A Double-Blind, Randomized, Placebo-Controlled Trial of Quetiapine Addition in Patients With Obsessive-Compulsive Disorder Refractory to Serotonin Reuptake Inhibitors

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Background: Although serotonin reuptake inhibitors (SRIs) are the most effective pharmacologic treatment currently available for patients with obsessive-compulsive disorder (OCD), 40% to 60% of patients do not respond to this treatment. This study was conducted to evaluate the efficacy and tolerability of quetiapine in addition to an SRI for treatment-refractory patients with OCD.

Method: Forty patients (10 men/30 women, mean ± SD age = 35.2 ± 12.1 years; range, 18–60 years) with primary OCD according to DSM-IV criteria who were recruited between February 2001 and December 2002 were randomly assigned in an 8-week, double-blind, placebo-controlled trial to receive dosages titrated upward to 300 mg/day of quetiapine (N = 20) or placebo (N = 20) in addition to their SRI treatment. At entry, all patients were unresponsive to courses of treatment with at least 2 different SRIs at a maximum tolerated dose for 8 weeks. During the study, primary efficacy was assessed according to change from baseline on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). A responder was defined as having a final Clinical Global Impressions-Improvement scale rating of "very much improved" or "much improved" and a decrease of ≥ 35% in Y-BOCS score.

Results: An intent-to-treat, last-observation-carried-forward analysis demonstrated a mean ± SD decrease in Y-BOCS score of 9.0 ± 7.0 (31%) in the quetiapine group and 1.8 ± 3.4 (7%) in the placebo group ($F = 16.99$, $df = 1,38$; $p < .001$). Eight (40%) of 20 patients in the quetiapine group and 2 (10%) of 20 patients in the placebo group were responders ($\chi^2 = 4.8$, $df = 1$, $p = .028$). The most common side effects in the quetiapine group were somnolence, dry mouth, weight gain, and dizziness.

Conclusion: The results of this study show that quetiapine in addition to an SRI is beneficial for patients with OCD who do not respond to SRI treatment alone.

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Obsessive-compulsive disorder (OCD) is a common and severe, but still underrecognized, psychiatric disorder. Although serotonin reuptake inhibitors (SRIs) are currently the most effective pharmacologic treatment for OCD, up to 40% to 60% of OCD patients do not respond to treatment.[1] Even after a switch to treatment with a second SRI, 30% to 40% of OCD patients fail to respond.[2] In case of refractoriness to SRIs, addition of antipsychotics might lead to symptom improvement.

To date, risperidone, olanzapine, and quetiapine have been shown to be effective as add-on treatment to SRIs in a number of case reports and open studies. Four open-label studies have reported on the use of risperidone[3–6]; 6, on olanzapine[7–12]; and 3,[13–15] 1 of which was negative,[15] on quetiapine. Two double-blind, placebo-controlled studies have confirmed the efficacy of risperidone for patients with SRI-refractory OCD, and 1 single-blind, placebo-controlled study has confirmed the efficacy of quetiapine in these patients.[16–18] To the best of our knowledge, no double-blind, placebo-controlled study has been conducted to evaluate the efficacy of quetiapine addition in OCD. Moreover, as the aforementioned studies have included OCD patients with comorbid disorders, such as chronic tic disorder, body dysmorphic disorder, and hypochondria, the beneficial effect of the addition of atypical antipsychotics to SRIs for treatment-refractory OCD patients without concomitant DSM-IV Axis I comorbidity still needs to be determined.

The objective of the present study was to assess the efficacy of quetiapine addition to SRIs for patients with OCD who were refractory to at least 2 SRI treatments and free of major comorbid disorders. We report here the results of a double-blind, placebo-controlled study of 40

patients with OCD who entered an 8-week trial to receive quetiapine or placebo in addition to their current SRI.

METHOD

Subjects

Forty patients gave consent to participate in this study and signed an informed consent form. The study was approved by the University of Utrecht Medical Ethical Review Committee (Utrecht, the Netherlands). Participants were female or male outpatients, aged between 18 and 65 years, who were diagnosed with primary OCD according to DSM-IV criteria. All patients were recruited between February 2001 and December 2002. The diagnosis was ascertained by means of the Mini-International Neuropsychiatric Interview.[19] Only patients with a score of at least 18 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),[20] or at least 12 if only obsessions or compulsions were present, were included. Another inclusion criterion was the failure of at least 2 treatments with an SRI at a maximum tolerated dose and adequate duration (at least 8 weeks). Failure was defined as an improvement of less than 25% on the Y-BOCS. Patients with comorbid tics or Tourette's disorder were excluded. Patients were required to be free of major depressive disorder, the diagnosis of which was ascertained by a score of less than 15 on the 17-item Hamilton Rating Scale for Depression (HAM-D)[21] at admission. Pregnant women and female patients with childbearing potential who were not using adequate methods of contraception were excluded, as were patients with organic mental disorders; epilepsy; any structural central nervous system disorder or stroke within the last year; DSM-IV diagnoses of bipolar disorder, schizophrenia, or any other psychotic condition; substance-related disorders within the past 6 months; other anxiety disorders; or severe personality disorders, the presence of which was assessed during clinical interview. Other reasons for exclusion from this study were evidence of clinically significant and unstable cardiovascular, gastrointestinal, pulmonary, renal, hepatic, endocrinologic, or hematologic conditions; glaucoma; myocardial infarction within the last year; being at risk for suicide; multiple drug allergies or known allergy to quetiapine; use of a concomitant psychotropic drug; behavioral or cognitive therapy 3 months prior to the screening visit; and any contraindication to the use of quetiapine. Patients were judged to be physically healthy based on the results of a physical examination, an electrocardiogram, and blood and urine screening tests.

