Quetiapine Augments the Effect of Citalopram in Non-Refractory Obsessive-Compulsive Disorder: A Randomized, Double-Blind, Placebo-Controlled Study of 76 Patients

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Objective: To assess the efficacy of quetiapine addition to citalopram in treatment-naive or medication-free obsessive-compulsive disorder (OCD) patients.

Method: Seventy-six patients who met DSM-IV criteria for OCD and who were drug-free or drug-naive at entry were randomly assigned in a 10-week, double-blind trial with citalopram (60 mg/day) plus quetiapine (300–450 mg/day) or placebo; treatment-refractory OCD patients were excluded. Of the 76 eligible patients, 66 patients completed the trial—31 in the quetiapine and 35 in the placebo group. The change from baseline to endpoint on the total Yale-Brown Obsessive Compulsive Scale (YBOCS) and the response to treatment in the quetiapine addition compared with the placebo addition group were the primary outcome measures. Response was defined as a 35% or greater reduction on the YBOCS and a Clinical Global Impressions-Improvement (CGI-I) score at endpoint of 1 or 2. The study was conducted from November 2003 to June 2005 at the University Medical Centre Utrecht, The Netherlands.

Results: As measured by the mean reduction in YBOCS scores following an intent-to-treat, last-observation-carried-forward analysis, quetiapine addition (11.9) was significantly superior to placebo (7.8; p = .009). Quetiapine addition was also significantly superior to placebo on the CGI-I scale, with a mean ± SD CGI-I score of 2.1 ± 1.3 versus 1.4 ± 1.2, respectively (p = .023). Quetiapine addition (N = 22, 69%) was also associated with a significantly greater number of patients responding to treatment compared with placebo addition (N = 15, 41%; p = .019). More patients receiving quetiapine (N = 8) than placebo (N = 2; NS) discontinued treatment due to adverse events.

Conclusions: The combination of quetiapine and citalopram was more effective than citalopram alone in reducing OCD symptoms in treatment-naive or medication-free OCD patients.

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Serotonin reuptake inhibitors are currently the mainstay for treatment of obsessive-compulsive disorder (OCD). Selective serotonin reuptake inhibitors (SSRIs), with a better side-effect profile and tolerability than clomipramine, have greatly improved the outlook of patients with OCD when combined with cognitive-behavioral therapy. However, a substantial number of patients fail to respond to SSRIs even after switching to another effective treatment. It is estimated that 30% to 40% of OCD patients are nonresponders to treatment, and patients who do respond to treatment are commonly left with residual symptoms.[1,2] In addition, it takes patients at least 8 to 12 weeks to respond to SSRI treatment. A higher response rate and/or an earlier and greater improvement are therefore unmet needs in the treatment of OCD.

To date, several studies have reported on the usefulness of atypical antipsychotics to augment the response to SSRIs in patients with refractory OCD. Randomized clinical trials have revealed the efficacy of risperidone, olanzapine, and quetiapine in combination with an SSRI.[3–11] These findings have recently been confirmed by 3 meta-analyses showing that adding atypical antipsychotics to SSRIs is an effective strategy with which to augment the response in treatment-refractory OCD patients.[12–14] Treatment-refractory OCD patients, however, may constitute a subgroup of OCD patients, and the results of augmentation trials in refractory

OCD patients can therefore not readily be expanded to all OCD populations. To the best of our knowledge, no controlled clinical trial on the efficacy of atypical antipsychotics as add-on medication to SSRIs has been conducted in nonrefractory OCD patients.

The aim of the present study was to evaluate the usefulness of combining an atypical antipsychotic with an SSRI in OCD patients who had never received appropriate treatment for their condition. The study was conducted with quetiapine because of its low propensity to elicit extrapyramidal and neuroendocrine side effects. Its efficacy in treatment-refractory OCD patients was reported in a controlled study; the response rate in this population of OCD patients amounted to 40%.[5]

