on tasks.

Visual processing

Visual processing, visual perception and visuo-construction are the basic processes of the brain's visual system. Visual processing is the sequence of events that allows information to flow from visual sensors in the retina to cognitive processing in the brain. Visual perception is the ability to precieve the immediate environment by processing information that has entered the eye as visible light. The resulting perception is also known as eyesight, sight, or vision (adjectival form: ocular, optical, visual, respectively). Visuo-construction is a skill that involves the ability to organize and reconstruct spatial information to make a design. Sometimes it is defined as one of the general intelligence factors (Carrol 1986).

Heinrichs and Zakzanis (1998) reported that individuals with schizophrenia score between 0.5 to almost 1.5 standard deviations below the control mean in various visual /spatial ability tests. However, compared with other domains of neurocognition, visual/spatial problems seem to be somewhat smaller. The problematic part of this evaluation is the fact that executive functions are to some extent part of visual processing, especially when constructing designs from observed stimuli or when choosing strategies for either visuo-

constructive or spatial processes. Executive functions are part of the total process in these cases, and its execution is often significantly disturbed in schizophrenia.

Motor skills

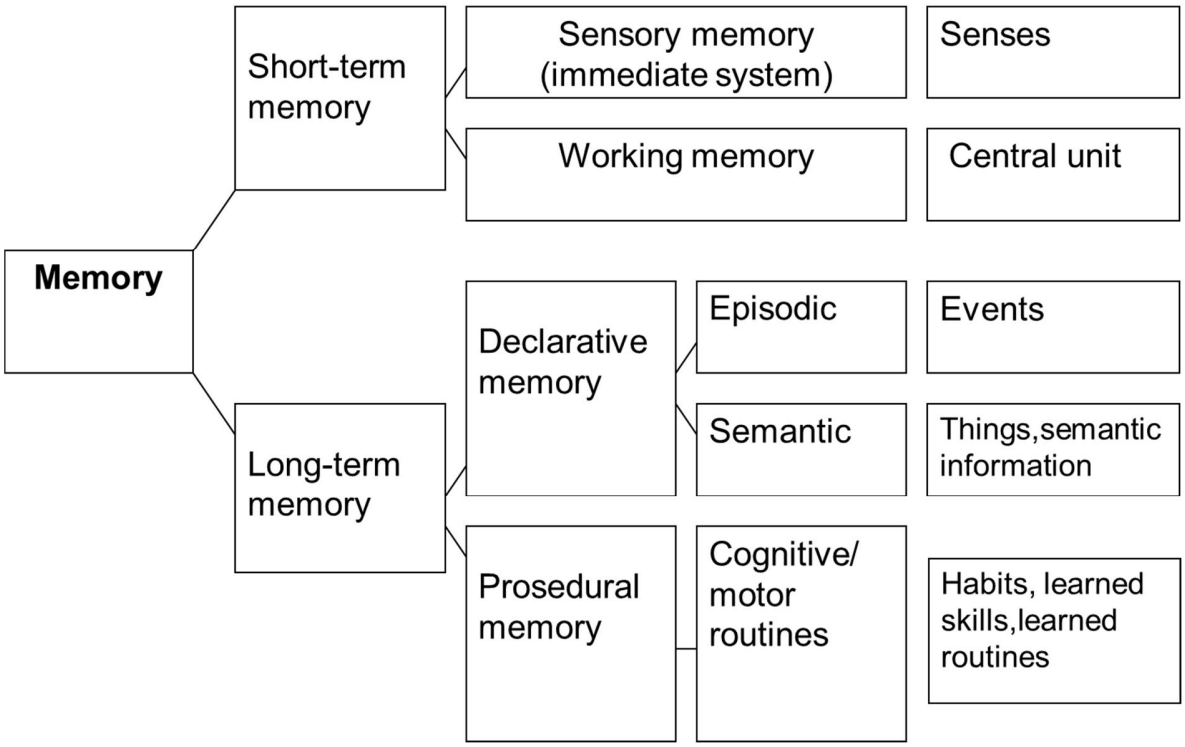
Motor dysfunction is a consistent finding in retrospective high-risk and archive-using studies of schizophrenia (Jones et al. 1994; Jones and Done 1997; Walker et al. 1999; Mittal et al. 2010). Delayed motor development, and at least mild motor dysfunctions that persist throughout infancy, have been observed in those individuals who later developed schizophrenia, and in their unaffected adult first-degree relatives (Kinney et al. 1986; Fish et al. 1992; Cantor-Graae et al. 1994; Ismail et al. 1998). It is a constant and obvious finding that movement abnormalities and motor dysfunctions are related to the emergence of schizophrenia, and longitudinal studies indicate that these features precede the onset of clinical symptoms (Walker 1994; Rosso et al. 2000). In addition to congenital motor dysfunctions, medication, and especially the first-generation antipsychotics (FGAs) may generate problems with motor functioning.

Memory

Memory is a complex system that allows an individual to register, encode, store, retain, and eventually retrieve information (Lezak et al. 2004). The first phase in memory is registering the stimuli, which is followed by editing the information for storage in the memory. As a result of this encoding, external information is processed physically and chemically in sensorial systems. The second phase in processing a memory is the storage of encoded information. This property makes it possible to retain information over time. Retrieval, in the final phase, allows us to use the retained information. Initially, when trying to remember something, we must locate stored information and return it to our consciousness. Memory and learning are close concepts, and memory can be considered as a result of learning.

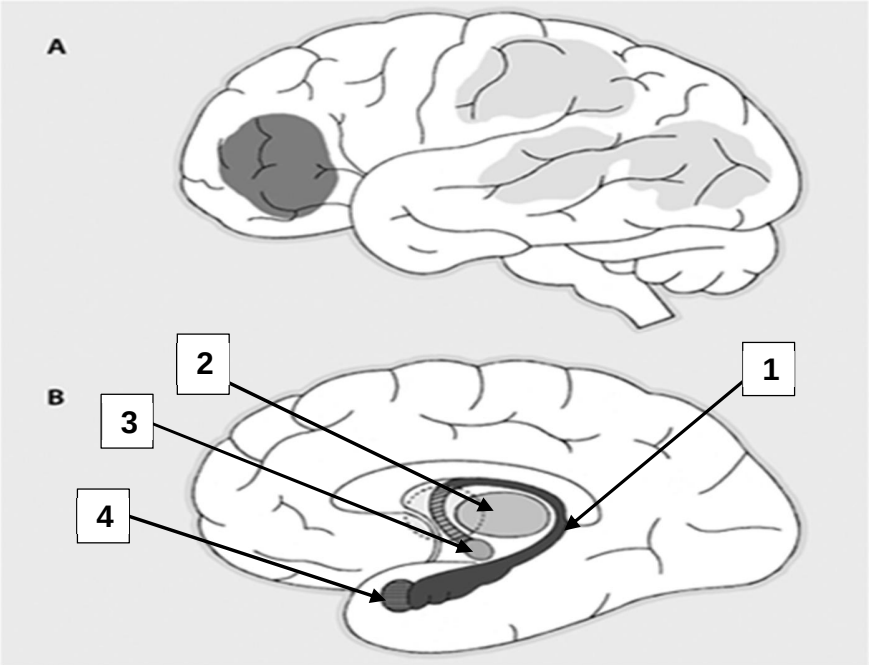
The memory system is often divided into short-term and long-term memories. Short-term memory can be divided into immediate and working memory, while long-term memory includes declarative (explicit) memory and non-declarative (implicit) memory (Figure 1).

Figure 1. Human memory system.



Memory cannot be localized to any specific area of the brain, and is the result of co-work between multiple neural networks. However, some parts of the brain may have more significance for remembering when compared with others. Different brain areas are activated in different types of memory (Figure 2).

Figure 2



A. Sensory memory systems, are located mostly in parietal and occipital cortex (colored light gray). Working memory (associated with executive functions) are processed mainly in frontal lobe (colored dark grey).
B. Inner occipital lobe, hippocampus (1) and thalamus (2) process events and things before storage it in cortical systems. Basal ganglia (3) comprise a group of structures that are involved remembering movements and skill learning. The amygdala (4) is involved in fear-learning (in addition to complex processing of emotions).

It has been known at least since the 1990s that there are consistent and comprehensive memory impairments in schizophrenia (Aleman et al. 1999). Verbal memory, including story recall and word list learning, seems to be more severely affected than non-verbal memory (Saykin et al.1991). Memory impairments are detected in both episodic and semantic forms of memory (Saykin et al. 1991; Saykin et al. 1994; Heinrichs and Zakzanis 1998; Cirillo and Seidman 2003). In their meta-analysis, Cirillo and Seidman (2003) proposed that verbal declarative memory is among the most defected neuropsychological functions in patients with schizophrenia. While the recognitive memory of patients with schizophrenia tends to be more or less intact (Conklin et al. 2002), the major problems are found in learning and

especially the use of effective learning strategies, which means more impairment in explicit than implicit memory systems (Sponheim et al. 2004). However, impaired recognition is sometimes detected, at least in the patients who have a severe decline in memory function (Clare et al. 1993; Landrø 1994), which may indicate that consolidation process of information could also be impaired.

Executive functions

The executive functions comprise the capacities for volitional activity, forward planning and self-regulation (Lezak et al. 2004). Executive functions control and manage other cognitive processes and are often described as a central executive unit of the brain and the whole cognitive system. Executive functions are a part of the process an individual uses to achieve purposeful behavior (Lezak et al. 2004). Executive functions include the ability to evaluate situations, choose and formulate strategies and solve problems, which provide the ability to adaptively shift to new situations or strategies. Some definitions of executive functions include even more dimensions. For example, according to Chan et al. (2008), executive functions are an umbrella term for neurocognitive processes such as planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility, multi-tasking, and both the initiation and monitoring of actions. These functions are largely carried out by brain prefrontal areas, and sometimes executive functions are even called frontal functions. However, other areas of brain (for example the parietal lobe) are also involved in executive functions, and there is no exclusive relationship between executive functions and frontal lobe activity. Patients suffering schizophrenia have impairments in many areas of executive functioning, and the degree of decline is usually severe in schizophrenia (Heinrichs and Zakzanis 1998).

Summary of neurocognitive dysfunctions associated with schizophrenia

The neurocognitive deficits in schizophrenia are especially pronounced in many domains of information processing. While no particular type of neurocognitive deficit is unique to schizophrenia, tasks that require active retrieval of verbal material from long-term memory, visual-motor processing, attention, vigilance or integrity of executive functions seem to be significantly difficult for most patients with schizophrenia (Blanchard and Neale 1994; Heinrichs and Zakzanis 1998; Nopoulos et al. 1994; Raine et al. 1992; Saykin et al. 1994; Sullivan et al.1994). It is now thought that impaired neurocognitive deficits may be a core finding in schizophrenia.

The nature of the neurocognitive deficits in schizophrenia

Neurocognitive impairment in schizophrenia is diffuse and pervasive, with performance deficits of approximately 1 to 2 standard deviations below non-psychiatric control samples across most cognitive domains; i.e., memory, attention, processing speed, vigilance, and executive functions (Gold 2004; Green 2006; Heinrichs and Zakzanis 1998). Although there are reports of individuals with schizophrenia demonstrating neurocognitive performance within the normal range, these high-functioning individuals do appear to show impairments relative to their estimated premorbid abilities (Reichenberg et al. 2005), and particularly for speeded tasks and working memory tests (Wilk et al. 2005).

Course of the neurocognitive deficits in schizophrenia

Two contrasting hypotheses have been argued on the course of neurocognitive deficits in schizophrenia. Some studies have suggested that cognitive function deteriorates over time, whereas others have reported stability or even an improvement in some functions (Delisi et al. 1995; Rund 1998). This question on the longitudinal course of schizophrenia is important in considering schizophrenia as a neurodegenerative (progressive) disorder or as a stable disease that result from a developmental defect. Moreover, neurocognitive deficits have become potential biological markers, or endophenotypes, that might ease in the identification of genetic factors that are involved in vulnerability to schizophrenia. To serve as reliable endophenotypes for schizophrenia, neurocognitive factors should be stable over time, and the non-genetic factors affecting its severity could be identified and used to obtain standardized values. There is also an increasing interest to improve neurocognitive functions in patients with schizophrenia through pharmacological treatments or cognitive remediation programs.

Recent evidence has suggested that neurocognitive deficits are independent of both clinical state and medication, and they are present at the initial episode of the disease (Saykin et al. 1994; Heinrichs and Zakzanis 1998; Albus et al. 2006). In patients with schizophrenia, neurocognitive deficits are present even before the first psychotic episode (Caspi et al. 2003). In fact, evidence points towards existing cognitive deficits already in childhood, before any psychotic illness (Osler et al. 2007; Maccabe 2008). Most studies point to a course of neurocognitive deficits being relatively stable without any significant worsening (Maccabe 2008; Frangou et al. 2008; Szöke et al. 2008). However, in addition to these facts, which supporting the idea of neurocognitive deficits as a sign of neurodevelopmental vulnerability factors, there are also findings that show neurocognitive deterioration at the time of the first psychotic episode (Lieberman et al. 1996). Furthermore, most experienced clinicians can readily identify a deteriorating course of neurocognition in their patients over time. Controversial results may be due to different subgroups of patients with

neurocognitive deficits, and different courses of illness in these subgroups. Over all, people with schizophrenia have been shown to have a wide range of cognitive deficits, but at least part of the longitudinal course of these deficits remains unclear, and further longitudinal studies are still needed to clarify this issue.

