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The Tolerability of Mirtazapine Augmentation in Schizophrenic Patients Treated with Risperidone: A Preliminary Randomized Placebo-controlled Trial

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Objective: Some patients with schizophrenia may need mirtazapine augmentation to improve negative and cognitive symptoms. However there have been a few studies about the tolerability of mirtazapine augmentation to antipsychotics such as akathisia, extrapyramydal symptoms, weight gain, and body mass index (BMI).
Methods: This study was an eight-week double-blind, randomized controlled trial (RCT) of mirtazapine augmentation to risperidone. Twenty-one stabilized participants diagnosed with schizophrenia and undergoing treatment with risperidone were randomized to adjunctive treatment with mirtazapine (15 mg/day for the first two weeks, 30 mg/day for the next six weeks) or placebo. Eleven patients were assigned to the mirtazapine group, and nine patients were given placebo.
Results: There was no significant difference between the mirtazapine and placebo groups with respect to Barnes Akathisia rating Scale (BAS) and Sympsom-Angus Scale (SAS). However, the mirtazapine group exhibited a statistically significant increase in weight and BMI ($p<0.05$).
Conclusion: These results suggest that mirtazapine augmentation can be tolerable in schizophrenic patients treated with risperidone; however, we should pay attention to the weight gain with mirtazapine. Our results should be replicated in a large-scale lengthy trial.

KEY WORDS: Schizophrenia; Mirtazapine; Risperidone; Augmentation; Tolerability.

INTRODUCTION

Mirtazapine, the first of a new class of noradrenergic and serotonoergic antidepressants (NASSA), has been shown to inhibit 5-HT_2, α_2 adrenergic, 5-HT_3, histaminergic H_1 receptors as well as 5-HT_{1a} receptor. It is an effective, safe, and well tolerated drug.[1,2)]

Adding mirtazapine to certain antipsychotic drugs may improve the negative and cognitive symptoms of some patients with schizophrenia. Several randomized controlled trials (RCT) showed that mirtazapine augmentation was of some benefit. Berk *et al.*[3)] augmented the haloperidol treatment of schizophrenia patients with mirtazapine and showed an improvement in their negative symptoms. Joffe *et al.*[4)] showed mirtazapine augmentation's antipsychotic effect in schizophrenia patients treated with various antipsychotic drugs. Risperidone is a novel atypical antipsychotic drug with dopamine D_2 and 5-HT_2 receptor antagonistic properties that is effective in the treatment of schizophrenia. Our group also showed an improvement of negative and cognitive symptoms after mirtazapine augmentation in schizophrenia patients treated with risperidone.[5)]

However, only one of those studies showed tolerability of mirtazapine augmentation to risperidone in patients with schizophrenia.[6)] It mentioned extrapyramidal symptom (EPS) dimension and somatic complaints with respect to the side effects of mirtazapine augmentation to risperidone. Also, it did not study the changes of akathisia severity, which mirtazapine could reduce in patients treated with antipsychotics.[7,8)]

Therefore, we investigated the side effects of mirtazapine augmentation including akathisia and EPS with appropriate scales.

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METHODS

Study Design and Subjects

This study was an eight-week double-blind, RCT of patients with schizophrenia treated by mirtazapine augmentation to risperidone in Korea, from October 2008 to March 2009. This study results were published elsewhere in part.[5)]

We recruited 74 schizophrenic patients who had been treated by risperidone. Inclusion criteria were as follows: 1) age between 21 and 70 years; 2) diagnosis of schizophrenia based on the Structured Clinical Interview for DSM-IV[9)] (SCID) after receiving a physical (neurological) exam, electroencephalography, and magnetic resonance imaging; and 3) score of at least four on the Clinical Global Impressions scale[10)] (CGI) and stable, with no changes in CGI or medication dosage and side effects, for eight weeks (as determined by two investigators, SH Lee and TK Choi).

Exclusion criteria were as follows: 1) evidence of organic mental disorder; 2) drug or alcohol dependence that required inpatient treatment and/or detoxification; 3) presence of a depressive episode based on the SCID; and 4) other conditions, such as a serious medical condition, history of bipolar or schizoaffective disorder, suicidality, possibility of pregnancy, and lactation. After the screening, we enrolled 21 patients. Of these, twelve were randomly prescribed mirtazapine and nine were given placebo. One female patient withdrew her consent one day after taking mirtazapine and 20 patients remained at the end of the study. Seven patients of the placebo group and six of the mirtazapine group took benztropine (mean dose 0.78 mg/day and 0.55 mg/day in the respective groups) at baseline. After the study began, no other psychotropic agents were allowed.