METHOD

Patient Selection

Patients were recruited through clinical referrals to the outpatient clinic for Anxiety Disorders at the University Medical Centre Utrecht from November 2003 to June 2005. Patients, male or female, aged 18 years or older, met DSM-IV criteria for OCD based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[15] and had baseline scores of 17 or more on the total Yale-Brown Obsessive Compulsive Scale (YBOCS)[16,17] or of at least 11 if only obsessions or compulsions were present. Patients were in good physical health based on medical history, physical examination, vital signs, an electrocardiogram (ECG), and laboratory testing (hematology, blood chemistry, and urinalyses). Patients were excluded from the study for any of the following reasons: (1) current or past use of antipsychotics and/or serotonin reuptake inhibitors (including clomipramine) at an effective dose for at least 8 weeks; (2) current but not lifetime major depressive disorder or a rating of more than 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D)[18]; (3) a positive pregnancy test or nursing; (4) not using a medically accepted contraceptive for fertile women; (5) current or past history of 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 psychotic disorder; substance-related disorders within the past 6 months; or personality disorders based on the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II)[19]; (6) comorbid tic or Tourette's disorder; (7) any clinically significant acute or unstable medical condition or clinically significant ECG or laboratory abnormalities; (8) known allergy to quetiapine or citalopram; (9) behavioral or cognitive therapy 3 months prior to screening; or (10) suicide risk. The Utrecht Medical Ethical Review Committee of the University Medical Center (The Netherlands) approved the study and, after complete description of the study to the patients, written informed consent was obtained before enrollment.

Study Design

A double-blind, placebo-controlled, 10-week study design was used to compare the efficacy and tolerability of quetiapine addition to citalopram in OCD patients. Patients were randomly assigned to receive either citalopram with quetiapine or citalopram with placebo using a fixed-dose schedule. Citalopram treatment was initiated at 20 mg/day and gradually increased every 2 weeks with 20 mg/day up to a maximum dosage of 60 mg/day. The dosage of quetiapine was escalated gradually from 50 mg/day on day 1 to 100 mg/day on day 2, 200 mg/day on day 15, and 300 mg/day on day 43. In case of insufficient response, the dosage could be increased to 450 mg/day on day 57. Quetiapine was administered in capsules of 25 mg and 100 mg and patients took the study drug once or twice daily, depending on the tolerability. Both placebo and quetiapine were packaged identically, and each subject received the appropriate dosage.

Efficacy Measures

The primary outcome measure was the mean change from baseline to endpoint on the total score of the YBOCS in the intent-to-treat (ITT) population using the last-observation-carried-forward (LOCF) analysis. The YBOCS assessment was performed at screening, baseline, and at study weeks 2, 3, 4, 6, 8, and 10. Two trained, blinded investigators (N.C.V. and S.B.F.) completed YBOCS ratings at baseline and endpoint with intraclass correlation coefficients ranging from 0.96 to 0.99 at baseline and endpoint, respectively.

Other outcome measures were the Clinical Global Impressions-Severity of Illness scale (CGI-S),[20] the Clinical Global Impressions-Improvement scale (CGI-I),[20] the Hamilton Rating Scale for Anxiety (HAM-A),[21] the Brown Assessment of Beliefs Scale (BABS),[22] the Padua Inventory,[23] the Schizotypal Personality Questionnaire (SPQ),[24] the self-report version of the YBOCS (YBOCS-SR),[25,26] and the Sheehan Disability Scale (SDS).[27] These measures were completed at the screening and baseline visits and at study weeks 2, 3, 4, 6, 8, and 10 by a trained, blinded investigator. The HAM-D was completed at the screening and baseline visits and at study weeks 6 and 10 by a trained, blinded investigator. Response to treatment was defined as (1) a $\geq 35\%$ decrease in YBOCS score and (2) a final CGI-I rating of 1 ("very much improved") or 2 ("much improved").

