The development of therapeutic strategies to effectively treat negative symptoms remains one of the primary goals in the treatment of schizophrenia. Mirtazapine is the first of a new class of dual action compounds, the noradrenergic and specific serotonergic antidepressants (NaSSa), whose activity is related to the enhancement of noradrenergic and serotonergic transmission by a presynaptic α2 antagonism and postsynaptic 5-HT2 and 5-HT3 antagonism, respectively. This study was a 8-week double-blind, randomized, placebo-controlled trial of 30 mg adjunctive mirtazapine to clozapine therapy in 24 patients with DSM-IV schizophrenia. The main finding at the end of the trial was a significant reduction on the Scale for the Assessment of Negative Symptoms (SANS) total scores in the mirtazapine group compared to placebo ($P < 0.01$) with a significant improvement on the SANS subscales avolition/apathy and anhedonia/asociality. The Brief Psychiatric Rating Scale total score at week 8 showed superiority of mirtazapine over placebo. These findings suggest a potential role for mirtazapine as an augmentation strategy in the treatment of negative symptoms of schizophrenia. Int Clin Psychopharmacol 19:71–76 © 2004 Lippincott Williams & Wilkins.

Keywords: clozapine, mirtazapine, negative symptoms, schizophrenia

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Introduction

Negative symptoms have long been recognized as a central schizophrenic feature. From the earliest descriptions of dementia praecox, it has been clear that a population of schizophrenic patients suffered from ‘a weakening of those emotional activities which permanently form the mainsprings of volition…’ (Kraepelin, 1919). Operational criteria for negative symptoms have been established (Andreasen, 1982); blunted affect, poverty of thought content and speech, avolition or apathy and social withdrawal are the core symptoms, shared by almost all the rating scales used to assess the negative syndrome of schizophrenia (Buchanan and Carpenter, 1994).

Systematic studies have demonstrated that negative symptoms respond poorly to antipsychotic therapies; there is some evidence that conventional neuroleptics can improve negative symptoms secondary to psychotic symptoms, while they show no efficacy on primary negative symptoms (Möller, 1993). Moreover, it has been observed that conventional neuroleptics may even exacerbate negative symptomatology (Carpenter, 1996; Evins and Goff, 1996). Atypical antipsychotics show a better efficacy on negative symptoms when compared to conventional neuroleptics, although the evidence for an improvement in primary negative symptoms is controversial (King, 1998). The proposed mechanisms underlying this improved profile of activity involve a low affinity for D2 receptors, a selective antagonism on serotonin 5-HT2 and/or α1 adrenoreceptors and, moreover, a differential effect on regional dopamine transmission (Linnér et al., 2002). It is assumed that atypical antipsychotics preferentially enhance the release of dopamine more potently in mesolimbic and mesocortical brain regions and particularly in the medial prefrontal cortex (Nomikos et al., 1994; Westerink et al., 2001); moreover, this effect appears to be partially dependent on serotonergic properties, since 5-HT2 blockade increases available dopamine (Meltzer, 1999). The enhancement of cortical dopamine may underlie the efficacy of these drugs to treat negative symptoms because these symptoms have been hypothesized to be associated with a functional impairment of mesocortical dopaminergic transmission (Weinberger and Lipska, 1995; Kuroki et al., 1999). Despite this evidence, an effective treatment
of primary negative symptoms still remains limited, although these symptoms partially respond to atypical antipsychotics.

