CLINICAL EFFECTS OF MIRTAZAPINE ADDED TO FIRST GENERATION ANTIPSYCHOTICS IN SCHIZOPHRENIA.

Viacheslav Terevnikov

ACADEMIC DISSERTATION

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ABSTRACT

Although a number of add-on treatment strategies have been studied to improve the outcome of antipsychotic-treated chronic schizophrenia, none of them have thus far proved to be conclusively effective. Mirtazapine, an antidepressant with a unique receptor profile, improves the clinical effect of first generation antipsychotics (FGAs), in terms of negative and extrapyramidal symptoms (EPS) in some published studies, when used in conjunction with FGAs. The present study aimed to explore the efficacy of adjunctive mirtazapine on the symptoms of schizophrenia in patients with an insufficient response to different FGA monotherapies at adequate stable dosages.

Thirty-nine patients who met the DSM-IV-TR criteria for schizophrenia or schizoaffective disorder depressive type, and who were at least moderately ill (as measured by the Clinical Global Impression Scale) despite their FGA treatment, received add-on mirtazapine 30 mg/day (n=20) or placebo (n=19) in a 6-week double-blind randomized controlled trial (RCT). Thirty-seven completers of the double-blind phase were treated in an open-label design with mirtazapine 30 mg/day during an additional 6 weeks. Dosages of current antipsychotics remained unchanged. The Positive and Negative Syndrome Scale (PANSS) total score (primary outcome), as well as secondary outcomes, which included PANSS subscales, Simpson-Angus Scale for Extrapyramidal Side-effects (SAS) and Calgary Depression Scale for Schizophrenia (CDSS) were measured prospectively. Patients underwent a physical examination (weight, vital signs) and a range of laboratory measures that included fasting glucose and total cholesterol. Within group and between group differences were compared on the Modified Intent-to-Treat basis with Last Observations Carried Forward. Correlation analyses and regression analyses were used to measure relationships between clinical and metabolic parameters.

In the within group analyses, mirtazapine add-on treatment led to a statistically significant improvement of all measured clinical parameters during the double-blind phase. Improvement in PANSS total scores was as large as 12.5% (p<0.001), whereas the improvement in PANSS positive symptoms was 17.2% (p<0.001) while the improvement in PANSS negative symptoms was 12.0% (p<0.001). SAS scores improved by 9.8% (p=0.017) and CDSS scores improved by 52% (p=0.003). The latter change exhibited a direct correlation with several subscales of PANSS. In the mirtazapine group, the effect size was 1.00 (95%CI 0.34-1.67) on the primary outcome parameter. The between-group difference favoured mirtazapine on PANSS total scores (p=0.004), PANSS positive subscale (p=0.001) and PANSS negative subscale (p=0.001). No significant differences were found in other parameters. Mirtazapine treatment led to an increase in body weight and cholesterol levels, and the latter change was associated with a clinical improvement on all PANSS subscales, where an increase in total cholesterol by 1 mmol/L predicted a reduction on the PANSS total score by 7 points [r=0.85, p=0.001].
During the open-label phase, patients who switched to mirtazapine demonstrated an improvement in PANSS (effect size 0.94 on PANSS total scores), CDSS and SAS scores in a manner similar to their mirtazapine-treated counterparts in the double-blind phase. The incidence of adverse events did not differ between mirtazapine and placebo.

These findings indicate that add-on mirtazapine to current FGA treatment is significantly more efficacious in the reduction of positive, negative and depressive symptoms than a placebo add-on. This is the first RCT report of a statistically significant additive antipsychotic effect from an adjunctive antidepressant. Mirtazapine induced changes in body weight and lipid metabolism were similar to those seen with the most effective antipsychotics, and this metabolic effect may even contribute to its clinical efficacy.

The main limitation of the study was its small sample size. Thus, larger and longer follow up trials are undoubtedly needed to confirm these results. Further research should also consider combinations of mirtazapine with second generation antipsychotics, and especially comparisons with clozapine.
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LIST OF ORIGINAL PUBLICATIONS

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


### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>5-HT</td>
<td>5-Hydroxytryptamine, serotonin</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AIMS</td>
<td>Abnormal Involuntary Movement Scale</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>BAS</td>
<td>Barnes Akatisia Scale</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BPRS</td>
<td>Brief Psychiatric Rating Scale</td>
</tr>
<tr>
<td>CATIE</td>
<td>Clinical Antipsychotic Trials of Intervention Effectiveness Study</td>
</tr>
<tr>
<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
</tr>
<tr>
<td>CGI</td>
<td>Clinical Global Impression Scale</td>
</tr>
<tr>
<td>CUtLASS</td>
<td>Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study</td>
</tr>
<tr>
<td>COX</td>
<td>Cycloxygenase</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P-450</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text-Revized</td>
</tr>
<tr>
<td>ECT</td>
<td>Electroconvulsive Therapy</td>
</tr>
<tr>
<td>EPS</td>
<td>Extrapyramidal Symptoms</td>
</tr>
<tr>
<td>EUFEST</td>
<td>The European First Episode Schizophrenia Trial</td>
</tr>
<tr>
<td>FGA</td>
<td>First-Generation Antipsychotic</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-Aminobutyric Acid</td>
</tr>
<tr>
<td>GAF</td>
<td>The Global Assessment of Functioning</td>
</tr>
<tr>
<td>HRSD</td>
<td>Hamilton Rating Scale for Depression</td>
</tr>
<tr>
<td>IMAO</td>
<td>Inhibitor of the Monoamine Oxidase</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>MITT</td>
<td>Modified Intent to Treat</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-Methyl-D-aspartic acid</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>mPFC</td>
<td>Medial Prefrontal Cortex</td>
</tr>
<tr>
<td>QHS</td>
<td><em>quaque hora somni</em> [L.] (every night at bedtime)</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>SANS</td>
<td>Scale for the Assessment of Negative Symptoms</td>
</tr>
<tr>
<td>SAPS</td>
<td>Scale for the Assessment of Positive Symptoms</td>
</tr>
<tr>
<td>SAS</td>
<td>Simpson &amp; Angus Scale for Extrapyramidal Symptoms</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
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<tr>
<td>SGA</td>
<td>Second-Generation Antipsychotic</td>
</tr>
<tr>
<td>SNRI</td>
<td>Selective Noradrenaline Reuptake Inhibitor</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-Photon Emission Tomography</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>Tricyclic Antidepressant</td>
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1 INTRODUCTION

Schizophrenia is a serious psychiatric disease that affects approximately 0.5-0.9% of the world population (Tandon et al., 2008), and causes considerable suffering to the individual, the individual’s family and an enormous economic burden to society (Csernansky and Schuchart, 2002). Antipsychotic drugs currently remain the cornerstone for the pharmacological treatment of schizophrenia (Leucht et al., 2012). All antipsychotics are antagonists of dopamine D2 receptors (Butcher, 2000). Atypical antipsychotics (e.g., clozapine and a group of novel compounds) demonstrate higher efficacy against negative symptoms, a lower incidence of extrapyramidal side effects, improved outcome and a better quality of life (Meltzer, 2012). These advantages of atypical antipsychotics over conventional antipsychotics have been often attributed to their high affinity to postsynaptic serotonin 5HT2a receptors and a relatively low affinity to dopamine D2 receptors, in contrast to conventional antipsychotics, whose D2 affinity is high (Meltzer, 1994). Some antidepressants, such as trazodone, mianserine, nefazodone and mirtazapine are also potent inhibitors of postsynaptic 5HT2a receptors. They are, however, lacking noteworthy D2 receptor affinity and, thus, antipsychotic efficacy. Combinations of these antidepressants with conventional antipsychotics could result in the atypical-like receptor blockade with additional antidepressive effects and, hereby, improvement the negative, depressive, and quality of life domains in schizophrenia, with better tolerance.

Preliminary support to this assumption was indicated by several published studies, where the addition of 5HT2a-blocking antidepressants to ongoing therapy with first-generation antipsychotics (FGAs) reduced negative symptoms of schizophrenia (Decina et al., 1994, Hayashi et al., 1997). Such antidepressants also improved the antipsychotic-induced extrapyramidal symptoms (Hayashi et al., 1997, Wynchank and Berk, 2003). In addition to 5HT2a receptor blockade, mirtazapine demonstrates inhibitory effects at alpha-2 and 5HT3 receptors, as well as indirect agonism at serotonin 5HT1 receptors (Berendsen and Broekkamp, 1997). Moreover, these receptors appear to be involved in the schizophrenic process (Hertel et al., 1999, Meltzer and Huang, 2008) and participate in the mechanism of action of clozapine, which is the most efficacious antipsychotic (Asenjo-Lobos et al., 2010). Indeed, in some preclinical studies adjunctive mirtazapine enhanced the antipsychotic-like effects and tolerability of conventional drugs in an atypical fashion (Berendsen et al., 1998, Pinder et al., 1998). In a previous randomized controlled trial (RCT), adjunctive mirtazapine appeared to be superior to placebo in terms of improving negative symptoms in haloperidol-treated schizophrenic patients (Berk et al., 2001).
2 REVIEW OF LITERATURE

2.1 SCHIZOPHRENIA.

2.1.1 DEFINITION AND EPIDEMIOLOGY.
Schizophrenia is a serious mental disorder affecting about 24 million people worldwide (World Health Organization, 2009). It is among the top ten leading causes of disease-related disability in the world (Tandon et al., 2008). Due to an early age of onset, and a subsequent tendency to persist chronically, schizophrenia generates great suffering for patients and causes significant social and economical burdens. A comprehensive survey estimated that schizophrenia is responsible for 1.1% of the total disability adjusted life years worldwide, and for 2.8% of the years lived with disability worldwide (Jablenski, 2000).

According to systematic reviews, the incidence of schizophrenia is approximately 15.2/100000, with a prevalence of approximately 7.2/1000 (McGrath et al., 2004, Saha et al., 2005). The incidence of schizophrenia has long been estimated to be relatively similar worldwide. However, recent epidemiological studies revealed a considerable heterogeneity in the incidence of schizophrenia, which is thought to be related to a range of socioeconomic factors; e.g., urban vs. rural settings, the level of local social resources and the proportion of migrants in a host society, which represents a newly emerged risk group for schizophrenia (Pedersen and Mortensen, 2001, Cantor-Graae and Selten, 2005, Coid et al., 2008, Kirkbride et al., 2008). In Finland the lifetime prevalence for schizophrenia is estimated to be 0.87% (Perälä et al., 2007).

2.1.2 THE MAIN CLINICAL DOMAINS OF SCHIZOPHRENIA, ITS COURSE AND OUTCOME
Schizophrenia is characterized by three main symptom domains: positive symptoms, negative symptoms and cognitive dysfunction (Tamminga and Holcomb, 2005). Positive symptoms typically include delusions, hallucinations (most commonly, auditory), a lack of insight and thought disorder. These symptoms tend to be more easily controlled than negative symptoms provided that antipsychotic medication is adequate.

Negative symptoms of schizophrenia include social withdrawal, avolition, loss of motivation, emotional blunting and paucity of speech. In population-based samples, patients with primary negative symptoms comprise 15–20% of the patient population (Kirkpatrick et al., 2006). Negative symptoms contribute to a diminished level of daily functioning and quality of life, with increased social isolation. It is widely accepted that
negative symptoms generally respond less definitely to pharmacological treatment than positive symptoms (Erhart et al., 2006).

Schizophrenia-related cognitive impairment particularly includes the domains of attention, working memory and executive function (Goff et al., 2011). A growing body of evidence suggests that in schizophrenia, cognitive dysfunction may be an even more important determinant of outcome than either positive or negative symptoms (Keefe et al., 2005, Szöke et al., 2008). It is so far unclear whether or not the remediation of cognitive impairment in patients with schizophrenia can be achievable (Harvey et al., 2008).

In addition to these core symptom domains, schizophrenia generally presents with a number of other symptoms, including depression, anxiety, mania, aggression, self harm and suicidal behavior.

During the course of schizophrenia, comorbid depression can be diagnosed in approximately 50% of patients (Buckley et al., 2009). The prevalence of depressive symptoms vary in different epidemiological studies, being from 5% (Lindenmayer et al., 1991) to 83% (Hafner et al., 2005). Depressive symptoms are estimated to be more common in the acute phase and lower in the chronic phase of schizophrenia (Emsley et al., 1999, Lancon et al., 2001, An der Heiden et al., 2005). Comorbid depression significantly increases the risk for suicide (Heilä et al., 1997, Radomsky et al., 1999). It also negatively affects quality of life and level of functioning (Zizook et al., 1999), and is associated with more frequent relapses (Conley et al., 2007).

Schizophrenia may be characterized as a life-long disease with recurrent acute symptom exacerbations, and extensively varying degrees of functional disability (Robinson et al., 1999). Schizophrenia often has an acute onset, is episodic in its course, with some level of satisfactory recovery between episodes. Other patterns of this illness are characterized by an insidious onset, partial recovery, or a lack of recovery between episodes. In the most severe cases of this disease, a profound deterioration in psychosocial function occurs during the first few years of its course (van Haren et al., 2012). In a large epidemiological study by An der Heiden and co-authors (1996), 60.7% of patients were symptomatic 14 years after the first hospital admission, 12.5% were symptom-free while treated with antispsychotics, and 26.8% were in remission.

2.1.3 PATHOPHYSIOLOGICAL BACKGROUND OF SCHIZOPHRENIA

A number of disparate pathophysiological models have been proposed for an explanation of schizophrenia symptomatology. The most widely held neurochemical hypothesis is the classic hyperdopaminergic model (Carlsson and Lindquist, 1963, van Rossum, 1966), which postulates that psychotic symptoms in schizophrenia result from an excess of dopamine transmission. This theory emerged on basis of the observation that inhibition of dopamine metabolism in the brain improved psychotic symptoms (van Rossum, 1966) and this finding gained additional support from SPECT- and PET-based studies conducted in 1990 (Knable and Weinberger, 1997). According to this hypothesis,
patients with schizophrenia have an increased dopamine release into the synapse in mesolimbic areas during the acute phase of the disease, compared to healthy controls (Martinot et al., 1990, Kegeles et al., 2010). Functional neuroimaging studies also suggested that negative symptoms and cognitive dysfunction in schizophrenia may be connected to a deficit in dopamine neurotransmission at D₁ dopamine receptors in medial prefrontal cortex (mPFC) (Goldman-Rakic et al., 2004, Castner and Goldman-Rakic, 2004). Taken together, these theories formed a more complex and integrative model which postulates that schizophrenia is characterized by an imbalance between subcortical and cortical dopamine systems; e.g., subcortical mesolimbic dopamine projections may be hyperactive, thus resulting in hyperstimulation of D₂ receptors and positive symptoms, while mesocortical projections to the mPFC may be hypoactive, thus resulting in hypostimulation of D₁ receptors, the negative symptoms and cognitive impairment (Knable and Weinberger, 1997).

