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Quetiapine augmentation in patients with treatment resistant obsessive–compulsive disorder: a single-blind, placebo-controlled study

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Recently, atypical antipsychotics have been used for the management of the patients with refractory obsessive–compulsive disorder (OCD). The aim of the present study was to evaluate the results of quetiapine augmentation to a serotonin reuptake inhibitor (SRI) in the patients with refractory OCD. Fifty-two patients with OCD according to DSM-IV entered 3 months of an open-label phase treatment with a SRI with or without concomitant adjunctive treatment regimen. Of them, 27 patients were refractory OCD. These patients were randomly divided into two groups, SRI plus quetiapine and SRI plus placebo, for an 8-week single-blind phase. The course of OCD was evaluated by Yale–Brown Obsession–Compulsion (Y-BOCS) and Clinical Global Impression–Severity of Illness and Improvement (CGI-SI and I) Scales every other week for 8 weeks. Of the 14 patients in group I, nine (64.4%) showed significant improvement with 60% or greater improvement on the Y-BOCS and one (7.1%) partial improvement with 30% or greater improvement on the Y-BOCS, whereas no improvement was observed in group II. The addition of quetiapine to ongoing SRI therapy has been found to be effective and well-tolerated approach in patients with refractory OCD. Int Clin Psychopharmacol 17:115–119

Keywords: augmentation, OCD, quetiapine, refractory, SRI

INTRODUCTION

Serotonin reuptake inhibitors (SRI) are used in the treatment of the patients with obsessive–compulsive disorder (OCD) as the first choice. However, approximately 40–60% of patients do not response to this treatment and obsessive–compulsive symptoms persist (Goodman *et al*., 1989b). One of the approaches in treatment of refractory OCD is to add to another group of drug to SRIs. Addition of central serotonin (5-HT) enhancers such as lithium (McDougle *et al*., 1991) and buspirone (McDougle *et al*., 1993) plus SRI has not been found effective, whereas adding dopamine receptor antagonists, such as pimozide and haloperidol, has been shown to be effective in the treatment of refractory OCD with comorbid schizotypal personality disorder or chronic tic disorder (McDougle *et al*., 1990; McDougle *et al*., 1994).

Atypical antipsychotics have also been tried in the patients with treatment resistant OCD (Patil, 1992; Young *et al*., 1994). The addition of risperidone or olanzapine to SRI has been shown to be considerably beneficial (Saxena *et al*., 1996; Weiss *et al*., 1999). On the one hand, to the best of our knowledge, there is no available information about using quetiapine (alone or with a SRI), a new atypical antipsychotic derived dibenzothiazepine, in the treatment of OCD. On the other hand, although they differ in some pharmacologic properties [e.g. quetiapine has high affinity for α_1 adrenergic and histamine H_1 receptors, lower affinity for α_2 adrenergic and dopamine D_1 receptors and no muscarinic M_1 activity (Saller and Salama, 1993), olanzapine has high affinity for α_1 adrenergic, histamine H_1, dopamine D_1 receptors and muscarinic M_1 activity (Bymaster *et al*., 1996) and risperidone's pharmacologic profile demonstrates a somewhat lower affinity for α_1 and α_2 adrenergic and histamine H_1 receptors (Leysen *et al*., 1988)], quetiapine has some similarities with risperidone and olanzapine in regard to receptor binding profile, such as greater affinity for

serotonin-2 (5-HT_2) receptors than dopamine D_2 receptors. Therefore, we decided to evaluate the results of quetiapine augmentation to SRI in the patients with treatment resistant OCD.

METHODS

Patients

Of the patients who had applied to Firat University Medical Faculty Department of Psychiatry, and who were diagnosed with OCD without psychotic features according to DSM-IV (APA, 1994) between September and December 2000, 52 gave their written informed consent to take part after receiving a complete description of the study. The study protocol was approved by the Firat University School of Medicine Ethics Committee.

First, 52 patients entered 3 months of an open-label screening phase. All patients received at least one adequate SRI trial before this phase. The SRI treatment was started at the dose of 37.5 mg/day for clomipramine, 50 mg/day for fluvoxamine or 20 mg/day for fluoxetine, and titrated up to 300 mg/day for clomipramine, 300 mg/day for fluvoxamine and 80 mg/day for fluoxetine according to clinical response and experienced side-effects [fluoxetine (maximum 80 mg/day, mean 46.6 mg), fluvoxamine (maximum 300 mg/day, mean 140.8 mg) and clomipramine (maximum 300 mg/day, mean 185.5 mg)]. In some patients, either a combination of SRI and anxiolytic (clonazepam in two patients and alprazolam in one patient), pimozide (in one patient) or lithium carbonate (in two patients) was given. Nineteen patients responded to this treatment regimen. Four patients dropped out of the study due to treatment incompliance and two were excluded from the study due to intolerance. Therefore, 27 patients entered the 8-week, single-blind and placebo-controlled phase.

Refractoriness to treatment were accepted when all following criteria were met: (i) still having a Yale–Brown Obsession–Compulsion Scale (Y-BOCS) (Goodman *et al.*, 1989a) score of 18 or greater (Goodman *et al.*, 1989b); (ii) the agreement of three of the authors (M.A., M.K. and E.T.) that the patient was not enough improved; and (iii) minimal improvement on Clinical Global Impression–Improvement Scale (CGI-I).