Safety, Tolerability Measures

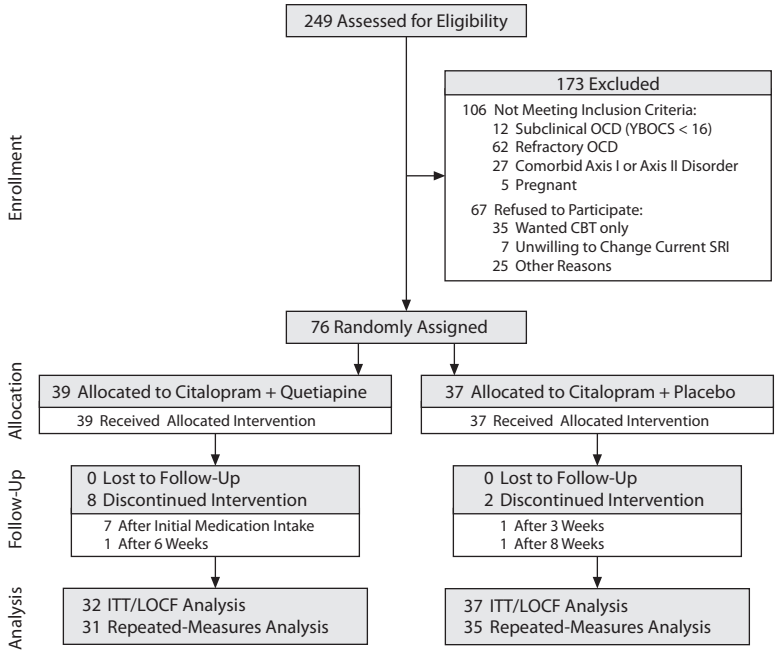
Any spontaneously reported or observed adverse events were recorded at each visit with regard to time of onset, duration, and severity. No concomitant medications were allowed. Vital signs, including blood pressure, pulse rate, and weight were obtained at each visit. The St. Hans Rating Scale for extrapyramidal syndromes (SHRS)[28] was used to evaluate extrapyramidal side effects at each visit, and the Arizona Sexual Experience Scale (ASEX)[29] was

administered to evaluate sexual function at baseline, study week 6, and endpoint. Blood samples for plasma drug-level determinations were collected at each assessment. Plasma levels of citalopram and quetiapine were determined by using high-performance liquid chromatography with fluorescence detection.

Data Analysis

All primary and secondary outcome measures were analyzed in the ITT population, consisting of all randomly assigned patients who took at least 1 dose of medication and who had at least 1 valid postbaseline assessment. For continuous variables the mean change from baseline to endpoint, using the LOCF principle, was analyzed using a 2-way analysis of variance (ANOVA). Appropriate tests for normality and homogeneity were also performed. In addition, repeated-measures ANOVAs with baseline value as covariate further tested time effects, treatment effects, and the time-by-treatment interactions on the dependent measures between groups for the completer data sets. The univariate statistics were applied to the repeated-measures analyses unless the test for compound symmetry failed, in which case the Huynh-Feldt statistics were used. For continuous variables, the sample t tests for independent groups or the Mann-Whitney U test, when tests of homogeneity were violated, was used to compare groups. The χ^2 analysis or the Fisher exact test was used for dichotomous variables. The Pearson product moment correlation coefficient was used to examine correlations between variables. The incidence of adverse events was based on the number of patients who reported a given treatment-emergent event. All tests were 2-tailed, and an α level of .05 was used to determine statistical significance. Data were analyzed with SPSS software version 14.0 (SPSS Inc., Chicago, Ill.).

Figure 1. Patient Flow Diagram



Abbreviations: CBT = cognitive-behavioral therapy, ITT = intent to treat, LOCF = last observation carried forward, OCD = obsessive-compulsive disorder, SRI = serotonin reuptake inhibitor, YBOCS = Yale-Brown Obsessive Compulsive Scale.

RESULTS

Patient Characteristics

Two-hundred forty-nine patients were screened for eligibility, of whom 143 met the entrance criteria for the study. Seventy-six out of 143 eligible patients were randomly assigned and received study medication; the remainder of patients refused to participate in the study for various reasons (Figure 1). Thirty-nine patients were randomly assigned to the quetiapine group and 37 to the placebo group. Seven patients randomly assigned to the quetiapine group discontinued treatment after the first administration of the drug because of adverse events (severe sedation, N = 4; palpitations, N = 1; and dizziness, N = 2). Three other patients discontinued treatment because of adverse events or lack of motivation, 1 in the quetiapine group (after 6 weeks of treatment) and 2 in the placebo group (after 3 and 8 weeks of treatment). Sixty-six patients (31 in the quetiapine and 35 in the placebo group) completed the 10-week trial.

Baseline demographic and clinical characteristics are summarized in Table 1. Besides significantly higher BABS scores at baseline in the quetiapine group ($p = .05$), no statistically significant differences were found in baseline characteristics among the groups. About 50% of the patients in both treatment groups were psychotropic drug–naive and the remainder had been treated with SSRIs in the past but not in an effective OCD dosage and for at least 8 weeks. There were no notable differences in demographic or clinical variables between patients who discontinued treatment and those who completed the study.