A more recently pathophysiological model for the etiology of schizophrenia focuses on an alteration in the glutamate neurotransmitter system, especially involving N-Methyl-D-aspartic acid (NMDA) receptor function (Javitt and Zukin, 1991, Olney and Farber, 1995). This idea has emerged on the base of observations from reduced glutamate levels in the spinal fluid of patients with schizophrenia (Kim et al., 1980). A later observation noted that phencyclidine (PCP) abuse causes symptoms closely resembling schizophrenia (Lodge and Anis, 1982), which provided further support for the “glutamatergic” theory of schizophrenia. Recent SPECT studies in medication-free schizophrenic patients found NMDA receptor hypofunction in the hippocampus (Pilowsky et al., 2006). Antipsychotic treatment, especially with clozapine, attenuated this deficit (Bressan et al., 2005). Specific medications that therapeutically modify the glutamate system showed promising results in preclinical trials, but confirmation from RCTs has note yet been obtained (Buchanan et al., 2007, Tandon et al., 2010).

Some evidence indicates that gamma-Aminobutyric acid (GABA) neurotransmission is impaired in schizophrenia (Benes and Berretta, 2001, Lewis and Hashimoto, 2007). It has also been suggested that the cognitive deficits in schizophrenia may be related to alterations in GABA neurotransmission (Costa et al., 2001; Brigman et al., 2006). The potential role of GABAergic agents in the treatment of schizophrenia has not yet been established (Menzies et al., 2007). However there are add-on studies on mood stabilizers (see chapter 4.2.4).

Interest in a role for the serotonin system in the pathophysiology of schizophrenia began in the early 1960s (Axelrod and Inscoe, 1963), and developed further after the introduction of second-generation antipsychotics (SGAs), which are characterized by potent 5-HT₂A receptor antagonism and relatively weak dopamine D₂ receptor antagonism (Meltzer et al., 2008). However, in postmortem studies no consistent changes in the serotonin system of schizophrenia patients have been found (Harrison, 1999), which makes it unclear as to what extent the serotonin system is involved in the pathophysiology of schizophrenia. It has been proposed that the antipsychotic effect of the SGAs may result from a serotonin-mediated modulation of dopamine release into the synapses (Marcus et al., 2000). This supposition is supported by the observation
that 5 HT\textsubscript{2a} receptor antagonists, without any affinity to dopamine receptors, exhibit antipsychotic activity both in animal and human studies (Kuroki et al., 2003).

Although the proposed pathophysiological theories of schizophrenia seem rather disparate and inconclusive, there may be a common ground for several neurotransmitter abnormalities occurring at the same time. A growing body of evidence suggests that alterations in glutamate receptor functioning may, in turn, contribute to the development of the GABAergic pathology associated with schizophrenia (Keshavan, 2011). Both glutamatergic and GABAergic disfunction may lead to severe imbalances between the excitatory and inhibitory systems of the brain, possibly forming a fundamental deficit for schizophrenia, while monoaminergic dysfunction could be a secondary result of this imbalance (Miyamoto et al., 2012).

2.2 PHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIA

2.2.1 ANTIPSYCHOTIC TREATMENT: CURRENT RECOMMENDATIONS

A number of treatment guidelines exist for schizophrenia (APA, 2004, Suomen psykiatriyhdistys, 2008, APA, 2009, NICE, 2009, Barnes et al., 2011). Though varying in detail, these treatments generally accept that dopamine antagonists (antipsychotics) represent the only class of drugs that have a widely proven efficacy in the treatment of schizophrenia (Barnes et al., 2011). It has been recommended that treatment with antipsychotics should begin at the early stages of schizophrenia, thus forming a critical part of early intervention strategy. This approach is based on the presumption that treatment should begin at an early and relatively treatment-responsive stage of the disease, to minimize possible negative consequences of an active morbid process, and to subsequently improve both symptomatic and functional outcomes (Marshall et al., 2005, Perkins et al., 2005). 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, 2008). Consensus guidelines recommend the continuation of antipsychotic treatment in patients with established schizophrenia for at least one or two years (Buchanan et al. 2010; NICE, 2009).

Several naturalistic studies have demonstrated that only 20% of patients did not experience another episode during a 5-year follow-up after the first psychotic episode, (Shepherd et al., 1989, Robinson et al., 1999). In patients with a history of multiple episodes, the expected frequency of relapse is presumably higher, which justifies continuous maintenance treatment with antipsychotics (Leucht et al., 2012). It has been established that maintenance treatment with antipsychotics reduces relapse rates. For instance, Gilbert and co-authors (1995) found the reduction of relapse risk from 53% to 16% within 10 months of maintenance treatment. Intermittent treatment has been found to be less efficacious when compared to continuous treatment in several studies (Carpenter et al., 1990, Schooler et al., 1997, Gaebel et al., 2010).
First-generation antipsychotics (FGAs).

FGAs emerged in the early 1950s, when the efficacy of chlorpromazine in the treatment of psychotic symptoms was first described (Delay, 1952). In the following decades, a large number of other phenothiazine compounds and antipsychotics of other chemical classes (e.g., butyrophenones, tioxantenes, etc.) were introduced. Although nearly six decades have passed since the introduction of the first FGA, this group of psychotropic drugs is still in wide use, and is still considered to be effective in treating schizophrenia, especially the psychotic symptoms (Lieberman et al., 2005, Leucht et al., 2009). The clinical efficacy of FGAs is believed to result from their ability to inhibit the brain dopamine D2 receptors (Carlsson and Lindqvist, 1963), although these drugs affect some other neurotransmitter systems, e.g. serotonin and acetylcholine.

While generally effective in the treatment of psychosis, FGAs are associated with numerous adverse effects; for example, extrapyramidal symptoms (EPS), hyperprolactinemia, anticholinergic effects and others (see Section 4.2.2.). Another problem is that the efficacy of FGAs on negative symptoms of schizophrenia has been repeatedly questioned (Meltzer, 1999).

Second-generation antipsychotics (SGAs).

Attempts to develop effective antipsychotics with a better tolerability profile led to the introduction of the second-generation antipsychotics, which are also known as the “atypical” antipsychotics. The era of SGAs began in 1959 with the introduction of clozapine, the first SGA and, in a pharmacological sense, the prototypical SGA (Meltzer, 2012). In recent decades, SGAs became the most widely prescribed pharmacological treatment for schizophrenia (Aparasu et al., 2005). Despite reliable experience in the use of SGAs, an uncertainty regarding the definition of their “atypicality” still exists (Meltzer et al., 2001). The most commonly used principle for distinguishing between typical and atypical antipsychotics is based on the differences between their mechanisms of action. In particular, SGAs are believed to exhibit a more potent blockade of 5-HT2a (Meltzer et al., 1994), while FGAs function primarily by blocking the dopamine D2 receptor. SGAs are considerably less associated with EPS, yet also have their own collection of adverse effects, e.g. negative influence on lipid and glucose metabolism, weight gain, haematological side-effects (with clozapine), along with some other unwanted effects (Volavka et al., 2002, see section 4.2.2).

The comparative efficacies of FGAs and SGAs have been a subject of extensive research, as can be seen in modern meta-analyses of this topic, which include hundreds of RCTs. Despite an enormous number of comparative RCTs, the question regarding the relative efficacy of FGAs and SGAs still appears to be unanswered. Some meta-analyses of RCTs that compare FGAs and SGAs found the latter group to be superior in terms of overall efficacy. For example, a meta-analysis by Davis and co-authors (2003) found that clozapine, amisulpride, risperidone, and olanzapine were more effective than FGAs. In another meta-analysis, Leucht and co-authors (2009) found that these same four SGAs were superior to FGAs with regard to general efficacy. Worth mentioning is that the magnitude of this favourable efficacy was defined by the authors as small, with the frequency of adverse effects for the FGAs being much more prominent (Leucht et al.,
Geddes and co-authors did not find any difference in their meta-analysis (2000) when the efficacy between FGAs and SGAs was compared. Moreover, in several large effectiveness studies, namely Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE) (Lieberman et al., 2005), Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (Jones et al., 2006) and The European First Episode Schizophrenia Trial (EUFEST) (Kahn et al., 2008), no clear superiority was found in the effectiveness of SGAs over FGAs. In CATIE, olanzapine-treated patients showed a slightly longer time for discontinuation than other antipsychotics, while perphenazine (an FGA comparator) showed a comparable degree of effectiveness when compared with other SGAs (Lieberman et al., 2005). Similarly in CUtLASS, no major differences in effectiveness were found between FGAs and SGAs (Jones et al., 2006). In EUFEST, olanzapine was superior to haloperidol with regard to the time to discontinuation, while another outcome measure, symptom reduction, was nearly indistinguishable in all treatment groups (Kahn et al., 2008). Taken together, these results suggest that there may not be any significant overall differences between FGAs and SGAs in regard to improvement in psychopathology. The only exception from this is clozapine, which has been consistently shown to be superior to other antipsychotics in treatment-resistant schizophrenia (McEvoy et al., 2006, Leucht et al., 2009). Given the lack of a significant efficacy between antipsychotics, the key issues influencing the choice of an antipsychotic for an individual patient with schizophrenia should be the side-effect profile, the potential to improve cognition and the prevention of relapse (Meltzer, 2012).

2.2.2 MAIN RISKS DUE TO ANTIPSYCHOTIC TREATMENT

The use of FGAs is associated with a broad range of adverse effects, which are often severe and sometimes irreversible, as is in the case of tardive dyskinesia, which impairs general health, level of functioning and quality of life for the FGA-treated person, and also negatively affects the adherence to treatment (Kane and Correll, 2010). FGAs are known to cause different extrapyramidal symptoms; i.e., parkinsonism, dystonia, akatisia and tardive dyskinesia (Miyamoto et al., 2012). The estimated overall prevalence of EPS in patients with schizophrenia varies widely between 29 and 74% according to different reports (McCreadie et al., 1992, van Harten et al., 1996, Modestin et al., 2000). In the Nithsdale schizophrenia survey, which assessed the prevalence of antipsychotic-induced parkinsonism, akatisia and tardive dyskinesia among patients with schizophrenia, the corresponding prevalences were 27%, 18% and 25%, respectively, (McCreadie et al., 1992). These EPS are thought to result from a blockade of dopamine D2 receptors located in the nigrostriatal area. This is why the more potent D2 blockers are associated with a more significant risk of both acute and late-onset EPS (Agnoli et al., 1983). Other side-effects of FGAs include anticholinergic effects (such as dry mouth), postural hypotension, weight gain, hyperprolactinemia (with subsequent sexual dysfunction) and a lowering of the seizure threshold (Meyer, 2007). A potentially
lethal, yet fortunately rare complication of FGA treatment is the malignant neuroleptic syndrome (Trollor, 2012).

For these reasons, the introduction of SGAs was accompanied with much optimism in regard to their advertised safety and tolerability profiles. Indeed, the lower degree of D₂ antagonism, when compared to FGAs, makes SGAs seem less prone to cause neurological side-effects (Meltzer, 2012). However, later RCTs showed that SGAs are not fully devoid of EPS (Miller et al., 2008), the risk of neuroleptic malignant syndrome (Trollor et al., 2012) and hyperprolactinemia (Cookson et al., 2012). Moreover, SGAs are associated with their own set of detrimental side-effects; i.e., metabolic complications that include weight gain, hyperglycaemia and dyslipidemia (Newcomer, 2007, De Hert et al., 2009). Clozapine, the most effective SGA, also bears an inherent range of harmful side-effects, such as haematological complications, myocarditis, seizures, weight gain, constipation and excessive sedation (Kane, 1998). In particular, the risk of agranulocytosis has led to limitations of clozapine’s use, which is currently restricted in many countries to refractory patients (NICE, 2009).

Interestingly, there appears to be a relationship between the efficacy and metabolic effects of antipsychotics, at least in the case of SGAs. Clozapine and olanzapine both have an untoward profile of metabolic side-effects. Clozapine has repeatedly showed superiority in efficacy over other antipsychotics and, in some reviews olanzapine also demonstrated similar properties (Leucht et al., 2009). It has been repeatedly shown in RCTs that these antipsychotic-related metabolic adverse effects are directly associated with an improvement in psychopathology. Meltzer and co-authors (2003), for example, reported an association between weight gain and clinical improvement in clozapine-treated patients. In an RCT by Procyshyn and co-authors (2007), clozapine-induced changes in lipid profile were correlated with its clinical efficacy, yet independently of weight change. In a study by Ascher-Svanum and co-authors (2005) olanzapine-induced weight gain significantly correlated with better treatment response. More recently Hermes et al. (2011) reported similar results for various FGAs and SGAs in the CATIE study, where a 0.28 point decrease in PANSS total score was associated with a 1% increase in body mass index (BMI). The nature of this relationship is unclear (Procyshyn et al., 2007). It has been hypothesised that low serum cholesterol may contribute to poor treatment response in patients with schizophrenia by decreasing central serotonin function (Hawton et al., 1993). Thus, clozapine might “repair” this dysfunction by increasing lipid levels. However, it remains unclear whether or not such changes in weight and metabolic parameters directly influence clinical improvement, are a consequence of this, or are a covariate or some other mediating factor (Ascher-Swanum et al., 2005). Clearly, this particular issue also requires further investigation (Meltzer, 2012).

There appears to be only very modest differences in clinical efficacy between different antipsychotic drugs (with the sole exception of clozapine and, with some degree of controversy, olanzapine), and no convincing data exists to support an effective targeting strategy for treating particular symptoms of schizophrenia with particular antipsychotics. Thus, the available data on the specific adverse effect profiles of
antipsychotics have a considerable influence on drug choice for the treatment of schizophrenia (Barnes et al., 2011).

### 2.2.3 TREATMENT-RESISTANT SCHIZOPHRENIAS: CURRENT CLINICAL APPROACHES

The term “treatment-resistant” is generally attributed to cases where schizophrenia has not responded sufficiently to treatment. There still exist some controversies in defining this phenomenon. According to one of the definitions, treatment-resistant patients “had previously failed to respond to, or were intolerant of at least two different classes of antipsychotic drugs given in appropriate doses for at least 4 weeks each” (Bondolfi et al., 1998). Another definition uses a wider clinical concept of “incomplete recovery”, which means that the presence of “lasting disability in functional and psychosocial aspects despite psychological/psychosocial and pharmacological interventions” (Pantelis and Lambert, 2003).