Phenomenic similarities and partial overlap between negative and depressive symptoms (anhedonia, motor retardation, social withdrawal, apathy) tend to suggest that a serotonergic dysfunction might be involved in the pathogenesis of negative symptoms of schizophrenia (Meltzer, 1989). For these reasons, the tendency in recent literature is to suggest the use of antidepressant drugs as augmentation strategies for the treatment of negative symptoms (Evins and Goff, 1996). As tricyclic antidepressants added to clozapine showed little benefit and an increased risk of toxicity (Chong and Remington, 2000), the evidence from literature is more in favour of selective serotonin reuptake inhibitor augmentation (Silver et al., 2000; Zullino et al., 2002). Controlled and open trials of antidepressant augmentation strategies have reported controversial results. Buchanan et al. (1996) and Takahashi et al. (2002) found no clinical efficacy in adding fluoxetine and fluvoxamine to ongoing clozapine and risperidone treatments, respectively, while other studies reported beneficial effects. In the first controlled trial of fluvoxamine 100 mg/day as augmentation therapy for the negative symptoms of schizophrenia, Silver and Nassar (1992) highlighted a significant improvement of negative symptoms in the fluvoxamine group compared to placebo. Further studies conducted by the same researchers confirmed these early results (Silver et al., 2003). Spina et al., (1994) observed a significant improvement in Scale for the Assessment of Negative Symptoms (SANS) total scores in a controlled trial of fluoxetine add-on therapy versus placebo. A placebo-controlled trial conducted by Goff et al. (1995) showed that fluoxetine augmentation improved Brief Psychiatric Rating Scale (BPRS) negative scores, although an exacerbation of psychotic symptoms was registered in 19% of fluoxetine-treated patients. An open study of mianserin addition to ongoing haloperidol treatment in a sample of drug-resistant, chronically hospitalized schizophrenic patients significantly improved the core symptoms of schizophrenia with a prominent reduction in anxiety levels (Grinshpoon et al., 2000). Moreover, mianserin added to typical antipsychotic agents in chronic schizophrenic in-patients showed a cognitive-enhancing effect not related to improvement in clinical symptomatology, primarily in negative symptoms (Poyurovsky et al., 2003a).

Mirtazapine is the first of a new class of dual action compounds, the noradrenergic and specific serotoninergic antidepressants (NaSSa), whose activity is related to the enhancement of noradrenergic and serotonergic transmission by a presynaptic α2 antagonism and postsynaptic 5-HT2 and 5-HT3 antagonism, respectively (De Boer et al., 1988). The serotonin release induced by mirtazapine is specifically mediated postsynaptically via 5-HT1A receptors, as mirtazapine selectively blocks the 5-HT2A and 5-HT3 receptors. The potential use of mirtazapine as augmentation strategy for the treatment of negative symptoms of schizophrenia has been highlighted in a double-blind, randomized, placebo-controlled study (Berk et al., 2001). This study showed a significant decrease in negative symptoms when mirtazapine was added to haloperidol in a group of schizophrenic patients. In addition, a recent double-blind, randomized, placebo-controlled study has demonstrated the therapeutic effect of low-dose mirtazapine in the treatment of neuroleptic-induced akathisia (Poyurovsky et al., 2003b). A similar therapeutic effect on neuroleptic-induced extrapyramidal symptoms and akathisia has been found using nefazodone at a dose of 100 mg/day (Wynchank and Berk, 2003).

Based on this background, the aim of this study was to assess, using a double-blind, placebo-controlled design, the efficacy and tolerability of adjunctive mirtazapine to an ongoing treatment with clozapine for the negative symptoms of schizophrenia.

**Methods**

**Subjects**

Twenty-four outpatients, 15 males and nine females, aged 21–53 years, who met DSM-IV criteria for schizophrenia and demonstrated persistent negative symptoms despite an adequate trial of clozapine, were included in this study. The patients age, gender and duration of illness are shown in Table 1. The mirtazapine and placebo groups were comparable with respect to the different variables.

All patients had been on clozapine monotherapy 150–650 mg daily for at least 1 year; the dose had been stable for at least 1 month prior to the study and was left unchanged throughout the study. Patients with any other major psychiatric disorder, significant concurrent medical illnesses, organic brain disorder, history of substance and alcohol abuse, mental retardation, and pregnant or lactating women were excluded. To exclude the presence of a depressive episode, subjects who scored more than 20 on the Hamilton Rating Scale for Depression (Hamilton, 1967) were excluded from the study. The patients provided written informed consent after a full explanation of the protocol design which had been approved by the local ethic committee.

<table>
<thead>
<tr>
<th>Table 1 Demographic and clinical characteristics of the sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Patients entered</td>
</tr>
<tr>
<td>Patients evaluable</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
</tr>
<tr>
<td>Duration of illness (years), mean ± SD</td>
</tr>
<tr>
<td>Clozapine dose (mg/day), mean ± SD</td>
</tr>
<tr>
<td>HAM-D (mean ± SD)</td>
</tr>
</tbody>
</table>

* Two-tailed Student’s t-Test.
Study design
This trial was an 8-week double-blind, randomized, placebo-controlled trial of adjunctive mirtazapine to clozapine therapy in schizophrenia. The following rating scales were used: Hamilton Rating Scale for Depression administered only at baseline as an exclusion instrument; BPRS (Overall and Gorham, 1962) scored 1–7 at baseline and at the end of the trial (week 8); the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984); and SANS (Andreasen, 1983), both administered at baseline and at the end of weeks 2, 4 and 8 by two independent raters. While inter-rater reliability for these assessments was not established by formal training, it is important to note the assessments were conducted by psychiatrists with at least 5 years clinical experience and who were well versed with the use of the rating scales.