Efficacy Endpoints

The primary efficacy parameter was the change in total YBOCS score from baseline to endpoint in the ITT population. Statistical analysis showed that quetiapine addition was superior to placebo with a mean decrease of 11.9 and 7.8 ($F = 7.4$, $df = 1$, $p = .009$) for quetiapine and placebo, respectively (Table 2). Twenty-two patients in the quetiapine group

Table 1. Baseline Demographic and Clinical Characteristics of Patients With Non-Refractory Obsessive-Compulsive Disorder Treated With Quetiapine or Placebo

Variable	Quetiapine (N = 39)	Placebo (N = 37)	
Sex, N (%)			
Male	17 (44)	20 (54)	(χ^2 = 0.83, df = 1, p = .36)
Female	22(56)	17 (46)	
Age at trial entry, mean (SD), y	35 (12)	34 (11)	(F = 0.34, df = 1,74; p = .56)
Age at onset, mean (SD), y	16 (8)	17 (9)	(F = 0.29, df = 1,74; p = .41)
Duration of illness, mean (SD), y	19.0 (12.1)	16.9 (12.3)	(F = 0.57, df = 1,74; p = .45)
Drug-naive patients, N (%)	14 (36)	17 (46)	(χ^2 = 0.79, df = 1, p = .37)
Patients who ever used SSRIs, N (%)	25 (64)	20 (54)	(χ^2 = 0.79, df = 1, p = .37)
Patients who ever received CBT, N (%)	13 (33)	12 (32)	(χ^2 = 0.007, df = 1, p = .93)
Patients with comorbid disorders present at time of intake, N (%)	17 (44)	23 (62)	(χ^2 = 1,94, df = 1, p = .16)
Depression	5 (13)	8 (22)	
Dysthymic disorder	1 (3)	1 (3)	
Panic disorder without agoraphobia	3 (8)	2 (5)	
Panic disorder with agoraphobia	1 (3)	3 (8)	
Social phobia	3 (8)	4 (11)	
Generalized anxiety disorder	1 (3)	0 (0)	
Body dysmorphic disorder	3 (8)	2 (5)	
Hypochondria	2 (5)	5 (14)	
Trichotillomania	1 (3)	2 (5)	
Kleptomania	0 (0)	1 (3)	
Skin picking	3 (8)	3 (8)	
Tics	3 (8)	2 (5)	
Rating scale scores, mean ± SD			
YBOCS			
Obsessions	13.7 ± 2.9	13.8 ± 1.8	(F = 0.89, df = 1,74; p = .76)
Compulsions	12.7 ± 4.7	13.7 ± 2.1	(F = 1.38, df = 1,74; p = .24)
Total score	26.4 ± 5.7	27.5 ± 3.4	(F = 1.05, df = 1,74; p = .31)
HAM-A	13.3 ± 7.0	13.2 ± 7.2	(F = 0.01, df = 1,74; p = .92)
HAM-D	9.0 ± 4.0	9.0 ± 4.3	(F = 0.04, df = 1,74; p = .84)
GAF	56.2 ± 6.4	56.8 ± 7.7	(F = 0.137, df = 1,74; p = .71)
SDS work	7.0 ± 2.4	6.0 ± 2.4	(F = 2.61, df = 1,74; p = .11)
SDS social	6.5 ± 2.4	6.0 ± 2.5	(F = 0.72, df = 1,74; p = .40)
SDS family	7.0 ± 2.3	7.0 ± 2.0	(F = 0.01, df = 1,74; p = .91)
BABS	5.3 ± 4.8	7.1 ± 4.5	(F = 3.85, df = 1,55; p = .05)

Abbreviations: BABS = Brown Assessment of Beliefs Scale, CBT = cognitive-behavioral therapy, GAF = Global Assessment of Functioning scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, SDS = Sheehan Disability Scale, SSRIs = selective serotonin reuptake inhibitors, YBOCS = Yale-Brown Obsessive Compulsive Scale.

versus 15 in the placebo group were classified as responders to treatment; the difference was statistically significant (χ^2 = 5.5, df = 1, p = .019). Repeated-measures analysis for the total YBOCS scores revealed a significant treatment-by-time interaction (F = 3.32, df = 6, p = .003), indicating that quetiapine was more effective than placebo in augmenting the effect of citalopram. Repeated-measures analyses for the YBOCS obsession and compulsion subscores revealed a significant time-by-treatment interaction for the obsession subscore (F = 3.01, df = 6, p = .012) but not for compulsions (F = 1.33, df = 6, p = .31).

