Quetiapine Addition to Serotonin Reuptake Inhibitor Treatment in Patients With Treatment-Refractory Obsessive-Compulsive Disorder: An Open-Label Study

Damiaan Denys, M.D.; Harold van Megen, M.D., Ph.D; and Herman Westenberg, Ph.D.

Objective: Although patients with obsessive-compulsive disorder (OCD) benefit from treatment with serotonin reuptake inhibitors (SRIs), it is estimated that 40% to 60% of the patients remain unimproved. The objective of this study was to examine whether addition of the atypical antipsychotic quetiapine to SRIs is useful for patients with OCD who do not respond to SRI monotherapy.

Method: Ten patients with OCD (DSM-IV criteria) who had not responded to at least 3 previous treatments with an SRI at maximum dose and duration were assigned to receive quetiapine in addition to an SRI for 8 weeks. Treatment response was assessed using the Yale-Brown Obsessive-Compulsive Scale (YBOCS).

Results: Seven of 10 patients responded to the quetiapine addition. The mean ± SD baseline YBOCS score of 31.4 ± 7.8 dropped to a mean of 20.8 ± 8.4 at endpoint with a mean reduction of 35.4%.

Conclusion: This is the first study to show that treatment-refractory OCD patients may benefit from addition of quetiapine to ongoing SRI therapy.

(J Clin Psychiatry 2002;63:700–703)

Received July 30, 2001; accepted Dec. 17, 2001. From the Department of Psychiatry, University Medical Center, Utrecht, the Netherlands.

The authors report no financial affiliation or other relationship relevant to the subject matter of this article.

Corresponding author and reprints: D. Denys, M.D., UMC, HP B.01.206, P.O. Box 85500 3508 GA Utrecht, the Netherlands (e-mail: D.A.J.P.denys@azu.nl).

Serotonin reuptake inhibitors (SRIs) are the most effective drug therapy available for obsessive-compulsive disorder (OCD). Nevertheless, 50% to 60% of patients with OCD fail to respond to a single trial of an SRI, and 20% to 40% do not respond sufficiently after several medication trials.[1] Therapeutic strategies in these resistant cases consist of augmentation therapies with, e.g., tryptophan, buspirone, clonazepam, and lithium or the addition of antipsychotics such as haloperidol and pimozide. Controlled studies using the former approach have yielded discouraging results. The latter approach involves the addition of low-dose antipsychotics to standard antidepressant treatment and has been shown to be effective in cases with comorbid chronic tic disorders.[2] Unfortunately, extrapyramidal side effects have limited the use of typical antipsychotics. Therefore, treatment with atypical antipsychotics that show fewer extrapyramidal symptoms might be a useful alternative for treatment-refractory OCD patients.

To date, a number of studies have been carried out with atypical antipsychotics in addition to SRIs for treatment-refractory OCD patients. Four open-label studies and 1 double-blind, placebo-controlled study have reported on the efficacy of risperidone, and 4 open-label studies and 1 double-blind, placebo-controlled study have reported on olanzapine. We have compared decreases in scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS)[3] between these studies (Table 1). The addition of risperidone for 72 patients produced a mean decrease in YBOCS score of 33%, while addition of olanzapine for 65 patients produced a mean decrease in YBOCS score of 28%. The effect of risperidone addition in the double-blind, placebo-controlled study of McDougle et al.[7] was higher than those observed in the open studies with risperidone. Interestingly, the mean decrease in YBOCS score in the double-blind, placebo-controlled trial with risperidone (31%) was substantially higher than that reported in the double-blind, placebo-controlled study with addition of olanzapine (19.5%).[12]

The atypical antipsychotic quetiapine has a receptor-binding profile similar to those of risperidone and olanzapine. Quetiapine has a binding affinity for serotonin 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} and dopamine D_1, D_2, and D_4 receptors.[13] Quetiapine has a lower receptor-binding affinity for 5-HT_{2A}, 5-HT_{2C}, and D_2 than olanzapine and risperidone.[14] However, the 5-HT_2/D_2 receptor affinity ratio of olanzapine and quetiapine is equal. Because of the similarities in receptor-binding profiles, one may expect quetiapine addition to be efficacious in relieving obsessive-compulsive symptoms in therapy-refractory patients. In this report, we describe a series of 10 patients with SRI-refractory OCD who were treated with quetiapine as an add-on to SRI treatment.