Treatment resistance is a relatively common phenomenon in schizophrenia. It has been estimated that between a fifth and a third of patients with schizophrenia demonstrate a poor response to adequate regimes of antipsychotic treatment (Liebermann et al., 1996; Conley and Buchanan, 1997, Pantelis and Lambert, 2003). This proportion seems to increase with the progression of the disease, as the failure to achieve remission among first-episode patients is estimated to be at about 10% (Crow et al., 1986; Lambert et al., 2008), and with every new relapse one of six patients will not remit from the episode of illness, despite pharmacological treatment (Wiersma et al., 1998). There is a growing body of evidence to suggest that treatment resistant schizophrenia has its own neurobiological correlates, with an underlying pathophysiology that most likely involves other neurochemical abnormalities than a dopamine imbalance (Altamura et al., 2005, Stone et al., 2010).

The efficacy of clozapine for treatment-resistant schizophrenia has been clearly demonstrated by Kane and co-authors (1988, 2001), and a few subsequent meta-analyses have supported the superiority of clozapine over both FGAs and SGAs (Wahlbeck et al., 1999, Chakos et al., 2001, Asenjo-Lobos et al., 2010). Thus, clozapine remains the “gold standard” for treatment-resistant schizophrenia (Leucht et al., 2011, Volavka, 2012) and is recommended for this purpose by the most clinical guidelines.

Another treatment strategy for treatment-resistant schizophrenia employs combinations of antipsychotic drugs (including combinations with clozapine), but evidence supporting the feasibility of this approach is both limited and contradictory (Goodwin et al. 2009). This also seems to be true for the augmentation of antipsychotic therapy with medications from other classes of drugs, with the only probable exception of clozapine augmentation with lamotrigine (Tiihonen et al., 2009). This apparent exception is discussed in Section 4.2.4.

To summarize, clozapine remains the most effective treatment option for treatment-resistant schizophrenia, while other treatment strategies have not yet gained enough
support from clinical studies. However, the available evidence suggests that only 30 to 60% of patients with treatment-resistant schizophrenia will achieve a satisfactory response to clozapine (Iqbal et al., 2003). Moreover, treatment with clozapine is associated with a number of adverse effects, some of them serious and potentially fatal. Thus, a need remains for effective treatment strategies.

2.2.4 ADD-ON TREATMENTS FOR SCHIZOPHRENIA

As stated earlier, treatment with antipsychotics alone is not always enough to achieve a good clinical outcome in schizophrenia. This observation corresponds to a need for new pharmacological strategies that improve treatment results. One such strategy is adjuvant treatment, where ongoing antipsychotic therapy is augmented with a drug from another class of medicines. The most widely used augmentation strategies that target schizophrenic symptoms include mood stabilizers; e.g. valproate (Schwarz et al., 2008), lamotrigine (Tiihonen et al., 2009), lithium (Leucht et al., 2007) and antidepressants; e.g., tricyclic antidepressants (TCAs, Siris, 1993), selective serotonin reuptake inhibitors (SSRIs, Sepehry et al., 2007) and other receptor-blocking antidepressants (Singh et al., 2010). Other augmentation strategies include sex hormones (Ko et al., 2008), cyclo-oxygenase (COX) inhibitors (Riedel et al., 2005), glutamatergic drugs (Tuominen et al., 2006), acetylcholine esterase inhibitors (Keefe et al., 2008) and sildenafil (Akhondzadeh et al., 2011).

Only a few adjuvant medicines have so far been included in the international treatment guidelines. These include the augmentation of ongoing clozapine treatment with lamotrigine (Barnes et al., 2011) and the augmentation of FGA or SGA treatment with antidepressants for either symptoms of depression (APA, 2004) or persistent negative symptoms (Barnes, 2011). Mood stabilizers are recommended by the APA for prominent mood lability and aggression (APA, 2004). Overall, the evidence regarding efficacy and tolerability of adjunctive treatments is still inconclusive and requires further investigation (Leucht, 2011).

2.3 THE ROLE OF ADJUNCTIVE ANTIDEPRESSANTS IN THE TREATMENT OF SCHIZOPHRENIA

The existing treatment guidelines do not yet suggest antidepressants for the treatment of negative or positive symptoms of schizophrenia. For instance, the Practice Guideline for the Treatment of Patients with Schizophrenia by the APA recommends the consideration of antidepressants for treating comorbid major depression, yet suggests caution due to a possible risk for an exacerbation of the psychosis (APA, 2004). Similarly, the NICE guideline by the British Royal College of Psychiatrists suggests limiting the antidepressant augmentation of antipsychotics only for the treatment of
“comorbid or secondary psychiatric problems, such as depression and anxiety” (NICE, 2009).

Nevertheless, in actual practice clinicians widely use antidepressants to treat co-occurring depression, posttraumatic stress disorder or anxiety in psychotic patients (Zink et al., 2010, Himelhoch et al., 2012). For example in the CATIE study, approximately a third of the participants with schizophrenia were receiving an antidepressant at the study baseline (Chakos et al., 2006).

2.3.1 EFFICACY OF ANTIDEPRESSANTS IN THE TREATMENT OF POSITIVE, NEGATIVE AND AFFECTIVE SYMPTOMS

Antidepressants as an adjuvant treatment for schizophrenia have been a subject of extensive clinical research for many years. The results of RCTs with add-on antidepressants are summarized in Table 1.

In earlier studies, the rationale for the use of adjuvant antidepressants was based on the observation of an existing clinical overlap between some symptoms of schizophrenia and depression; e.g., apathy, anhedonia and avolition, and a presumption of stimulating effects from antidepressants (Waehrens and Gerlach, 1980). Studies with TCAs in the 1980s yielded mainly positive results, but their conclusions seem to be questionable, mainly due to some substantial methodological limitations, especially in regard to the applied outcome measures (Rummel-Kluge et al, 2006).

In the 1990s, the focus of research on biological mechanisms in schizophrenia targeted the serotonin system. In particular, the adjunctive SSRIs were hypothesized to affect negative symptoms by enhancing synaptic availability of serotonin for neurotransmission, with a subsequent re-setting of the dysfunctional serotonergic system (Laruelle et al., 1993, Dean et al., 1996). The efficacy of individual SSRIs as an add-on treatment for schizophrenia vary widely, and most evidence exists for their efficacy on negative symptoms (Zullino et al., 2002, Rummel-Kluge et al., 2006), while no support exists from RCTs to justify their use in their treatment of positive or depressive symptoms. A theoretical basis for the probable efficacy of selective noradrenaline reuptake inhibitors (SNRIs) in the adjunctive treatment of schizophrenia relies on the assumption that noradrenergic hypoactivity may be associated with negative symptoms (Yamamoto and Hornykiewicz, 2004). Therefore, enhancing the transmission in noradrenergic pathways of the brain may lead to a corresponding reduction in negative symptoms.

The available evidence regarding the efficacy of add-on treatment with SNRIs in schizophrenia is also mixed and scarce (Table 1).

Another group of antidepressants – the so-called receptor blocking antidepressants act via the inhibition of various monoamine receptor subtypes. The rationale for the combining of these antidepressants with antipsychotics in the treatment is based on the theory of atypicality; e.g., antipsychotics with 5HT2-receptor blockade prevailing over
D$_2$-receptor blockade (from atypical, or SGAs) are more effective in regard to positive, negative, and cognitive symptoms than the pure D$_2$-blockers (typical, or FGAs, Meltzer, 1999, Meltzer et al., 2011). According to this assumption the combination of a 5HT$_2$-inhibitor with a D$_2$-inhibitor would mimic or, at least resemble the receptor binding profile of SGAs with corresponding favorable clinical effects with less side effects (Berendsen et al., 1998, Berk et al., 2001).

Of these drugs, trazodone, mianserin and mirtazapine have been studied in several RCTs (Table 1). The vast majority of these studies point to the efficacy of add-on treatment with receptor-blocking antidepressants on the negative symptom domain of schizophrenia. Mirtazapine appears to have demonstrated the most consistent findings.

To summarize, Rummel-Kluge and co-authors concluded in their Cochrane review (2006) that “the combination of antipsychotics and antidepressants may be effective in treating negative symptoms of schizophrenia...”, though the information from RCTs can still be characterized as limited. In their meta-analysis on the same topic, Singh and co-authors (2010) based their comparison of effect sizes for different antidepressants, and suggested that the most effective drugs for treating the negative symptoms are ritanserin, trazodone and fluoxetine (NNT 5, 6 and 11, correspondingly). It should be noted, however, that ritanserin (an antagonist of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors) is not currently marketed as an antidepressant.

Current evidence is still insufficient to recommend any of the existing antidepressants for the treatment of positive symptoms in schizophrenia. Nevertheless, the use of add-on antidepressants appears to be a safe treatment strategy, because in the above listed RCTs no additional risk worsening psychosis has emerged. This seems to be true at least for chronic schizophrenia, while it has been recommended to avoid the use of antidepressants during the acute stage of psychosis (Leucht et al., 2011).

Add-on antidepressants may be beneficial in the treatment of depression in the patients with schizophrenia (Leucht et al., 2011, Whitehead et al., 2012), although this research data is far from convincing and further research is needed.
Table 1. Antidepressants as add-on treatment for schizophrenia: a review of double-blind, placebo-controlled studies.

<table>
<thead>
<tr>
<th>Antidepressant/Study</th>
<th>Antipsychotic</th>
<th>No of subjects</th>
<th>Dose, mg/day</th>
<th>Duration, weeks</th>
<th>Efficacy measures</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCA</strong>s</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amitryptiline</td>
<td>Perphenazine</td>
<td>87</td>
<td>n/d*</td>
<td>12</td>
<td>Wing scale</td>
<td>Significant improvement in amitryptiline group.</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Different FGAs</td>
<td>20</td>
<td>n/d</td>
<td>6</td>
<td>n/d</td>
<td>No difference between groups.</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Depot FGAs</td>
<td>14</td>
<td>n/d</td>
<td>24</td>
<td>n/d</td>
<td>Improvement in negative symptoms in imipramine group, no improvement in placebo group.</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
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<tr>
<td>Fluoxetine</td>
<td>Different FGAs</td>
<td>34</td>
<td>20</td>
<td>12</td>
<td>SANS, SAPS, HDRS</td>
<td>Improvement in favour of fluoxetine in SANS scores. No improvement in SAPS scores in either group. Improvement of HDRS scores in fluoxetine, but not in placebo group.</td>
</tr>
<tr>
<td></td>
<td>Depot FGAs</td>
<td>41</td>
<td>20</td>
<td>6</td>
<td>BPRS, SAS</td>
<td>Improvement in favour of fluoxetine in BPRS negative subscale. No change on other parameters.</td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
<td>33</td>
<td>20</td>
<td>8</td>
<td>BPRS, HDRS</td>
<td>No change on either parameter in either group.</td>
</tr>
<tr>
<td></td>
<td>Different FGAs</td>
<td>32</td>
<td>20-40</td>
<td>8</td>
<td>BPRS, HDRS, SANS, MIMS1</td>
<td>No change on any parameter in either group.</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>30</td>
<td>20</td>
<td>8</td>
<td>SAPS, SANS, HDRS</td>
<td>Greater reduction of SAPS scores in placebo group than in fluoxetine group.</td>
</tr>
<tr>
<td>Study Details</td>
<td>Treatment</td>
<td>Sample Size</td>
<td>Duration (weeks)</td>
<td>Efficacy Measures</td>
<td>Results</td>
<td></td>
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<tr>
<td>Bustillo et al, 2003</td>
<td>Olanzapine</td>
<td>31</td>
<td>60</td>
<td>PANSS, HDRS, SAS, BAS, AIMS</td>
<td>No change on either parameter in either group.</td>
<td></td>
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<tr>
<td>Fluvoxamine</td>
<td></td>
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<tr>
<td>Silver and Nassar, 1992</td>
<td>Different FGAs</td>
<td>30</td>
<td>50-100</td>
<td>SANS, SAPS, HDRS</td>
<td>Improvement in favour of fluvoxamine on SANS scores. No improvement on SAPS scores in either group.</td>
<td></td>
</tr>
<tr>
<td>Silver et al, 2000</td>
<td>Different FGAs</td>
<td>53</td>
<td>50-100</td>
<td>SANS, SAPS, BPRS</td>
<td>Improvement in favour of fluvoxamine on SANS scores. No improvement on SAPS scores in any group.</td>
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<tr>
<td>Sertraline</td>
<td></td>
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<tr>
<td>Lee et al, 1998</td>
<td>Haloperidol</td>
<td>36</td>
<td>50</td>
<td>PANSS, SAS</td>
<td>No change on either parameter in either group.</td>
<td></td>
</tr>
<tr>
<td>Mulholand et al, 2003</td>
<td>Different FGAs, risperidone</td>
<td>26</td>
<td>50</td>
<td>BPRS, SANS, HDRS, BDI, SAS, BAS</td>
<td>No change in BPRS or SANS scales in either group. Improvement of HDRS and BDI scores in favour of sertraline. No change in EPS symptoms in sertraline group, worsening of SAS scores in placebo group.</td>
<td></td>
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<tr>
<td>Citalopram</td>
<td></td>
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<tr>
<td>Salokangas et al, 1996</td>
<td>Different FGAs</td>
<td>90</td>
<td>20-40</td>
<td>PANSS</td>
<td>Decrease on PANSS total in both groups with no difference between groups in PANSS positive or negative subscales.</td>
<td></td>
</tr>
<tr>
<td>Friedman et al, 2005</td>
<td>Different SGAs</td>
<td>19</td>
<td>40</td>
<td>PANSS</td>
<td>No change in either group.</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Jockers-Schenul et al, 2005</td>
<td>Different FGAs and SGAs</td>
<td>29</td>
<td>30</td>
<td>PANSS, HDRS, SAS, BAS, AIMS</td>
<td>Decrease on PANSS negative in paroxetine group, no difference between groups on PANSS positive subscale. No improvement on HDRS scores in any group. No change in EPS symptom severity in either group.</td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td>Receptor-blocking antidepressants</td>
<td>n</td>
<td>Dose</td>
<td>BPRS, SANS</td>
<td>Improvement in duloxetine group on PANSS negative and negative subscale. Improvement on CDSS in duloxetine group.</td>
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<tr>
<td>Duloxetine</td>
<td>Mico et al., 2011</td>
<td>Clozapine</td>
<td>33</td>
<td>60</td>
<td>6</td>
<td>PANSS, CDSS</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Schutz and Berk, 2001</td>
<td>Haloperidol</td>
<td>30</td>
<td>8</td>
<td>8</td>
<td>PANSS, HDRS</td>
</tr>
<tr>
<td></td>
<td>Poyurovksi et al, 2003</td>
<td>Olanzapine</td>
<td>26</td>
<td>4</td>
<td>6</td>
<td>SANS, SAPS, HDRS</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Decina et al, 1994</td>
<td>Not defined</td>
<td>47</td>
<td>n/d</td>
<td>6</td>
<td>BPRS, SANS</td>
</tr>
<tr>
<td></td>
<td>Hayashi et al, 1997</td>
<td>N/d</td>
<td>39</td>
<td>50-200</td>
<td>5</td>
<td>BPRS, SANS</td>
</tr>
<tr>
<td></td>
<td>Hayashi et al, 1997</td>
<td>N/d</td>
<td>39</td>
<td>20-60</td>
<td>5</td>
<td>BPRS, SANS</td>
</tr>
<tr>
<td>Mianserin</td>
<td>Shiloh et al, 1992</td>
<td>Haloperidol, perphenazine</td>
<td>18</td>
<td>30</td>
<td>6</td>
<td>BPRS, SANS, HDRS</td>
</tr>
<tr>
<td></td>
<td>Poyurovski et al, 2003</td>
<td>Different FGAs</td>
<td>30</td>
<td>15</td>
<td>4</td>
<td>SAPS, SANS, HDRS</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Berk et al, 2001</td>
<td>Haloperidol</td>
<td>30</td>
<td>30</td>
<td>6</td>
<td>PANSS</td>
</tr>
<tr>
<td></td>
<td>Zocali et al, 2004</td>
<td>Clozapine</td>
<td>24</td>
<td>30</td>
<td>8</td>
<td>SANS, SANS,</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment Details</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Study Parameters</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Berk et al, 2009</td>
<td>Different SGAs (including clozapine)</td>
<td>40</td>
<td>30</td>
<td>PANSS, HDRS</td>
<td>No difference in either parameter between groups.</td>
<td></td>
</tr>
<tr>
<td>Abbasi et al, 2009</td>
<td>Risperidone</td>
<td>40</td>
<td>30</td>
<td>PANSS</td>
<td>Improvement on PANSS negative and PANSS total in mirtazapine group, no difference on other PANSS subscales</td>
<td></td>
</tr>
</tbody>
</table>