Study Design

Patients were randomly assigned to receive either quetiapine or placebo for 8 weeks in addition to their current SRI in a single-center, double-blind, placebo-controlled, parallel-group study design. Dosing schemes of SRI treatment of patients are shown in Table 2. The patients taking SRI drug dosages below maximal dosages had taken the maximal dosage but preferred lower dosages because of lack of efficacy and side effects with the higher dosage. The target dose of quetiapine was 200 mg/day, and quetiapine treatment was initiated at a dose of 50 mg/day at day 1 and increased to a dose of 300 mg/day in week 8 using a fixed dosing schedule (100 mg/day for weeks 1 and 2, 200 mg/day for weeks 3–6, and 300 mg/day for weeks 7 and 8). Quetiapine was administered in capsules of 25 mg and 100 mg. The study drug was packaged so that the units were identical and each subject received the appropriate dosage. All patients received 2 capsules per day from week 0 to week 8.

Ratings and Treatment Response

Patients were evaluated at weeks 0, 2, 4, 6, and 8. The rating of global improvement was made with the Clinical Global Impressions-Improvement scale (CGI-I),[22] on which 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, and 5 = minimally worse. Obsessive-compulsive symptoms were measured with the Y-BOCS.[20] Depression was rated with the 17-item HAM-D,[21] and anxiety was evaluated with the Hamilton Rating Scale for Anxiety (HAM-A).[23] The Brown Assessment of Beliefs Scale (BABS)[24] was used to assess delusional characteristics of obsessions. The Sheehan Disability Scale (SDS)[25] was used as a measure of overall symptomatic and functional impairment. The SDS consists of 3 separate ratings to evaluate the extent to which the symptoms disrupt work, social life, and family life. A trained blinded investigator completed the scales at baseline and at each visit. The primary efficacy parameter was the Y-BOCS score. A patient was rated as a responder on the basis of (1) ≥ 35% decrease in Y-BOCS score and (2) a final CGI-I rating of 1 (very much improved) or 2 (much improved).

Assessment of Physiologic Measures, Adverse Events, and Blood SRI Levels

Physical examination, routine hematology, biochemistry profile, urinalysis, and electrocardiogram were performed on the patient's first visit. Vital signs, including blood pressure and pulse rate, were obtained at each visit. Any adverse event reported by the patient or observed by the investigator was recorded at each visit. Blood for plasma drug level determinations was collected at each assessment, i.e., at weeks 0, 2, 4, 6, and 8. Blood levels of the compounds were determined by high-performance liquid chromatography with fluorescence detection in the laboratory of the Department of Psychiatry (University Medical Center Utrecht, Utrecht, the Netherlands).[26]

Statistical Analysis

The primary efficacy parameter, Y-BOCS score, was analyzed for all patients with at least 1 assessment

after baseline, following an intent-to-treat (ITT), last-observation-carried-forward (LOCF) procedure with 1-way analysis of variance (ANOVA). In addition, a 2-way ANOVA with a repeated-measures analysis was calculated for the Y-BOCS scores of the completers at all points in time to assess the main effect of time and the drug-time interaction. Of the 40 patients randomly assigned to receive treatment (ITT), 37 (92.5%) completed the study and were included in the repeated-measures ANOVA analysis. Patient 7 from the quetiapine group dropped out at week 2 because of lack of motivation and worsening of OCD symptoms. Patients 21 and 39 from the placebo group were excluded from the repeated-measures analysis because of inconsistent Y-BOCS ratings: both patients reported obsessions at one time but reported none at another. For significant 2-way ANOVAs, 1-way ANOVAs were calculated to determine if significant differences between quetiapine and placebo were present at each visit. As some reports suggest that the clinical significance of severity may be evaluated better by considering the Y-BOCS subscales individually rather than globally,[27,28] we conducted similar analyses on the separate Y-BOCS compulsive and obsessive subscale scores.

Pearson χ^2 tests, Fisher exact tests, or 1-way ANOVAs were used to compare clinical characteristics and the rate of responders for the treatment groups. An analogous procedure was performed for the HAM-A and HAM-D. Finally, Pearson correlations were calculated between the baseline rating scale measures and the change in ratings to assess possible correlations between the pretreatment severity and the subsequent clinical improvement. The data are presented as mean ± SD at a 5% level of significance. All statistical analyses were conducted with the SPSS statistical package, version 9.0 (SPSS Inc., Chicago, Ill.).