Table 1. Decrease in Yale-Brown Obsessive Compulsive Scale (YBOCS) Scores in Trials in Which Atypical Antipsychotics Were Added to Serotonin Reuptake Inhibitors[a]

Study	Drug	Type of Trial	Patients (N)	Decrease in YBOCS Score, % Mean	Median	SD
McDougle et al[2]	Risperidone	Open	3	54	56	10
Saxena et al[4]	Risperidone	Open	21	NA[a]	NA[a]	NA[a]
Stein et al[5]	Risperidone	Open	8	22	10	29
Pfanner et al[6]	Risperidone	Open	20	30	32	9
McDougle et al[7]	Risperidone	Double-blind	20	31	30	27
Weiss et al[8]	Olanzapine	Open	10	40	42	25
Koran et al[9]	Olanzapine	Open	10	16	9	22
Bogetto et al[10]	Olanzapine	Open	23	30	NA[a]	NA[a]
Francobandiera[11]	Olanzapine	Open	9	37	42	25
Bystritsky[12]	Olanzapine	Double-blind	13	20	NA[a]	NA[a]

[a]Individual YBOCS scores were not available.

METHOD

Subjects

Ten outpatients (7 women and 3 men) gave written informed consent for participation in the study, which had been approved by the University of Utrecht Medical Ethical Review committee (Utrecht, the Netherlands). The mean ± SD age of the subjects included in the study was 40.2 ± 12.8 years. Patients were diagnosed with primary OCD according to DSM-IV criteria; diagnoses were ascertained using the Mini-International Neuropsychiatric Interview.[15,16] Only patients with OCD symptoms of at least 5 years' duration and a score on the YBOCS of at least 18, or at least 12 if they exhibited only obsessions or only compulsions, were included. The subjects' mean ± SD baseline score on the YBOCS was 31.4 ± 7.8, and the mean duration of illness was 17.6 ± 8.6 years (Table 2). Nine patients had both obsessions and compulsions. Patients were asked to specify their principal symptoms (see Table 2). One patient (patient 10) had only obsessions with a predominant aggressive content and limited insight. Two patients met DSM-IV criteria for comorbid Axis I diagnoses: patient 9 had a history of chronic motoric tics and patient 10, generalized anxiety disorder. Three patients carried a comorbid DSM-IV Axis II disorder: patients 3 and 6, obsessive-compulsive personality disorder and patient 5, schizotypal personality disorder.

All patients failed at least 3 adequate treatments with an SRI at maximum dose (clomipramine 250 mg/day, fluvoxamine 300 mg/day, fluoxetine 80 mg/day, sertraline 225 mg/day, paroxetine 60 mg/day, venlafaxine 300 mg/day) and duration (12 weeks). Failure was defined as a less than 25% improvement on the YBOCS. Eight SRI-treatment–resistant patients had previously participated at our department in a double-blind, controlled comparison trial (N = 100) of 2 antidepressants (paroxetine, 60 mg/day, and venlafaxine, 300 mg/day, each for 12 weeks) to which they had failed to respond. Two patients came directly from physician referrals. Patients were healthy on the basis of results of physical examination, electrocardiogram, and screening tests of blood and urine.

Treatment

In an 8-week trial, all patients continued to take their current SRI at the maximum dose during addition. Nine patients received paroxetine, 60 mg/day, and 1 patient received venlafaxine, 300 mg/day. Quetiapine addition was initiated at a dose of 75 mg/day and gradually increased to 200 mg/day in week 4, using a fixed schedule of dosing (100 mg/day in week 2, 150 mg/day in week 3, 200 mg/day in week 4). From week 4, patients were kept on 200 mg/day.

No other psychotropic drugs were administered, and patients were not instructed in formal behavior techniques. Subjects were seen by the same trained rater at baseline and at the end of weeks 2, 4, 6, and 8, at which times clinical response and adverse events were evaluated. The rater was not blind to treatment and study hypotheses.

Assessment

The primary efficacy parameter was YBOCS score. Full response to treatment was prospectively defined as ≥ 50% decrease in YBOCS score and partial response, as ≥ 25% decrease in YBOCS score from the beginning. In addition, we administered at each visit the Hamilton Rating Scale for Anxiety (HAM-A) and the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[17,18] Adverse events were assessed at each visit by means of patients' spontaneous reports.