The decrease in YBOCS total score (r = –0.24, p = .046) and the decrease in YBOCS obsession subscore (r = –0.23, p = .048) correlated negatively with the pretreatment YBOCS obsession severity score. The decrease in YBOCS compulsion subscore (r = .24, p = .036) positively correlated with pretreatment YBOCS total score. No statistically significant correlation was found between any of the other outcome measures. Responders and nonresponders did not differ on any of the baseline measures.

The mean change from baseline to endpoint on the CGI-I in the ITT population was significantly larger for quetiapine compared to placebo (F = 5.4, df = 1, p = .023). In the quetiapine group, 11 patients were "very much improved," and 14 were "much improved," whereas in the placebo group, 5 were rated as "very much improved" and 16 were "much improved." Repeated-measures analysis for the completer set revealed a significant mean treatment effect (F = 7.0, df = 6, p = .0001), but no treatment-by-time interaction (F = 1.3, df = 6, p = .25) (Figure 2).

Baseline scores, endpoint scores, and mean changes in HAM-A, HAM-D, BABS, SPQ, YBOCS-SR, Padua Inventory, and SDS scores are listed in Table 2. Repeated-measures analysis revealed a significant treatment-by-time interaction for the HAM-A (F = 2.2, df = 6, p = .05) and HAM-D (F = 4.5, df = 2, p = .013) scores. The univariate ANOVA analysis revealed superior efficacy in the quetiapine group versus the placebo group for the reduction in SPQ scores (F = 6.5, df = 2, p = .013). No significant differences were found in the reduction in YBOCS-SR, Padua Inventory, SDS, and BABS scores between the quetiapine group and the placebo group.

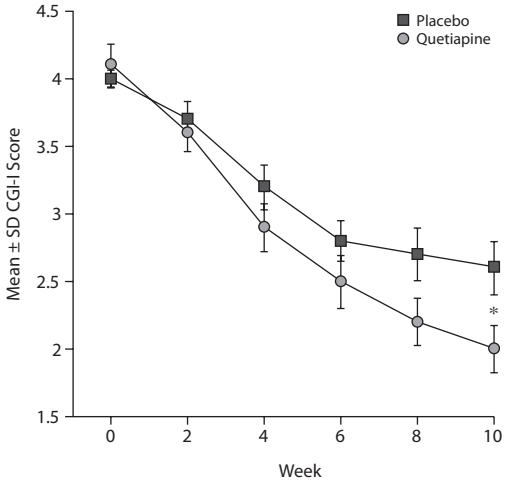
Significant correlations were found between total YBOCS scores and total YBOCS-SR scores at all study

Table 2. Differential Efficacy (ITT, LOCF) in Citalopram Plus Placebo and Citalopram Plus Quetiapine Groups

	Citalopram + Placebo (N = 37)			Citalopram + Quetiapine (N = 32)				
Rating Scale Scores, Mean ± SD	Baseline	Endpoint	Change	Baseline	Endpoint	Change	F (U)	p
YBOCS	26.4 ± 6.1	18.4 ± 8.0	7.8 ± 6.5	27.5 ± 3.5	15.7 ± 6.5	11.9 ± 7.0	7.4	.009
CGI-S	5.5 ± 0.7	4.2 ± 1.1	1.3 ± 1.0	5.4 ± 0.5	4.0 ± 1.2	1.4 ± 1.2	U = 540.5	.98
CGI-I	4.0 ± 0.4	2.5 ± 1.2	1.4 ± 1.2	4.1 ± 0.8	2.0 ± 1.0	2.1 ± 1.3	5.4	.023
HAM-A	13.4 ± 6.9	9.6 ± 6.8	3.8 ± 7.0	13.2 ± 7.4	6.9 ± 3.9	6.6 ± 6.0	2.2	.05
HAM-D	9.1 ± 4.0	6.9 ± 5.4	2.1 ± 5.8	8.9 ± 4.3	4.8 ± 2.3	4.2 ± 4.1	4.5	.013
SDS work	7.0 ± 2.4	4.4 ± 3.3	2.7 ± 3.3	5.9 ± 2.3	3.8 ± 2.9	2.3 ± 2.5	0.29	.59
SDS social	6.4 ± 2.4	4.3 ± 3.0	2.4 ± 3.2	5.7 ± 2.7	2.9 ± 2.4	3.1 ± 2.3	1.0	.32
SDS family	7.1 ± 2.2	4.8 ± 3.0	2.0 ± 3.1	7.0 ± 2.0	4.0 ± 2.7	2.8 ± 2.7	1.3	.27
BABS	5.1 ± 4.4	2.7 ± 3.2	3.0 ± 4.7	7.0 ± 4.4	3.3 ± 3.2	3.6 ± 3.8	0.2	.69
YBOCS-SR	31.9 ± 9.5	25.5 ± 9.9.	6.9 ± 8.6	32.2 ± 7.0	21.8 ± 10.5	10.5 ± 10.7	1.6	.21
Padua	59.7 ± 22.0	51.4 ± 26.5	9.6 ± 22.6	64.5 ± 23.0	46.8 ± 27.3	19.8 ± 21.7	2.0	.16
SPQ	19.6 ± 11.0	17.9 ± 10.7	1.5 ± 7.0	18.4 ± 11.9	13.0 ± 11.5	7.0 ± 9.6	6.5	.013