This study was conducted in accordance with the Declaration of Helsinki and institutional review board. Informed consents were provided by all participants. The CHA Bundang Medical Center Institutional Review Board (Ethics Commmittee) approved this research. Only patients and their families who signed an informed consent document were chosen to participate in this study.

Medication

The dose of risperidone ranged from 2 mg/day to 6 mg/day, and the mean dose was 3.52 mg/day. Doses of risperidone were fixed for the duration of the study. Mirtazapine was added to the ongoing pharmacotherapy with risperidone in the mirtazapine group. The initial dosage was 15 mg/day at bedtime for the first two weeks. Thereafter, a daily dose of 30 mg/day was given at bedtime through the remainder of the study. Drug adherence was judged by a self-report checklist and capsule count during the study. Benztropine or prapranolol were not allowed after the study commenced.

Outcome Measures

Primary outcome measures were the scales for the assessment of akathisia and EPS, Barnes Akathisia rating Scale (BAS),[11)] Sympsom-Angus Scale (SAS),[12)] weight, abdominal circumstance, and Body Mass Index (BMI). These were collected for each patient at baseline and after two, four, and eight weeks. BAS is a rating scale that assesses the severity of drug-induced akathisia. This scale consists of a set of four questions, comprising one objective item, two different subjective items such as the level of the patient's restlessness, and a global rating item. The global item score may be used as an overall severity measure and has a diagnostic threshold, with a score of two or more indicating the presence of akathisia.[13,14)] SAS is a 10-item instrument used to evaluate the presence and severity of parkinsonian symptomatology. The 10 items focus on rigidity rather than bradykinesia, and do not assess subjective rigidity or slowness. Items are rated for severity on a 0-4 scale. The conventional scoring system for the SAS is to calculate a global score by summing the individual item scores and then dividing by the total number of items. Simpson and Angus considered that a final score of up to 0.3 was "within the normal range." All scales were evaluated by two experienced psychiatrists and the inter-rater reliability (0.80-0.84) of the project staff was ensured. A secondary outcome was the Positive and Negative Symptom Scale (PANSS).[15)] Side effects are measured by the Toronto Side Effects Scale (TSES)[16)] dimension, a 32-item instrument that includes central nervous system (CNS), gastrointestinal (GI), sexual and other side effects.

Statistical Analysis

Sociodemographic variables were compared between mirtazapine and placebo groups using a Mann Whitney U test. Fisher's exact test was used to determine gender associations. For side effects, we used a repeated-measure ANOVA to evaluate and compare the tolerability of mirtazapine over time in the two groups, considering the time main effect and the time×treatment interaction. All data analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Significance was defined as p

< 0.05.

RESULTS

Sociodemographic Characteristics

There were no significant differences between mirtazapine and placebo groups with respect to age, gender, education, duration of illness, risperidone dosage and PANSS scores. PANSS negative scores improved between baseline and week 8 (F=12, df=1.18, $p < 0.01$). Table 1 shows the demographic data.

Side Effects of Mirtazapine Augmentation in Schizophrenia Patients Treated with Risperidone

During this eight-week trial, there was no significant difference between mirtazapine and placebo groups with respect to BAS scores or SAS scores (Table 2, Fig. 1). Additionally, when we compared BAS scores or SAS scores within groups between the baseline and week eight using paired t-test in each group, no significant differences were found (mirtazapine group, BAS: p=0.234, SAS: p=0.126; placebo group, BAS: p=0.549, SAS: p=0.362). Also, when we compared between group effects at week eight using independent t-test, no significant differences were found (BAS: p=0.327, SAS: p=0.096). In terms of weight, five patients gained weight in the mirtazapine group. The mean body weight increased 5.83 kg during the study in the mirtazapine group. An increase of body weight and BMI from baseline to week eight was observed over time (body weight F=12, df=1.18, $p < 0.05$; BMI F=9.34, df=3, p=0.01), an effect that was significantly different statistically from that of the placebo group after considering the time×treatment interactions (body weight F=3.3, df=1.18, $p < 0.05$; BMI F=4.17, df=4, p=0.023). Although a similar outcome was expected for abdominal circumference, there was no difference between groups (Table 3, Fig. 1). The other side effects are reported in Table 4.

Table 1. Demographic characteristics of participants

	Mirtazapine (n=11) Mean (SD)	Placebo (n=9) Mean (SD)	p
Age (year)	35.08 (13.58)	36.44 (9.57)	0.80
Gender (male/female)	5/6	5/4	0.55
Duration of illness (month)	83.33 (97.90)	71.56 (89.81)	0.78
Education (year)	13.08 (2.15)	13.11 (3.33)	0.98
Risperidone (mg)	3.00 (1.94)	4.22 (1.83)	0.50
Benztropine (N/mg)	6/0.55 (0.63)	7/0.78 (0.48)	0.90
Benzodiazepine (N/mg)	7/0.63 (0.67)	4/0.67 (0.87)	0.91
PANSS total	79.91 (10.16)	88.22 (15.61)	0.40
Positive scale	17.58 (2.11)	20.00 (4.90)	0.20
Negative scale	21.42 (4.54)	24.22 (3.99)	0.16
General scale	40.92 (4.48)	44.00 (8.08)	0.28

N, number; SD, standard deviation; PANSS, positive and negative syndrome scale.