*n/d – not defined*
2.3.2 EFFICACY OF ANTIDEPRESSANTS IN THE TREATMENT OF EPS

The supposition that add-on antidepressants may alleviate antipsychotic-induced EPS derives from the idea of dopamine deficit in the basal ganglia of brain. According to this theory, pharmacological agents that increase available dopamine in this area may be used to treat EPS (Meltzer et al., 2003, Ohno, 2011). Another possible effective mechanism could be through 5HT2 receptor antagonism – a common feature of several receptor-blocking antidepressants (Berk et al., 2001).

The research data regarding the efficacy of receptor-blocking antidepressants on antipsychotic-induced EPS are contradictory (Table 1). Findings from several RCTs with add-on mirtazapine, mianserin and trazodone to existing antipsychotic therapy suggest a probable efficacy of these antidepressants, while findings from some other studies with the same agents do not.

There is no proven mechanism for the possible efficacy of TCAs, SSRIs or SNRIs in the treatment of antipsychotic-induced EPS. Moreover, these antidepressants may themselves even cause EPS in patients with major depressive disorder (MDD, Madhusoodanan et al., 2010). Nevertheless, the influence on EPS was a secondary variable in a number of studies with SSRIs and SNRIs, as listed in the section 4.3.1. Perhaps, not surprisingly, all these studies gained negative results.

2.3.3 EFFECTIVENESS OF ANTIDEPRESSANTS IN SCHIZOPHRENIA

Only a few effectiveness studies have focused on adjuvant antidepressants in schizophrenia. In a large study by Tiihonen and co-authors (2012), relationships between polypharmacy and mortality rates were investigated in a nationwide cohort of 2588 patients suffering from schizophrenia and hospitalized for the first time between January 2000 and December 2007. According to their results, concomitant antidepressant treatment was associated with lessened mortality from all causes (HR 0.57; 95% CI 0.28-1.16) and particularly from suicide (HR 0.15; 95% CI 0.03-0.77).

In another recent prospective study conducted by Laengle and co-authors (2012), the effects of psychotropic polypharmacy (including antidepressants, benzodiazepines, and mood stabilizers) on clinical outcomes and quality of life were analyzed in a cohort of 374 patients with schizophrenia and schizoaffective disorder who received different SGAs. Patients were assessed with the PANSS, the Global Assessment of Functioning (GAF), the Lancashire Quality of Life Profile, SAS, and Abnormal Involuntary Movement Scale (AIMS) in a 24 month follow-up. In that study, patients receiving combinations of SGAs with antidepressants did not differ in terms of clinical outcomes, as measured by PANSS, from patients receiving antipsychotic monotherapy. Moreover, therapy with a SGA-antidepressant combination was associated with a more significant improvement in EPS than all other treatments, including monotherapy with SGAs. Worth noting from the same study is the mean baseline PANSS scores ranging from
49.8 to 57.7, thus making it unclear whether or not these findings can be extrapolated to patients with more severe illness.

Glick and co-authors (2006) evaluated the clinical effect for the gradual discontinuation of antidepressant treatment in a sample of 22 patients stabilized on an antipsychotic medication. The outcome was measured with the Clinical Global Impression-Improvement Scale (CGI-I) during a 3 to 12 months of follow-up. Tapering off an antidepressant led to a decline of a patient’s mental condition in one case, whereas in 18 cases the situation remained stable, while in 3 cases the patients’ mental state improved. This led the authors to conclude that tapering off the concomitant antidepressant treatment does not change the outcome. Based on this observation, clinicians are now encouraged to try and withdraw stabilized chronic patients from their adjunctive antidepressant medications, provided that their antipsychotic dosage is adequate. These authors did not use other outcome measures, nor did they report on other patient characteristics (e.g., presence of depressive symptoms or EPS, severity and duration of the disease, etc), which makes it difficult to extrapolate this finding on to certain patient groups, for example, patients with schizophrenia and depression, patients with predominantly negative symptoms, etc.

In a recent large (n= 16,083) nationwide study in Finland, Suokas and co-authors (2012) found that antidepressant use was associated with a decreased risk of antipsychotic polypharmacy in patients with schizophrenia. This finding was statistically significant in patients with chronic schizophrenia, and there was also a trend towards improvement in patients with recent-onset schizophrenia.

Thus, it can be concluded that in real-life clinical settings there should be no reasons for concern about the safety of antidepressants in schizophrenia patients. Moreover, antidepressants seem to decrease mortality in schizophrenia patient cohorts, presumably by the prevention of suicide and other forms of self harm.

### 2.4 MIRTAZAPINE

#### 2.4.1 PHARMACOLOGICAL PROFILE AND CLINICAL EFFICACY

Mirtazapine is a pharmacological agent from the group of second generation antidepressants (SGAs). Mirtazapine has a unique receptor profile, being an antagonist of central pre-synaptic alpha-2-adrenoreceptors, postsynaptic 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, and histamine H<sub>1</sub> receptors. In addition, mirtazapine exhibits indirect agonism at 5-HT<sub>1A</sub> receptors (de Boer, 1996).

Through blockade of central alpha-2-adrenergic autoreceptors, mirtazapine causes an increase in the release of noradrenaline. The subsequent stimulation of somatodendritic alpha-1-receptors, which mediate the firing of serotonin neurons, along with a direct blockade of inhibitory alpha-2-heteroreceptors on 5-HT terminals is thought to lead to an increase in hippocampal serotonin release (Gillman, 2006). Enhanced serotonin neurotransmission is, in this case, specifically mediated via the 5-
HT₁ receptor, which is thought to be responsible for the therapeutic effects of some antidepressants. Unlike other antidepressants (SSRIs, SNRIs, TCAs, Inhibitors of the Monoamine Oxidase [IMAOs]) that stimulate serotonergic receptors by increasing available serotonin, mirtazapine selectively blocks 5-HT₂ and 5-HT₃ receptors, which makes this antidepressant free of the adverse effects typical for other classes of antidepressive drugs (e.g., sexual dysfunction, gastrointestinal problems, etc.) (Gillman, 2006). Moreover, inhibition of 5-HT₂ and 5-HT₃ receptors may contribute to the anxiolytic and somniforic effects of mirtazapine (de Boer, 1996). Histamine H₁ receptor blockade is believed to contribute to side-effects of mirtazapine, e.g., sedation, increased appetite and weight gain (Stimmel et al., 1997).

Mirtazapine is an antidepressant with established efficacy in the treatment of major depression (Benjamin and Doraiswamy, 2011). According to a Cochrane review by Watanabe and co-authors (2011), the effect of mirtazapine is comparable to TCAs (OR 0.89, 95% CI 0.72 to 1.10) and superior over both SSRIs (OR 1.19, 95% CI 1.01 to 1.39) and SNRIs (OR 1.53, 95% CI 1.03 to 2.25), in terms of response during the acute-phase treatment (6 to 12 weeks) of MDD. Mirtazapine has been listed as being among the most effective antidepressants in some (Watanabe et al., 2008, Cipriani et al., 2009), though not all (Hansen et al., 2005) systematic reviews. Furthermore, there is consistent evidence from a number of RCTs demonstrating that mirtazapine has a faster onset of action in patients with MDD than the majority of other antidepressants (Gartlehner et al., 2011).

2.4.2 SAFETY AND TOLERABILITY OF MIRTAZAPINE

Mirtazapine is generally well tolerated, with an overall incidence of reported adverse effects comparable to that of a placebo (Montgomery, 1995), and most adverse events seen with mirtazapine treatment are mild and transient, and as a rule decreasing in both intensity and frequency over time (Fawsett and Barkin, 1998). Adverse events that are most frequently encountered with mirtazapine vs. placebo are dry mouth (25% vs. 16%), drowsiness (23% vs. 14%), excessive sedation (19% vs. 5%), increased appetite (11% vs. 2%) and weight gain (10% vs. 1%) (Montgomery, 1995). Noticeably, sedation and drowsiness are related to low doses and either diminish or gradually disappear during titration to higher doses (Bremner, 1995). It has been hypothesized that the noradrenergic activation induced by mirtazapine at higher dosages overrides its antihistaminic activity (Barkin et al., 1999). The incidence of serotonin-related adverse gastrointestinal effects (e.g., nausea, vomiting, diarrhea) are either comparable or somewhat lower in mirtazapine than in placebo, and the incidence of agitation, restlessness or insomnia are comparable with both mirtazapine and placebo (Fawsett and Barkin, 1998). Treatment with mirtazapine is associated with a much lower risk of sexual dysfunction when compared with SSRIs (Benkert et al., 2000) and SNRIs (Gartlehner et al., 2011). Interestingly, in a study by Gelenberg and co-authors (2000),
patients suffering from SSRI-related sexual dysfunction did benefit from a switch to mirtazapine treatment, with no loss in antidepressive response.

Mirtazapine has a wide therapeutic index and is relatively safe in overdose situations (Montgomery, 1995). Being a very weak inhibitor of cytochrome P450 hepatic isoenzymes, it has a low propensity for drug–drug interactions (Timmer et al., 2000, Dodd et al., 2001).

During the clinical development program, no significant changes in laboratory parameters or cardiovascular vital signs (e.g., heart rate, blood pressure) occurred with mirtazapine treatment (Montgomery, 1995). Data from more recent studies mainly confirmed the established safety of mirtazapine from the viewpoint of glucose metabolism (Laimer et al., 2006, Hennings et al., 2012). However, there is a growing body of evidence that point to an unfavorable effect of mirtazapine on serum lipid parameters; i.e., LDL-cholesterol and triglycerides (Laimer et al., 2006, McIntyre et al., 2006). This effect is thought to be a secondary to the well-established propensity for mirtazapine to induce weight gain, rather than a direct influence of mitrazapine on lipid metabolism (McIntyre et al., 2006).

2.4.3 RATIONALE FOR THE USE OF MIRTAZAPINE AS AN ADD-ON TREATMENT FOR SCHIZOPHRENIA

The explanation for the efficacy of mirtazapine as an adjunctive treatment for schizophrenia is based on its receptor profile. As stated previously, mirtazapine is a potent inhibitor of postsynaptic 5-HT2a receptors that lacks noteworthy D2 receptor affinity, and thus antipsychotic efficacy. Subsequently, the combination of mirtazapine with a D2 antagonist (i.e., FGA) may provide a beneficial strategy with improved efficacy and tolerability. Other pharmacodynamic properties of mirtazapine, e.g. inhibition of 5-HT3 and alpha adrenoreceptors, may also be useful. In addition, mirtazapine can presumably be safely combined with most conventional antipsychotics, as it does not significantly inhibit liver CYP 450 enzymes, which are responsible for the metabolism of many antipsychotics. To date however, there is not enough data on the feasibility of this strategy. The only previous RCT on a mirtazapine-FGA combination (Berk et al., 2001) examined just one antipsychotic (haloperidol 5 mg daily) in a group of 15 patients. Thus, more studies are needed, especially in settings that resemble clinical practice (i.e., treated with different FGAs), before adjunctive mirtazapine in schizophrenia can be recommended.
3 AIMS OF THE STUDY

1. To explore the effect of short- and middle-term adjunctive mirtazapine on the positive and negative symptoms of schizophrenia in patients with no or only sub-optimal response to different FGAs in stable dosages.

2. To obtain data on the effects of short- and middle-term adjunctive mirtazapine on affective symptomatology in FGA-medicated patients with schizophrenia.

3. To evaluate whether or not adjunctive mirtazapine is able to diminish FGA-induced side effects.

4. To investigate safety and tolerability of mirtazapine in patients with schizophrenia.
4 SUBJECTS AND METHODS

4.1 STUDY DESIGN

The study was a single-center add-on placebo-controlled RCT. Patients were recruited from the Psychiatric Hospital and the Day Treatment Unit of the Psychoneurological Dispensary of the Karelian Republic, Petrozavodsk, Russia.

4.2 INCLUSION AND EXCLUSION CRITERIA

4.2.1 INCLUSION CRITERIA

Male or female in- or out-patients who met the following criteria:

1) aged 18 - 65 years,
2) a diagnosis of DSM-IV (APA, 1994) defined schizophrenia (disorganized, catatonic, paranoid, residual, or undifferentiated) 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 has remained unchanged (also in terms of dosage) for at least six last weeks prior to screening (eight weeks for depot antipsychotics),
4) have demonstrated less than optimal clinical outcome, i.e. experience either positive or negative symptoms (disability due to only general symptoms was insufficient for inclusion) resulting in an illness of at least moderate severity (i.e. a rating of 4, moderately ill, or more on the CGI severity item, Guy, 1970),
5) the clinical condition has remained stable during the last six weeks prior to the baseline visit,
6) the patient had a level of understanding that enabled reasonable cooperation with the investigator,
7) the patient had given written informed consent.

4.2.2 EXCLUSION CRITERIA

1) a history of allergy or serious adverse events due to mirtazapine,
2) a previous lack of response to a trial with mirtazapine at a daily dosage of 30 mg or more during four or more weeks, when added to the patient’s current or earlier conventional antipsychotic medication,
3) a previous lack of response to another antidepressant with affinity to postsynaptic 5-HT2 receptors (e.g.; mianserine, trazodone, or nefazodone,) used at adequate doses during four or more weeks,
4) current atypical antipsychotic medication (e.g., clozapine, risperidone, olanzapine, sertindole, quetiapine, zotepine, ziprasidone, etc.)