Abbreviations: BABS = Brown Assessment of Beliefs Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness 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, SPQ = Schizotypal Personality Questionnaire, YBOCS = Yale-Brown Obsessive Compulsive Scale, YBOCS-SR = Yale-Brown Obsessive Compulsive Scale–Self-Report.

Figure 2. CGI-I Scores by Visit for OCD Patients Receiving Citalopram Plus Quetiapine (N = 32) or Citalopram Plus Placebo (N = 37)



*Significant difference from the placebo group: F = 5.4, df = 1, p = .024.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, OCD = obsessive-compulsive disorder.

Table 3. Adverse Events Reported in Treatment Groups

Side Effect, N (%)	Citalopram + Placebo (N = 37)	Citalopram + Quetiapine (N = 39)	χ^2	df	p
Somnolence	21 (57)	33 (86)	8.48	1	.003
Sexual problems	16 (43)	16 (41)	0.008	1	NS
Weight gain	8 (22)	21 (54)	9.02	1	.003
Headache	13 (35)	10 (26)	0.446	1	NS
Dry mouth	5 (14)	13 (33)	4.79	1	.026
Tremor	10 (27)	6 (15)	1.122	1	NS
Nausea	14 (38)	2 (5)	10.80	1	.001
Sweating	10 (27)	5 (13)	1.89	1	NS
Dizziness	4 (11)	9 (23)	2.43	1	NS
Increased appetite	4 (11)	7 (18)	1.03	1	NS
Sleeplessness	11 (30)	0 (0)	12.40	1	< .001
Muscular pain	6 (16)	2 (5)	2.11	1	NS
Palpitations	4 (11)	3 (8)	0.13	1	NS
Concentration problems	4 (11)	3 (8)	0.13	1	NS

Abbreviation: NS = not significant.

weeks (r = 0.516–0.884, p < .0001) and between change in total YBOCS scores and change in YBOCS-SR scores (r = 0.760, p = .0001).

When we compared drug-naive and drug-free patients, no significant differences were found in mean changes of YBOCS, CGI, HAM-A, HAM-D, BABS, and SPQ scores.

Safety

The quetiapine treatment was well tolerated, and no serious adverse events occurred. Patients taking quetiapine reported a mean of 5 adverse events each, and patients taking placebo reported a mean of 4 adverse events each over the course of the trial. The most prevalent adverse events are presented in Table 3. Patients taking quetiapine significantly more often reported somnolence, weight gain, and dry mouth, whereas patients in the placebo group more often reported nausea and sleeplessness. The majority of adverse events in both treatment groups were mild or moderate in severity.

The mean ± SE increase in weight from baseline to endpoint was 2.7 ± 0.4 kg for patients treated with quetiapine, whereas in the placebo group the mean ± SE weight decrease was 0.7 ± 0.5 kg (F = 27.8, df = 1, p = .0001). The mean ± SE heart rate increased significantly more in the quetiapine group compared with placebo from baseline to endpoint (mean ± SE 6.5 ± 1.7 vs. 0.7 ± 2.1, F = 4.5, df = 1, p = .039). No ECG changes or other clinically significant laboratory changes or vital signs changes were found throughout the study. Interestingly, a significant increase, which was not clinically relevant as endpoint scores were still low, was found only in the placebo group on the SHRS to evaluate extrapyramidal side effects. Furthermore, an increase of ASEX scores was found in the quetiapine group, but ANOVA did not reveal significant differences between placebo and quetiapine.