RESULTS

Demographic and Clinical Characteristics

Twenty patients were randomly assigned to the quetiapine group, and 20 were assigned to the placebo group. Demographic and clinical characteristics for the patients are summarized in Table 1. The patient groups did not differ statistically in age ($F = 0.34$, $df = 1,38$; $p = .56$), sex distribution ($\chi^2 = 0.5$, $df = 1$, $p = .46$), age at onset ($F = 0.002$, $df = 1,38$; $p = .97$), duration of illness ($F = 3.2$, $df = 1,38$; $p = .58$), baseline ratings of outcome measures (Table 2), previous drug trials ($\chi^2 = 6.6$, $df = 4$, $p = .16$), or behavioral therapies ($\chi^2 = 2.4$, $df = 4$, $p = .6$).

Global Treatment Response

Following an ITT-LOCF analysis, quetiapine addition was superior to placebo at the end of the study, with mean CGI-I scores of 2.9 ± 1.0 and 3.8 ± 0.8, respectively ($F = 8.2$, $df = 1,38$; $p = .007$). Two patients in the quetiapine group were "very much improved," and 6 were "much improved," whereas in the placebo group 2 were rated as "much improved" ($\chi^2 = 4.8$, $df = 1$, $p = .028$). The general pattern of improvement is depicted in Figure 1, which illustrates the observed mean change in CGI-I scores across the 8 weeks of treatment for both groups. Analysis of variance revealed a significant treatment effect over the 8-week trial period for time ($F = 5.7$, $df = 1,35$; $p = .001$) and for drug and time interaction ($F = 2.9$, $df = 1,35$; $p = .02$). A statistically significant difference in CGI-I scores in the quetiapine group compared with the placebo group was observed from week 6 onward ($F = 8.5$, $df = 1,35$; $p = .006$).

Change in Obsessive-Compulsive Symptoms

As measured by the reduction in total Y-BOCS scores, following an ITT-LOCF analysis, quetiapine addition was superior to placebo at the end of the study with a mean decrease of 9.0 ± 7.0 and 1.8 ± 3.4 ($F = 16.99$, $df = 1,38$; $p < .001$), respectively (Table 3). Eight patients in the quetiapine group compared with 2 in the placebo group had a ≥ 35% decrease on the Y-BOCS ($\chi^2 = 4.8$, $df = 1$, $p = .028$). The pattern of improvement in obsessive-compulsive symptoms is depicted in Figure 2, which illustrates the observed mean change in total Y-BOCS scores across the 8 weeks of treatment for both groups. Analysis of variance revealed a significant treatment effect over the 8-week trial period for time ($F = 9.5$, $df = 1,35$; $p < .001$) and for drug and time interaction ($F = 4.5$, $df = 1,35$; $p = .005$). The quetiapine group revealed a statistically significant difference in total Y-BOCS scores from the placebo group from week 4 onward ($F = 4.7$, $df = 1,35$; $p = .036$). Analyses of variance of the Y-BOCS obsessions and compulsions subscale scores both revealed a significant treatment effect for time (obsessions: $F = 7.9$, $df = 1,35$; $p < .001$; compulsions: $F = 8.7$, $df = 1,35$; $p < .001$) and for the interaction of time and drug (obsessions: $F = 3.6$, $df = 1,35$; $p = .01$; compulsions: $F = 3.3$, $df = 1,35$; $p = .02$).

The decreases in Y-BOCS total ($r = 0.3$, $p = .02$) and obsession subscale ($r = 0.4$, $p = .007$) scores were both significantly correlated with pretreatment Y-BOCS obsession severity scores but not with pretreatment Y-BOCS total or compulsion subscale scores. The pretreatment severity of obsessions was the only significant parameter ($F = 7.8$, $df = 1.18$, $p = .01$) in discerning responders (mean Y-BOCS obsession subscale score = 15.5 ± 2.2) from nonresponders (mean Y-BOCS obsession subscale score = 11.1 ± 4.6) to quetiapine addition. The decrease in Y-BOCS scores was not correlated with pretreatment HAM-A, HAM-D, or BABS scores.

Change in Other Outcome Measures

Baseline scores, endpoint scores, and mean changes in HAM-A, HAM-D, BABS, and SDS scores are listed in Table 3. The univariate ANOVA analysis revealed supe-

Table 1. Baseline Demographic and Clinical Characteristics of Obsessive-Compulsive Disorder Patients Receiving an SRI Plus Quetiapine or an SRI Plus Placebo[a]