All patients scored 3 or more on at least one of the five global SANS subscales at the baseline evaluation, while positive symptoms were mild or absent in the whole group. Patients were randomly allocated to receive, in a double-blind design, either mirtazapine 30 mg/day or a placebo. Improvement in negative symptomatology was considered clinically relevant if patients experienced a reduction of over 20% on SANS total score from baseline to the final test at 8 weeks. Moreover, because HAM-D was only performed at baseline, change in depressive symptoms was assessed at final visit extracting the depressive factor of the BPRS; this factor consists of two items measuring depressed mood and guilt feelings (Brar et al., 1997).

Information about adverse events was obtained by interviewing the patients at each visit. In addition to a physical examination, systolic and diastolic blood pressure, heart rate and body weight were all measured at each visit. A complete set of laboratory investigations was performed in all patients on admission and at the end of the study.

Statistical analysis
The within-group differences in efficacy ratings between baseline and final test were analysed by the Wilcoxon rank sum test. Comparison between the groups at baseline was performed using the Mann–Whitney U-test. Comparison between the groups at end of weeks 2, 4 and 8 was performed using analysis of covariance. All tests were two-tailed and \( P < 0.05 \) was considered statistically significant.

Results
Twenty patients completed the study and were included in the analyses of efficacy. There were four premature dropouts, two in the placebo group and two in the mirtazapine group for causes unrelated to the treatment (one patient for concurrent illness, three patients did not comply with the visits). At the baseline visit (day 0), there was no significant difference between active and control group on SANS, SAPS, BPRS and HAMD scores (Tables 1 and 2).

Table 2 summarizes the baseline and final values of the different efficacy variables for the mirtazapine and placebo groups. Negative symptomatology, as assessed by the SANS, improved significantly over the time of treatment (from baseline to week 8) in the mirtazapine group, but not in the placebo group. At the end of the trial (week 8), the SANS total scores were significantly lower in the mirtazapine group than in the placebo group (39.0 versus 51.0; \( P < 0.01 \), \( F = 6.64 \), d.f. = 1). Moreover, mirtazapine-treated patients showed a significant improvement compared to the placebo group for the SANS subscales avolition/apathy (6.3 versus 9.7; \( P < 0.05 \), \( F = 4.48 \), d.f. = 1) and anhedonia/asociality (8 versus 10.6, \( P < 0.05 \), \( F = 5.49 \), d.f. = 1). Mean SANS total scores at each assessment point in the two treatment groups are shown in Fig. 1.

Table 2  Clinical changes in patients receiving mirtazapine versus placebo at baseline and Week 8

<table>
<thead>
<tr>
<th></th>
<th>Mirtazapine (n=10)</th>
<th>Placebo (n=10)</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 8</td>
<td>Baseline</td>
</tr>
<tr>
<td>SANS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogia</td>
<td>11.4 ± 3.4</td>
<td>8 ± 2.7c</td>
<td>10.4 ± 2.1</td>
</tr>
<tr>
<td>Affective flattening</td>
<td>12.9 ± 5.8</td>
<td>8.8 ± 3.1a</td>
<td>13.5 ± 4.6</td>
</tr>
<tr>
<td>Avolition/apathy</td>
<td>7.9 ± 2.11</td>
<td>6.3 ± 0.6</td>
<td>8.5 ± 2</td>
</tr>
<tr>
<td>Anhedonia/asociality</td>
<td>10.5 ± 1.8</td>
<td>8.2 ± 0.5c</td>
<td>10.8 ± 1.9</td>
</tr>
<tr>
<td>Attention</td>
<td>6.8 ± 1.8</td>
<td>5 ± 2.3c</td>
<td>7.8 ± 2</td>
</tr>
<tr>
<td>Total SANS score</td>
<td>48.9 ± 6.9</td>
<td>36.1 ± 4.7</td>
<td>51 ± 5.3</td>
</tr>
<tr>
<td>Total SAPS score</td>
<td>6.9 ± 3.6</td>
<td>6.6 ± 2.2</td>
<td>7.9 ± 3.3</td>
</tr>
<tr>
<td>BPRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum of depressive symptoms</td>
<td>2.90 ± 0.9</td>
<td>2.50 ± 0.8</td>
<td>2.90 ± 0.8</td>
</tr>
<tr>
<td>Total BPRS scores</td>
<td>45.5 ± 4.1</td>
<td>25.4 ± 3.2c</td>
<td>45.3 ± 3.8</td>
</tr>
</tbody>
</table>

Data are means ± SD.