5) a history of non-response to either clozapine or other atypical antipsychotics,

6) a medical or neurological condition or drug treatment which might cause a serious risk for the patient, 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 or current bipolar disorder or schizoaffective disorder, bipolar type (patients with schizoaffective disorder, depressive type could participate in the study).

8) substance addiction or abuse within the last three months prior to screening,

9) clearly predictable poor compliance,

10) suicidality,

11) for females of child-bearing potential: pregnancy, lactation, or an inability or unwillingness to use medically acceptable methods of contraception during the study,

12) treatment with any antidepressant, mood stabilizer, regular (i.e. four or more times within one week) use of sumatriptan, naratriptan, zolmitriptan, or drugs with a similar mechanism of action, or buspirone or drugs with a similar mechanism of action - within four weeks (for fluoxetine six weeks) prior to baseline. Accidental use of the above listed drugs for the treatment of migraine was not allowed on the day of clinical assessment or just before the assessment,

13) treatment with antipsychotics other than those currently used within 6 weeks prior to baseline,

14) treatment with benzodiazepines as follows:

- regular use (i.e. four or more times weekly) of any benzodiazepines at any dosage during the last four weeks prior to baseline, if they have been started for less than two months ago. However, regular use of benzodiazepines was permitted if they were absolutely necessary, and if they had been continued during two or more months prior to baseline in stable daily dosages not exceeding 30 mg of diazepam or comparable dosages of other benzodiazepines,

- occasional use (i.e., three or less times weekly) of benzodiazepines in daily dosages exceeding 30 mg of diazepam or comparable dosages of other benzodiazepines. Use of benzodiazepines on the day of clinical assessment was not allowed before the assessment,

15) electroconvulsive therapy (ECT) within three months prior to baseline,

16) any clinically relevant abnormality detected during the physical examination or laboratory screening tests that were likely to interfere with the conduct of the study.
4.3 MAIN STUDY PROCEDURES

4.3.1 GENERAL OUTLINE
Patients who complied with all selection criteria were enrolled to the trial and after a one-week single-blind placebo run period, they were randomly assigned to either mirtazapine 30mg or placebo *quaque hora somni* (QHS) in a double-blind fashion for six weeks. After that, patients eligible and willing to participate entered the six week open-label phase, where they received mirtazapine 30mg QHS (Figure 1).

4.3.2 DEMOGRAPHICS AND OTHER GENERAL SUBJECT CHARACTERISTICS
The following data were obtained 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 and reason of hospitalization (if appropriate)
- date and reason of possible drop-out
- history of antipsychotic medication use (what antipsychotics, in what dosages, and for how a long time have they been used prior to the study).

4.3.3 EFFICACY ASSESSMENTS
Clinical efficacy was assessed with the PANSS (Kay et al., 1987), the CGI and CDSS (Addington et al., 1993). For evaluation of depressive symptoms the depression/anxiety factor of PANSS and the PANSS depression item were used. Subjective attitudes of the patients to the study medication were further assessed with the Patient Global Impression Scale (PGI, Guy, 1976).

Clinical assessments were performed at week –1 (screening), week 0 (baseline) and after 1, 2, 4, 6, 7, 8, 10, and 12 weeks of treatment.

4.3.4 SAFETY AND TOLERABILITY ASSESSMENTS
The FGA-induced extrapyramidal symptoms were evaluated with the SAS (Simpson & Angus, 1970) simultaneously with the clinical assessments. Physical examination and laboratory tests (including complete blood count, fasting levels of glucose and total cholesterol) were performed at screening and at end-point. In addition to this the subjects were asked about any adverse events, while using the study medication.
4.3.5 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) Regular (i.e. four or more times within one week) use of sumatriptan, naratriptan, zolmitriptan or drugs with a similar mechanism of action. Even occasional use of these drugs was not allowed on the days of clinical assessments and before the assessments.
5) Buspirone or drugs with a similar mechanism of action
6) Benzodiazepines:
   - regular use (i.e. four or more times weekly) of any benzodiazepines at any dosages were not allowed if they have not been started for the two or more last months prior to baseline (week 0) in stable dosages not exceeding 30 mg of diazepam or equivalent. The investigators will be encouraged to keep the regular benzodiazepine medication unchanged during the study. A decrease in dosages was, however, allowed due to ethical reasons, while an increase dosage was not allowed.
   - occasional use (i.e. three or less times weekly) of benzodiazepines in daily doses exceeding 30 mg of diazepam or equivalent was not allowed. Occasional use of benzodiazepines at any dosage was not allowed on the days of clinical assessments and before the assessments.
7) Zopiclon, zolpidem and zaleplon were permitted as hypnotics if necessary, in dosages not exceeding recommendations of the manufacturer.

4.4 STATISTICAL METHODS

4.4.1 EFFICACY VARIABLES

The primary efficacy variables were the PANSS total scores. Secondary efficacy parameters included the PANSS subscale scores, number of responders (persons with ≥ 20 % decline on the total and/or negative PANSS scores and/or those scoring much improved or very much improved on the CGI improvement item), CDSS and Simpson-Angus Scale scores. The analysis was made on a Modified Intent-to-Treat (MITT) basis (i.e. all randomized patients with ≥1 on-therapy evaluations) with the last observation carried forward (LOCF). An observation was considered to be on-therapy if it occurred within 3 days of the patient’s final full dose of the study medication.

Initial calculations indicated that 17 patients per treatment group would be required to guarantee power of 0.80 in detecting of difference (alpha=0.05) when comparing therapies (mirtazapine vs. placebo) with underlying success rate of 20 points decrease on the PANSS total score from the estimated initial score of 100 (SD 20). Since a
substantial drop-out rate was expected, the number of patients entering each treatment group was increased to 20.

### 4.4.2 STATISTICAL MODELS

Cross-sectional statistical differences between the study groups (between-group differences) were analyzed using an independent samples t-test for continuous variables and the chi-square test for categorical variables. Within-group changes in the efficacy variables over time were tested by the paired sample t-test. Post hoc type comparisons of the treatments were based on estimated marginal means when repeated measures ANOVA were used. Spearman correlation analysis was performed for calculations of correlations between measured values. Relationships between the changes in the metabolic parameters and PANSS-measured changes of psychopathology were analyzed using the linear regression model, which included changes in each of the PANSS (sub)scales as dependent variables and changes in body weight, fasting glucose and total cholesterol levels as independent variables.

Two-tailed p-values less than 0.05 were considered statistically significant. Analyses were performed using SPSS for Windows 19.0 software (SPSS Inc.).

### 4.4.3 DEFINED PATIENT SAMPLES FOR COMPARISONS

The primary comparisons were between the mirtazapine and placebo groups. Three patient samples were defined for the purposes of analysis.

The safety sample comprised all patients who had received at least one dose of study medication, and had at least one post-dose safety assessment.

The primary sample was the “modified intent-to-treat” sample with the last observations carried forward (LOCF). This sample included all randomly assigned patients with at least one on-therapy evaluation.

The per-protocol sample comprised all patients in the intent-to-treat population who had completed 12 weeks of the study without a major protocol violation.

### 4.5 ETHICS

The present study was conducted in compliance with the current revision 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 beginning of the trial.

After a complete description of the study, a written informed consent was obtained from each patient. Patients were able to withdraw their consent at any time.
were recruited only if add-on treatment was considered appropriate for them from a clinical point of view.
5 RESULTS

5.1 THE PATIENT POPULATION: CLINICAL AND DEMOGRAPHIC CHARACTERISTICS

5.1.1 THE DOUBLE-BLIND PHASE (STUDIES I, III AND IV):

The recruitment of patients took place during the period from 1.9.2004 to 31.7.2007. Approximately two hundred patients were selected for the pre-screening phase. Of these selected patients, we considered about 140 patients not to meet the inclusion criteria and about 90 patients declined to participate. Forty six patients were found to be eligible for the study and signed the informed consent. During the placebo run-in period, five withdrew the informed consent and, thus, 41 patients were randomized. One patient from the placebo group was withdrawn from the study immediately after the randomization, as the baseline assessments were not performed. Another patient from the same group was excluded due to a protocol violation (FGA dose lower than 200mg of chlorpromazine equivalent). Thus the modified intent to treat (MITT) population consisted of 39 patients: 20 of them formed the mirtazapine group and 19 formed the placebo group (Fig. 1).

All other patients had a diagnosis of schizophrenia, except for one patient in the placebo group who had a diagnosis of schizoaffective disorder, depressive type. Patients received therapy with chlorpromazine (n=5), flupentixol (n=2), fluphenazine decanoate (n=8), haloperidol (n=14), haloperidol decanoate (n=10), levomepromazine (n=6), pericazine (n=2), sulpiride (n=1), trifluoperazine (n=13), zuclopentixol decanoate (n=5) or zuclopentixol (n=4). The majority of the patients in this study received polypharmacy, with the number of concomitantly used FGAs varying from two to four. These patients had received numerous antipsychotic trials during previous years of their treatment.

Baseline demographic and clinical characteristics, medication history or current FGA dosages did not significantly differ between the mirtazapine and placebo groups, with the exception of higher PANSS positive scores in the mirtazapine group (Table 2).

At baseline, there were no statistically significant differences between the groups for weight, blood pressure or any metabolic parameters (i.e., fasting glucose and cholesterol).
Table 2. Baseline demographics and clinical data of patients.

<table>
<thead>
<tr>
<th></th>
<th>Mirtazapine (n=20)</th>
<th>Placebo (n=19)</th>
<th>Test statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>43.4 (9.24)</td>
<td>48.21 (9.68)</td>
<td>t=1.59, p=0.121</td>
</tr>
<tr>
<td>Gender, males: n (%)</td>
<td>11 (55%)</td>
<td>9 (47.4%)</td>
<td>χ²=0.23, p=0.63</td>
</tr>
<tr>
<td>Inpatients</td>
<td>11 (55%)</td>
<td>7 (36.8%)</td>
<td>χ²=1.29, p=0.26</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>23.45 (6.47)</td>
<td>24.11 (6.69)</td>
<td>t=0.31, p=0.76</td>
</tr>
<tr>
<td>Duration of disease, years</td>
<td>19.95 (9.08)</td>
<td>24.95 (9.43)</td>
<td>t=1.69, p=0.100</td>
</tr>
<tr>
<td>Number of previous psychotic episodes</td>
<td>7.85 (4.13)</td>
<td>6.71 (5.03)</td>
<td>t=0.79, p=0.44</td>
</tr>
<tr>
<td>Current FGA dose, CPZ equivalents, mg</td>
<td>330.75 (123.53)</td>
<td>316.58 (164.87)</td>
<td>t=0.31, p=0.76</td>
</tr>
<tr>
<td>Number of previous antipsychotic trials</td>
<td>8.50 (2.69)</td>
<td>8.11 (3.49)</td>
<td>t=0.40, p=0.69</td>
</tr>
<tr>
<td>PANSS positive</td>
<td>22.15 (4.10)</td>
<td>18.89 (5.13)</td>
<td>t=2.20, p=0.03</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>30.90 (4.68)</td>
<td>29.26 (5.06)</td>
<td>t=1.05, p=0.30</td>
</tr>
<tr>
<td>PANSS general</td>
<td>53.05 (6.20)</td>
<td>51.42 (8.65)</td>
<td>t=0.68, p=0.50</td>
</tr>
<tr>
<td>PANSS total</td>
<td>106.10 (10.20)</td>
<td>99.58 (16.06)</td>
<td>t=1.52, p=0.14</td>
</tr>
<tr>
<td>CGI</td>
<td>4.45 (0.61)</td>
<td>4.21 (0.42)</td>
<td>t=1.43, p=0.16</td>
</tr>
<tr>
<td>SAS</td>
<td>12.05 (5.18)</td>
<td>10.00 (4.70)</td>
<td>t=1.29, p=0.20</td>
</tr>
<tr>
<td>CDSS</td>
<td>5.00 (5.18)</td>
<td>4.5 (4.87)</td>
<td>t=0.31, p=0.75</td>
</tr>
</tbody>
</table>

5.1.2 THE OPEN-LABEL PHASE (STUDY II)

Of the completers from the double-blind phase, 39 patients consented to participate in the open-label extension phase. Of these, 20 patients were previously treated with mirtazapine (further referred as the continuation group) and 19 patients were previously treated with placebo (further referred as the switch group). Two patients (both from the switch group) discontinued mirtazapine treatment during the open-label phase due to adverse events; i.e., excessive sedation (which emerged at week 7, n=1) or agitation, anxiety and aggressive behavior (which emerged at week 10, n=1). Due to a protocol violation, this same patient was excluded from the analysis, as in the double-blind phase of the study. The remaining continuation group patients (n=20) and switch group patients (n=16) were eligible for the MITT analysis.
Figure 1. Patients' flow in the double-blind and open-label phases.

* same patient as in the double-blind phase, included at baseline of the open-label phase.
5.2 DOUBLE-BLIND PHASE (STUDIES I, III AND IV): THE MAIN FINDINGS IN WITHIN-GROUP AND BETWEEN-GROUP COMPARISONS.

5.2.1 THE EFFECT OF MIRTAZAPINE ON POSITIVE AND NEGATIVE SYMPTOMS.

The double-blind phase results for the mirtazapine and placebo groups are presented in Table 3.

In the mirtazapine group, a statistically significant improvement in all PANSS subscales was registered. Treatment with placebo led to a slight improvement (3%) only in the PANSS negative subscale.

The effect size of $d=1.00$ (CI95% 0.34-1.67) on the PANSS total scores for clinical significance during the double-blind phase was observed.

In the between-group comparison, mirtazapine clearly outperformed placebo on PANSS positive, negative and total subscales. On the PANSS general subscale, there was also a trend in favor of mirtazapine, which did not reach statistical significance. No comparisons in favor of placebo were revealed. In post hoc tests, the difference between treatments became evident at week 4.

There were four responders (20.0%) in the mirtazapine group and one responder (5.3%) in the placebo group ($p=0.342$).