Patient	Sex	Age (y)	Age at Onset (y)	Duration of Illness (y)	No. of Previous SRI Trials	No. of Previous Behavioral Therapy Trials	Principal Symptoms
Placebo							
3	F	27	5	22	2	0	Fear of harming others; checking and repeating rituals
4	F	36	22	14	2	0	Fear of harming others, moral obsessions
5	F	22	5	17	3	1	Perfectionism and doubt; checking, repeating, ordering
8	M	39	19	20	2	2	Aggressive, sexual obsessions; checking, washing
11	F	25	17	8	2	1	High risk assessment; checking
12	F	30	14	17	3	2	High risk assessment, contamination fear; washing
14	F	54	22	32	4	2	Contamination fear; checking
15	F	52	13	39	2	1	High risk assessment; checking
17	F	25	16	9	4	0	Contamination fear; checking
20	F	38	18	20	4	1	Perfectionism; washing, checking, counting
21	F	44	23	21	2	1	Contamination fear; washing
23	F	23	6	18	4	1	Perfectionism; washing, repeating, checking
25	F	41	22	19	> 5	5	Contamination fear, perfectionism; washing
26	M	50	22	28	2	0	Fear of harming others; checking
29	M	24	4	20	2	1	High risk assessment; washing, checking, counting
31	M	31	8	23	2	1	Perfectionism, doubt; checking
33	M	36	8	28	3	2	Perfectionism, doubt; checking
36	F	19	14	5	2	0	Fear of dying; checking and repeating rituals
38	M	38	4	34	2	0	Fear of loss of control; washing, checking
39	F	27	12	15	2	1	Perfectionism; rituals
Quetiapine							
1	M	59	15	44	3	0	Afraid of forgetting things; checking
2	F	24	12	12	2	1	Contamination fear; washing
6	F	52	27	26	2	1	Contamination fear, perfectionism; washing, checking
7	F	47	12	35	4	3	Perfectionism, doubt; washing, checking
9	M	20	7	13	2	0	Fear of harming others; repeating, hoarding, ordering
10	M	39	13	26	3	1	Perfectionism; checking, repeating, ordering
13	F	36	27	9	3	1	Fear of loss of control; checking, repeating, ordering
16	M	18	12	6	3	1	High risk assessment; mental rituals, washing
18	F	43	15	28	3	2	High risk assessment; repeating
19	F	29	5	24	3	2	Fear of being harmed by others; checking, washing
22	F	24	19	5	3	1	Perfectionism, doubt; washing, checking, repeating
24	F	52	22	30	2	0	Aggressive obsessions, perfectionism, doubt; checking
27	F	48	11	37	> 5	1	Religious obsessions, contamination; repeating, washing
28	F	24	7	17	2	1	Aggressive obsessions, contamination; washing, checking
30	F	41	20	21	6	1	Aggressive obsessions, morality; checking
32	F	33	14	21	3	0	Contamination fear; repeating
34	F	38	15	23	2	1	Fear of harming others; checking
35	F	60	10	50	2	0	Fear of harming others; washing, checking
37	F	20	11	9	2	1	Sexual, aggressive obsessions; repeating
40	F	19	8	11	3	2	Aggressive obsessions; repeating, mental rituals

[a]Mean ± SD values were as follows for placebo and quetiapine, respectively: age, 34 ± 10 years and 36 ± 14 years (for all patients, 35.2 ± 12.1 years); age at onset, 14 ± 7 years and 14 ± 6 years; duration of illness, 20 ± 9 years and 20 ± 13 years; number of previous SRI trials, 3 ± 1 and 3 ± 1; number of previous behavioral therapy trials, 1 ± 1 and 1 ± 1.
Abbreviations: F = female, M = male, SRI = serotonin reuptake inhibitor.

rior efficacy in the quetiapine group versus the placebo group for the reduction in HAM-A ($F = 6$, $df = 1,38$; $p = .019$), HAM-D ($F = 5.4$, $df = 1,38$; $p = .025$), and SDS work scores ($F = 12.5$, $df = 1,38$; $p = .001$), but not for the BABS ($F = 3.7$, $df = 1,15$; $p = .074$), SDS social life ($F = 2.9$, $df = 1,38$; $p = .092$), or SDS family life scores ($F = 2.7$, $df = 1,38$; $p = .1$).

Tolerability of Quetiapine, Dropouts, and Plasma Drug Concentrations

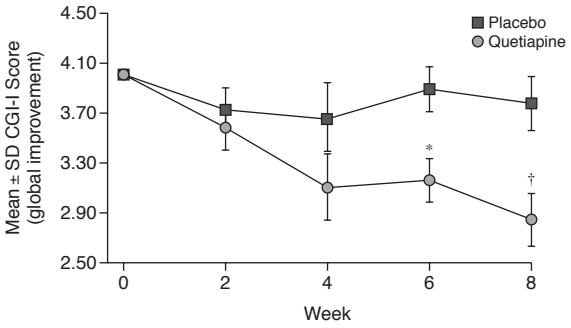
All patients reported at least 2 or 3 adverse experiences throughout the 8 weeks of treatment. The most prevalent side effects are presented in Table 4. The most prominent side effect, somnolence, was observed in almost all patients from the quetiapine group and was frequently rated as moderate or severe. The vast majority of the other side effects in both treatment groups were mild or moderate in severity. The number of adverse events experienced in the quetiapine group did not increase in a dose-dependent manner. Although all patients reported adverse experiences, these did not provoke dropout of any of the patients. One patient discontinued quetiapine treatment at week 2 due to worsening of OCD symptoms and lack of motivation. No clinically significant labora-