*Mirtazapine versus placebo difference at week 8.

aBaseline to week 8 change statistically significant (\( P < 0.05 \)).

bBaseline to week 8 change statistically significant (\( P < 0.01 \)).
At the final evaluation, two out of 10 patients on mirtazapine add-on experienced a reduction of over 20% from baseline on SANS total score, while no subject showed a clinically relevant improvement in negative symptoms in the placebo group. Compared with baseline values, the improvement in negative symptoms was evident in mirtazapine-treated patients after 4 weeks of therapy ($P < 0.05$) and continued at week 8 ($P < 0.01$).

In the mirtazapine group, there was a statistically significant improvement in the SANS subscales affective flattening ($P < 0.05$), alogia and anhedonia/asociality ($P < 0.01$) from baseline values to final evaluation. Positive symptoms, as measured by SAPS, were not modified in both mirtazapine and placebo groups during the observation period. At endpoint, BPRS total scores resulted lower in mirtazapine group compared to placebo. Depressive symptomatology, assessed using the extracted factor of the BPRS, was unchanged at final visit in both groups.

In the mirtazapine group, three patients experienced mild and transient drowsiness while, in two patients, a weight increase of 2 kg was registered at the final evaluation. No clinically relevant changes in heart rate, blood pressure or laboratory tests were observed in either treatment group during the observation period.

**Discussion**

The results of the present study show that mirtazapine added to stable clozapine treatment may have a beneficial effect on the negative symptomatology in a sample of schizophrenic patients with persistent negative symptoms. Mirtazapine was significantly more efficacious than placebo in reducing negative symptoms as measured by change on the SANS total scores after 8 weeks of therapy. However, clinical changes from mirtazapine add-on therapy showed a certain degree of inter-individual variability, as a reduction of over 20% in SANS total scores was obtained only by two patients. However, because the mean reduction in SANS total scores was 17.7%, other patients were close to reaching the cut-off for being considered as responders.

With regard to SANS subscales, improvement was evident in avolition/apathy and anhedonia/asociality, while no significant changes have been registered in the core negative symptoms alogia and affective flattening between groups. However, in the mirtazapine group, comparison of SANS total score and subfactors at week 8, controlling for baseline scores, demonstrated significantly greater reduction in the negative symptoms subscale alogia, affective flattening and anhedonia/asociality besides the SANS total score. Furthermore, in the mirtazapine group, the improvement in negative symptoms began after 4 weeks of therapy and continued until the end of the trial, at week 8. SAPS scores did not change during mirtazapine treatment; on the other hand, the study had focused on schizophrenic patients selected for the presence of persistent negative symptomatology, in the absence of significant positive symptoms.

The improvement in overall psychopathological state is highlighted by changes in BPRS scores during mirtazapine treatment. It may be hypothesized that this amelioration could be a consequence of the improvement in negative symptoms because the sample chosen for the study was characterized by neither depressive nor positive symptoms. Nevertheless, the lack of improvement in the key negative symptoms affective flattening and alogia between groups, together with changes in many ‘nonspecific’ items on the BPRS, suggests that improvement may involve anxiety and other general symptoms rather than primary negative symptoms. The possibility that the improvement in negative symptoms was due to an effect on depressive symptomatology could be ruled out because depressive symptoms, controlled at final visit with the extracted factor of the BPRS, were unchanged in both groups. Conversely, in placebo-treated patients, no significant changes in the overall clinical state and in negative symptoms were observed. Consistent with previous findings (Loonen et al., 1999; Berk et al., 2001), mirtazapine was well tolerated, as no significant side-effects were noted and none of the patients dropped out due to adverse events.
Adjunctive treatment of antidepressant to an ongoing antipsychotic therapy can raise blood levels of antipsychotic drugs, as demonstrated for fluvoxamine (Hiemke et al., 1994), fluoxetine and paroxetine (Spina et al., 1998; Spina et al., 2000). By contrast, mirtazapine causes only minimal, insignificant changes in steady-state plasma concentrations of clozapine, as well as risperidone and olanzapine, as demonstrated by an open study performed on a sample of 24 schizophrenic patients (Zoccali et al., 2003). This finding is also consistent with an earlier open-label, non-randomized, pilot study showing that mirtazapine add-on did not affect plasma concentrations of risperidone and its active metabolite in six psychiatric patients (Loonen et al., 1999).