When designing studies to examine the possible enhancing effects of pharmacological agents, practice effects should be taken into account. The observable neurocognitive improvements in the patients with schizophrenia may result from real improvements in neurocognition, a practice (learning) effect, or a combination of the two. However, the practice effect alone might explain a perceptible improvement in neurocognition when tests are repeated several times, and this might also mask a concurrent worsening in some neurocognitive processes. This means that the practice effect may either simulate neurocognitive improvement, or attenuate the real-life impairment. To avoid these distortional effects of cognitive measurements, and to ensure that results can be correctly interpreted, the practice effect should be taken into account in the design of neurocognitive studies. For this reason, the use of a control group is of principal importance. It may also be important to match the groups, not only in terms of basic demographic characteristics (e.g., age, gender, education etc.), but also for familiarity with the tests and, more generally, for familiarity with testing circumstances in general.

Neurocognitive impairment as a determinant of outcome

In general, neurocognitive deficits in schizophrenia are related to poor global functioning (Velligan et al. 2000), and in particular to impaired community functioning, decreased instrumental and problem-solving skills, poor success in psychosocial rehabilitation programs (Green et al. 2000), and failure in long-term employment (Bryson and Bell 2003).

It has been progressively recognized that the severity of neurocognitive impairment is a major determinant to outcome in schizophrenia. It has been reported that neurocognitive deficits can account for up to 20 - 60% of the functional outcome in patients with schizophrenia (Green et al. 2000; Keefe and Fenton 2007; Keefe et al. 2007; Weinberger and Gallhofer 1997). This relationship is even more pronounced in chronic, highly symptomatic patients (Verdoux et al. 2002). Despite the use of different pharmacological treatments and psychosocial strategies, most patients with schizophrenia are still suffering from neurocognitive impairments that severely limit their social and vocational functioning. Therefore, interventions to improve neurocognitive function also have the capacity to improve quality of life. Thus, development of social and occupational outcomes remains one of the primary goals in the treatment of schizophrenia (Hyman and Fenton 2003).

Pathophysiological background of neurocognitive impairment in schizophrenia

As discussed previously, both the etiology and validity of schizophrenia, as single etiological category of mental disorders, is debatable (Dutta et al. 2007; Tandon et al. 2008). Lacking of a substantial knowledge of the etiology, entity and neurobiology of schizophrenia means that it is also difficult to characterize the specific neurobiological abnormalities underlying the disease, and the neurocognitive impairments associated with it.

The classic hyper-dopaminergic model (Carlsson and Lindquist 1963; van Rossum 1966), postulated that psychotic symptoms in schizophrenia were the result of too much dopamine transmission. Subsequent studies with functional neuroimaging suggest that negative symptoms, as well as neurocognitive dysfunctions in schizophrenia, may be partly due to a dysfunction in dopamine neurotransmission at D1 dopamine receptors in the medial prefrontal cortex (Goldman-Rakic et al. 2004; Castner et al. 2004). An integrative approach originally based on single-photon emission computed tomography- and positron emission tomography-based studies postulated that schizophrenia is characterized by an imbalance between subcortical and cortical dopamine systems (Knable and Weinberger, 1997). . According to this idea, subcortical mesolimbic dopamine projections may be hyperactive, thus resulting in hyper-stimulation of D2 receptors (and positive symptoms), while mesocortical projections to the prefrontal cortex (PFC) may be hypoactive, thus resulting in a concurrent hypostimulation of D1 receptors, which could lead to neurocognitive deficits or negative symptoms (Knable and Weinberger 1997). There are also etiological theories that have focused attention on a possible alteration in the glutamate neurotransmitter system, especially involving *N*-Methyl-D-aspartic acid (NMDA) receptor function (Javitt and Zukin 1991; Olney and Farber 1995) or impaired *gamma*-aminobutyric acid (GABA) neurotransmission (Benes and Berretta 2001; Lewis and Hashimoto 2007). Some studies have suggested that neurocognitive deficits in schizophrenia may be related to alterations in GABA neurotransmission (Costa et al. 2001; Brigman et al. 2006). Some recent studies suggest that alterations in glutamate receptor function may contribute to the development of the GABAergic pathology associated with schizophrenia (Keshavan et al. 2011).

Dysfunctions in glutamatergic and GABAergic systems may lead to severe imbalances between the excitatory and inhibitory systems of the brain, possibly forming a fundamental deficit for schizophrenia, while monoaminergic (including 5-HT, dopamine and other monoamines) dysfunction could be a secondary result of this imbalance (Miyamoto et al. 2012).

While neurocognitive dysfunction probably reflects the core pathological processes in schizophrenia, a comprehensive theory to integrate the complex pattern of positive symptoms, negative symptoms, neurocognitive decline and neurobiology in schizophrenia remains obscure. Despite the paucity of neurobiological data for this disease, any dysfunction in the major neurotransmitter systems (e.g., dopaminergic, glutamatergic,

cholinergic, serotonergic and GABAergic) is of importance to the functional neurobiology of schizophrenia (Galletly 2009).

When trying to understand the neurobiology of schizophrenia, and the neurocognitive impairment in schizophrenia, the challenge remains to integrate a growing body of evidence that relates neurotransmitter systems with genetic and other risk factors. Such efforts stimulate the development of hypotheses that account for these findings, in order to discover new treatments for neurocognitive dysfunction (Galletly 2009).

Strategies to enhance neurocognition in schizophrenia

Established treatment guidelines for schizophrenia (American Psychiatric Association 2004 and 2009; National Institute for Health and Care Excellence (NICE) 2009, Galletly 2009, Barnes et al. 2011) generally consider dopamine antagonists (antipsychotics) as the most effective way to diminish active positive symptoms of schizophrenia. It has been recommended that antipsychotic medications should be administered at the earliest stages of schizophrenia, thus forming a critical part of early intervention amenities. This approach is also based on the presumption that early treatment- will minimize possible negative consequences of active neuronal morbidity, and subsequently improve both symptomatic, neurocognitive and functional outcomes (Marshall et al. 2005; Perkins et al. 2005; Galletly 2009). It has also been hypothesized that antipsychotic treatment at the first episode of schizophrenic psychosis can prevent the progression of structural brain changes (Li and Xu 2007; Lieberman et al. 2005 and 2008).

There are two central approaches to enhance neurocognitive performance in patients with schizophrenia: non-pharmacological (for example neuropsychological rehabilitation) and pharmacological. Most of these patients are treated pharmacologically. Over 60 years have passed since the synthesis of chlorpromazine, on 11 December of 1950, and dopamine receptor D2 blockade is still an important objective in the psychopharmacological treatment of schizophrenia. However, these antipsychotic drugs have only a limited efficacy on the negative and neurocognitive symptoms of schizophrenia. The inadequate response to treatment is more apparent in subgroups of symptoms. In particular, while antipsychotic drugs are often effective at controlling the positive psychotic symptoms, they are less able to ameliorate the negative and cognitive symptoms of schizophrenia. These include social withdrawal, blunted mood, lack of self-care and deficits in both executive function and working memory. When combined with depressed mood, this spectrum of symptoms is more problematic for integrating the patient into society. As no single antipsychotic agent has been consistently shown to be a neurocognitive enhancer, various adjunctive psychopharmacological agents have been studied, yet so far with inconsistent and evasive results (Keefe et al. 2007; Galletly 2009).

Some of the possible neuro-enhancing adjunctive agents that have been studied are antidepressants. Within this class of drugs, mirtazapine has demonstrated a unique, wide-range mechanism of action that includes antagonism of the noradrenaline alpha-2 receptor, serotonin 5-HT2 and 5-HT3 receptors, and indirect agonism of the 5-HT1A receptor (Anttila and Leinonen 2001). All of these monoaminergic receptors seem to be involved in the modulation of neurocognition (Akhondzadeh et al. 2009; Galletly 2009; Sumiyoshi et al. 2007). The pro-neurocognitive effect of adjunctive mirtazapine was first reported in an open label study by Delle Chiaie et al. (2007), which has subsequently been replicated in a limited randomized controlled trial (RCT) (Cho et al. 2011).

The effects of antipsychotic drugs on neurocognition

FGAs emerged in the early 1950s, when the efficacy of chlorpromazine was first described in the treatment of psychotic symptoms (Delay et al. 1952). FGAs are still in wide use, although are other types of antipsychotics are currently available. The desired effect of FGAs on the positive psychotic symptoms has been shown to result from their ability to inhibit dopamine D_2 receptors in the brain (Carlsson and Lindqvist 1963; Lieberman et al. 2005; Leucht et al. 2009). Unlike the other FGAs, chlorpromazine has high affinity for D1 receptors.

The endeavour to develop effective antipsychotics with a better tolerability profile, and with a more comprehensive profile of effects, led to the advent of SGAs, which are also known as atypical antipsychotics. Clozapine, the prototypical SGA, has demonstrated a higher efficacy in treatment-refractory schizophrenia and a lower incidence of extrapyramidal symptoms (EPS) than FGAs. These unique features are referred to as atypical. These advantages from clozapine are probably attributed to its high affinity to serotonin 5HT2 receptors and relatively low affinity to dopamine D2 receptors, as opposed to FGAs, which generally have high affinity for D2 and relatively less interaction with 5HT receptors (Meltzer 1994). Based on this concept of serotonin dopamine antagonism, a number of novel SGAs have been developed to replace clozapine, due to its serious adverse effects.

Much optimism accompanied the early reports that favored SGAs over FGAs in the vast majority of clinical domains. However, the supremacy of SGAs has recently been questioned, as large independent studies have failed to show that most SGAs are safer or more effective than most FGAs (Jones et al. 2006; Tiihonen et al. 2006). Nevertheless, evidence exists in favor of SGAs in terms of negative symptoms of schizophrenia (Davis et al. 2003), chronic schizophrenia with a history of suboptimal response to treatment (Volavka et al. 2002), adverse effect profile (Dossenbach et al. 2004), treatment adherence (Kahn et al. 2008) and discontinuation of treatment (Lieberman et al. 2005).

Various interventions to improve neurocognition in schizophrenia have provided equivocal results (Galletly 2009; Keefe et al. 2007). In the 1990s, the first reports on SGAs as probable neurocognitive enhancers led to an enthusiasm that has eventually turned into a growing uncertainty. In contrast, it seems that FGAs may be either neutral or even able to recover rather than impair neurocognition (Keefe et al. 2006). In the Clinical Antipsychotic Trials of Intervention Effectiveness study (CATIE) (Keefe et al. 2007) FGAs have even slightly outperformed some SGAs in some cases.

Aside from the FGAs vs. SGAs controversy, the modest and disappointing neurocognitive effects of all antipsychotics has brought the basic research back to evaluate pharmacological adjuncts with possible neurocognition-enhancing properties. As a result, antidepressants with monoamine receptor-mediated mechanisms of action such as mianserine or mirtazapine, have become a promising candidate group (Poyurovsky et al. 2003). This is in contrast to the vast majority of both old and new antidepressants, e.g., SSRIs, that inhibit the action of monoamine transporters, which are technically not receptors.

Mirtazapine as a plausible neurocognitive enhancer

The neurocognitive effects from add-on antidepressants in schizophrenia have been studied in only a small number of RCTs, and with contradictory results. For instance, the serotonin reuptake inhibitor citalopram did not yield any benefits (Friedman et al. 2005), while adjunctive mianserine, a serotonin receptor-blocking antidepressant with a mechanism of action fairly close to mirtazapine, did improve neurocognition in FGA-treated schizophrenia patients (Poyurovsky et al. 2003). One explanation for this beneficial effect of mianserin might be due to its inhibition of serotonin 5-HT2 receptors – a feature that FGAs [in contrast to SGAs] are lacking.

Mirtazapine is an antidepressant with a distinct mechanism of action that includes antagonism of presynaptic noradrenaline a2, serotonin 5-HT2 and 5-HT3 receptors, and indirect agonism of the 5-HT1A receptor (Anttila and Leinonen 2001), which have all been shown to enhance neurocognition (Akhondzadeh et al. 2009; Galletly 2009; Sumiyoshi et al. 2007). Adjunctive mirtazapine has been frequently promoted to improve negative symptoms of schizophrenia (Berk et al. 2001; Joffe et al. 2009; Zoccali et al. 2004), and even positive symptoms in FGA-treated schizophrenia patients (Joffe et al. 2009). However, it is currently unknown whether or not adjunctive mirtazapine would also have a beneficial effect on neurocognitive processes.

Aims of the study

1. To explore the effect of 6-week adjunctive mirtazapine treatment on neurocognitive symptoms of schizophrenia in patients with no response, or only a sub-optimal response, to different FGAs in stable dosages.