Mean ± SE plasma levels of quetiapine were 40 ± 8.5 pg/mL at week 2 and 63 ± 8.9 pg/mL at week 10. The mean ± SE plasma citalopram levels were 50 ± 4.4 pg/mL at week 2, 140 ± 9.5 pg/mL at week 10 in the quetiapine group, 48 ± 6.0 pg/mL at week 2, and 81 ± 11.0 pg/mL at week 10 in the placebo group. The mean plasma levels of citalopram in the quetiapine group were significantly higher than in the placebo group ($t = -3.2$, $df = 53$, $p = .002$). No correlation was found between clinical improvement and plasma levels.

DISCUSSION

The present study shows that low doses of quetiapine can augment the efficacy of the SSRI citalopram in non-refractory OCD patients. Quetiapine addition to citalopram treatment was more effective than placebo addition on primary outcome measures. Twenty-two patients (69%) were rated as responders in the quetiapine group versus 15 (41%) in the placebo group. Administration of quetiapine, however, led to a higher number of patients discontinuing treatment prematurely because of adverse events. This is, to the best of our knowledge, the first randomized controlled clinical trial demonstrating the efficacy of atypical antipsychotic addition to SSRIs in drug-naive and drug-free OCD patients.

The response rate for citalopram alone in the present study is comparable to response rates (ranging from 25%–50%) reported for other SSRIs and clomipramine in OCD patients.[30–33] The only controlled clinical trial with citalopram in OCD patients reported rates slightly higher than found in the current study, i.e., 52% for 40 mg/day and 65% for 60 mg/day.[34] The latter study, however, had a relatively high placebo response rate (36.6%) in comparison to other clinical trials with SSRIs in OCD, which may have inflated the response rate. Furthermore, Montgomery et al.[34] used a less stringent response criterion (decrease in YBOCS score of ≥ 25%) compared to the present study (a decrease in YBOCS score of ≥ 35% and a CGI-I rating of 1 or 2), which could be another explanation for higher response rates in their study. Another variable that might affect the response rate is the duration of treatment. Given the steady decline in YBOCS scores between 8 and 10 weeks of treatment, it is likely that a full response had not yet been reached and that longer duration of treatment could have increased the number of responders.

Our results support and extend results of previous reports of successful treatment with quetiapine addition for treatment-refractory OCD patients. Three of 5 open-label studies and 1 single-blind, placebo-controlled study have shown a beneficial response of quetiapine addition to SSRIs in OCD.[35–39] In a placebo-controlled study from our group with quetiapine (300 mg/day), using the response criterion of a decrease on the YBOCS of ≥ 35% and a CGI-I rating of 1 or 2, 40% and 10% of the refractory OCD patients in the quetiapine and placebo group, respectively, were rated as responders.[5] Two other placebo-controlled studies with quetiapine in patients who were refractory or nonresponsive to treatment could not confirm this finding.[4,7] In the study of Carey et al.,[4] 40% and 48% of the patients in the quetiapine and placebo group, respectively, responded to treatment. In contrast to Denys et al.,[5] the latter study included predominantly nonresponders to a single SSRI trial rather than refractory patients. Another difference was that patients were treated for a much shorter period of time at a lower dose level. In a small placebo-controlled study, Fineberg et al.[7] found a response rate of 27% in the quetiapine group versus 10% in the placebo group; the difference between the 2 treatment conditions was not statistically significant. The latter study also included nonresponders but had a longer duration (16 weeks) than the trial reported by Carey et al.[4] However, 2 recent meta-analyses based on the raw data of these 3 controlled studies confirmed the efficacy of quetiapine addition in refractory OCD patients.[13,14]