Table 2. Baseline and Endpoint Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Clinical Global Impressions Scale (CGI) Data for Patients Receiving an SRI Plus Quetiapine or an SRI Plus Placebo[a]

Patient	Current SRI	Daily Dose (mg)	Y-BOCS Score			CGI Score at Endpoint
			Baseline	Endpoint	Change, %	
Placebo						
3	Venlafaxine	300	32	30	–6.3	4
4	Paroxetine	60	19	10	–47.4	2
5	Fluoxetine	40	18	19	+5.6	4
8	Citalopram	60	32	27	–15.6	3
11	Citalopram	60	34	32	–5.9	4
12	Fluoxetine	60	32	28	–12.5	3
14	Paroxetine	60	34	31	–8.8	4
15	Citalopram	60	22	24	+9.1	4
17	Paroxetine	20	30	25	–16.7	3
20	Citalopram	20	30	31	+3.3	4
21	Fluvoxamine	200	33	32	–3.0	4
23	Imipramine	150	23	24	+4.3	4
25	Venlafaxine	300	30	30	0	4
26	Paroxetine	60	21	11	–47.6	2
29	Paroxetine	40	27	27	0	4
31	Fluvoxamine	200	18	20	+11.1	5
33	Paroxetine	60	22	24	+9.1	4
36	Citalopram	50	16	16	0	5
38	Venlafaxine	300	21	20	–4.8	4
39	Citalopram	40	34	31	–8.8	4
Quetiapine						
1	Citalopram	60	33	22	–33.3	3
2	Paroxetine	60	30	28	–6.7	4
6	Fluvoxamine	50	32	12	–62.5	1
7	Citalopram	60	33	30	–9.1	4
9	Venlafaxine	300	29	13	–55.2	2
10	Venlafaxine	300	25	21	–16.0	4
13	Paroxetine	20	27	16	–40.7	2
16	Paroxetine	60	27	29	+7.4	4
18	Paroxetine	40	33	24	–27.3	3
19	Fluoxetine	20	32	16	–50.0	2
22	Venlafaxine	300	25	25	0	4
24	Citalopram	60	24	16	–33.3	3
27	Paroxetine	50	21	20	–4.8	4
28	Citalopram	60	19	16	–15.8	4
30	Fluoxetine	20	26	12	–53.8	2
32	Clomipramine	75	27	5	–81.5	1
34	Paroxetine	30	25	20	–20.0	4
35	Paroxetine	60	34	17	–50.0	2
37	Paroxetine	40	31	18	–41.9	2
40	Citalopram	40	31	24	–22.6	3

[a]Mean ± SD values were as follows for placebo and quetiapine, respectively: Y-BOCS baseline score, 26.4 ± 6.3 and 28.2 ± 4.3; Y-BOCS endpoint score, 24.6 ± 6.7 and 19.2 ± 6.0; Y-BOCS change %, –6.7 ± 16.0 and –31.0 ± 23.4; CGI endpoint score, 3.8 ± 0.8 and 2.9 ± 1.0.
Abbreviation: SRI = serotonin reuptake inhibitor.

Figure 1. CGI-I Scores by Visit for OCD Patients Receiving an SRI Plus Quetiapine (N = 19) or an SRI Plus Placebo (N = 18)



*Significant difference from the placebo group: F = 8.5, df = 1,35; p = .006.
†Significant difference from the placebo group: F = 7.8, df = 1,35; p = .008.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, OCD = obsessive-compulsive disorder, SRI = serotonin reuptake inhibitor.

tory abnormalities were found throughout the study, and no serious adverse events associated with vital sign changes were observed.

Plasma levels of quetiapine increased with dosage until week 6 (week 2: 120 ± 89 ng/mL, week 4: 135 ± 151 ng/mL, week 6: 284 ± 326 ng/mL, week 8: 150 ± 189 ng/mL). No linear relationship between clinical improvement and plasma levels was found. The plasma levels were obtained mainly to confirm compliance.

DISCUSSION

This study is the first double-blind, placebo-controlled trial to demonstrate that quetiapine in addition to SRIs for treatment-refractory OCD is significantly more efficacious than SRI monotherapy in reducing obsessive-compulsive symptoms. Eight (40%) of 20 patients were rated as responders with a CGI-I score of 1 or 2 and a mean decrease on the Y-BOCS (ITT, LOCF) of ≥ 35% within 6 weeks.