2. To evaluate predictors and mediators of a possible enhancing effect from adjunctive 6-week mirtazapine treatment on neurocognition in patients with schizophrenia with no or only a sub-optimal response to different FGAs in stable dosages.

3. To investigate whether or not a prolonged 12-week exposure to mirtazapine could further improve neurocognition in patients with schizophrenia with no or only a sub-optimal response to different FGAs in stable dosages.

4. To determine whether or not 12-week mirtazapine treatment is associated with any improvement in clinical symptoms of patients with schizophrenia with no or only a sub-optimal response to different FGAs in stable dosages.

Patients and Methods

Study design

This study was the neurocognitive arm of a larger single-center, randomized, add-on, double-blinded, placebo-controlled study. Study participants were recruited from the Psychiatric Hospital and the Day Treatment Unit of the Psychoneurological Dispensary in the Karelian Republic, Petrozavodsk, Russia.

Patients who fulfilled all selection criteria were enrolled into the trial. After a one-week single-blind placebo run-in period, patients were randomized to receive either mirtazapine 30 mg or placebo every night at bedtime (QHS) in a double-blinded paradigm for 6 weeks (Studies I and II). Subsequently, patients who were willing to continue, and who were eligible to participate in an extension phase, entered the 6-week open-label phase, where they also received mirtazapine 30 mg QHS (Studies III and IV). Study drug codes for the double-blind phase were revealed only after all participants had completed both phases of the study, and after the database was closed.

Inclusion and exclusion criteria

Inclusion criteria

Patients of the study were of both genders, and included both in- and out-patients who fulfilled the following criteria:
1) An age between 18 - 65 years,
2) A diagnosis of schizophrenia (disorganized, catatonic, paranoid, residual, or undifferentiated), as determined by the DSM-IV (American Psychiatric Association 1994), or schizoaffective disorder (depressive type),
3) Currently receiving one or more FGA, at a cumulative daily dose of at least 200 mg chlorpromazine equivalents which had remained unchanged (also in terms of dosage) for at least six last weeks prior to screening. This criterion was extended to eight weeks for depot antipsychotics,
4) Presenting less than optimal clinical outcome; i.e., suffering from either positive or negative symptoms, where a disability due to only general symptoms was insufficient for inclusion. This insured that the resulting illness was at least of moderate severity (i.e., a moderately ill rating of 4 or more on the Clinical Global Impression Scale (CGI) severity item) (Guy 1970),
5) The clinical condition remained stable during the six weeks prior to the baseline visit,

6) The patient had a level of understanding that made reasonable cooperation with the investigator possible,
7) A written informed consent given by the patient.

Exclusion criteria

1) A previous allergy or a serious adverse event due to mirtazapine,
2) A history of unresponsiveness to a previous trial with mirtazapine at a daily dosage of 30 mg or more during four or more weeks, augmented to the patient's current or earlier conventional antipsychotic medication,
3) A previous lack of response to another antidepressant (e.g.; mianserine, trazodone, or nefazodone,) that has affinity to postsynaptic 5-HT_2 receptors, which were used at sufficient dosages during four weeks or more,
4) Current atypical antipsychotic medication (e.g.; clozapine, risperidone, olanzapine, sertindole, quetiapine, zotepine, ziprasidone.)
5) A previous non-response to either clozapine or other atypical antipsychotics,
6) A medical or neurological illness, or drug treatment that might cause a serious risk for the patients, or bias the assessment of their clinical or mental status (e.g.; serious unstable physical illness, epilepsy, "organic" brain syndrome, etc.),
7) A history of current bipolar disorder or schizoaffective disorder, bipolar type (patients with schizoaffective disorder, depressive type were able to participate in the study).
8) Substance addiction or abuse during the last three months prior to screening,
9) Poor medication compliance that is clearly predictable,
10) Suicidality,
11) For women of child-bearing age; pregnancy, lactation, or an inability or unwillingness to use medically acceptable methods of contraception during the study,
12) Treatment with any antidepressant, mood stabilizer, systematic (i.e., four or more times within one week) use of sumatriptan, naratriptan, zolmitriptan, or drugs with a similar mechanism of action, or either buspiron or drugs with a similar mechanism of action within four weeks (for fluoxetine, six weeks) prior to baseline. Inadvertent use of any above-listed drugs for the treatment of migraine was prohibited on the day of clinical assessment, or just before the assessment,
13) Treatment with antipsychotic drugs other than those currently used within the 6 weeks prior to baseline,
14) Treatment with benzodiazepines as follows:
- Systematic use (i.e., four or more times weekly) of any benzodiazepines at any dosage during any of the last four weeks prior to baseline, if they have been used for less than two months. However, systematic use of benzodiazepines was permitted if this treatment was considered to be absolutely necessary, and if they had been using benzodiazepines during two or more months before baseline in stable daily dosages not exceeding 30 mg of diazepam, or equivalent dosages of other benzodiazepines,

- Accidental use (i.e., three or less times weekly) of benzodiazepines in daily dosages exceeding 30 mg of diazepam or equivalent dosages of other benzodiazepines. Use of benzodiazepines on the day of clinical assessment was prohibited before the assessment,
15) Electroconvulsive therapy (ECT) within three months prior to baseline,
16) Any clinically meaningful abnormality identified during the physical examination, or laboratory screening that was likely to interfere with the conduct of the study.

Main study procedures

Demographic data collection

The following data were derived from the patient and primary clinical documents:
• date of birth
• diagnosis (DSM-IV)
• time of onset of the illness
• date of onset of the current episode
• number of previous psychotic episodes
• date of hospitalization and its reason (if appropriate)
• the date and the reason of possible drop-out
• history of antipsychotic medication use (what antipsychotics, in what dosages, and for how a long, and if have they been used prior to the study).

Neuropsychological assessment

At weeks 0, 6, and 12, a trained psychologist performed individual neuropsychological examinations to determine neurocognitive function. Russian translations (latest available versions) of commonly used and validated neuropsychological tests were employed to cover a broad range of neurocognitive domains (Szöke et al. 2008).

To ensure the same level of basic intelligence functions in both study groups, all patients were first tested with four subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler 1981). When assessing general intelligence domains, verbal intellectual function was measured with the Information and Similarities subtests, and non-verbal intelligence was evaluated with the Block Design and Digit Symbol subtests of the WAIS-R. Three subscales of the WMS (Wechsler 1945) were used to assess memory, where verbal memory was evaluated with the Logical Memory and Verbal Paired Associations subscales, and visual memory with the Visual Reproduction subscale. Executive functions were assessed with the Trail Making Test, part B (TMT-B) (Lezak, 1995; Reitan & Wolfson 1985), the Stroop coloured colour-names part of the Stroop test (Stroop words; Jensen & Rohwer 1966; Lezak 1995) and

the Digit Symbol subtest of the WAIS-R (Lezak 1995). To investigate initiation and conduct strategic mnemonic processing, verbal fluency was examined with a semantic category (animals) and letter word-list generation (words beginning with K) within a time limit of 60 seconds (Lezak 1995). The Block Design of WAIS-R was used to evaluate visual-spatial ability and fluency. General mental speed/attention control was evaluated with the Trail Making Test, part A (TMT-A) (Reitan & Wolfson 1985) and with the naming of coloured dots in the Stroop test (Stroop Dots; Jensen & Rohwer 1966; Lezak 1995). All neuropsychological tests were efficacy variables in this study. Table 2 displays the use of different neuropsychological assessment scales in Studies I-IV.

Clinical assessments

Clinical assessments were carried out at week –1 (screening), week 0 (baseline) and after 1, 2, 4, 6, 7, 8, 10, and 12 weeks of treatment. Clinical efficacy was evaluated by PANSS (Kay et al. 1987), CGI and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al. 1993). The Patient Global Impression Scale (PGI) (Guy 1976) was used to further analyze the patients' subjective attitudes to the study medication. The Simpson-Angus Scale for Extrapyramidal Side-effects (SAS) was used to investigate the FGA-induced extrapyramidal symptoms (Simpson and Angus 1970). Different clinical assessment scales used in Studies I-IV are shown in Table 2.

Table 2. Neuropsychological and clinical assessment scales used in Studies I-IV

Neuropsychological/clinical assessment scale	Reference	I	II	III	IV
CDSS, Calgary Depression Scale for Schizophrenia	Addington at al.1993		x		
CGI, Clinical Global Impression Scale	Guy 1976				x
Letter word-list generation (words beginning with K)	Lezak 1995	x		x	
PANSS, The Positive and Negative Syndrome Scale	Kay et al. 1987		x		x
PGI, Patient Global Impression Scale	Guy 1976				x
SAS, Simson-Angus Scale for Extrapyramidal Side Effects	Simson and Angus 1970		x		x
Semantic Category (animals)	Lezak 1995	x		x	
Stroop test, coloured colour-names part	Lezak 1995; Reitan and Wolfson 1985	x		x	
Stroop test, naming of coloured dots	Jensen and Rohwer 1966; Lezak 1995	x	x	x	
TMT-A, Trail Making Test, part A	Reitan and Wolfson 1985	x		x	
TMT-B Trail Making Test, part B	Reitan and Wolfson 1985; Lezak 1995	x		x	
WAIS-R, Wechsler Adult Intelligence Scale, Block Design	Wechsler 1981	x	x	x	
WAIS-R, Wechsler Adult Intelligence Scale, Digit Symbol Subtest	Wechsler 1981; Lezak 1995	x		x	
WAIS-R, Wechsler Adult Intelligence Scale, Information and Similarities Subtest	Wechsler 1981	x			
WMS, Wechsler Adult Memory Scale, Logical Memory Subscale	Wechsler 1945	x		x	
WMS, Wechsler Adult Memory Scale, Visual Reproduction Subscale	Wechsler 1945	x		x	
WMS, Wechsler Adult Memory Scale, Verbal paired Associates Subscale	Wechsler 1945	x		x	

Safety and tolerability assessments

Physical examination and laboratory tests (including complete blood count, fasting levels of glucose and total cholesterol) were carried out at screening and end-point. In addition, the participants were asked about any adverse events while on the study medication.

Concomitant medications

The following medications were not allowed during the study:
1) Antidepressants other than the study drug (mirtazapine) as defined in this protocol.
2) Antipsychotics other than the patient's pre-existing FGA(s).
3) Mood stabilizers.
4) Systematic (i.e., four or more times within one week) use of sumatriptan, naratriptan, zolmitriptan or drugs with a similar mechanism of action. Accidental use of these drugs was prohibited on the days of clinical assessments and before the assessments.
5) Buspiron or drugs with a same kind of mechanism of action.
6) Benzodiazepines:
Regular use (i.e., four or more times weekly) of any benzodiazepines at any dosage was prohibited if the patient not received any benzodiazepine for two or more months prior to baseline (week 0) in stable dosages not exceeding 30 mg of diazepam or equivalent. The investigators were encouraged to keep the regular, pretrial benzodiazepine medication unchanged during the study. A decrease in dosages was, however, permitted due to ethical reasons, while any increase was not allowed .
Accidental use (i.e., three or less times weekly) of a benzodiazepine in daily doses that exceeded 30 mg of diazepam or equivalent was not allowed. Accidental use of benzodiazepines at any dosage was prohibited on the days of clinical assessments and before these assessments.
7) If necessary, zopiclon, zolpidem and zaleplon were permitted as hypnotics, in dosages not exceeding recommendations of the manufacturer.

Statistical methods

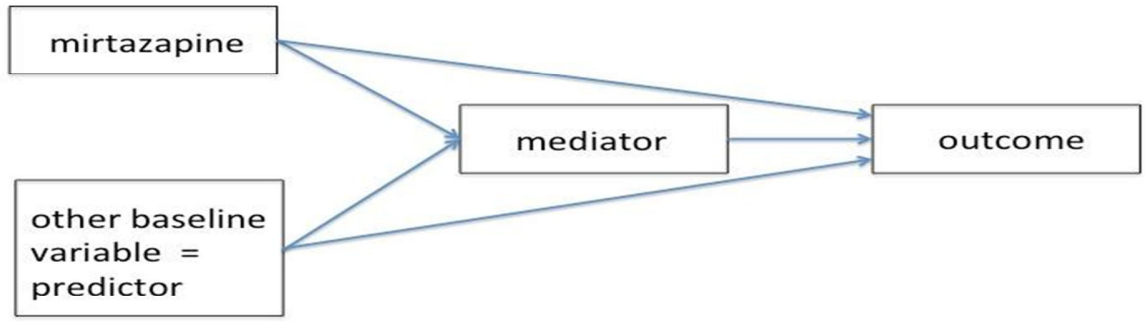
Analyses were carried out on a Modified Intent-to Treat (MITT) basis, with Last Observations Carried Forward (LOCF). False discovery rate (FDR) was applied to correct for multiple testing, and FDR controlled for the expected proportion of incorrectly rejected null hypotheses (type I errors). The q-value software (http://genomics.princeton.edu/storeylab/qvalue/manual.pdf) was employed for the FDR procedure, according to Storey (2002).