5.2.2 THE EFFECT OF MIRTAZAPINE ON DEPRESSIVE SYMPTOMS.

The CDSS scores, the depression/anxiety factor of PANSS and the PANSS depression item score decreased significantly in the mirtazapine group (Table 3), while no significant changes were observed in the placebo group. The between-group comparison favored mirtazapine on the depression/anxiety factor of PANSS. On two other measures, a similar trend was noticed, but did not reach statistical significance. The same depression scores did not decrease in the placebo group. The changes in the CDSS scores, in the depression/anxiety factor of PANSS and in the PANSS depression item score were, correspondingly, 0.81 (SD=2.40, $t=1.35$, $p=0.196$), 0.75 (SD=2.02, $t=1.49$, $p=0.158$) and 0.06 (SD=0.93, $t=0.27$, $p=0.79$).
Table 3. Changes in clinical parameters during the double-blind add-on treatment with mirtazapine (n=20) vs. placebo (n=19).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change within the mirtazapine group, week 0 – week 6, mean (sd)</th>
<th>Change within the placebo group, week 0 – week 6, mean (sd)</th>
<th>Between-group comparison of changes: mirtazapine vs. placebo, week 0 – week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS positive</td>
<td>4.05 (3.59), t=5.04, p&lt;0.001</td>
<td>0.47 (2.25), t=0.92, p=0.370</td>
<td>3.58, t=3.71, p&lt;0.001</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>3.60 (2.58), t=6.23, p&lt;0.001</td>
<td>0.89 (1.73), t=2.26, p=0.037</td>
<td>2.71, t=3.82, p&lt;0.001</td>
</tr>
<tr>
<td>PANSS general</td>
<td>5.65 (7.03), t=3.60, p&lt;0.002</td>
<td>1.84 (5.24), t=1.53, p=0.143</td>
<td>3.81, t=1.91, p=0.064</td>
</tr>
<tr>
<td>PANSS total</td>
<td>13.30 (11.31), t=5.26, p&lt;0.001</td>
<td>3.21 (8.03), t=1.74, p=0.098</td>
<td>10.09, t=3.20, p=0.003</td>
</tr>
<tr>
<td>CDSS*</td>
<td>2.60 (3.41), t=3.41, p=0.003</td>
<td>0.84 (2.36), t=1.55, p=0.138</td>
<td>1.76, t=1.86, p=0.071</td>
</tr>
<tr>
<td>PANSS, depression/anxiety factor**</td>
<td>2.65 (2.41), t=4.91, p&lt;0.001</td>
<td>0.72 (2.01), t=1.54, p=0.164</td>
<td>1.93, t=2.52, p=0.017</td>
</tr>
<tr>
<td>PANSS, depression item***</td>
<td>0.60 (0.88), t=3.04, p=0.007</td>
<td>0.20 (1.08), t=0.85, p=0.41</td>
<td>0.40, t=1.57, p=0.092</td>
</tr>
</tbody>
</table>

* For CDSS range was 0 – 27.
** PANSS depression/anxiety factor = PANSS items 15 (somatic concern), 16 (anxiety), 17 (guilt feelings), and 20 (depression) (range 4 - 28).
*** For PANSS depression item range was 1-7.
5.2.3 THE EFFECT OF MIRTAZAPINE ON EPS

During the double-blind phase the severity of extrapyramidal symptoms (EPS), as measured by the SAS, decreased from 12.05 to 10.0 points (t=2.62, p=0.017) in the mirtazapine group, and from 10.0 to 9.58 points (t=0.69, p=0.501) in the placebo group. In the between-group comparison of changes, no statistically significant differences were noted between mirtazapine and placebo (t=1.64, p=0.112).

5.2.4 SAFETY AND TOLERABILITY OF MIRTAZAPINE ADD-ON TREATMENT IN THE STUDY POPULATION

5.2.4.1 Adverse effects during the double-blind phase

In the safety sample, 12 adverse events were registered with mirtazapine and 10 with placebo. In the mirtazapine group these were: hypersedation (n=3), weight gain (n=3), increased appetite (n=1), weakness (n=1), hypersedimentation (n=1), arrhythmia (n=1), uterine myoma (n=1), dizziness (n=1). In the placebo group these were headache (n=2), hypersalivation (n=1), weight gain (n=1), collapse (n=1), acute respiratory disease (n=1), nausea (n=1), agitation (n=1), conjunctivitis (n=1), sleep disturbance (n=1). None of these adverse events led to a withdrawal from the study.

5.2.4.2 Changes in metabolic parameters (Study IV)

During the double-blind phase, there was a statistically significant increase in body weight and total cholesterol in the mirtazapine group (Table 4). A growth trend in both systolic and diastolic blood pressure was observed in the mirtazapine group, but this did not reach statistical significance. None of these parameters changed in the placebo group.

In the between-group comparison of longitudinal changes, a statistically significant difference in weight, systolic blood pressure and total cholesterol was revealed (Table 4).
Table 4. Changes in weight, blood pressure and metabolic parameters in FGA-treated patients with schizophrenia during the 6 week double-blind treatment with add-on mirtazapine (n=20) or placebo (n=19).

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Baseline</th>
<th>Change, week 6 – week 0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mirtazapine group</td>
<td>Placebo group</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.13 (5.97)</td>
<td>71.05 (12.18)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm.hg.</td>
<td>119.21 (10.17)</td>
<td>122.75 (11.29)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm.hg.</td>
<td>76.32 (5.97)</td>
<td>77.00 (4.97)</td>
</tr>
<tr>
<td>Glucose, mmol/l.</td>
<td>4.96 (0.69)</td>
<td>4.98 (0.73)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l.</td>
<td>4.68 (0.99)</td>
<td>5.22 (0.83)</td>
</tr>
</tbody>
</table>

*Data given as mean (sd).

5.3 DOUBLE-BLIND PHASE: THE RELATIONSHIPS BETWEEN CLINICAL, DEMOGRAPHIC AND LABORATORY PARAMETERS (STUDIES III AND IV).

5.3.1 RELATIONSHIPS BETWEEN IMPROVEMENT IN DEPRESSIVE SYMPTOMS AND OTHER CLINICAL DOMAINS OF SCHIZOPHRENIA.

In the mirtazapine group, the changes in the CDSS scores correlated positively with those in the PANSS positive, negative and total (sub)scales (Table 5). In the same group the changes in the PANSS depression/anxiety factor correlated positively with those in the PANSS positive, general and total (sub)scales. Changes in the PANSS depression item correlated positively with those in the PANSS general and total (sub)scales.

In the placebo group, changes in the CDSS and PANSS depression item correlated positively with those in the PANSS negative subscale.
Table 5. Correlations between changes in depressive symptoms and PANSS-measured clinical symptoms in FGAs-treated patients with schizophrenia during the 6-week double-blind treatment with add-on mirtazapine (n=20) vs. placebo (n=19).

<table>
<thead>
<tr>
<th>Change in:</th>
<th>Mirtazapine group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDSS</td>
<td>(\Delta)CDSS</td>
<td>(\Delta)CDSS</td>
</tr>
<tr>
<td>PANSS depression/anxiety factor</td>
<td>(\Delta)PANSS depression/anxiety factor</td>
<td>(\Delta)PANSS depression/anxiety factor</td>
</tr>
<tr>
<td>Positive</td>
<td>0.52**</td>
<td>0.51*</td>
</tr>
<tr>
<td>Negative</td>
<td>0.49*</td>
<td>0.24</td>
</tr>
<tr>
<td>General</td>
<td>0.36</td>
<td>0.83**</td>
</tr>
<tr>
<td>Total</td>
<td>0.55**</td>
<td>0.77**</td>
</tr>
</tbody>
</table>

\(\Delta\) = change.

*correlation is significant at the 0.05 level (Spearman’s rho).

**correlation is significant at the 0.01 level

5.3.2 RELATIONSHIPS BETWEEN MIRTAZAPINE-INDUCED METABOLIC CHANGES AND IMPROVEMENT IN CLINICAL PARAMETERS: RESULTS OF CORRELATION AND REGRESSION ANALYSES.

In the mirtazapine group, a change in total cholesterol level correlated negatively with changes in all (sub) scales of PANSS (Table 6). In the same group, the change in body weight correlated in the same manner with changes in the PANSS general scores and PANSS total scores, i.e. weight and total cholesterol increased with decreases in the PANSS scores.

In the placebo group, a change in total cholesterol correlated negatively with changes in the PANSS positive subscale, and a change in glucose level correlated negatively with changes in the negative and general PANSS subscale scores.
Table 6. Correlations between changes in metabolic parameters and changes in PANSS scores in FGA-treated patients with schizophrenia during the double-blind phase of an add-on treatment with mirtazapine vs. placebo.

<table>
<thead>
<tr>
<th></th>
<th>Mirtazapine group (n=20)</th>
<th>Placebo group (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∆Weight</td>
<td>∆Systolic blood pressure</td>
</tr>
<tr>
<td>∆PANSS positive</td>
<td>-0.39</td>
<td>-0.19</td>
</tr>
<tr>
<td>p=0.11</td>
<td>p=0.94</td>
<td>p=0.56</td>
</tr>
<tr>
<td>∆PANSS negative</td>
<td>-0.19</td>
<td>-0.31</td>
</tr>
<tr>
<td>p=0.44</td>
<td>p=0.19</td>
<td>p=0.50</td>
</tr>
<tr>
<td>∆PANSS general</td>
<td>-0.50</td>
<td>0.03</td>
</tr>
<tr>
<td>p=0.03</td>
<td>p=0.89</td>
<td>p=0.7</td>
</tr>
<tr>
<td>∆PANSS total</td>
<td>-0.48</td>
<td>-0.14</td>
</tr>
<tr>
<td>p=0.04</td>
<td>p=0.57</td>
<td>p=0.975</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>∆PANSS positive</td>
<td>0.02</td>
</tr>
<tr>
<td>p=0.51</td>
<td>p=0.92</td>
<td>p=0.81</td>
</tr>
<tr>
<td>∆PANSS negative</td>
<td>-0.26</td>
<td>-0.27</td>
</tr>
<tr>
<td>p=0.39</td>
<td>p=0.25</td>
<td>p=0.56</td>
</tr>
<tr>
<td>∆PANSS general</td>
<td>-0.42</td>
<td>-0.05</td>
</tr>
<tr>
<td>p=0.08</td>
<td>p=0.85</td>
<td>p=0.76</td>
</tr>
<tr>
<td>∆PANSS total</td>
<td>-0.41</td>
<td>-0.19</td>
</tr>
<tr>
<td>p=0.1</td>
<td>p=0.43</td>
<td>p=0.84</td>
</tr>
</tbody>
</table>

∆ = change.
*Spearman rho is significant at the 0.05 level.

Linear regression analysis revealed that in the mirtazapine group changes in total cholesterol were associated with changes in all PANSS (sub)scales scores (Figure 2). Namely, an increase of total cholesterol by 1 mmol/L predicted a reduction of 1.7 points (r=0.72, p=0.03) in the PANSS positive, 1.8 points (r=0.73, p=0.004) in the PANSS negative, 3.5 points (r=0.83, p=0.005) in the PANSS general and 7 points (r=0.85, p=0.001) in the PANSS total scores. No other significant associations were found between the measured physical and metabolic variables and PANSS (sub)scale scores. In the placebo group, linear regression analysis did not reveal any statistically significant relationships between metabolic parameters and symptoms of psychosis.
Figure 2. Regression scatter plots of total cholesterol changes vs. changes in the PANSS scores in FGA-treated schizophrenia patients during double-blind treatment with add-on mirtazapine (n=20) or placebo (n=19).
5.4 THE OPEN-LABEL PHASE: THE MAIN FINDINGS (STUDY II, III AND IV)

5.4.1 THE EFFECT OF MIRTAZAPINE ON POSITIVE, NEGATIVE AND DEPRESSIVE SYMPTOMS

In the continuation group, prolongation of mirtazapine treatment led to additional improvement in all PANSS (sub) scales (Table 7). The additional improvement was 10.8%, 13.8%, 8.1% and 11.2% for PANSS total, positive, negative and general scores, respectively.

In the switch group, a statistically significant improvement was registered in all PANSS (sub) scales. PANSS total scores decreased by 16.6%, and PANSS positive, negative and general scores dropped respectively by 20.3%, 17.0% and 15.0%.

For the total population of the study (i.e., pooled continuation and switch groups), the effect size during the open-label phase was 0.94 (CI 95%=0.45–1.43) as assessed by the PANSS total score.

Table 7. Changes in PANSS-measured clinical parameters during the open-label add-on treatment with mirtazapine (n=20) vs. placebo (n=19).

<table>
<thead>
<tr>
<th></th>
<th>Within-group change, week 6-12, mean (SD)</th>
<th>Between-group change, week 6-12, continuation vs. switch group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuation group</td>
<td>Switch group</td>
</tr>
<tr>
<td>PANSS total</td>
<td>10.00 (7.32)</td>
<td>15.63 (8.17)</td>
</tr>
<tr>
<td></td>
<td>t=6.11</td>
<td>t=7.65</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PANSS positive</td>
<td>2.50 (2.37)</td>
<td>3.68 (2.06)</td>
</tr>
<tr>
<td></td>
<td>t=4.71</td>
<td>t=7.17</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>2.20 (2.50)</td>
<td>4.68 (3.11)</td>
</tr>
<tr>
<td></td>
<td>t=3.93</td>
<td>t=6.02</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PANSS general</td>
<td>5.30 (3.87)</td>
<td>7.25 (4.01)</td>
</tr>
<tr>
<td></td>
<td>t=6.13</td>
<td>t=7.24</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

During the open-label phase, depressive symptoms measured with CDSS and the PANSS depression item decreased with statistical significance in both treatment groups. In the continuation group, the mean CDSS score decreased by 1.45 points (SD=1.67, t=3.88, p=0.001), the depression/anxiety factor of PANSS decreased by 1.20 (SD=1.51, t=3.56, p=0.002) and the
PANSS depression item decreased by 0.45 points (SD=0.60, t=3.3, p=0.004). In the switch group, depression measures also began to improve. By the endpoint, the mean CDSS score decreased by 2.75 (SD=3.99, t=2.76, p=0.02), PANSS depression/anxiety factor by 3.13 (SD=1.78, t=7.0, p=0.001) and the PANSS depression item by 0.88 (SD=1.02, t=3.4, p=0.004).

In the between-group comparison of changes, only the depression/anxiety factor improved significantly more in the switch group (t=3.50, p=0.002), while no significant differences were found in the two other parameters.

Changes in the CDSS scores were approximately of the same magnitude for the switch group in the open-label phase, and for the continuation group in the double-blind phase (2.75 and 2.6 points, respectively).

Correlation analysis did not reveal any significant relationships between changes in the depression scores and those from the PANSS (sub)scales’ scores for either group.

5.4.2 THE EFFECT OF MIRTAZAPINE ON FGA-INDUCED EPS DURING THE OPEN-LABEL PHASE

During the open-label phase, SAS scores decreased by 2.60 points (SD=1.98, t=5.86, p<0.001) in the continuation group, and decreased by 3.69 points (SD=2.87, t=5.14, p<0.001) in the switch group.