Comparison With Similar Trials

Our results are consistent with previous reports of successful treatment with quetiapine addition for treatment-refractory OCD patients in 2 open studies and 1 single-blind, placebo-controlled study. In the open study by Mohr et al.[13] (quetiapine 50–300 mg/day), 4 of 8 patients were responders (CGI-I score of 1 or 2) with a mean Y-BOCS score decrease of 32% within 4 weeks. In our previous open-label study[14] (quetiapine 200 mg/day), 3 of 10 patients were responders with a mean Y-BOCS decrease of 35% within 4 weeks. Finally, in the single-blind, placebo-controlled study by Atmaca et al.[18] (quetiapine 50–200 mg/day), 10 of 14 patients were responders with a mean Y-BOCS decrease of 44% (time of onset of response was not available). On the other hand, in an open study by Sevincok and Topuz,[15] only 2 of 8 patients responded to quetiapine (150 mg/day).

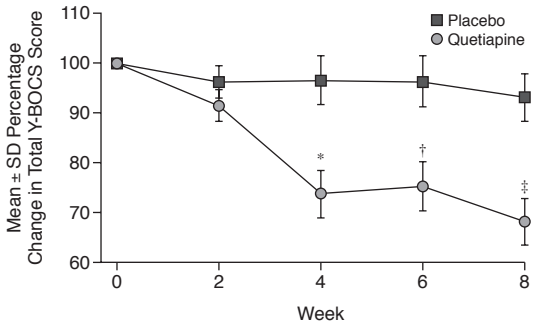
The response rates in our study are also in agreement with other double-blind, placebo-controlled addition trials in treatment-refractory OCD patients. In the haloperidol addition study by McDougle et al.,[29] 11 of 17 patients were rated as responders with a mean Y-BOCS decrease

Table 3. Changes From Baseline to Endpoint (ITT, LOCF) in Outcome Measures for Patients Receiving an SRI Plus Quetiapine (N = 20) or an SRI Plus Placebo (N = 20)[a]

	Baseline		Endpoint		Change	
Scale	Quetiapine	Placebo	Quetiapine	Placebo	Quetiapine	Placebo
CGI-I[b]	4.0 ± 0.0	4.0 ± 0.0	2.9 ± 1.0	3.75 ± 0.8	1.1 ± 1.0**	0.3 ± 0.8
Y-BOCS						
Obsessions	13.5 ± 4.1	13.2 ± 4.0	9.0 ± 3.6	12.5 ± 4.0	4.5 ± 4.0**	0.7 ± 2.4
Compulsions	14.6 ± 2.3	13.1 ± 4.1	10.1 ± 3.9	12.0 ± 4.4	4.5 ± 3.6**	1.1 ± 2.0
Total	28.2 ± 4.3	26.4 ± 6.3	19.2 ± 6.4	24.6 ± 6.7	9.0 ± 7.0**	1.8 ± 3.4
HAM-A	14.8 ± 7.4	12.5 ± 3.7	9.5 ± 5.2	11.3 ± 7.0	5.3 ± 5.0*	1.2 ± 5.7
HAM-D	12.6 ± 6.6	11.4 ± 5.3	5.7 ± 4.8	8.7 ± 5.8	6.8 ± 5.7*	2.6 ± 5.7
BABS[c]	8.5 ± 4.6	9.5 ± 5.8	5.4 ± 5.2	8.8 ± 6.4	3.1 ± 1.5	0.5 ± 1.0
SDS						
Work	7.0 ± 1.7	5.9 ± 3.0	4.9 ± 2.3	6.1 ± 2.9	2.1 ± 2.3**	0.0 ± 1.9
Social life	5.5 ± 2.8	5.5 ± 2.3	4.2 ± 1.8	5.4 ± 2.5	1.3 ± 2.5*	0.0 ± 2.0
Family life	5.6 ± 2.6	5.9 ± 2.6	4.1 ± 2.5	5.8 ± 2.4	1.4 ± 2.7*	0.0 ± 2.6

[a]Data are shown as mean ± SD. Statistical analysis was performed using an analysis of variance comparing changes for quetiapine and placebo.
[b]The baseline score of 4.0 ± 0.0 was not actually measured, but was inferred post factum as a reference point to the later changing scores.
[c]N = 29.
*p < .05.
**p < .01.
Abbreviations: BABS = Brown Assessment of Beliefs Scale, CGI-I = Clinical Global Impressions-Improvement scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, ITT = intent to treat, LOCF = last observation carried forward, SDS = Sheehan Disability Scale, SRI = serotonin reuptake inhibitor, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 2. Change in Y-BOCS Total Scores by Visit for OCD Patients Receiving an SRI Plus Quetiapine (N = 19) or an SRI Plus Placebo (N = 18)



*Significant difference from the placebo group: F = 11.1, df = 1,35; p = .002.
†Significant difference from the placebo group: F = 8.6, df = 1,35; p = .006.
‡Significant difference from the placebo group: F = 13.8, df = 1,35; p = .001.
Abbreviations: OCD = obsessive-compulsive disorder, SRI = serotonin reuptake inhibitor, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Table 4. Side Effects Reported in Treatment Groups

	SRI + Placebo (N = 20)		SRI + Quetiapine (N = 20)	
Side Effect	N	%	N	%
Somnolence	7	35	19	95
Dry mouth	8	40	11	55
Weight gain	…	…	6	30
Dizziness	…	…	6	30
Increased appetite	…	…	4	20
Problems with concentration	…	…	3	15
Sweating	6	30	2	10
Change in mood	3	15	2	10
Nightmares	…	…	2	10
Asthenia	…	…	2	10
Muscular pain	…	…	2	10
Palpitations	2	10	…	…
Diarrhea	2	10	…	…

Abbreviation: SRI = serotonin reuptake inhibitor.

of 49% within 4 weeks of treatment. It is of note that 8 of 11 had a comorbid chronic tic disorder. In the risperidone addition study by McDougle et al.,[16] 9 of 18 patients were rated as responders with a mean Y-BOCS decrease of 31% within 3 weeks of treatment. Three of 9 patients had a comorbid chronic tic disorder, and there was no difference in response between patients with and without comorbid tics.