Cross-sectional statistical differences between the study groups were tested by using Chi-Square (Studies I, III, IV) or by Fisher's exact test (Study IV) for categorical variables. Cross-sectional statistical differences between the study groups were analyzed by using the Mann-Whitney U-test (Studies I and III) and by the independent samples *t*-test (Study IV) for continuous variables.

Possible within-group changes in efficacy variables over time were assessed with the Wilcoxon test, and differences between treatments over time were evaluated with the Mann-Whitney U-test (Studies I and III). Within-group changes in the efficacy variables over time were analyzed by the paired sample *t*-test (Study IV). Spearman's correlation coefficient was used *post hoc* to investigate possible associations between longitudinal changes in neurocognitive measures (Study I).

A path analysis model was used for the identification of predictors and mediators In Study II. Path analysis method has important advantages over multiple regressions, and served as a method that allowed testing a system of regression equations where variables can serve as predictors, mediators and outcome. This also enabled multiple outcomes to be studied at the same time and the parsing of effects into their direct, indirect and total components. A robust maximum likelihood (MLR) estimator was used as an estimator, to correct for any non-normality in the variable distributions, in addition to providing an unbiased estimate of the standard errors (Muthén and Muthén 1998–2010). Each path analysis model was first conducted by including all possible paths, as shown in Figure 3. Because of the small sample size (n=19 in the mirtazapine group and n=18 in the placebo group), the final model for each mediator-/outcome-combination was calculated with a minimal number of paths from "other baseline variables than mirtazapine" to the mediator, and the outcome that was not statistically significant in the initial model.

Figure 3
A path-analytic approach was used to evaluate for possible predictors and mediators of a putative enhancing effect from adjunctive mirtazapine on neurocognition in schizophrenia. The path analysis model included all possible paths from treatment to outcome.



In Studies I, III, and IV, a p-value less than 0.05 was considered to be statistically significant. All analyses in Studies I, III, and IV were performed by using SPSS for Windows 14.0 software. In Study II, a statistical significance of $p < 0.10$ was applied instead of the normal $p < 0.05$, due to the small sample size, and this was decided *a priori*. Mplus 5.21 software was used to perform the path analysis in Study II.

Ethics

This study was made in compliance with the current version of the Declaration of Helsinki, Guideline for Good Clinical Practice (ICH_GCP) and with the current National Regulations in the Russian Federation Karelian Republic. The study protocol was considered and approved by the Ethical Committee of the Karelian Republic and the local Institutional Review Board before the start of the trial. After a complete description of the study, a written informed consent was received from each patient. Individuals were allowed to withdraw their consent at any time. Patients were recruited only if add-on mirtazapine treatment was considered appropriate and useful from a clinical point of view.

Results

Study outline, baseline demographics with neurocognitive and clinical profiles

This study included a double-blind, add-on, randomized, placebo-controlled, with a 6-week main period and an open-label 6-week extension phase. Studies I and II are based on data of the double-blind main phase (6 weeks), and Studies III and IV incorporate data from both the double-blind main phase (6 weeks) and the extension phase (6 weeks).

Table 3 displays the number of patients included in Studies I-IV. Of the 46 individuals screened, 41 were randomized. In Studies I and II, after randomization, one patient allocated to placebo was excluded due to a protocol violation and one patient (placebo assigned) withdrew consent. Two patients, one in each study group, were excluded due to their inability to perform in neurocognitive tests. Thus, a modified intent-to-treat population resulted in 19 individuals in the mirtazapine and 18 in the placebo groups in Studies I and II.

The study population in Study III consisted of completers from the 6-week double-blind phase who were capable and willing to proceed to the 6-week open label phase, and who were capable of at least one assessment after exposure to mirtazapine treatment. One individual in the continuation group could not be tested at week 12 and was excluded. Thus, data on 18 patients were analyzed at week 12, both for the continuation group (12-week mirtazapine exposure) and for the switch group (initially 6 weeks on placebo and thereafter 6 weeks on mirtazapine).

In Study IV, all 20 individuals originally assigned to the mirtazapine group completed the extension phase. In the placebo group, out of 21 assigned to placebo, four patients withdrew and one was excluded due to a protocol violation.

Table 3. Participant assignment in Studies I-IV

	Studies I and II (n)	Study III (n)	Study IV (n)
Screened	46	46	46
Randomized	41	41	41
Assigned mirtazapine	20	20	20
Assigned placebo	21	21	21
Analyzed mirtazapine double-blind phase, week 6	19	x	x
Analyzed placebo double-blind phase, week 6	18	x	x
Analyzed continuation group mirtazapine open-label phase, week 12	x	18	20
Analyzed switch from placebo to mirtazapine group open-label phase, week 12	x	18	16

There were no differences between the mirtazapine and placebo groups at baseline in age (44.05±9.00 vs. 48.11±9.95 years, p=0.19), gender/males (52.6% vs. 50.0%, p=0.87), in-patient status (52.6% vs. 33.3%, p=0.24), duration of illness (23.84±6.40 vs. 24.44±9.45 years, p=0.29), antipsychotic dose in chlorpromazine equivalents (319.21±115.31 vs. 300.83±154.26, p=0.25) or number of previous antipsychotics (8.74±2.76 vs. 7.78±3.28, p=0.34).

No difference emerged in the neuropsychological performance tests (WAIS-R, WMS, Stroop test, TMT, Word fluency) (Table 4) or clinical characteristics (PANSS total 105.63±10.26 vs. 97.50±13.64 points, p=0.15; PANSS positive 22.32±4.14 vs. 18.67±5.18 points, p=0.13; PANSS negative 30.32±3.99 vs. 28.50±3.93 points, p=0.32; PANSS general 53.00±6.37 vs. 50.33±7.44 points, p=0.37) at baseline between the mirtazapine and placebo groups.

Table 4. Baseline neuropsychological profile of the study population (completers of the double-blinded phase)

	Mirtazapine (n=19) mean (S.D.)	Placebo (n=18) mean (S.D.)	Test statistics
WAIS-R, information (points)	15.16 (5.94)	13.72 (4.60)	z=1.16, p= 0.404
WAIS-R, similarities (points)	13.58 (5.48)	12.39 (3.18)	z=0.58, p=0.497
WAIS-R, block design (points)	28.28 (8.66)	27.17 (9.76)	z=0.32, p=0.564
WMS, digit symbol (points)	25.28 (9.72)	23.24 (8.33)	z=0.79, p=0.444
WMS, digit span forward (points)	5.32 (0.89)	5.11 (1.08)	z=1.01, p=0.421
WMS, digit span backward (points)	3.72 (0.96)	3.72 (0.83)	z=0.19, p=0.614
WMS, digit span total (points)	8.84 (1.80)	8.83 (1.62)	z=0.48, p=0.536
WMS, logical memory (points)	8.47 (4.23)	8.28 (4.01)	z=0.11, p=0.638
WMS, logical memory delayed (points)	6.78 (3.52)	6.22 (3.77)	z=0.32, p=0.564
WMS, verbal paired associations (points)	17.84 (7.57)	19.67 (5.57)	z=0.61, p=0.497
WMS, verbal paired associations delayed (points)	6.78 (2.46)	7.17 (2.18)	z=0.35, p=0.559
WMS, visual reproduction (points)	6.83 (2.94)	6.56 (3.81)	z=0.03, p=0.659
WMS, visual reproduction delayed (points)	4.59 (2.90)	3.94 (3.35)	z=0.58, p=0.497
Stroop Dots (84) (time)	122.05 (55.40)	108.39 (45.56)	z=0.91, p=0.437
Stroop Dots (84) (number of mistakes)	1.11 (1.37)	1.00 (1.91)	z=0.59, p=0.497
Stroop coloured words (84) (time)	152.94 (61.13)	192.41 (119.95)	z=0.84, p=0.438
Stroop coloured words (84) (number of mistakes)	2.44 (2.01)	3.29 (2.62)	z=0.91, p=0.437
TMT-A (time)	97.11 (53.90)	107.41 (54.71)	z=0.78, p=0.444
TMT-A (number of mistakes)	0.11 (0.32)	0.24 (0.75)	z=0.12, p= 0.638
TMT-B (time)	152.47 (65.08)	162.71 (78.47)	z=0.38, p=0.559
TMT-B (number of mistakes)	1.59 (1.50)	1.35 (1.66)	z=0.68, p=0.491
Word fluency, letter words (points)	6.26 (3.02)	6.89 (2.68)	z=0.83, p=0.438
Word fluency, semantic (points)	7.79 (3.38)	9.17 (3.73)	z=1.16, p=0.404

The effect of 6-week adjunctive mirtazapine on neurocognitive symptoms of schizophrenia (Study I)

In Study I, after 6 weeks of treatment, when retests and initial tests were compared, 5/21 cognitive parameters (i.e. WAIS-R Block Design, p=0.021; WMS Logical Memory, p=0.044; WMS Logical Memory Delayed, p=0.044; Stroop Dots, p=0.044; TMT-A, p=0.018) were significantly improved in the mirtazapine group, compared to 1/21 statistically significant parameters (WMS Logical Memory, p=0.039) in the placebo group (Table 5). No worsening was observed in any of the neurocognitive parameters in either of the study groups.

Mirtazapine was better than placebo on the Block Design and Stroop Dots tests in the between-group comparisons (Table 5). The difference in the degree of change; i.e., the change while on mirtazapine minus that on placebo was 18.6% for Block Design and 11.1% for Stroop Dots (p=0.044 for both). This improvement was not associated with age, gender, duration of illness, out-or in-patient status, dose of antipsychotics or with improvements in negative, positive or general symptoms. Depression scores (item 20 of PANSS) were similar and not statistically significant between the mirtazapine and placebo groups at baseline (p=0.667). Changes in Block Design or Stroop Dots did not correlate with baseline depression scores (r=–0.08, p=0.649 and r=–0.085, p=0.629, respectively).

Table 5. Change in neurocognitive parameters between week 6 and baseline (Study I)

	Change within continuation mirtazapine group (n=19), p-value	Change within placebo group (n=18), p-value	Change between groups, mirtazapine vs. placebo, p-value
WAIS-R block design (points)	p=0.021	p=0.313	p=0.044
VMS digit symbol (points)	p=0.437	p=0.347	p=0.543
VMS digit span forward (points)	p=0.421	p=0.438	p=0.494
VMS digit span backward (points)	p=0.206	p=0.528	p=0.327
VMS digit span total (points)	p=0.233	p=0.659	p=0.377
VMS logical memory (points)	p=0.044	p=0.039	p=0.588
VMS logical memory delayed (points)	p=0.044	p=0.200	p=0.438
VMS verbal paired associations (points)	p=0.123	p=0.496	p=0.404
VMS verbal paired associations delayed (points)	p=0.091	p=0.437	p=0.421
VMS visual reproduction (points)	p=0.206	p=0.559	p=0.421
VMS visual reproduction delayed (points)	p=0.065	p=0.072	p=0.614
Stroop Dots (84) (time)	p=0.044	p=0.525	p=0.044
Stroop Dots (84) (number of mistakes)	p=0.421	p=0.559	p=0.249
Stroop coloured words (84) (time)	p=0.164	p=0.421	p=0.543
Stroop coloured words (84) (number of mistakes)	p=0.208	p=0.497	p=0.444
TMT-A (time)	p=0.018	p=0.421	p=0.233
TMT-A (number of mistakes)	p=0.659	p=0.421	p=0.438
TMT-B (time)	p=0.053	p=0.659	p=0.091
TMT-B (number of mistakes)	p=0.421	p=0.540	p=0.614
Word fluency letter words (points)	p=0.199	p=0.659	p=0.169
Word fluency semantic (points)	p=0.313	p=0.421	p=0.168

Predictors and mediators of enhancing effect of adjunctive 6-week mirtazapine treatment on neurocognition (Study II)

In Study II, a path model analyses revealed that add-on mirtazapine had an independent enhancing effect on the Block Design-measured visuo-spatial functioning. Overall, the fit was good in models that were conducted with no significant statistical differences between the models and data.

Path model analysis results

The results for each explored mediator are presented in Figure 4. The paths of mirtazapine → mediator, mirtazapine → outcome and mediator → outcome were always included in the final path analysis models, whether they were statistically significant or not. These paths are at all times of theoretical interest. A solid line indicates that the path is statistically significant, while a dashed line in the model designates that a path was not statistically significant. (*nota bene*; all figures and tables in this section are reprinted with permission).

Block Design

Model for PANSS negative subscale

Mirtazapine treatment indicated an independent effect on both the Block Design and negative symptoms (Figure 4 and Table 6). The change in negative symptoms did not mediate the improvement in Block Design. A better baseline level of Block Design functioning predicted less improvement in this particular test.