5.4.3 SAFETY AND TOLERABILITY OF MIRTAZAPINE DURING THE OPEN-LABEL PHASE: THE INFLUENCE OF MIRTAZAPINE TREATMENT ON WEIGHT AND METABOLIC PARAMETERS

The total number of adverse events (AE) during the open-label phase was 11. Three of these events (i.e., acute respiratory disease, weight gain and headache, n=1 for each AE) were registered in the continuation group and eight were registered in the switch group (i.e., headache (n=2), weight gain (n=2), excessive sedation (n=2), increased appetite (n=1) and marked agitation (n=1)). Agitation, which developed in one patient in the continuation group, led to withdrawal from the study in week 10. No serious AEs were registered during the open-label phase.

In the continuation group, there were no significant changes in weight, blood pressure or metabolic parameters.

In the switch group, weight increased by 2.72 kg (SD=3.47, t=-3.04, p=0.009) and cholesterol increased by 0.49 mmol/l (SD=0.97, t=-2.09, p=0.05). No changes in other measured parameters were registered. In the between-group comparison, no statistically significantly differences were found between the treatment groups. Weight gain in the switch group was approximately the same during the open-label phase as in the continuation group during the double-blind phase.
5.5 BOTH PHASES: CHANGES IN CLINICAL PARAMETERS DURING MIDDLE-TERM (12 WEEKS) VERSUS SHORT-TERM (6 WEEKS) OF ADD-ON TREATMENT WITH MIRTAZAPINE (STUDY II)

Middle-term treatment (the continuation group) led to an improvement of 27.7%, 18.7%, 20.0% and 21.6% in the PANSS positive, negative, general and total scale scores, respectively. The between-group comparison of a longitudinal change revealed a significant difference in favor of the middle-term mirtazapine treatment, but only for the PANSS positive scores (t=2.31, p=0.027). No differences in other clinical parameters were found.

The number of responders for both phases was twelve in the continuation group and seven in the switch group. No statistical differences were found in the number of responders between groups (χ²=0.942, p=0.332).
6 DISCUSSION

6.1 THE MAIN FINDINGS

This study was designed to explore the possible influence of mirtazapine added to ongoing treatment with different FGAs on the main clinical domains of schizophrenia. The influence of mirtazapine on FGA-related EPS was also studied. In addition, this study focused on safety and tolerability aspects of mirtazapine treatment in schizophrenia. As compared to the previous studies of mirtazapine add-on treatment in schizophrenia, the present study used a wider range of assessments, especially in regard of depressive symptoms. This study was the first to analyse the correlations between the effects of mirtazapine on positive and negative symptoms and its antidepressive effect. This study was also the first to report the relationships between clinical effects of mirtazapine and its metabolic influences.

The study population consisted of patients who suffered from a prolonged disease and had a previous history of insufficient response to a number of antipsychotic trials. At the stage of enrollment, study patients were at a relatively stable stage of their disease, and their FGA treatment had remained unchanged during a period of six previous weeks. Patients were highly symptomatic in both mirtazapine and placebo groups.

This study was the first to report a statistically significant favorable effect of mirtazapine-FGA combination on a wide range of clinical parameters. During the double-blind phase, clear-cut differences in all PANSS (sub)scales favored mirtazapine treatment in comparison with placebo in both the within group and between group analyses. A large effect size of $d=1.00$ (CI95% 0.34-1.67) on the PANSS total scores for clinical significance was observed. In an previous RCT by Berk et al. (2001) the effect-size on PANSS negative scores was 0.28 (-0.36 – 0.92).

Augmentation with mirtazapine also alleviated FGA-induced EPS, and led to decreases in depression scores. Treatment with mirtazapine raised weight and cholesterol levels, which being a negative change from the viewpoint of general health, was though directly correlated with the degree of clinical improvement.

In the open-label phase, patients who switched to mirtazapine treatment demonstrated clinical improvement in the same manner as their mirtazapine-treated counterparts in the double-blind phase. Prolonged (12 weeks) treatment with mirtazapine led to more prominent improvements in clinical parameters than short-term (6 weeks) treatment.

Mirtazapine was in general well-tolerated, with no serious adverse events during the study, and only one dropout due to a worsening of the patient’s mental condition.
6.2 EFFICACY OF ADD-ON MIRTAZAPINE IN SCHIZOPHRENIA: PANSS-MEASURED CLINICAL PARAMETERS

In the double-blind phase of the study, a statistically significant improvement was registered in regard to both negative and positive symptom domains. The difference in favor of mirtazapine was found both in within-group and between-group analyses. Improvement in negative symptoms due to mirtazapine add-on treatment have been reported in several RCTs. Three of the four RCTs conducted so far have demonstrated the superiority of mirtazapine over placebo on PANSS negative subscale scores when added to haloperidol (Berk et al., 2001), clozapine (Zoccali et al., 2004) and risperidone (Abbasi et al., 2010). The magnitude of the negative symptoms reduction in the RCT of Berk and co-authors was more significant, with a 42% drop in PANSS negative subscale scores. This difference could be explained by a less chronic patient population (mean age 29.5 years vs. 43.8 years in our study), not selected for signs of treatment resistance, which included patients with both first episode and recurrent illness. The studies by Zoccali and co-authors, and by Abbasi and co-authors, also reported results that favored mirtazapine add-on treatment. The results from the present study support these earlier findings, as we also found a substantial reduction in negative symptoms. However, our data differ from these earlier reports in terms of the newly found effect on positive psychotic symptoms. This new phenomenon could be explained by several factors; e.g., differences in antipsychotic medication in terms of both drugs and their dosages (in our study, a number of different FGAs were used in moderate dosages), study population (patients with a predominantly chronic course of the disease and signs of treatment resistance, not especially selected for negative symptoms) and relatively high retention rates. Indeed, according to a meta-analysis of Rabinowitz et al. (2009), drop-out rates in RCTs with antipsychotics vary from 19.3 to 75.5%, while in the present study the drop-out rate was only 7.5%.

In a RCT by Berk and co-authors (2009), no favorable effects of add-on mirtazapine in schizophrenia were found. However, in that study mirtazapine was added to treatment with SGAs, mostly clozapine, which definitely makes a direct comparison of these studies impossible.

Patients in the switch group, demonstrated a marked degree of improvement that was comparable the improvement seen in their counterparts from the continuation group during the double-blind phase. This tendency was seen in all the measured parameters, thus providing more evidence of mirtazapine’s favorable effect on schizophrenia symptoms.

In the continuation group, treatment with add-on mirtazapine for six additional weeks resulted in a further reduction of all PANSS (sub)scales scores. In between-group comparison the difference was statistically significant only in the PANSS positive subscale. During the 12-week
treatment, there were more responders in the continuation group than in the switch group. Thus, prolonged add-on treatment with mirtazapine can be beneficial, at least in regard to positive symptoms. This finding is also novel, as in earlier studies (all of which were of a shorter duration – from six to eight weeks) no similar relationships between the efficacy and duration of treatment were reported.

The effect of mirtazapine on schizophrenia symptoms, as elucidated in the present study, may be explained by its receptor profile. Regarding the influence on negative symptoms, there are several possible mechanisms that may contribute to mirtazapine’s beneficial effect. The first is the blockade of 5-HT₂₅ receptors – a common characteristic of both mirtazapine and SGAs, which is also evidently responsible for the better efficacy of the SGAs on the negative symptomatology of schizophrenia (Meltzer, 2012). In this sense, the addition of mirtazapine to FGAs imitates the SGAs’ receptor profile, which was a main hypothesis in this study. Blockade of central 5-HT₂₅ receptor results in a number of effects on dopaminergic activity in the mesocortical, mesolimbic, and nigrostriatal areas of the brain. It has been demonstrated in several preclinical studies that a combined 5-HT₂₅ and D₂ receptor inhibition may have a stimulating effect on the mesocortical pathway of the frontal cortex, thus increasing dopamine in this area (Volonte et al., 1997, Kuroki et al., 1999, Rollema et al., 2000). This effect is known to be selective, i.e. no concurrent stimulation of dopaminergic neurotransmission in the striatum occurs (Bonaccorso et al., 2002). Furthermore, Liegeois and co-authors (2002) based their dose–response relationship study of haloperidol combined with the highly selective 5-HT₂₅ antagonist M100907. The idea being that FGAs coupled with 5-HT₂₅ antagonists may promote dopamine release in mPFC, with only a slight impact on nigrostriatal function. The result was that M100907 did potentiate the ability of low dose (0.01–0.1 mg/kg) haloperidol to increase dopamine release in mPFC, whereas no such effect were observed with higher (0.3–1.0 mg/kg) dose of haloperidol (Liegeois et al., 2002). Dopamine deficiency in the mPFC 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 having a diminished risk for EPS (Meltzer et al., 2003).

This hypothesis was encouraged from an earlier study by Duinkerke and co-authors (1993), where adjuvant treatment with ritanserin, a pure 5HT₂ antagonist lacking antidepressive effects, led to an alleviation of negative symptoms in haloperidol-treated schizophrenia patients. Some additional evidence supporting this theory came also from a study with mianserin – another antidepressant with a similar receptor profile, blocking of 5-HT₂, 5-HT₃ and alpha-2 adrenoreceptors (Hayashi et al., 1997). In that study, adjuvant therapy with mianserin led to an improvement of negative symptoms in FGA-treated schizophrenia patients. This evidence, however, remains controversial, as two other studies failed to replicate this result (Shiloh et al., 2002, Poyurovski et al., 2003).
Mirtazapine’s indirect agonist effects on 5-HT$_{1a}$ receptors may also underlie its efficacy on negative symptoms. The 5-HT$_{1a}$ receptor may be involved in the mechanisms of negative and cognitive symptoms of schizophrenia (Kishi et al., 2011). In a preclinical study by Ichikawa and Meltzer (2000), a 5-HT$_{1a}$ agonist was shown to stimulate dopamine release in the prefrontal cortex and to enhance the effects of D$_2$ antagonists. In clinical studies, pure 5-HT$_{1a}$ agonists improved schizophrenia-related cognitive deficits (Sumiyoshi et al., 2001, Sumiyoshi et al., 2007). Direct or indirect agonism of 5-HT$_{1a}$ receptors is a common characteristic for the majority of SGAs (Meltzer, 2012) and is, along with 5-HT$_2$ blockade, responsible for their better efficacy on negative symptoms, compared to FGAs.

Another possible explanation for add-on mirtazapine’s efficacy on negative symptoms is its 5-HT$_3$ blocking properties. The role of 5-HT$_3$ receptors in the pathophysiology of negative symptoms was already proposed in early 1990s (Costall and Naylor, 1992). Research evidence supporting this theory first came from a clinical study by Zhang and co-authors (2006), in which the 5-HT$_3$ blocking agent ondansetron added to haloperidol improved negative symptoms, general psychopathology and cognitive functions in patients with chronic schizophrenia. No further research on this topic was reported after that, so this finding can be only considered as preliminary.

Interestingly, in a recent preclinical study by Masana and co-authors (2012), mirtazapine selectively increased dopamine function in the prefrontal cortex of rodents. Decreased dopamine activity in that area seems to be one of the key neurotransmitter abnormalities that underlies the negative symptoms in schizophrenia. This suggests another possible mechanism of mirtazapine effect on negative symptoms, which was elucidated in the present study.

It is challenging to outline possible explanations for the favorable effect of mirtazapine add-on treatment on positive symptoms in schizophrenia. Indeed, the antipsychotic effect of current medications has been mainly attributed to D$_2$ receptor antagonism (Yilmaz et al., 2012). There is, however, intriguing data from both preclinical and clinical studies that indicate a possible useful role for alpha-2-adrenoceptor inhibition in antipsychotic efficacy. In a preclinical study (Wadenberg et al., 2007), the alpha-2 antagonist idazoxan enhanced the therapeutic effect of haloperidol and olanzapine, and also reversed haloperidol-induced catalepsy. This result was supported by another preclinical study (Marcus et al., 2010), where idazoxan enhanced the efficacy of risperidone and facilitated both dopaminergic and glutamatergic neurotransmission in the prefrontal cortex. Earlier, in a clinical trial by Litman and co-authors (1996), idazoxan added to ongoing fluphenazine therapy produced clinical improvement comparable to that of clozapine in patients with schizophrenia. It has thus been proposed that alpha-2 inhibition enhances the antipsychotic effects of D$_2$ blockade (Choi et al., 2009).
According to a report of preclinical data (Berendsen et al., 1998), 5HT\textsubscript{1A} receptor agonism may also contribute to enhancing the effect of antipsychotics, although clinical support for this assumption is still lacking. An inhibition of histamine H\textsubscript{1} receptor, a common mechanism of action for mirtazapine and clozapine, may also contribute to the antipsychotic effect of mirtazapine (Mancama et al., 2002).

The pathophysiology of schizophrenia includes, among numerous other mechanisms, neurodegeneration and impaired neurogenesis (Inta et al., 2011). A growing body of evidence suggests that antidepressants may reactivate neuroplasticity (Castren and Rantamäki, 2010), which mechanism may provide a number of potential pharmacological contributors to the improved efficacy and better treatment outcomes in schizophrenia. According to both preclinical (Rogoz et al., 2005) and clinical data (Katsuki et al., 2012), mirtazapine appears to induce brain-derived neurotrophic factor (BDNF) gene expression and subsequently to raise BDNF serum levels, which points to its putative neuroprotective properties.

Interestingly, in a study by Katsuki and co-authors (2012) the raise in BDNF levels in responders to mirtazapine was observed during the first four weeks of treatment. This corresponds to the results of the present study, where statistically significant difference between mirtazapine and placebo started to be evident after four weeks of treatment. This suggests a possible role of enhanced neurogenesis in the clinical effects of mirtazapine. This, in turn, may eventually be of substantial benefit in the treatment of schizophrenia.

Mirtazapine is metabolized in part by the cytochrome P-450 (CYP) 2D6 liver enzyme (Dodd et al., 2001). Being a very weak inhibitor of the CYP-isoenzymes, mirtazapine is apparently not involved in the pharmacokinetic interactions of antipsychotics (Spina et al., 2008). Thus, its additional antipsychotic effect cannot be explained by an increase in the serum levels of the concomitantly used FGA.

### 6.3 EFFICACY OF ADD-ON MIRTAZAPINE IN THE TREATMENT OF DEPRESSION IN SCHIZOPHRENIA

In the double-blind phase of the present study depression scores measured by CDSS, depression/anxiety factor of PANSS and PANSS depression item decreased with statistical significance in the mirtazapine group, but not in the placebo-group.