Contrary to the results from our open-label quetiapine trial, a significant reduction in both HAM-A and HAM-D scores was observed in the current study. This finding is at odds with the haloperidol addition study,[29] which was not associated with a significant change in HAM-A or HAM-D scores, but is consistent with the risperidone addition trial,[16] in which a significant change in HAM-A and HAM-D scores was observed.

Clinical Features of Quetiapine Addition to SRIs

Although quetiapine was generally well tolerated, the majority of patients suffered from somnolence. This side effect, possibly due to the potent antihistaminergic prop-

erty of quetiapine, was repeatedly rated as moderate to severe. To counter this side effect, we adapted the dosing scheme by replacing the dose of 100 mg/day with doses of 25 mg 4 times per day. Eight patients reported benefiting from this change in dosing scheme. Furthermore, it is interesting to note that the response to quetiapine addition was similar to that reported in other addition trials and took place within 4 to 6 weeks. This rapid response is remarkable compared with the delay in effect seen with SRIs. Another clinical observation worth noting is that the pretreatment severity of obsessions predicted a favorable response. Responders to quetiapine addition were patients with higher Y-BOCS obsessional subscale scores. This finding appears compatible with the results of the recent risperidone addition study by Baxter et al.[30] Interestingly, Trethowan and Scott[31] observed a similar favorable outcome for obsessive symptoms in an early study with chlorpromazine monotherapy.

In contrast to what we expected, the reduction in Y-BOCS obsessional subscale scores was not accompanied by a statistically significant decrease in BABS ratings. Nevertheless, a mean reduction of 3.1 on the BABS might still be clinically significant, all the more since the decrease in the placebo group was negligible (0.5), which suggests that quetiapine addition had some effect. The BABS was felt to be a clinically valuable measure, but we were unable to rate all patients, as some of them were unable to express their obsessions explicitly. Hence, the lack of a significant decrease on the BABS might be due to our limited sample size (29 patients). Taken together, our observations suggest that response to addition of quetiapine takes place relatively rapidly and is especially promising for patients with severe obsessions. Our study confirms that "pure" OCD may be associated with serotonin-dopamine alterations and that patients with "pure" OCD might require conjoint SRI/antipsychotic therapy for effective symptom reduction rather than merely the subgroup of OCD patients with comorbid tic disorders or Tourette's disorder as was originally stated in the first placebo-controlled antipsychotic addition study.[29]

Mechanism of Action and Possible Implications for the Pathophysiology of OCD

There are several possible explanations for the efficacy of quetiapine addition for OCD patients refractory to SRIs. The first is a pharmacokinetic interaction between quetiapine and SRIs. Quetiapine and its metabolites are weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6, and 3A4 enzymes, albeit at concentrations 10- to 50-fold higher than were used in this study (maximum dose of 300 mg/day). Therefore, it is unlikely that quetiapine would enhance the efficacy of SRIs by inhibiting their metabolism. Unfortunately, we did not have blood levels of SRIs to rule out a possible pharmacokinetic interaction. Next, a number of possible pharmacodynamic hypotheses may be advanced. One is that the enhanced therapeutic response could be caused by a direct effect of quetiapine. Insofar as OCD has been linked to deficient serotonergic activity, it is tempting to ascribe the beneficial effect of quetiapine to its 5-HT_{2A}– and/or 5-HT_{2C}–blocking properties. The basal ganglia, which make up a brain region implicated in the pathophysiology of OCD, are heavily endowed with these receptors. However, the lack of efficacy of clozapine monotherapy in OCD, which also has a strong affinity for 5-HT_{2A} and 5-HT_{2C} receptors, argues against this reasoning.[32] Moreover, if the 5-HT_{2A} receptor were involved, one would expect mirtazapine, a 5-HT_{2A} antagonist, to be effective as well; however, this is not the case.[33] Another possibility is the antagonism on D_1 or D_2 receptors. It has been demonstrated in several animal models that both D_1 and D_2 receptors may play an important role in OCD.[34] Particularly, specific D_1 receptor blockade may be of interest, as this may decrease the "tone" in the orbitofrontal, ventromedial caudate direct pathway, which is hypothesized to be the cause of obsessive-compulsive symptoms.[35] However, given the weak affinity of quetiapine for D_1 and D_2 receptors compared with other antipsychotics, it is unlikely that this direct antagonism is the principal mechanism of action. To date, no studies have been published in which selective D_1 or D_2 antagonists were administered as monotherapy.