Figure 4. Model for PANSS negative subscale

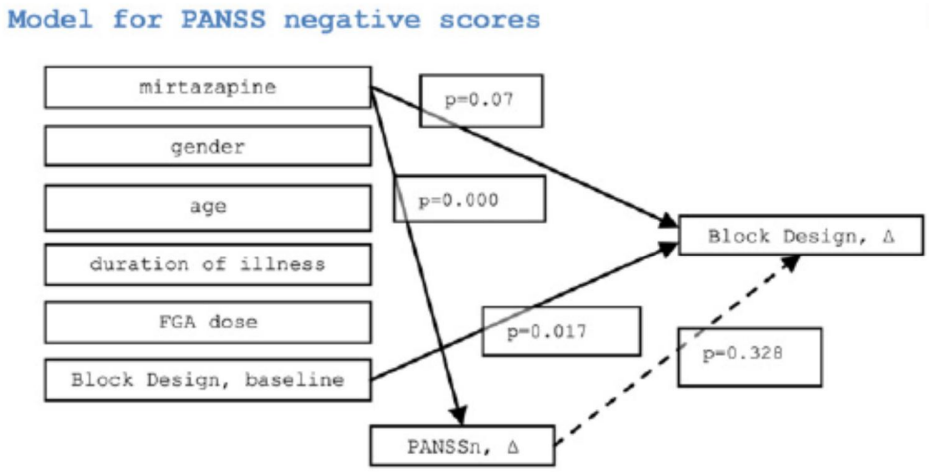


Table 6. Predictors and mediators of add-on mirtazapine-induced enhancement in Block Design measured neurocognitive function in schizophrenia- results of the path analysis; Model for PANSS negative scores.

Δ = change (scores at week 0 minus scores at week 6)

Path analysis model	Predictor or mediator	Value, Δ (s.e.)	t=	p= (two-tailed)	Overall model fit, p=
Model for PANSS negative scores					0.845
Block Design, Δ	mirtazapine	2.87 (1.58)	1.81	0.070	
	Block Design, baseline	-0.18 (0.08)	-2.39	0.017	
	PANSSn, Δ	-0.29 (0.29)	-0.98	0.328	

Model for PANSS positive subscale

Mirtazapine treatment showed a direct effect on the Block Design and PANSS positive scores (Figure 5 and Table 7). The effect of mirtazapine on changes in the Block Design was also mediated by changes in PANSS positive scores. Higher values for changes in PANSS positive scores were associated with higher values in the Block Design. Higher antipsychotic doses and shorter durations of illness were associated with larger improvements in the Block Design.

Figure 5. Model for PANSS positive subscale

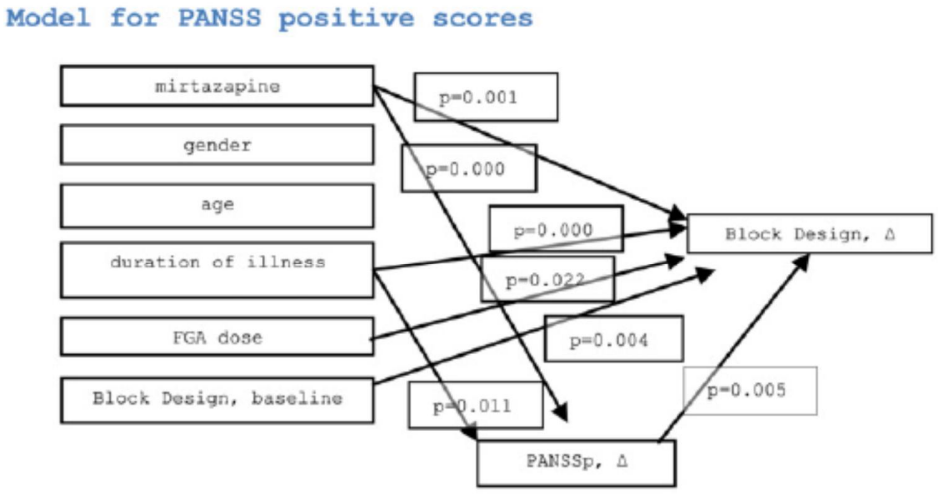


Table 7. Predictors and mediators of add-on mirtazapine-induced enhancement in Block Design measured neurocognitive function in schizophrenia- results of the path analysis; Model for PANSS positive scores.

Δ = change (scores at week 0 minus scores at week 6)

Path analysis model	Predictor or mediator	Value, Δ (s.e.)	t=	p= (two-tailed)	Overall model fit, p=
Model for PANSS positive scores					0.791
Block Design, Δ	mirtazapine	3.73 (1.09)	3.44	0.001	
	duration of illness	-0.23 (0.06)	-3.68	0.000	
	FGA dose	0.01 (0.01)	2.29	0.022	
	Block Design, baseline	-0.22 (0.08)	-2.85	0.004	
	PANSSp, Δ	0.35 (0.13)	2.82	0.005	

Model for PANSS total scale

Mirtazapine treatment showed an independent effect on both the Block Design and PANSS total scores (Figure 6 and Table 8). PANSS total scores, however, did not mediate the improvement in the Block Design. Better baseline functioning in the Block Design and longer duration of illness predicted only a minor improvement. Higher antipsychotic dosages predicted a larger improvement in the Block Design.

Figure 6. Model for PANSS total scale

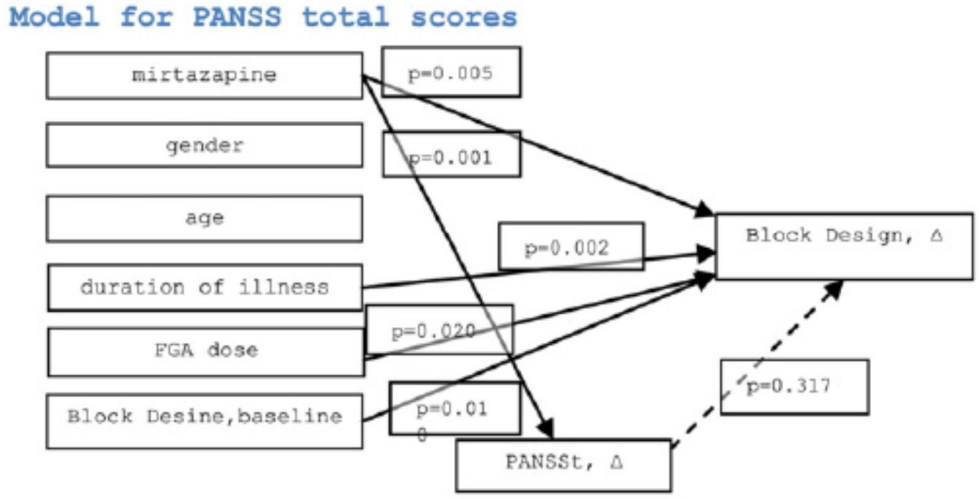


Table 8. Predictors and mediators of add-on mirtazapine-induced enhancement in Block Design measured neurocognitive function in schizophrenia- results of the path analysis; Model for PANSS total scores.

Δ = change (scores at week 0 minus scores at week 6)

Path analysis model	Predictor or mediator	Value, Δ (s.e.)	t=	p= (two-tailed)	Overall model fit, p=
Model for PANSS total scores					0.492
Block Design, Δ	mirtazapine	2.99 (1.06)	2.82	0.005	
	duration of illness	-0.20 (0.06)	-3.17	0.002	
	FGA dose	0.01 (0.01)	2.34	0.020	
	Block Design, baseline	-0.21 (0.08)	-2.59	0.010	
	PANSSt, Δ	0.04 (0.04)	1.00	0.317	
PANSSt, Δ	mirtazapine	-10.30 (3.18)	-3.24	0.001	

Models for CDSS and SAS

Mirtazapine treatment was associated with an improvement in the Block Design, both directly and *via* the CDSS (Figure 7 and Table 9). The same was true for the SAS in a separate model (Figure 7 and Table 9). In both the Model for the CDSS and the Model for the SAS, better baseline functioning in the Block Design and longer duration of illness predicted smaller improvements in the Block Design, while higher antipsychotic dosages predicted a larger improvement.

Figure 7. Models for CDSS and SAS

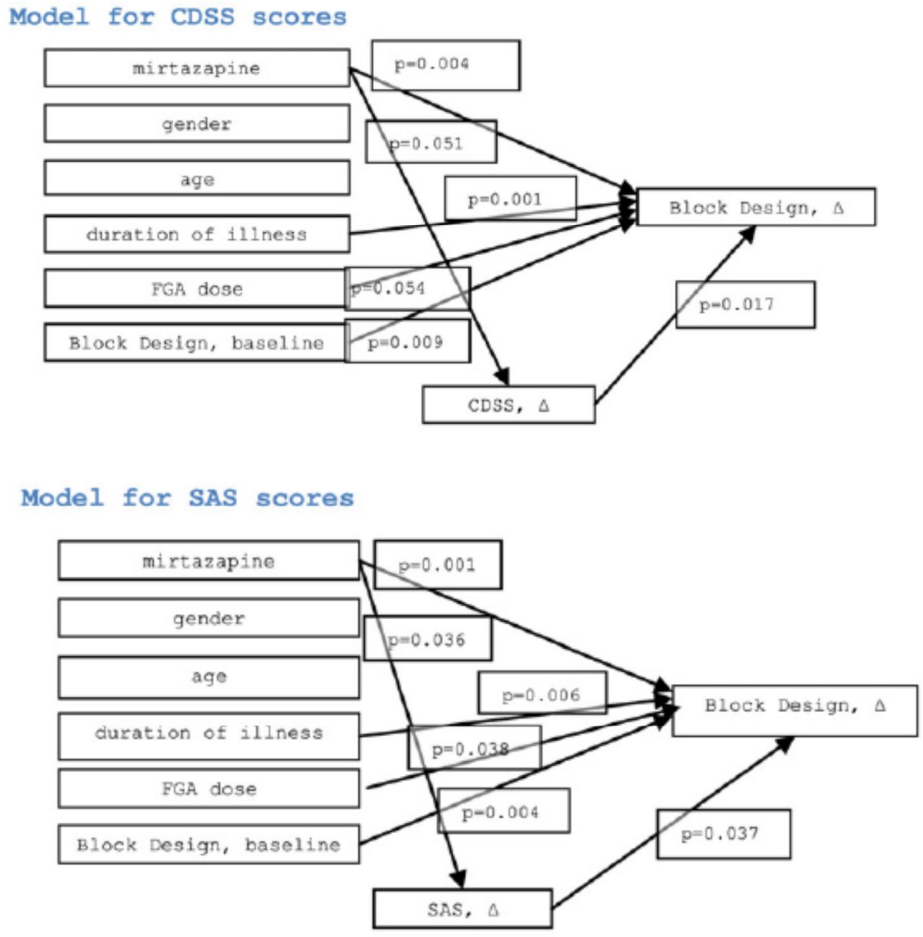


Table 9. Predictors and mediators of add-on mirtazapine-induced enhancement in Block Design measured neurocognitive function in schizophrenia- results of the path analysis; Models for CDSS and SAS.

Δ = change (scores at week 0 minus scores at week 6)

Path analysis model	Predictor or mediator	Value, Δ (s.e.)	t=	p= (two-tailed)	Overall model fit, p=
Model for CDSS					0.490
Block Design, Δ	mirtazapine	3.17 (1.09)	2.92	0.004	
	duration of illness	-0.20 (0.06)	-3.38	0.001	
	FGA dose	0.01 (0.01)	1.92	0.054	
	Block Design, baseline	-0.19 (0.07)	-2.62	0.009	
	CDSS, Δ	0.30 (0.12)	2.39	0.017	
CDSS, Δ	mirtazapine	-1.85 (0.95)	-1.94	0.051	
Model for SAS					0.518
Block Design, Δ	mirtazapine	3.50 (1.09)	3.22	0.001	
	duration of illness	-0.15 (0.06)	-2.77	0.006	
	FGE dose	0.01 (0.00)	2.08	0.038	
	Block Design, basline	-0.20 (0.07)	-2.89	0.004	
	SAS, Δ	0.41 (0.20)	2.08	0.037	
SAS, Δ	mirtazapine	-2.04 (0.97)	-2.10	0.036	

Stroop Dots

Results from the path model analysis show that mirtazapine treatment was not independently associated with an enhancement in the Stroop Dots for any model. In all models - except the model for SAS- better baseline performance (= smaller time) and higher dosages of FGAs predicted a minor improvement (= smaller drop in time) on the Stroop Dots. Of all measured parameters, only SAS mediated the effects of mirtazapine towards improvement in the Stroop Dots. In other words, decreases in the SAS scores were correlated with decrease in time in the Stroop Dots.

Effect of 12-week exposure to mirtazapine on neurocognitive symptoms of schizophrenia (Study III)

In Study III, patients who received mirtazapine in the double-blind phase, and continued on mirtazapine during the extension-phase (totally 12 weeks on mirtazapine), formed the "continuation group". Patients who were on placebo during the double-blind phase and received mirtazapine only during the extension-phase (totally 6 weeks on mirtazapine) formed the "switch group".

Those who switched from placebo to open label mirtazapine treatment achieved similar results in the 6 following weeks as the mirtazapine-treated individuals who had their first 6 weeks on mirtazapine treatment.

During the extension phase, 12 out of the 21 neurocognitive measured parameters improved in the continuation group, while 6 parameters showed improvement in the switch group (Table 10).