DISCUSSION

This is the first study to examine side effects using both BAS and SAS in patients with schizophrenia treated by mirtazapine augmentation. Akathisia and EPS symptoms were not significantly different between mirtazapine and placebo groups. But weight gain was higher in the mirtazapine group than the placebo group.

A few studies[7,17] mentioned that mirtazapine is efficacious in treating atypical antipsychotic (olanzapine, risperidone, aripiprazole)-induced akathisia, particularly in patients with coexisting depression. This discrepancy with our study may be due to the presence of comorbid depression in patients (our study excluded clinically depressive patients). Also, the inconsistency may come from the differences of the medication, diagnoses, and study design.

In terms of the EPS, our result is consistent with other RCTs. The differences between the mirtazapine and placebo groups did not reach statistical significance in six-week RCT studies,[3,4] while the mean SAS scores show a tendency to be improved with mirtazapine. Previously, mirtazapine had a potential to improve anti-

Table 2. Changes of akathisia and extrapyramidal symptom over time between mirtazapine and placebo groups

	Week 0 Mean (SD)	Week 2 Mean (SD)	Week 4 Mean (SD)	Week 8 Mean (SD)	p
Barnes-Akathisia					0.49
Mirtazapine	4.45 (3.05)	5.45 (3.05)	4.00 (3.66)	3.18 (2.44)	
Placebo	3.78 (2.39)	5.22 (2.68)	4.78 (3.60)	4.56 (3.64)	
Simpson-Angus					0.71
Mirtazapine	0.66 (0.27)	0.65 (0.27)	0.62 (0.26)	0.53 (0.29)	
Placebo	0.81 (0.34)	0.89 (0.18)	0.77 (0.21)	0.72 (0.17)	

SD, standard deviation.