Clinical Characteristics of Quetiapine Addition

An important difference between patients treated with quetiapine and those treated with placebo was tolerability. Patients reported substantially more severe side effects such as sedation while receiving quetiapine, resulting in premature discontinuation of quetiapine treatment in 8 patients. Seven patients already dropped out after the first administration, whereas only 2 patients taking placebo discontinued treatment due to adverse events. Sedation and somnolence were the most frequently reported side effects of quetiapine. Nevertheless, the total dropout rate of 13% due to adverse events is comparable to dropout rates due to adverse events in quetiapine addition trials in refractory-OCD patients (0%–17%),[4,5,7] and is also similar to those reported in a meta-analysis of pharmacologic trials with SSRIs in OCD patients (9%–13%).[40]

In contrast to the study by Denys et al.,[5] we did not observe a more rapid onset of action in the quetiapine group compared to the placebo condition. Differences in design and patient populations might explain this discrepancy. Another interesting clinical observation is that the difference between patients treated with quetiapine or placebo in total YBOCS scores at endpoint could be accounted for by the significant reduction of the obsession subscale score. This finding is in line with earlier studies suggesting a more favorable outcome for obsessive symptoms when antipsychotics are added to SSRIs.[5,9,41] This may suggest that the mechanism underlying obsessions and compulsions are different.

We also found significantly greater reductions in anxiety and depression symptoms as measured with the HAM-A and HAM-D scales in patients treated with quetiapine. This finding is in agreement with the results reported by Denys et al.[5] but at odds with the study of Carey et al.[4] Although there was a significant correlation between reductions on YBOCS and HAM-D scores, the therapeutic efficacy of

quetiapine addition was independent of mood, suggesting that the improvement of mood symptoms was secondary to the attenuation of OCD symptoms. We excluded patients with current primary major depressive disorder, and only 6 of 37 responders had a comorbid mood disorder.

A significant difference was also found in reductions of SPQ scores between patients taking quetiapine and patients taking placebo. Previous trials have already shown that the presence of schizotypal personality disorder is a good predictor of response to low-dose antipsychotic medication added to SRIs.[10,42] In addition, low-dose antipsychotic medication has been shown to be efficacious in treating non-OCD–related schizotypal personality disorder.[43,44] However, in the present study, patients with schizotypal personality disorder were excluded. Nevertheless, many patients of our sample showed some characteristics of schizotypal personality disorder that were effectively treated with quetiapine addition.

Study Limitations

The present study has several limitations. First, the study duration of 10 weeks could be criticized because the week 8 and 10 YBOCS slopes had not reached an asymptote. Second, although efforts were made to maintain blinding, differences in the rate and profile of adverse events may have partially unblinded the study and introduced bias. Third, common to most clinical OCD trials, patients with current major depressive disorder were excluded. We did include, however, patients with comorbid anxiety disorders, obsessive-compulsive spectrum disorders, and all lifetime anxiety and depressive comorbid disorders. Fourth, the beneficial response of quetiapine could be due to a general anxiolytic effect rather than a primary anti–obsessive-compulsive effect, as the decrease in HAM-A scores significantly correlated to the reduction in YBOCS scores. This finding corroborates the therapeutic efficacy of quetiapine addition in a number of anxiety and mood disorders. Fifth, sedation, as a side effect of quetiapine, could account for the therapeutic efficacy. However, almost all patients using quetiapine reported somnolence or sedation as a side effect, but not all patients were rated as responders. Furthermore, benzodiazepines do not yield therapeutic efficacy in OCD patients.[45,46] Sixth, a pharmacokinetic interaction between quetiapine and citalopram could account for the efficacy of quetiapine addition in OCD. Though quetiapine and its metabolites are only weak inhibitors of cytochrome P450 1A2, 2C9, 2C19, 2D6, and 3A4 isoenzymes, plasma citalopram levels in our quetiapine group were significantly higher after 10 weeks of treatment compared to placebo. However, there was no relationship between plasma citalopram level and response. Similar results were reported in a dose-effect study of citalopram in OCD patients, in which no linear relationship existed between steady-state plasma levels of citalopram and response.[47] On the other hand, citalopram metabolism is catalyzed by the CYP3A4 isoenzymes,[48–50] and this isoenzyme is also responsible for the metabolism of quetiapine. However, higher doses of quetiapine are not associated with a more beneficial response, and dose-response studies have not been performed.

CONCLUSIONS

In this study, the combination of quetiapine and citalopram was more effective than citalopram alone in reducing OCD symptoms in treatment-naive or medication-free OCD patients. These promising results should be duplicated in larger randomized, controlled trials of longer duration.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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