From week 0 to week 12 the continuation group demonstrated improvements in 17/21 parameters, and in 8/21 parameters for the switch group (Table 10). Twelve weeks of mirtazapine treatment indicated an advantage over the shorter, 6-week mirtazapine treatment on Stroop Dots time and TMT-B, according to the number of mistakes ($t = -2.562$, $p = 0.035$ and $t = -2.42$, $p = 0.043$, respectively) (Table 10).

Table 10. Change in neurocognitive parameters after the shift from 6 weeks double-blind treatment, with either mirtazapine or placebo, to 6 weeks (weeks 6 to 12, extension phase) treatment with open-label mirtazapine (Study III).

	Change within continuation group, (n=18), wk 6-12, p-value	Change within switch group, (n=18), wk 6-12, p-value	Change within whole population, (n=36), wk 6-12, p-value	Change within continuation group, (n=18), wk 0-12, p-value	Change within switch group, (n=18), wk 0-12, p-value	Change in continuation vs. change in switch group wk 0-12, p-value
WAIS-R block design (points)	0.529	0.044	0.397	0.023	0.006	0.256
VMS digit symbol (points)	0.001	0.18	0.006	0.024	0.073	0.544
VMS digit span forward (points)	0.028	0.034	0.006	0.009	0.020	0.541
VMS digit span backward (points)	0.133	0.334	0.117	0.017	0.490	0.104
VMS digit span total (points)	0.030	0.104	0.014	0.006	0.124	0.272
VMS logical memory (points)	0.052	0.503	0.196	0.009	0.014	0.566
VMS logical memory delayed (points)	0.039	0.052	0.006	0.001	0.026	0.257
VMS verbal paired associations (points)	0.118	0.028	0.013	0.012	0.050	0.503
VMS verbal paired associations delayed (points)	0.009	0.450	0.104	0.001	0.144	0.147
VMS visual reproduction (points)	0.014	0.132	0.009	0.023	0.331	0.231
VMS visual reproduction delayed (points)	0.035	0.273	0.043	0.001	0.031	0.544
Stroop Dots (time)	0.045	0.209	0.042	0.001	0.073	0.035
Stroop Dots (number of mistakes)	0.272	0.531	0.503	0.14	0.531	0.203
Stroop coloured words (time)	0.036	0.014	0.001	0.006	0.044	0.450
Stroop coloured words (number of mistakes)	0.290	0.104	0.079	0.073	0.334	0.431
TMT-A (time)	0.032	0.024	0.001	0.001	0.041	0.561
TMT-A (number of mistakes)	0.290	0.290	0.577	0.290	0.199	0.133
TMT-B (time)	0.013	0.006	0.001	0.001	0.294	0.124
TMT-B (number of mistakes)	0.06	0.542	0.150	0.006	0.577	0.043
Word fluency letter words (points)	0.045	0.050	0.014	0.032	0.031	0.503
Word fluency semantic points)	0.345	0.080	0.069	0.079	0.334	0.334

Effect of 12-week exposure to mirtazapine on clinical symptoms of schizophrenia (Study IV)

In Study IV, the first 6-week mirtazapine exposure resulted in a similar total PANSS score change in the continuation group (i.e., weeks 0-6) as in the switch group (i.e., weeks 6-12); i.e., 15.63 vs. 13.3, p=0.495.

PANSS total, PANSS positive, PANSS negative, PANSS general, CGI, and SAS significantly improved with mirtazapine treatment in the continuation and switch groups ($p<0.0001$) during the extension phase. CGI severity scale did not improve in the continuation group ($p=0.163$), but did improve in the switch group ($p<0.0001$). In the total population (pooled data for switch and continuation groups), all parameters that were measured improved with statistical significance. The effect size of this change was 0.94 (CI 95%=0.45–1.43), as determined by PANSS total score.

Patients who were on mirtazapine during both the 6-week double-blind and the 6-week open phases showed greater improvement in positive symptoms (29.6% versus 21.2%, p=0.027) than those who were on mirtazapine during open-label extension phase only.

Discussion

The main findings

This study was designed to explore the efficacy of 6-week mirtazapine add-on therapy with different FGAs in patients with schizophrenia. Neurocognitive functions were studied to evaluate the additional effects of a prolonged 12-week exposure to mirtazapine, and to determine whether or not this improved neurocognition in these patients. Predictors and mediators of an enhancing effect from adjunctive 6-week mirtazapine treatment on neurocognition were also explored. In addition, this study focused on whether or not 12-week mirtazapine treatment is associated with an improvement in clinical symptoms in patients with schizophrenia.

The population for this study comprised patients who suffered from a prolonged disease and had a previous history of insufficient response to antipsychotic medications. During the study enrollment, patients were at a moderately stable stage of their disease, and their FGA treatment had remained unchanged for at least six weeks prior to screening. Overall, patients were highly symptomatic and had severe neurocognitive impairments.

This study is the first to report a favorable effect of a mirtazapine-FGA combination on neurocognitive impairments in a RCT study design. Adjunctive mirtazapine treatment not only enhanced neurocognition, but also had some desirable effects on the overall clinical symptomatology in chronic schizophrenia.

Effects of add-on mirtazapine on neurocognition in schizophrenia

In the first part of this study, a statistically positive effect was achieved when mirtazapine was added to FGAs, and compared to placebo, in neurocognitive domains of visual-spatial ability and general mental speed/attention control according to results from the Block Design and Stroop Dots, respectively. The difference in the degree of change (i.e., the change from mirtazapine minus that of placebo) was almost 20% in the Block Design and more than 10% in Stroop Dots. Improvements were not related to either the changes in psychopathology or depression. In addition, 5 out of 21 measured parameters improved with statistical significance in within-group analyses after mirtazapine vs. only one parameter with placebo.

Delle Chiae et al. (2007) published the first clinical study with add-on mirtazapine in schizophrenia. The duration of this study was 8 weeks, with an open label study design and

included only 15 outpatients. In their study mirtazapine was added to clozapine and reported to improve neurocognition. Contrary to the findings of our study, Delle Chiae and co-authors (2007) reported an improvement in both immediate and delayed memories with the mirtazapine-clozapine combination. Nonetheless, visual-spatial abilities and psychopathological parameters remained unchanged.

The difference in the results between these two studies might be due to a difference in the study samples. For example, Delle Chiae et al. (2007) studied stable outpatients with a ten year duration of illness of, while the patients in our study were highly symptomatic in-patients with a 20 year duration of illness. Also, the different receptor affinity profiles from the mirtazapine-FGAs combinations (i.e., inhibition of a wide range of receptors, in addition to D2) in our study vs. the mirtazapine-clozapine combination may also account for some significant variation (i.e., through an additional inhibition in only a limited number of receptors for clozapine; e.g., alpha2). Other methodological issues are also worth mentioning; e.g., different neuropsychological measures and a smaller sample size or the open design of the earlier study may also provide reasons for different profiles of positive results between these two studies.

Both the Block Design and Stroop dots tests are, at least in some way, related to general executive functions, which were also measured by TMT-B in this study. In line with this assumption, TMT-B also tended to favor mirtazapine (improvement by 13% with mirtazapine vs. worsening by 4.8% with placebo). However, this difference did not reach statistical significance after the FDR correction (p=0.091).

The actual mechanism for a potential neurocognitive enhancing effect of mirtazapine in schizophrenia remains unknown, but it may be elucidated from its receptor binding profile. Like most SGAs, mirtazapine could also increase prefrontal dopaminergic and noradrenergic activity via 5-HT2A or 5-HT2C receptor blockade, as demonstrated in animal models (Liegeois et al. 2002; Meneses 2007; Zhang et al. 2000), and thus improve neurocognitive performance. Secondly, 5-HT3 receptor modulation by mirtazapine could also improve neurocognition (Akhondzadeh et al. 2009), presumably through increased release of acetylcholine (Ramirez et al. 1996). Thirdly, mirtazapine might improve neurocognition as a result of the indirect agonism of 5-HT1A receptors (Sumiyoshi et al. 2007). Moreover, mirtazapine is a more potent alpha-2 receptor antagonist than clozapine, which may explain its additional neurocognition-enhancing effect, even if it is added to clozapine (as in the study reported by Delle Chiae et al. 2007). The alpha-2 receptors remain an important target for neurocognitive research and its down-regulation may enhance neurocognition through a noradrenaline-mediated modulation of response to environmental stimuli (Friedman et al. 2004). Furthermore, alpha-2 receptor antagonism seems to boost hippocampal neurogenesis (Rizk et al. 2006). Also, mirtazapine may actually boost levels of brain-derived neurotrophic factor (BDNF) Rogoz et al. 2005), which is a major mediator of neurogenesis

and neuroplasticity. Correspondingly, those who suffer from schizophrenia often have abnormally low BDNF serum levels (Rizos et al. 2008).

Due to contemporary and large independent studies (Jones et al. 2006; Lieberman et al. 2005; Tiihonen et al. 2006), FGAs may return to everyday psychopharmacological use in the future, especially if mirtazapine-FGA combinations become established as neurocognitive enhancers in schizophrenia. The patents for both FGAs and mirtazapine have already expired, and are now relatively inexpensive, which is an important issue of enlarging significance.

These beneficial neurocognitive effects of mirtazapine did not depend on baseline demographic, clinical parameters or its antidepressive effects. The most significant changes were seen in the positive symptoms domain, which appears to be independent of neurocognition (Heydebrand et al. 2004). The commonly experienced sedative effect of mirtazapine did not seem to prevent the development of its neurocognitive effects, at least by the endpoint (week 6) when the sedative effect of mirtazapine should have already weakened through the development of pharmacological tolerance (Ramaekers et al. 1998).

It is important to note that since mirtazapine binds to multiple types of receptors, and the affinity of mirtazapine to these different receptor types is differential (see Anttila & Leinonen 2001). Thus, it is possible that lower doses of mirtazapine have qualitatively (and not just quantitatively) different add-on effects, when compared to the dosages that are typically given in the clinical context such, as the 30 mg/d dose utilized in the present study.

Predictors and mediators of mirtazapine-induced cognitive enhancement in schizophrenia - a path model investigation

Block Design

In this part of the present study, mirtazapine treatment demonstrated a noticeable, (35 – 38 %) independent and direct beneficial effect on the visuo-spatial ability, as measured by the Block Design in all path analysis models.

Alterations in the PANSS positive, CDSS and SAS scores mediated the effect of mirtazapine on the visuo-spatial ability, as measured by the Block Design, while changes in the PANSS negative or PANSS total scores did not. Higher dosages of FGAs and shorter duration of illness predicted more noticeable improvement in the Block Design in all models except for one of the PANSS negative scores. A better baseline level of the Block Design predicted less improvement with add-on mirtazapine treatment.

Even though the PANSS positive, CDSS and SAS scores were better in these patients, the relationship of these scores to improvement in the Block Design was opposite. This means that a lesser degree of improvement in these clinical measures relates greater enhancements in the Block Design. Neither the interrelationship nor real life relationship between neurocognitive dysfunctions and clinical symptoms of schizophrenia are entirely understood. Particularly negative symptoms have been the focus of neuropsychological examinations, as these symptoms have a tendency to overlap with neurocognitive deficits.

Some researchers suppose that neurocognition and clinical symptoms are independent domains of schizophrenia (Green 1996; Harvey et al. 2006; Dominguez et al. 2009), while others maintain that neurocognitive deficits are secondary to clinical symptoms (Kerns and Berenbaum 2002; Nieuwenstein et al. 2001).

A current systematic review (Dominguez et al. 2009) and a later publication by Ventura et al. (2009) demonstrate that negative symptoms are significantly associated with cognitive deficits, while positive and depressive dimensions of psychopathology are not. However, in the CATIE study published by Keefe et al. (2007), neurocognitive enhancement was evidently, even if modestly, associated with symptom reduction in all PANSS dimensions.

The current study presents the mediation of positive neurocognitive effects from mirtazapine via changes in positive, depressive, and parkinsonism symptoms, with the absence of any statistically significant relationship between an improvement in neurocognition with improvements in negative symptoms. This result may be due to the particular features of our study sample. Patients in our study were chronically ill and severely psychotic, and the results showed the greatest improvements in positive and depressive symptoms (Joffe et al. 2009; Terevnikov et al. 2011). Additionally, an inverse relationship was seen between improvements in the Block Design results, and that a similar relationship between the positive, depressive and also parkinsonism symptoms might be entirely due to statistical reasons; i.e., the so-called regression to the mean phenomenon (Barnee et. al. 2005). If so, this means that in the beginning low clinical symptom scores in some patients could only allow for a lesser drop in clinical ratings, as the result of a ceiling effect, while their capacity for neurocognitive improvement could be higher than their more symptomatic matching parts. The probable role of clinical mediators in the effects of mirtazapine on neurocognition endures, at least somewhat, and requires more studies with statistical path analytical methods of larger and more varied patient populations.
FGAs tend to impair neurocognition in schizophrenia, at least when high dosages are used (Keefe et al. 2007). In the present study, higher dosages of FGAs predicted a favorable effect from mirtazapine on the Block Design. In other words, mirtazapine seemed to remediate the unpleasant neurocognitive effect of FGAs on neurocognition.