Alternatively, one might hypothesize that the enhanced therapeutic response with quetiapine addition is caused by a specific synergistic quality of the combination of SRIs with antipsychotics. Thus, both the enhancement of synaptic availability of 5-HT through blockade of the 5-HT transporter and serotonergic antagonism (5-HT_{2A}/5-HT_{2C}), dopaminergic antagonism (D_1/D_2), or both of the latter would be necessary for therapeutic efficacy. In the case of combined serotonin enhancement and serotonergic antagonism, the combination of an SSRI with mirtazapine or mianserin would be beneficial. Unfortunately, no studies have been published in which any of these selective drugs were used to augment SRIs. Recently, Marek et al.[36] suggested that the enhanced clinical efficacy of SRIs with atypical antipsychotics resulted from blockade of 5-HT_{2A} coincident with activation of non–5-HT_{2A} serotonergic receptors. This interesting hypothesis certainly may account for the efficacy of atypical antipsychotics such as risperidone, olanzapine, and quetiapine but not for the efficacy of haloperidol, which is 30-fold more potent at the D_2 receptor than at the 5-HT_{2A} receptor. The efficacy of haloperidol and pimozide as adjuncts to SSRIs favors the significance of a dopaminergic antagonism. On the other hand, if a combined 5-HT_{2A}/D_2 antagonism accounts for the efficacy of addition of atypical antipsychotics, one would expect that clozapine, loxapine, and chlorpromazine, which have higher ratios of affinity for the 5-HT_{2A} receptor over the D_2 receptor are as favorable

as augmenting agents as are risperidone, olanzapine, and quetiapine.[37] Unfortunately, no studies with these drugs have been published.

Determining the precise mechanism of the synergism of the combination of antipsychotics with SRIs presents a daunting challenge. Preclinical studies have revealed that the combination of olanzapine or clozapine with fluoxetine or sertraline resulted in a robust and sustained increase of extracellular dopamine and norepinephrine levels in the prefrontal cortex. These increases were significantly higher than the increases achieved with either drug in monotherapy.[38] Using similar microdialysis techniques as applied in the aforementioned studies, we found that the increase of extracellular dopamine in the prefrontal cortex following coadministration of fluvoxamine with quetiapine was higher than the increase detected after administration of either drug alone.[39] This synergistic effect on dopamine levels did not apply to changes in extracellular serotonin levels, nor was it observed in other brain areas such as the striatum and the nucleus accumbens. Although they are preliminary, we might infer from these observations that the combination of an SRI with an atypical antipsychotic results in a unique synergistic effect on extracellular dopamine levels in the prefrontal cortex. Changes in dopamine activity within the prefrontal cortex may be critical for OCD, as it is suggested that dopamine coordinates the long-term extinction of fear conditioning and modulates the neural interaction between the prefrontal cortex, hippocampus, and amygdala.[40] Additional research must be conducted to determine whether changes in extracellular dopamine levels may account for the clinical efficacy of addition strategies with atypical antipsychotics in treatment-refractory OCD.

Study Limitations

A limitation of the present study is that the observation of response to addition with quetiapine is restricted to an acute effect. It remains to be determined whether the addition of quetiapine is able to maintain a long-term response in patients with OCD. Recently, a study by Maina et al.[41] retrospectively evaluated whether antipsychotic discontinuation resulted in a relapse. Fifteen of 18 patients relapsed within 2 months of discontinuation (relapse was defined as a $>35\%$ increase on the Y-BOCS). Another limitation of our study design is that we cannot rule out that the effect we observed was due to quetiapine alone. This would be unexpected, in view of the lack of efficacy of clozapine monotherapy. Nevertheless, given the profusion of recently published studies with atypical antipsychotics in addition to SRIs, further controlled research on the issue remains indispensable to clarify this aspect. Furthermore, we cannot rule out that the beneficial response of quetiapine was due to a general anxiolytic effect rather than a primary anti–obsessive-compulsive effect. The decrease in HAM-A scores that was significantly correlated to the reduction in Y-BOCS scores lends support to this assumption. In addition, quetiapine addition to SRIs appears to be effective in a number of anxiety and mood disorders. Since most patients reported somnolence, it may also be argued that the effect of quetiapine was nonspecific due to sedation. However, in that case, we should expect all patients to have improved on quetiapine treatment, since 19 of 20 patients suffered from somnolence. Another limitation of the current study is that the OCD sample was free of comorbid diagnoses, and therefore our findings might not be generalizable to an OCD sample with comorbidity.

In summary, the results of this study indicate that addition of quetiapine to SRIs is a safe and effective treatment option for patients with SRI-refractory OCD. The response to addition with quetiapine takes place relatively rapidly and is especially promising for patients with severe obsessions.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclo, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), loxapine (Loxitane and others), mirtazapine (Remeron), olanzapine (Zyprexa and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft).

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