In order to determine the response to 8-week treatment, the following criteria were used: (i) 60% or greater improvement on the Y-BOCS (significant improvement); (ii) 30% or greater improvement on Y-BOCS (partial improvement); and (iii) the agreement of three of the authors (M.A., M.K. and E.T.) that the patient was enough improved.

Dose and procedure

The subjects were randomly assigned to two groups: SRI plus quetiapine (group I) ($n = 14$, seven females and seven males) and SRI plus placebo (group II) ($n = 13$, six females and seven males). The random assignment was single-blind. Quetiapine (50 mg/day) or placebo was added to SRI at the beginning of the study. Quetiapine was increased to a dose of 25 mg/day in each 2-week period, if the Y-BOCS score did not decrease by 2 or more. Placebo remained stable throughout the study period. SRI doses were stabilized (fluoxetine 40 mg/day in five patients in both group I and II; fluvoxamine 200 mg/day in five patients in group I and in four patients in group II; and clomipramine 150 mg/day in four patients in group I and in four patients in group II). No other drugs and formal behaviour therapy were given. The course of OCD was evaluated by Y-BOCS and CGI every other week for 8 weeks. The instruments were administered by the same rater (M.A.) throughout the study.

Statistical analysis

Data were evaluated by the SPSS Statistical Package, version 9.05. (SPSS, Chicago, IL, USA). Comparisons were performed using the chi-square test and Student's *t*-test where appropriate.

RESULTS

Fourteen patients were randomized to quetiapine and 13 patients to placebo administered group. The mean age of the patients was 28.6 years (SD 8.5; range 18–44 years) and 28.1 years (SD 8.7; range 20–49 years) in groups I and II, respectively ($P > 0.05$). The mean age at onset was 21.3 years (SD 5.2) and 22.1 years (SD 4.7) in groups I and II, respectively ($P > 0.05$). The mean previous failed adequate SRI trial was 1.9 (SD 0.7; range 1–3) in group I and 2.1 (SD 0.6; range 1–3) in group II before starting open-label phase ($P > 0.05$). Eight patients from group I and six from group II had failed trials of behaviour therapy. The most frequent obsession and compulsion were dirt contamination ($n = 13$) and washing ($n = 12$) for entire sample.

Of the patients, 14(51.9%) had comorbid axis I disorder. These comorbid disorders were major depressive disorder ($n = 8$), social phobia ($n = 2$), hypochondriasis ($n = 2$) and panic disorder ($n = 2$). There is no statistically significant difference between treatment groups with respect to the distribution of comorbid

Table 1. Comparison of scale scores (mean ± SD) both at baseline and endpoint of the quetiapine or placebo addition phase and that of responders at endpoint

	Baseline		*P*	Endpoint		*P*
	Group I ($n=14$)	Group II ($n=13$)		Group I ($n=14$)	Group II ($n=13$)	
Y-BOCS	24.1 ± 4.9	23.8 ± 4.1	> 0.05[a]	13.4 ± 3.2	21.4 ± 4.3	< 0.05[a]
CGI-SI	4.58 ± 1.5	4.47 ± 1.7	> 0.05[a]	2.42 ± 0.8	3.76 ± 1.4	< 0.01[a]
Responders	–	–	–	71.4%	0%	< 0.0001[b]

[a]Student's *t*-test. [b]Chi-square test. Y-BOCS, Yale–Brown Obsession–Compulsion Scale; CGI-I, Clinical Global Impression–Improvement Scale.

diagnoses ($P>0.05$). No patient had comorbid tic disorder.

At the beginning of the 3-month period before the addition of quetiapine or placebo, the mean Y-BOCS score for total patients in groups I and II was 28.4 ± 5.2 whereas it was 23.9 ± 4.6 at the end of this period, with a mean Y-BOCS score of 24.1 ± 4.9 in group I and 23.8 ± 4.1 in group II ($P>0.05$). The comparisons of Y-BOCS and Clinical Global Impression–Severity of Illness (CGI-SI) scores both at baseline and endpoint is summarized in Table 1. In addition, the mean Y-BOCS scores at each evaluation point are presented in Fig. 1.

Of the group I patients, nine (64.3%) exhibited significant improvement and one (7.1%) partial improvement. In the patients with significant improvement, the mean Y-BOCS score was 24.2(SD 5.3) and 12.2 (SD 4.8) before and after the addition of quetiapine, respectively. Of them, five were considered as very much improved and four much improved by CGI-I. In the patient with 'partial' improvement, the mean Y-BOCS score was 22 and 14 before and after quetiapine addition, respectively. This patient was evaluated as much improved by CGI-I. None of the group II patients showed partial or significant improvement. There was a statistically significant difference between treatment groups with respect to treatment response ($P<0.0001$) (Table 1).