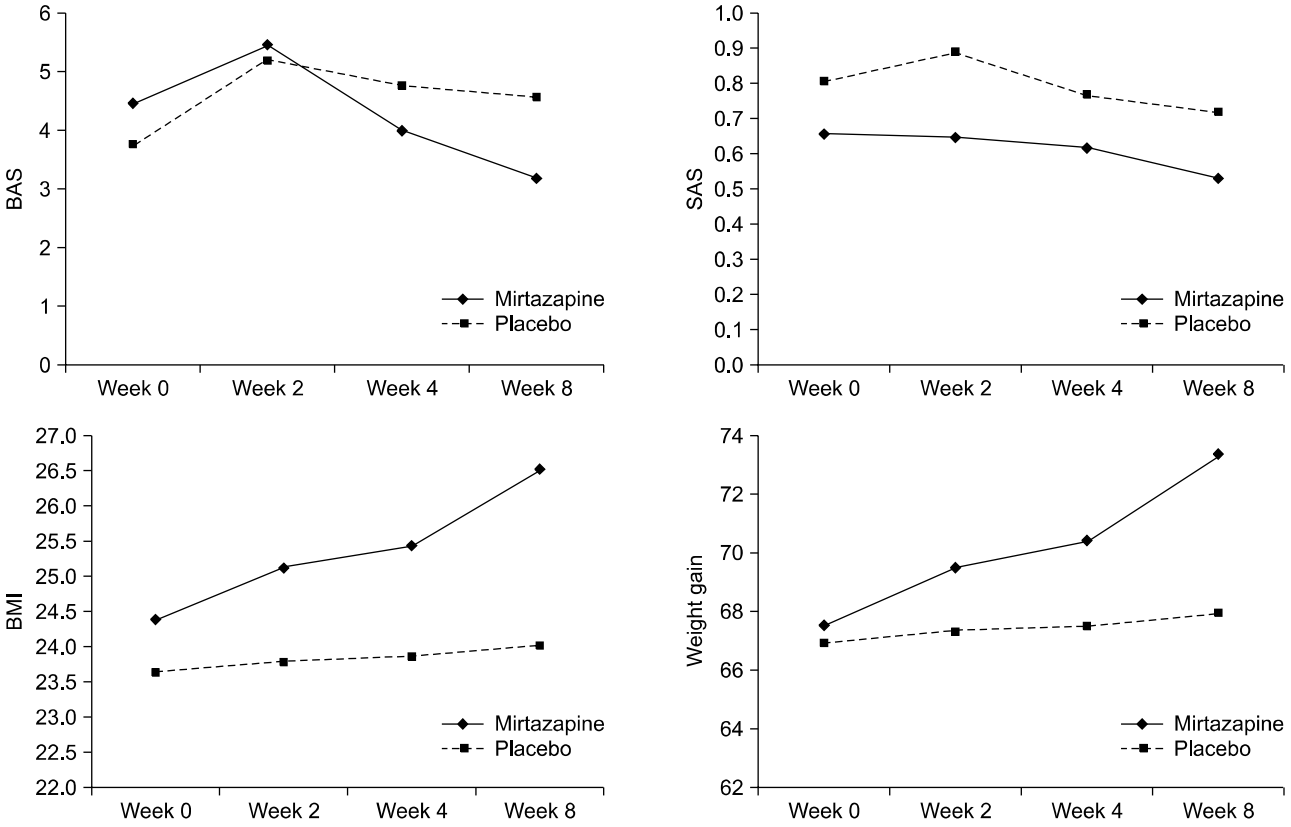

Fig. 1. Changes of akathisia, extrapyramidal symptom, body mass index and weight over time between mirtazapine and placebo groups.

Table 3. Changes of body mass index, weight gain, and abdominal circumstance over time between mirtazapine and placebo groups

	Week 0 Mean (SD)	Week 2 Mean (SD)	Week 4 Mean (SD)	Week 8 Mean (SD)	*p*
Body mass index					0.03
Mirtazapine	24.42 (4.69)	25.17 (4.63)	25.45 (4.58)	26.55 (5.37)	
Placebo	23.67 (4.36)	23.83 (4.47)	23.90 (4.40)	24.05 (4.32)	
Weight gain					0.03
Mirtazapine	67.53 (17.93)	69.55 (17.12)	70.36 (17.24)	73.36 (18.77)	
Placebo	66.94 (16.69)	67.33 (16.75)	67.50 (16.50)	67.96 (16.44)	
Abdominal circumstance					0.22
Mirtazapine	87.00 (10.43)	89.45 (10.87)	90.00 (11.25)	91.73 (11.93)	
Placebo	85.78 (10.16)	84.56 (10.11)	86.00 (10.22)	86.33 (10.28)	

SD, standard deviation.

psychotic induced movement disorder by blocking the α_2 and 5 HT_2 receptor in animal studies.[18] Poyurovsky *et al.*[8] suggested that mirtazapine is characterized by potent presynaptic alpha-2 adrenergic antagonism, which accounts for its antidepressant activity, and marked 5-HT_{2A} blockade that seems to preponderate in a low dose and contribute to its anti-akathisia properties after reviewing the human subject studies. However, RCT studies including our research suggest that mirtazapine would be not sufficiently potent to reduce the EPS in schizophrenic patients.

In regard to weight gain or BMI, it seems our study is in contrast with that of Abbasi *et al.*[6] A possible explanation for the inconsistency in the weight gain and BMI may be derived from the differences of the duration of illness, gender, mean dose of risperidone, symptom severity, and sample size. Notably, Abbasi *et al.*[6] studied the effects of mirtazapine 30 mg/day add-on therapy to risperidone 6 mg in high male/female ratio (about 2 : 1) of schizophrenic patients, while the female to male ratio was about 1 : 1 in our study. Generally, weight gain is more common

Table 4. Other side effects according to Toronto Side Effects Scale (TSES)

	Mirtazapine (n=11) N (%)	Placebo (n=9) N (%)
Nervousness	1 (9.1)	0 (0)
Agitation	0 (0)	1 (11.1)
Muscle twitching	1 (9.1)	0 (0)
Diarrhea	0 (0)	1 (11.1)
Increased appetite	1 (9.1)	0 (0)
Weakness or fatigue	1 (9.1)	0 (0)
Postural hypotension	1 (9.1)	0 (0)
Drowsiness/daytime somnolence	1 (9.1)	2 (22.2)
Decreased sleep	0 (0)	1 (11.1)
Premature ejaculation	1 (9.1)	0 (0)
Erectile dysfunction	1 (9.1)	0 (0)

N, number.

in females than males among patients taking psychotropic drugs.[19)]

It is important to note that our study has certain limitations. First, the sample size of this study was small, thus limiting its power. Second, the eight-week duration of this study may have prevented exploring the full side effects of mirtazapine. Third, since we permitted benztropine or prapranolol before the initiation the study, the subjects may be already clinically stabilized in terms of akathisia and EPS.

In conclusion, these results suggest that mirtazapine augmentation can be tolerable in schizophrenic patients treated with risperidone; however, we should pay attention to the weight gain from mirtazapine. Our results should be replicated in a large-scale lengthy trial.

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