According to a recent meta-analysis (Szöke et al. 2008), the remaining capacity for neurocognitive recovery in patients with long-term schizophrenia is limited. Consequently, it was not surprising to find in our study that the duration of illness correlated negatively with mirtazapine-induced neurocognitive improvement in most path analysis models. This could mean that the more extended duration of the illness, the more likelihood of cognitive deterioration, which seems to be more or less treatment resistant. One explanation for this effect might be that schizophrenia has often been considered as a disorder of connectivity between components of large-scale brain networks (Lynall et al. 2010). Consequently, there may be impaired interactive connectivity between different brain regions, which could cause executive dysfunctions and dysfunctions between different domains of neurocognition, and subsequent metacognitive problems.

Stroop Dots

Mirtazapine did not have an independent effect on the Stroop Dots. Higher dosages of FGAs predicted a minor improvement (= smaller drop in time) on the Stroop Dots test, and positive change in the SAS scores did mediate the effect of mirtazapine treatment on the Stroop Dots. This means that mirtazapine-induced improvements in general mental speed and attention control, as measured by Stroop Dots, were most likely indirect and due to an improvement in the FGA-related symptoms of parkinsonism, thus resulting in a better naming speed in this test.

Effects of prolonged 12-week adjunctive mirtazapine

After the six week extension phase of previous 6-week double blind phase, both groups showed significant improvements on several neurocognitive tests. Moreover, the prolonged treatment with mirtazapine (12 weeks) led to additional benefits by improved results (either newly or further improved) for the continuation group on most tests (i.e., 17 tests vs. eight tests for the switch group). Patients from the placebo group, who received open label mirtazapine for the 6-week extension achieved similar results as those in the mirtazapine group at the end of their initial 6-week period (i.e., six of the 21 parameters improved) This was the first period of active mirtazapine treatment for the placebo group, and their improvement was similar to the initial mirtazapine group (i.e., eight of the 21 parameters improved).

Overall, the open label design of the extension phase did not seem to further increase the performance levels. This means a low rate of placebo response or regression to the mean, or both. The weak placebo effect was actually expected in this chronic, clinically stable population.

A 12-week period of mirtazapine treatment resulted in a better neurocognitive outcome than the 6-week mirtazapine treatment, as evaluated by Stroop Dots time and TMT-B (number of mistakes). Both tests are associated with general mental speed and attention control, and executive functions. This could mean that the neurocognitive effects of mirtazapine are principally related to attention and executive functions, and thus may also have desirable effects on the functional outcome.

Results of prolonged treatment replicate our previous findings (Joffe et al. 2009; Studies I and IV). Thus, to the best of the author's knowledge, the neurocognition data for add-on mirtazapine in schizophrenia reported until now are encouraging, aside from a study by Berk et al. (2009), which was of shorter duration. These results might also indicate that 12-week mirtazapine add-on to antipsychotic treatment results in additional neurocognitive improvements when compared to shorter duration of treatment.

In Study I, mirtazapine was more effective than placebo during the first six weeks of treatment, according to the Block Design and Stroop Dots. However, the Block Design results did not differ any longer between the 6-week and 12-week treatments, indicating that the neurocognitive function measured by the Block Design had reached its maximum after six weeks of mirtazapine treatment, with no supplementary benefit after extended treatment. In contrast, Stroop Dots results continued to improve after the 12 weeks of mirtazapine treatment. Moreover, an improvement on TMT-B scores appeared only during the continuation treatment (i.e., the 6-week extension phase). Thus, it seems that some aspects of neurocognition may require less time to achieve noticeable changes while other changes may develop slower, as with antidepressants.

All three tests; i.e., Block design, Stroop Dots and TMT-B are somehow associated with attention and executive functions, even though Block Design predominantly measures visuo-spatial ability. Stroop Dots and TMT-B measures that improved after the 12-week mirtazapine treatment, compared to the 6-week treatment, are strongly associated with general mental speed/attention control and executive functions which, show an clear association with work performance, normal activities of daily life, outpatient service utilization (McGurk et al. 2004; Velligan et al. 2000), and general treatment success (Bowie and Harvey 2006; McKee et al. 1997).

Above all, adjunctive mirtazapine enhanced neurocognition in long term patients, who were generally difficult to treat and whose neurocognitive decline tended to be even more profound and more detrimental to functional outcome than in the earlier stages of their illness (Harvey et al. 1998; Medalia and Richardson 2005; Spaulding et al. 1999).

Even though neuropsychological domains are not directly localized to specific brain regions or biochemical pathways in cortex, both attention and executive functions have mostly been

attributed to the frontal areas (Pantelis et al. 2005). Mirtazapine, as well as some SGAs have strong antagonist properties to alpha 2-adrenergic receptors, which may enhance dopaminergic transmission in the frontal cortex (Gobert et al. 1998; Millan et al. 2000).

Effects of add-on mirtazapine on clinical symptoms in schizophrenia

It has been reported earlier, from another part of this study, that clear-cut differences in all PANSS subscales and a large effect size of 1,00 (CI95% 0,23-1,67) on the PANSS total scores resulted from mirtazapine treatment when compared with a placebo in both within group and between group analyses during the double-blind phase (Joffe et al. 2009). In the open-label phase, patients who switched to mirtazapine treatment demonstrated a clinical improvement in the same manner as their mirtazapine-treated counterparts in the double-blind phase. Prolonged treatment with mirtazapine led to more prominent improvements in clinical parameters than short-term treatment. A trend towards improvement was seen in all measured parameters, therefore providing more evidence of mirtazapine's beneficial effect on schizophrenia symptoms.

As in the case of neurocognitive enhancing effects, the effect of mirtazapine on clinical symptoms may be explained by its unique receptor profile. Concerning the influence on negative symptoms, there are several possible mechanisms of action that may explain mirtazapine's beneficial effect. Blockade of central 5-HT2a receptor results in a number of effects on dopaminergic activity in the mesocortical, mesolimbic, and nigrostriatal areas of the brain, and it has been demonstrated in several preclinical studies that a combined 5-HT2a and D2 receptor inhibition may have a stimulating effect on the mesocortical pathway of the frontal cortex, thus increasing dopamine in this area (Volonté et al. 1997; Kuroki et al. 1999; Rollema et al. 2000). This effect is highly selective, with no simultaneous stimulation of dopaminergic neurotransmission in the striatum (Bonaccorso et al. 2002). A dopamine deficit in the medial PFC area is known to underlie the negative and cognitive symptoms of schizophrenia (Howes and Kapur 2009), and thereby such a drug combination may lead to better treatment outcomes that have a diminished risk for EPS (Meltzer et al. 2003). Mirtazapine also has indirect agonistic effects on 5-HT1a receptors, which may also explain at least part of its efficacy on negative symptoms. The 5-HT1a receptor may also be involved in the manifestation of negative and cognitive symptoms of schizophrenia (Kishi et al. 2011). Direct or indirect agonism of 5-HT1a receptors are a common characteristic for the majority of SGAs (Meltzer 2013), and combined with 5-HT2a blockade could deliver better efficacy on negative symptoms when compared to FGAs. Another preliminary hypothesis for the efficacy of add-on mirtazapine on negative symptoms may be due to its antagonism of 5-HT3 receptors. For example, adding the 5-HT3 blocking agent ondasetron to haloperidol improved negative symptoms, the general psychopathology and cognitive functions in patients with chronic schizophrenia (Zhang et al. 2006).

The beneficial effect of add-on mirtazapine on the positive symptoms of schizophrenia was more surprising than its effect to negative symptoms. Patients in this study were treated with FGAs, which are potent antipsychotics for treating positive symptoms, because of their antagonism of D2 receptors (Yilmaz et al. 2012).

The preclinical and clinical data indicate that alpha-2 inhibition enhances the antipsychotic effects of D2 blockade (Choi et al. 2010). In a preclinical study (Wadenberg et al. 2007), the alpha-2 antagonist idazoxan enhanced the therapeutic effect of haloperidol and olanzapine combined. This finding was supported by a preclinical study by Marcus et al. (2010), in which idazoxan improved the efficacy of risperidone and enhanced both dopaminergic and glutamatergic neurotransmission in the PFC. In addition, inhibition of the histamine H1 receptor, a shared mechanism of action for mirtazapine and clozapine, may also contribute to the antipsychotic effects of mirtazapine (Mancama et al. 2002).

Main limitations of the study

Although our sample size was one of the largest add-on mirtazapine trials to date, this relatively small sample limits the ability to draw definite conclusions for the clinical treatment of schizophrenia. However, the detriments of sample size in this study were balanced by the low discontinuation rate, the controlled design of the first phase, the desired and clear effect observed in chronic, difficult-to-treat patients with schizophrenia, consistency of mirtazapine-induced changes across a range of parameters and the time-span and, finally, the extended longevity of the intervention.

The size of the open label design of the second phase apparently did not suffer from sample size, as the observed effect of the initial exposure to mirtazapine in the double-blind and open label phases did not differ. Yet, one could argue that observed neurocognitive benefits were due to practice effects (see Goldberg et al. 2010), especially in the open-label phase. However, there is some evidence to suggest that the practice effect could be small in relatively old, chronic FGA-treated patients with schizophrenia (as in our study), and that FGAs could even suppress the practice effect (Harvey et al. 2005).

During the past years, the MATRICS CCB has become the golden standard in psychopharmacological studies of neurocognition in schizophrenia (Nuechterlein et al. 2008, Buchanan et al. 2011). Though the use of the MATRICS CCB would be undoubtedly desirable in this study, the consensus on this test battery was not achieved by the time of our trial. Moreover, all components of the MATRICS CCB had not been yet validated in Russian, nor were there normative data from the Russian population for all tests. For the same reason, composite scores could not be calculated in this study, which limits the comparability of these findings with to those in other studies. Nonetheless, all tests applied in the current trial were verified neuropsychological instruments that are used internationally (Lezak 1995;

Szöke et al. 2008). This study did not explore potential economic health aspects of the intervention, yet both FGAs and mirtazapine are now available as generic products, and such treatment would obviously be cost-effective.

Implications for future research

Further neurocognition studies with adjunctive mirtazapine in patients with schizophrenia should: 1) comprise larger study samples; 2) extend over a longer time span that elucidates whether or not some additional improvements could be achieved with prolonged treatment; 3) also investigate treatments with SGAs, 4) apply MATRICS CCB as a verified test battery, and 5) include both functional and economical health outcomes.

Summary and Conclusions

1. Mirtazapine treatment was better than placebo in the neurocognitive domains of visual-spatial ability and general mental speed/attention control, as assessed by Block Design and Stroop Dots during the 6-week double-blind phase. Adjunctive mirtazapine treatment might also be an effective short-term option as a neurocognitive enhancer for FGA-treated schizophrenia patients with an initial inadequate treatment response.

2. Mirtazapine treatment demonstrated a perceptible and independent direct beneficial effect on the Block Design-measured visuo-spatial functioning. This neurocognitive enhancing effect was mediated through significant changes in positive, depressive symptoms and symptoms of parkinsonism, but not in negative symptoms. Higher doses of FGAs, longer durations of illness and lower initial Block Design scores also predicted this effect. Mirtazapine may have both direct and indirect influence on visuo-spatial functioning in FGA-treated schizophrenia patients with sub-optimal treatment response.

3. During the 6-week extension phase, patients who had previously received six weeks of mirtazapine and those on placebo both showed significant improvement on several neurocognitive tests. Twelve-week mirtazapine treatment demonstrated better neurocognitive outcome than just six weeks of mirtazapine treatment, as evaluated by Stroop Dots time and TMT-B, number of mistakes, which are associated with general improvement in mental speed/attention control and executive functions. Twelve-week mirtazapine add-on to antipsychotic treatment indicated additional neurocognitive improvements of just six weeks, which demonstrates a progressive therapeutic effect.

4. Patients who were on mirtazapine during both the 6-week double-blinded and the 6-week open phases demonstrated greater improvement in positive symptoms than those who received mirtazapine during open-label extension phase only. During the 6-week open-label phase, significant improvements on several clinical parameters of the PANSS total score were observed. Mirtazapine might have an additive antipsychotic effect in FGA-treated schizophrenia. The generalizability of these results is limited by the small sample size.

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Appendices

APPENDIX I. INFORMATION FOR A PATIENT AND INFORMED CONSENT (ENGLISH VERSION).

Information for a patient.

Introduction.
Dear .....

You are invited to participate in a study entitled "Efficacy of add-on mirtazapine on the clinical and neuropsychologic parameters in schizophrenic patients who are currently treated with conventional antipsychotics – a double-blind placebo-controlled trial with an open-label extension phase". This study is a collaborative scientific project between Russian and Finnish medical researchers. Please read this information and ask any questions that you may have before you agree to be involved into the study.