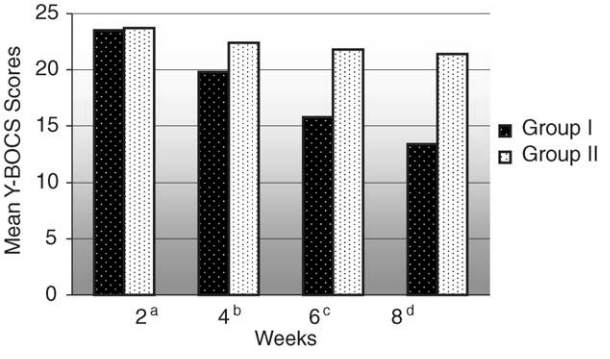

Figure 1. Yale–Brown Obsession–Compulsion Scale (Y-BOCS) Scores at 2, 4, 6 and 8 weeks in groups I and II. [a]$P>0.05$, [b]$P>0.05$, [c]$P<0.05$, [d]$P<0.05$.

The quetiapine doses received in group I were: 50 mg/day in three patients (21.5%); 75 mg/day in five patients (35.7%); 100 mg/day in four patients (28.6%); 150 mg/day in one patient (7.1%) and 200 mg/day in one patient (7.1%).

Nine of the patients (64.4%) in group I complained of side-effects. The most frequent side-effect was nausea ($n=6$), followed by sedation ($n=3$) and dizziness ($n=1$). In group I, the mean weight gain from baseline to endpoint in the 8-week phase was 1.9 kg (SD 1.8).

Four of the patients (30.7%) in group II reported side-effects, including sedation ($n=2$), headache ($n=1$) and nervousness ($n=1$). The mean weight gain was 1.6 kg in group II (SD 1.3).

No patient dropped out of the study in the 8-week quetiapine or placebo addition phase.

DISCUSSION

Our results reveal that quetiapine augmentation is effective and well-tolerated in the treatment of patients with refractory OCD. Of the patients, 71.4% (64.3% significant and 7.1% partial) demonstrated improvement. Antipsychotic drugs at low doses have been used in the treatment of refractory OCD as adjunctive treatment (McDougle *et al.*, 1990). Therefore, atypical antipsychotics such as clozapine, risperidone and olanzapine, have recently been tried in the patients with refractory OCD. In a case reported by Young *et al.* (1994), the patient with primary OCD, unresponsiveness to multiple drugs, ECT and psychosurgery, showed partial response to clozapine treatment. However, it has been reported that patients with schizophrenia during clozapine treatment developed obsessive–compulsive symptoms (Baker *et al.*, 1992; Patil, 1992; Patel and Tandon, 1993). In addition, it has been reported that risperidone, when used alone,

exacerbated obsessive and compulsive symptoms in the patient with comorbid bipolar disorder and OCD (Remington and Adams, 1994) or with comorbid OCD and schizophrenia (Kopala and Honer, 1994). When risperidone was combined with a SRI, the complaints considerably improved in the latter case. As can be seen, the descriptions of exacerbation in obsessive–compulsive symptoms occurred in patients with primary psychotic disorder or comorbid OCD and psychotic or bipolar disorder rather than primary OCD. Weiss *et al*. (1999) added olanzapine to SSRI in 10 patients with refractory OCD. Of these, 70% of patients (40% almost full responder) responded to this treatment regimen. In another study performed by Saxena *et al*. (1996), 87% of the patients with SRI refractory OCD showed clinically significant improvement after risperidone augmentation to SRI treatment. In their double-blind, placebo-controlled study McDougle *et al*. (2000) reported that 50% of patients with refractory OCD who were given risperidone plus SRI, and none of the patients given placebo plus SRI, responded. In general, the response rate of our study is comparable with open-label studies (Saxena *et al*., 1996; Weiss *et al*., 1999) but higher than double-blind design studies (McDougle *et al*., 1994, 2000). This situation suggests that the study design itself may affect the response rate.

We have only been able to identify one case report regarding the relation between quetiapine and obsessive–compulsive symptoms in the literature. Khullar *et al*. (2001) reported quetiapine to exacerbate obsessive and compulsive symptoms in a case who had OCD and comorbid delusional disorder. Quetiapine, similar to risperidone, has strong antagonist effects on 5-HT_{1C} and 5-HT_2 receptors. Therefore, it might be expected to increase obsessions and compulsions. However, the existence of a complex relationship between obsessive–compulsive symptoms and atypical antipsychotics has been noted (Kopala and Honer, 1994). Moreover, the fact that atypical antipsychotics, including quetiapine addition to an SRI, are effective in patients refractory to a combination of SRI and typical neuroleptics might be explained by their strong antagonistic effects on many serotonin receptor subtypes (5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D} and 5-HT_7). These receptors are down-regulated by chronic SRI use and, consequently, the blockade of serotonin receptors by atypical antipsychotics, including quetiapine, can result in increased action of an SRI (Leysen, 1992; Richelson, 1994).

Several limitations should be taken into consideration when interpreting our results. The main limitation of our study was the single-blind design. In addition, because of the small sample size, our results could be considered preliminary.

In conclusion, the results of the present study suggest that quetiapine augmentation to a SRI may be effective and well-tolerated in patients with treatment resistant OCD. However, further double-blind studies involving a large group of patients are needed.

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