RESULTS

Seven of 10 patients completed the trial: patient 4 discontinued treatment after 4 weeks because of excessive sedation, patient 8 dropped out after 6 weeks because of hospital admission due to the severity of the disease, and patient 7 dropped out on week 6 because of lack of motivation. Three patients were full responders, with a mean decrease of 55% in YBOCS score. Four patients, of whom 1 had dropped out (patient 7), were partial responders with at least a 25% decrease. Three patients experienced no change in their obsessive-compulsive symptoms. In those who benefited from the treatment, improvement started within the first 2 weeks of the quetiapine addition. Three patients who were substantially impaired in their activities and social interaction due to obsessive-compulsive symptoms improved remarkably in their social skills. Patient 1, during treatment, went for the first time on a holiday and applied again for a job after several years of unemployment. Patient 3, who had severe ideas of precision that prevented him from opening his mail for 10 years, started

Table 2. Quetiapine Addition to Serotonin Reuptake Inhibitors (SRIs): Patient Characteristics and Outcome[a]

Patient No.	Age (y)	Sex	Duration of OCD (y)	Type of OCD Symptoms	Comorbid Diagnosis	Current SRI	Daily SRI Dose (mg)	Rating Scale Score: YBOCS Baseline	YBOCS Endpoint	HAM-A Baseline	HAM-A Endpoint	HAM-D-17 Baseline	HAM-D-17 Endpoint
1	37	F	10	Checking	None	Paroxetine	60	36	17	10	6	12	3
2	66	F	33	Contamination	None	Paroxetine	60	32	22	6	2	7	4
3	51	M	31	Precision	OCPD	Paroxetine	60	39	21	4	5	4	2
4[b] (NR)	23	M	10	Multiple	None	Paroxetine	60	30	30	0	3	0	1
5	41	M	17	Hoarding	Schizotypal personality disorder	Venlafaxine	300	32	24	5	5	5	4
6	38	F	20	Precision	OCPD	Paroxetine	60	36	13	8	6	6	3
7[b]	47	F	18	Precision	None	Paroxetine	60	32	18	13	5	14	5
8[b] (NR)	34	F	15	Checking	None	Paroxetine	60	40	37	22	30	21	21
9	23	F	15	Contamination	None	Paroxetine	60	23	19	18	2	13	8
10	42	F	7	Aggressive content	GAD	Paroxetine	60	14	7	28	10	20	15
Mean	40.2		17.6					31.4	20.8	11.4	7.4	10.2	7.5
SD	12.8		8.6					7.8	8.4	8.8	8.3	7.0	6.0

[a]Abbreviations: GAD = generalized anxiety disorder, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, NR = nonresponder, OCD = obsessive-compulsive disorder, OCPD = obsessive-compulsive personality disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.
[b]Dropout.

gradually to again read his letters. Patient 2, who had worried that an intruder may enter the house and repeatedly checked door and window locks, had avoided outdoors activities for a long time. During treatment, she visited her daughters several times.

In general, patients' mean YBOCS score (intent-to-treat analysis) decreased significantly (by 35.4%) from baseline to endpoint (paired 2-tailed t test: $t = 4.391$, $df = 9$, $p = .002$). In contrast to the data of McDougle et al.[7] and of Koran et al.,[9] we found no significant decrease in mean scores on the HAM-A and HAM-D-17 from baseline to endpoint. Nonetheless, 2 patients (patients 9 and 10) showed improvement as measured using the HAM-A, with a 50% reduction in score, while another patient (patient 8) got more anxious, resulting in a discontinuation from the study. These findings may indicate that the antiobsessive effect of the addition of quetiapine is independent of its antidepressant or anxiolytic activity.

Our findings show that quetiapine addition was generally well tolerated. The most common adverse effects were sedation (N = 7), followed by increased appetite (N = 2), mild akathisia (N = 2), and obstipation (N = 1). Two patients (patients 1 and 6) reported weight gain, but we failed to objectify the precise amount. As already mentioned, 1 patient dropped out because of excessive sedation (patient 4).

DISCUSSION

This study provides preliminary evidence that the addition of quetiapine to ongoing SRI treatment may be efficacious for therapy-refractory OCD patients. There are, however, limitations to the data presented due to the small sample size and the open-label design. In all, the results of our study are consistent with the findings of previous addition trials with risperidone and olanzapine. The rate of full responders in our sample with a cutoff of 50% decrease in YBOCS score was 30%, which is similar to the findings of Francobandiera[11] (33%) and approaches the results of Weiss et al.[8] (40%). With a cutoff of a 25% decrease in YBOCS score, the response rate in our study was 70%, comparable to the results of Pfanner et al.[6] (75%), Weiss et al.[8] (70%), and Francobandiera[11] (66%).