The purpose of the study.
During this study, a medicine called mirtazapine will be added to you current treatment. Mirtazapine is an antidepressant that has been used extensively for a long time in clinical practice in the majority of the European countries, in the USA, Canada and Russia. The main indication for the use of mirtazapine is depression (long-lasting and profound decrease in mood and interest in life, fatigue, feeling of apathy, weakness, sleep and appetite disturbances). The disease you are suffering from is often accompanied to some extent with depressive symptoms, and additional use of antidepressants is common in clinical practice. The mechanism of action of mirtazapine differs from that of the most other antidepressants. This difference supposes that this medicine is able to alleviate the depressed mood symptoms, and make your current medication more effective. Mitrazapine can also decrease possible side effects of your basic medication, such as unpleasant feelings in the muscles, tremor, irritability, feeling of rigidity or weakness, or concentration difficulties. The addition of mirtazapine will probably enable a decrease in the dosage of your basic medication. Supposedly, some properties of mirtazapine will improve the thought process, attention and memory, and increase your general level of functioning. The study you are invited to participate in will make the preliminary information, which the above assumptions are based upon, more accurate.

How the study will be conducted.

For the first 6 weeks of the study, after the appropriate and comprehensive medical examination of your health, you will be prescribed a new medication – either mirtazapine, or the so-called 'placebo' – medicine, which looks like mirtazapine but doesn't contain any pharmacologically active substances. Neither you, nor your doctor will know which medicine you will receive, but you will be provided with this information as soon as the whole study is over; i.e., when all the patients have completed their participation, and the data received during the study has been analyzed. During the second 6 weeks, placebo will not be administered, and all patients will receive mirtazapine. Mirtazapine will be administered in a recommended effective dose, once daily before bed. The capsules or tablets must be swallowed wholly, without grinding or chewing.
Your physician will possibly decrease the dosage of your basic medication in the second 6-week period of the study. Altogether, you will receive the study medication during 12 weeks (about 3 months).

Procedures of the study.
During the study your physician will examine you with certain regularity. In total, 10 assessments of your mental and physical health will be performed. These visits by your physician may differ from the ordinary assessments that you are used to. They may include psychiatric and psychological testing (sometimes rather time consuming) and both clinical and laboratory tests; such as ECG, blood and urine analyses.

Potential risk due to the participation in the study.
As all effective medicines, mirtazapine can cause side effects in some patients, such as dry mouth, sleepiness, an increase in both appetite and body weight. However, these symptoms are rare, usually mild and most often disappear without any specific intervention during the continuation treatment with mirtazapine. Your physician will monitor your health condition carefully during the treatment period, with regular assessments of your physical and mental state.
This study can present some other inconvenience: the participation in the study requires regular visits to a physician and each visit takes, at the average, more time than the ordinary visit to a physician. You will have to follow the dosing schedule very carefully, and not forget to return all unused tablets to your physician.

The expected benefit.
You can benefit from this study: the symptoms of your disease can improve or even disappear; you can experience improvements in memory, attention and information processing. In case you have had symptoms of depression, or suffered from side-effects of your basic medicine, these problems may also improve or even disappear. It is possible that during the treatment with mirtazapine you will need a smaller dose of your basic medicine. Your health condition will be monitored during the treatment very carefully, and you will see your physician regularly. In addition, your participation in this study may eventually help a large number of other patients for whom, supposedly, a safe and effective method of treatment is being developed.

How to contact your physician.

If you experience any symptoms of worsening your health condition (physical or mental), you should contact your physician immediately, by using the phone number that he or she will give you, or contact the physician on call at 74-35-60.

Additional information concerning the study.
Your participation in this study is completely voluntary. You have the right to refuse participation at any time during the study, without any negative consequences for your treatment. In this case, you will be prescribed ordinary treatment. From the point of view of the study it is very important, however, to have as large a number of patients as possible to complete the full course of treatment. If you decide to withdraw from the study, it is desirable that you meet your physician for the final assessment as soon as possible.
The participation in this study is based on the principle of mutual confidence, and your physician will guarantee that your anonymity is maintained. This means that your name will be seen only in your medical record, as with any usual treatment. No information will be disclosed and your identity will only be recorded in the study materials. In some special circumstances, however, this information may be required by local, federal or international authorities who monitor the quality and ethical issues of clinical studies. An open and diligent cooperation between you and your physician is crucially important for the successful progress of the study.

Please feel free to ask any questions you may have, especially if there is a word or phrase that you do not understand. After you have attentively read this information, you will be asked to sign THE INFORMED CONSENT FORM (see below).

THE INFORMED CONSENT FORM.

I, _____, born 19 _____
(surname, name, second name)
have had enough time to learn about the information concerning the study and the investigational medicine. I have a full understanding of this information, I am aware of the study purpose, its duration and conditions of my participation in it. I am aware of the expected benefit from the treatment, as well as its possible side-effects and potential risk to my health. I have received the answers to all the questions concerning my participation in the study.
With this statement I confirm my voluntary consent to participate in the study "Efficacy of add-on mirtazapine on the clinical and neuropsychologic parameters in schizophrenic patients treated with conventional antipsychotics – a double-blind placebo-controlled trial with an open-label extension phase".
I have the right to withdraw from the study at any time.

«_____» _____ 200__ .

Physician _____
(surname, name, second name)

Institution_____
(name)
The signature of the patient or his representative _____
The signature of the physician _____

APPENDIX II. INFORMATION FOR A PATIENT AND INFORMED CONSENT (RUSSIAN VERSION).

Информация для пациента.

Введение.
Глубокоуважаемый(-ая)……,

Вам предложено участие в научном исследовании «Влияние присоединения миртазапина к терапии типичными нейролептиками на клинические и нейропсихологические параметры у больных шизофренией – двойное слепое исследование с дополнительной «открытой» фазой». Исследование проводится как совместный научный проект ученых России и Финляндии. Пожалуйста, прочтите этот документ и задайте все интересующие вас вопросы, прежде чем дать ваше согласие на участие в исследовании.

Цель исследования.
В ходе этого исследования к лекарственному лечению, получаемому Вами в данный момент, будет добавлен миртазапин. Миртазапин – это препарат с антидепрессивным действием, широко и в течение многих лет применяемый как в большинстве стран Европы, в США и Канаде, так и в России. Основное показание для его применения – это депрессия (длительное и глубокое снижение настроения, интереса к жизни, утомляемость, чувство безразличия, слабость, нарушения сна и аппетита). Ваше заболевание нередко сопровождается в той или иной мере симптомами депрессии, и дополнительное применение антидепрессивных препаратов является обычным в клинической практике. Механизм действия миртазапина несколько отличается от большинства других антидепрессантов. Это отличие позволяет предполагать, что этот препарат может не только устранить сниженное настроение, но и сделать ваше основное лекарство более эффективным, снизив при этом его возможные побочные действия, такие как неприятные ощущения в мышцах, дрожь, раздражительность, ощущение скованности или слабости, трудности в сосредоточении. Сочетание с миртазапином позволит, возможно, уменьшить дозу вашего основного лекарства. Предполагается также, что особые свойства миртазапина могут улучшить процессы мышления, внимание и память, а также повысить Вашу активность и общий уровень деятельности. Исследование, в котором Вас приглашают участвовать, позволит уточнить уже имеющиеся предварительные данные, на основании которых выдвинуты эти предположения.

Как будет проводиться исследование.
В первые 6 недель исследования, после того, как проведено соответствующее полное клиническое и лабораторное обследование Вашего состояния, Вы будете получать

дополнительное лекарство – либо миртазапин, либо так называемое плацебо – лекарство, которое выглядит точно так же как миртазапин, но не заключает в себе какого-либо действующего вещества. Ни Вы, ни Ваш врач не будут знать, какое из двух лекарств Вы будете получать, но эта информация может быть Вам предоставлена по окончании всего исследования, то есть, в период, когда все пациенты закончат свое участие, и полученные данные будут проанализированы. В последующие 6 недель плацебо назначаться не будет, а все пациенты будут получать миртазапин. Миртазапин будет назначаться в рекомендуемой эффективной дозе (1 раз в день в вечернее время). Капсулы и таблетки должны проглатываться целиком, неизмельченными и неразжеванными.
Во второй части исследования Ваш врач, возможно, несколько уменьшит дозу Вашего основного лекарства. Всего Вы будете получать исследуемый препарат в течение 12 недель (около трех месяцев).

Процедуры исследования.
За время проведения исследования Ваш врач обследует ваше физическое и психическое состояние с заранее определенными интервалами – в общей сложности, десять раз. Эти посещения врача могут несколько отличаться от привычного для Вас хода обычных посещений и включать в себя проведение психиатрических и психологических тестов (порой довольно продолжительных), а также клинических и лабораторных обследований, таких как анализы крови и мочи, электрокардиограмма.

Возможный риск, связанный с участием в исследовании.
Как и все эффективные лекарства, миртазапин может у некоторых пациентов вызывать побочные явления, такие как сухость во рту, сонливость или повышение аппетита и увеличение массы тела. Эти симптомы наблюдаются, однако, довольно редко, не являются очень выраженными и, чаще всего, проходят сами по себе при продолжении лечения миртазапином. В ходе исследования за Вашим самочувствием будет внимательно наблюдать Ваш врач, который будет регулярно обследовать ваше физическое и психическое состояние.
Данное исследование может заключать в себе и некоторые дополнительные неудобства: участие в исследовании требует регулярного посещения врача, и каждое посещение занимает, в среднем, больше времени, чем обычный визит к врачу. Вам придется особенно внимательно следить за регулярностью приема лекарств, не забывая каждый раз возвращать оставшиеся таблетки Вашему врачу.

Ожидаемая польза.
Для Вас данное исследование может принести пользу: симптомы вашего заболевания могут уменьшиться или даже исчезнуть, Вы можете отметить улучшение памяти, внимания и осмысления информации. В случае, если Вы имели симптомы депрессии или нежелательные побочные действия от основного лекарства, может быть отмечено их уменьшение вплоть до полного исчезновения. Не исключено, что в результате

лечения Вам понадобится меньшая доза основного препарата. В ходе исследования за состоянием Вашего здоровья будут следить особенно тщательно, и Вы будете регулярно встречаться с вашим лечащим врачом. Кроме того, Ваше участие в данном исследовании может помочь большому количеству других пациентов, для которых, как предполагается, разрабатывается новый безопасный и эффективный метод лечения.

Как связаться с врачом.
В случае появления каких-либо симптомов ухудшения Вашего состояния (как физического, так и психического), Вы должны немедленно связаться с Вашим лечащим врачом, по телефону, который он или она Вам предоставит, либо с дежурным врачом по телефону 74-35-60.

Дополнительная информация об исследовании.
Участие в исследовании полностью добровольное. Вы имеете право прервать ваше участие в исследовании в любое время, что не будет иметь отрицательных последствий для вашего обычного лечения, которое будет Вам в этом случае назначено. С точки зрения исследования, важно все же, чтобы как можно большее количество пациентов прошли весь курс лечения от начала до конца. В случае если Вы все же решите прервать участие в исследовании, было бы желательно, чтобы Вы встретились как можно скороее с Вашим врачом для заключительного обследования.
Участие сторон в исследовании будет основано на взаимном доверии, и Ваш врач гарантирует вам полное соблюдение врачебной тайны. Это означает, что Ваше имя будет фигурировать только в Вашей истории болезни или амбулаторной карточке, как это бывает при обычном лечении. В то же время, никакие данные, позволяющие определить Вашу личность, не будут регистрироваться в научных материалах. Эти данные могут, однако, в случае особой необходимости, затребовать представители соответствующих местных, федеральных или международных инстанций, наблюдающих за научным качеством и этическими вопросами клинических исследований. Для успешного выполнения исследования, открытая и добросовестная совместная работа между Вами и Вашим врачом особенно важна.

Пожалуйста, задайте любые вопросы, которые у Вас возникли, особенно, если вам встретилось непонятное вам слово или фраза. После того, как Вы внимательно прочли это разъяснение, Вас попросят подписать СОГЛАСИЕ НА УЧАСТИЕ В ИССЛЕДОВАНИИ (см. ниже).

СОГЛАСИЕ НА УЧАСТИЕ В ИССЛЕДОВАНИИ.

У меня, _____ 19____ г. р.
(фамилия, имя, отчество)

было достаточно времени, чтобы ознакомиться с информацией об исследовании и об исследуемом препарате. Я понял суть изложенной информации, мне известно о целях исследования, его продолжительности и условиях моего участия в нем, также как и об ожидаемой пользе и о возможных побочных эффектах и риске для здоровья. Я получил ответы на все возникшие у меня вопросы.
Я утверждаю, что даю добровольное согласие на предложенное мне участие в клиническом исследовании «Влияние присоединения миртазапина к терапии типичными нейролептиками на клинические и нейропсихологические параметры у больных шизофренией – двойное слепое исследование с дополнительной «открытой» фазой»..
Я имею право прервать участие в исследовании в любое время.

«_____» _____ 200__ г.

Врач-психиатр _____
(фамилия, имя, отчество)
Учреждение _____
(наименование)
Подпись пациента или его законного представителя _____

Подпись врача-психиатра _____