The lack of significant kinetic interactions between mirtazapine and atypical antipsychotics led us to assume that the therapeutic effect shown by mirtazapine on negative symptoms is likely to result from a pharmacodynamic mechanism. Mirtazapine is a 5-HT2A/C and 5-HT3 antagonist, with centrally active presynaptic 52 receptor antagonism specificity and indirect agonistic properties on 5-HT1 receptors. Similarly, clozapine pharmacological profile includes antagonistic activity at 5-HT2A, 5-HT2C and 5-HT3 receptors and at the 51 receptor (less so at the 52) and agonistic activity at 5-HT1A receptors. Both 5-HT2A and 5-HT2C receptors are involved in the inhibitory modulation of dopaminergic neurotransmission (Kapur and Remington, 1996; Millan et al., 1998), exerting a tonic and phasic influence on mesocortical dopaminergic function. Although support from clinical data is still limited, it is increasingly evident that agonism at 5-HT1A receptors has a similar effect to 5-HT2A receptor antagonism (Meltzer and Maes, 1995; Arborelius et al. 1996) have highlighted that 5-HT1A agonists are able to preferentially increase the dopamine output in the prefrontal cortex.

With regard to the activity at 52 shown by mirtazapine and, to a lesser extent, by clozapine, it has been suggested that 52 antagonism enhances the noradrenergic transmission blocking presynaptic 52 autoreceptors. Noradrenaline acts on serotonergic neurones in a dual manner by inhibiting hippocampal serotonin release via an 52-mediated effect, and by increasing the serotonergic dorsal raphe cell firing via an 52-mediated effect (De Boer, 1995). Because mirtazapine blocks 52 heteroreceptors situated on serotonergic neurones, it prevents the inhibitory effect of noradrenaline on serotonin release (Fawcett and Barkin, 1998). On the other hand, it is quite evident that, besides serotonergic receptors, various receptor subtypes are involved in the enhancement of dopamine release induced by antipsychotic drugs in the medial prefrontal cortex (Westerink et al., 2001).

A number of studies indicate that the 52 adrenoreceptor is probably an important site in antipsychotic atypicality, exerting a tonic inhibitory influence on extracellular dopamine in the medial prefrontal cortex (Gresch et al., 1995; Yamamoto and Novotney, 1998). Evidence exists showing that 52 adrenoreceptor antagonism increases dopamine efflux specifically in the medial prefrontal cortex in animal models (Hertel et al., 1999a). Indeed, the addition of idaxodan, an 52 adrenoreceptor antagonist, to raclopride, a selective D2 antagonist, resulted in a significant enhancement of the dopamine output in the medial prefrontal cortex (Hertel et al., 1999b). As negative symptoms are presumably associated with impaired dopaminergic function in the medial prefrontal cortex, it can be hypothesized that the beneficial effect of mirtazapine, observed in this study and in previous researches (Berk et al., 2001), may be linked to its 52 adrenoreceptor antagonism, which enhances dopaminergic transmission in the prefrontal cortex.

It is of interest to note that both clozapine and mirtazapine share similar activities at 5-HT1A, 5-HT2A, 5-HT2C, 5-HT3 serotonergic receptors and at 52 adrenergic receptors. It appears possible that the association of mirtazapine with clozapine may exert a potentiating, synergistic action on the multiple receptor subtypes and on the neurotransmitter systems involved in the pathophysiology of negative symptoms. However, our results show certain limitations due to the small sample size, the inter-individual variability in the clinical response and the limited duration of the trial. Nevertheless, these findings provide evidence that the addition of mirtazapine to clozapine treatment is well tolerated and may be proposed as an useful therapeutic strategy to improve negative symptoms in chronic schizophrenic patients.

References