It is, however, difficult to compare the effect sizes between the different addition trials. Firstly, there is large variability in patient groups between studies. Saxena et al.[4] included OCD patients with comorbid schizophrenia, schizoaffective disorders, and Gilles de la Tourette's disorder, while Stein et al.[5] studied an uncomplicated OCD patient population. Supplementing SRIs with atypical antipsychotics shows benefits, but future studies should focus on patients with uncomplicated OCD. Secondly, there is some inconsistency in the definition of treatment refractoriness. Most studies included patients who had failed to respond to only 1 SRI trial. They should rather be qualified as treatment resistant. Only patients included in the study by Koran et al.[9] were truly treatment refractory, as they failed to respond to at least 3 adequate SRI treatments.[12] The more restrictive criterion for inclusion in the latter study may explain the lower mean decrease in YBOCS scores (16%). The problem of incomplete response is an area that merits further investigation, and clear criteria for nonresponse need to be agreed upon. Thirdly, the standards for response rates vary substantially. For responders, Weiss et al.[8] used a cutoff of 50% decrease in YBOCS score, while Francobandiera[11] chose a cutoff of 25%. McDougle et al.,[7] on the other hand, used a more restrictive criterion with a cutoff of 35% for YBOCS

decrease and a final score of 16 on the YBOCS in combination with a final Clinical Global Impressions scale rating of "much improved" or "very much improved." Such differences invalidate, unfortunately, the comparison of effect sizes between studies.

Regarding the mechanism of action, it is unlikely that pharmacokinetic interactions between atypical antipsychotics and SRIs account for the beneficial effect of the addition. As a result, several pharmacodynamic hypotheses have been advanced. Atypical antipsychotics may boost the action of SRIs through serotonin receptor blockade.[4] The broader range of effective treatment with the addition of atypical antipsychotics may be due to a D_2 blockade,[19] or a combined serotonergic-dopaminergic blockade may be required, particularly a 5-HT_{2A} and D_2 antagonism.[2]

On the basis of our preliminary experience, we have initiated a double-blind, placebo-controlled trial to establish the efficacy, tolerability, and safety of quetiapine in addition to SRIs for patients with SRI-refractory OCD. The addition of atypical antipsychotics to SRIs seems a promising pharmacotherapy intervention for treatment-refractory OCD patients. Besides the practical consequence of providing clinicians with a new pharmacologic approach, it should give impetus to new theoretical considerations on the pharmacologic treatment of OCD symptoms. Further investigations on the mechanism of action of these addition strategies for OCD are warranted.

Drug names: clonazepam (Klonopin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), olanzapine (Zyprexa), paroxetine (Paxil), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Goodman WK, Price LH, Rasmussen SA, et al. Efficacy of fluvoxamine in obsessive-compulsive disorder: a double-blind comparison with placebo. Arch Gen Psychiatry 1989;46:36–44
2. McDougle CJ, Fleischmann RL, Epperson CN, et al. Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. J Clin Psychiatry 1995;56:526–528
3. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 1: development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–1011
4. Saxena S, Wang D, Bystritsky A, et al. Risperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. J Clin Psychiatry 1996;57:303–306
5. Stein DJ, Bouwer C, Hawkridge S, et al. Risperidone augmentation of serotonin reuptake inhibitors in obsessive-compulsive and related disorders. J Clin Psychiatry 1997;58:119–122
6. Pfanner C, Marazziti D, Dell'Osso L, et al. Risperidone augmentation in refractory obsessive-compulsive disorder: an open-label study. Int Clin Psychopharmacol 2000;15:297–301
7. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2000;57:794–801
8. Weiss EL, Potenza MN, McDougle CJ, et al. Olanzapine addition in obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors: an open-label case series. J Clin Psychiatry 1999;60:524–527
9. Koran LM, Ringold AL, Elliott MA. Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry 2000;61:514–517
10. Bogetto F, Bellino S, Vaschetto P, et al. Olanzapine augmentation of fluvoxamine-refractory obsessive-compulsive disorder (OCD): a 12-week open trial. Psychiatry Res 2000;96:91–98
11. Francobandiera G. Olanzapine augmentation of serotonin uptake inhibitors in obsessive-compulsive disorder: an open study. Can J Psychiatry 2001;46:356–358
12. Bystritsky A. Augmentation of SSRI response in refractory OCD using adjunct olanzapine: a placebo-controlled trial. In: New Research Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 9, 2001; New Orleans, La. Abstract NR636:171–172
13. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors focus on newer generation compounds. Life Sci 2000;68:29–39
14. Kapur S, Seeman P. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics?: a new hypothesis. Am J Psychiatry 2001;158:360–369
15. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
16. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
17. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
18. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
19. Khullar A, Chue P, Tibbo P. Quetiapine and obsessive-compulsive symptoms (OCS): case report and review of atypical antipsychotic-induced OCS. J Psychiatry Neurosci 2001;26:55–59