The lack of a statistically significant difference favoring mirtazapine over placebo could have resulted the initial depression scores being relatively low in both groups, which has been found in earlier studies with chronic schizophrenia (Lancon et al., 2001, ). It is apparent that showing the antidepressive effect of mirtazapine in this particular population would require a separate study with more severe criteria for depressive symptoms.
DISCUSSION

The present study considerably deviates from previous RCTs that investigated the putative efficacy of mirtazapine on depression in schizophrenia. In the study by Berk and co-authors (2001), haloperidol-treated patients with schizophrenia also showed a noticeable improvement in depression scores, due to mirtazapine treatment, but these changes did not differ from the placebo group. A possible explanation for this difference in antidepressive effect is a less stable patient sample in the present study and, secondary to this, a phenomenon known as “regression to the mean”. The limited sample size in the study of Berk et al (2001) may also include a risk for type II error. In a more recent study by Berk and co-authors (2009), add-on mirtazapine did not improve symptoms of depression in SGA-treated schizophrenia. Actually, it has been proposed earlier that SGAs may improve depressive symptoms on their own in schizophrenia, even when used as monotherapy, thus making the potential effect of add-on treatment with antidepressants negligible or even unnecessary (Tollefson et al., 1999, Leucht, 2012). This might also be true for clozapine, as reported in a RCT by Zoccali and co-authors (2004) of add-on treatment with mirtazapine, which did not lead to an improvement in the depressive symptoms of clozapine-treated schizophrenia. In addition, it should be noted that none of the above listed RCTs was specifically designed as a depression study, which can be seen, for instance, in the scarce set of depression measuring instruments (e.g., only the depression factor extracted from the BPRS was included in a study of Zoccali and co-authors).

In the open-label phase of the present study, depressive symptoms continued to improve in the continuation group, with comparable changes in the switch group de novo. By the end-point, the CDSS scores decreased to a level lower than the threshold of three points for depression diagnosis (Addington et al., 1996) in both groups. Thus, it can be assumed that a period of six weeks may be enough to obtain the desirable antidepressive effect of mirtazapine in schizophrenia.

In the present study, the changes in CDSS, depression/anxiety factor of PANSS and the PANSS depression item for the mirtazapine group demonstrated several inconsistent direct correlations with desirable changes in PANSS scores during the double-blind phase. This finding makes it partially unclear whether or not the observed improvement in depressive scores registered in the present study was in fact due to a specific antidepressive effect of mirtazapine, or some non-specific halo effect of the global improvement. However, no reverse correlations were found; i.e., improvement in depressive scores was not accompanied by a decline in other symptom clusters. A worsening of psychosis due mirtazapine treatment was seen in one case in the present study, while in the majority of patients mirtazapine improved positive symptoms.
6.4 EFFICACY OF ADD-ON MIRTAZAPINE IN ALLEVIATING FGA-INDUCED EPS

In this study, improvement on SAS-measured EPS was registered in the mirtazapine group, but not in the placebo group. A between-group comparison did not, however, yield any statistically significant differences. This finding might be due to the FGA dosages that varied from low to moderate in the present study. This could have resulted in initially low SAS scores, which might have reduced the possibility for a noticeable change. One contributing factor to this could be the current trend to use lower doses of FGAs to prevent the EPS, which is important when considering the treatment safety.

Evidence from earlier studies that evaluated the efficacy of mirtazapine on antipsychotic-induced EPS remains controversial. In the study by Berk and co-authors (2001), mirtazapine was unable to outperform placebo in terms of its efficacy on haloperidol-related EPS. In that study, however, patients treated with add-on placebo also suffered from EPS and received anticholinergic medicines more frequently than patients receiving add-on mirtazapine. Similarly, in a study of Abbasi and co-authors (2010), adjunctive mirtazapine did not improve risperidone-induced EPS. There exist, however, two positive studies (Poyurovski et al., 2003, Poyurovski et al., 2008) in which add-on mirtazapine improved both SAS and BAS scores in patients treated with different FGAs and SGAs. Additional support comes from a recent preclinical study by Tatara et al. (2012), where mirtazapine attenuated haloperidol-induced EPS, while TCAs and SSRIs demonstrated opposite effect.

The influence of mirtazapine on EPS-symptoms is presumably associated with its 5-HT2 blocking properties. In earlier preclinical studies, the blockade of 5-HT2A/2C receptors has been shown to attenuate EPS, which is further related to the blockade of striatal D2 receptors (Meltzer and Massey, 2011, Ohno, 2011). This theory is also supported by studies with ritanserin, a potent 5-HT2A/2C blocker, which improved antipsychotic-induced EPS, both under preclinical (Tatara et al., 2012) and clinical conditions (Akhonzadeh et al., 2008). The same mechanism is plausibly associated with the lesser risk of EPS in SGAs, which are less potent D2 blockers than FGAs and also 5-HT2 blockers (Meltzer, 2012).

6.5 SAFETY AND TOLERABILITY OF MIRTAZAPINE ADD-ON TREATMENT IN SCHIZOPHRENIA

Mirtazapine was well tolerated during both study phases. The most frequent adverse effects were weight gain, increased appetite, and excessive sedation. A mirtazapine-provoked adverse effect led to discontinuation from the study in only one case. The other adverse effects were infrequent, mild and
transient. In general, the frequency and nature of mirtazapine adverse effects corresponded with the those described in major depression studies (Anttila and Leinonen, 2001).

Besides the general tolerability issues of mirtazapine treatment, the present study also explored the relationships between metabolic effects and clinical efficacy of mirtazapine. As expected, mirtazapine caused weight gain and an increase in total cholesterol during the double-blind phase. These results are in concordance with earlier findings from studies on major depression (Thase et al., 2001), in which mirtazapine also increased both body weight and total cholesterol. Similar to prior reports (Montgomery, 1995), mirtazapine did not cause any significant changes in fasting glucose levels.

Furthermore, one of the main findings of this study was that the increase in total cholesterol level in mirtazapine-treated patients was directly associated with the clinical improvement. In an RCT by Procyshyn and co-authors (2007), the clozapine-related increase in serum lipids was also linked with the improvement in psychopathology. The difference between these findings is, that in their study the increased cholesterol level was associated only with an improvement in PANSS negative subscale scores. At the same time, the decrease in PANSS total scores correlated with an increase in serum triglycerides, while no associations were found between the increase in serum lipids and improvement on either PANSS positive or PANSS general scores. In a secondary analysis of the CATIE patient sample, Hermes et al. (2011) did not reveal significant associations between lipid parameters (i.e., cholesterol and triglyceride) and change in PANSS scores. However, the range of antipsychotics used in CATIE did not include clozapine, medication with perhaps the most evident relationship between its clinical efficacy and the metabolic effects (Procyshyn et al., 2007). The present study did not reveal any relationships between body weight gain and favorable changes in psychopathology, which has previously been reported with antipsychotics (Meltzer et al., 2003, Ascher-Svanum et al., 2005, Hermes et al., 2011).

Clozapine (Lieberman et al., 2003) and olanzapine (Asenjo Lobos et al., 2010) have consistently demonstrated better efficacy than some other antipsychotics with less noticeable metabolic adverse effects. A mechanism for the assumed relationships between lipid metabolism, psychopathology of schizophrenia and mechanism of action for antipsychotic drugs remains obscure. There is some evidence that low cholesterol levels can be associated with maladaptive behaviors; i.e., aggression (Golomb, 1998), suicide and self-aggression (Muldoon et al., 1993). It has been proposed that a lowering of serum cholesterol levels may influence the composition of neuronal membranes with a consequent attrition of 5-HT receptors (Procyshyn, 2007). This may, in turn, contribute to an insufficient suppression of aggressive behavior and, according to some recent data, also contribute to the phenomenon of treatment-resistance in schizophrenia (Stone et al., 2010). Another mechanism that may possibly explain the relationship between
metabolic and psychotropic properties of mirtazapine, is an existing association between 5HT2-antagonism and insulin sensitivity. This phenomenon is thought to be associated with hypercholesterolemia and other forms of dyslipidemia (Bonora et al., 1998). In an RCT by Gilles and co-authors (2005), ketanserin, an agent with 5-HT2-antagonist properties, demonstrated ability to impaire insulin sensitivity. Therefore the clinical effects of mirtazapine can in part be explained by each of the aforementioned mechanisms, i.e. changes in lipid levels and blockade of serotonin receptors. Similarly to clozapine, mirtazapine also inhibits histamine-H1 receptors. This effect may not only contribute to the metabolic changes, but also be involved in the modulation of certain pathophysiological processes in schizophrenia (Mancama et al., 2002).

While probably lacking in antipsychotic efficacy itself, mirtazapine shares several metabolic side effects with the most effective antipsychotics, which may be at least some marker of its synergistic efficacy in improving positive psychotic symptoms.

As a candidate for effective adjunct treatment of schizophrenia (Phan et al., 2011), mirtazapine increases body weight and serum cholesterol level – both established to be serious risk factors for cardiovascular diseases. This observation dictates a need for a thorough evaluation of the pros and cons of this therapy in each individual case.

6.6 MAIN LIMITATIONS OF THE STUDY

The main limitation of the present trial was its small sample size, which may have adversely affected the statistical power of findings for secondary analyses. This weakness may, however, be compensated by the fact that the measured changes were large in magnitude and consistent with the wide range of different clinical parameters. Another limitation was the open-label design of the extension phase, which raises the question as to whether or not the observed favorable changes might be a result of a placebo effect or a spontaneous fluctuation of the disease (a so-called “regression to the means”). This does not appear very likely, because in the present study the changes in the measured parameters were essentially similar for the switch group in the extension phase as for the continuation group in the double-blind phase. This perspective might better reflect the specific clinical effect of the study drug, rather than the influence of non-pharmacological factors.

Several limitations of the present study were connected to the characteristics of the patients’ population. First, the criterion requiring the presence of a stable period before enrollment to the study, led to limiting the study population to predominantly chronically or subchronically ill patients. This limitation makes it difficult to extrapolate our results to patients in acute stage of schizophrenia. Second, the present study was initially planned to be possibly close to “real-life” conditions, which resulted in heterogeneity of
DISCUSSION

the study population, in terms of both anipsychotics used and of the duration of the disease. On the other hand, the above mentioned similarity of our patients’ population to the ones often met in real-life circumstances, can be considered as its strength.

For the depression branch of the study, the limitation was that the patients were not specifically selected for depression symptoms. This could be seen in the low depression scores at baseline, which initially means a limited potential for change. Due to this fact, the results gained in this study regarding the antidepressive effect of mirtazapine in schizophrenia should be interpreted with some caution.

The analysis of metabolic parameters was limited in the present study to fasting glucose and total cholesterol, while evaluations of other potentially important parameters (for instance, a broader panel of lipid parameters, e.g. LDL and HDL, body composition, leptin, insulin resistance index) were not conducted.

A strength of the present study is that the patients’ population was presented with initially high PANSS scores, which makes it possible to extrapolate its results to patients with difficult-to-treat schizophrenia. Another strength is that patients were investigated using a wide range of widely approved and validated clinical scales. The present study included an RCT phase, which makes its results reliable from the viewpoint of the evidence-based medicine. In the present study the drop-out rate was very low which also improves the reliability of the results.
In schizophrenia with suboptimal response to the FGAs, adjunctive mirtazapine appears to improve negative and depressive symptoms and to alleviate FGAs-induced extrapyramidal side effects. Moreover, add-on mirtazapine can also improve positive symptoms – to the best of the author’s knowledge, an effect never observed earlier for any antidepressant. The improvement in positive and negative symptoms may be independent on the antidepressive effect. The background of the additive efficacy is unknown but it may result from the atypical mechanism of action of mirtazapine – an inhibition of a certain combination of receptors (instead of inhibition of transporters as for the vast majority of other antidepressants).

As in unipolar depression, also in schizophrenia mirtazapine treatment causes body weight gain and an increase in the serum cholesterol levels. The metabolic changes, unwanted as such correlate, however, with improved psychopathology in a fashion, observed earlier for clozapine and some other SGAs.

These observations may have not only theoretical implications but, if confirmed in larger and longer studies affect current practices – an add-on mirtazapine trial may become a worthwhile option before switching to clozapine.

Further studies should focus on mirtazapine-SGA combinations, FGAs-mirtazapine-combinations vs. switch to SGAs, include schizophrenia patients with prominent depression, and comparison with clozapine.
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APPENDICES

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

Information for a patient.

Dear .......................................................................................... 

You are invited to participate in a 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”. This study is a collaborative scientific project of Russian and Finnish researchers. Please read this form and ask any questions 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 your current treatment. Mirtazapine is an antidepressant which has been extensively and for a long time used in clinical practice in the majority of the European countries, in the US and Canada, as well as in Russia. The main indication for the use of mirtazapine is depression (long-lasting and profound decrease of mood and interest to 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 the clinical practice. The mechanism of action of mirtazapine differs from that of the most part of other antidepressants. This difference supposes that this medicine is able to not only alleviate the depressed mood symptoms, but also make your current medication more effective. It 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 decrease of 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.
At 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 may be provided with this information as soon as the whole study is over, i.e., when all the patients have completed their participation in it, and the data received during the study have 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 at the night time. The capsules or tablets must be swallowed wholly, ungrinded and unchewed.

You physician will possibly decrease the dosage of your basic medication in the second 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 of 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 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, increase of 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 an ordinary visit to a physician. You will have to follow the dosing schedule very carefully and not to 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 improvement of memory, attention and information processing. In case you have had symptoms of depression or suffered from side-effects of your basic medicine, they 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 help a large number of other patients for whom, supposedly, a new 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, using the phone number that he or she will give you, or contact the physician on call 74-35-60.

**Additional information concerning the study.**

Your participation in this study is completely voluntary. You have right to refuse from 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, that as a greater number of patients as possible will have completed the full course of treatment. If you decide to withdraw from the study anyway, it is desirable that you meet your physician for the final assessment as soon as possible.

The participation in the study is based on the principle of mutual confidence and your physician will guarantee you anonymity being strictly kept. This means that your name will be seen only in your medical record, as at any usual treatment. No information able to disclose your identify will be recorded in the study materials. In some special circumstances however, this information may be required by local, federal or international authorities monitoring 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 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, ________________________________________________________________.
(surname, name, second name)

born 19 ______

have had enough time to learn the information concerning the study and
the investigational medicine. I have 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 of its possible side-effects and potential risk for 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 a 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 ________________________________
Информация для пациента.

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 применяющий 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 безразличича, 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.
APPENDICES

В первые 6 недель исследования, после того, как проведено соответствующее полное клиническое и лабораторное обследование Вашего состояния, Вы будете получать дополнительное лекарство – либо миRTазапин, либо так называемое плацебо – лекарство, которое выглядит точно так же как миRTазапин, 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 миRTазапин. МиRTазапин 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, миRTазапин 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 миRTазапином. 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, большие 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 скорее с Ващим 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, требовать представители соответствующих местных, федеральных или международных инстанций, наблюдающих за научным качеством и этническими 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, ____________________________________________________________
(фамилия, имя, отчество)

19____ г. р.

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 ____________________________________________