Quetiapine Augmentation in Obsessive-Compulsive Disorder Resistant to Serotonin Reuptake Inhibitors: An Open-Label Study

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Background: The response of obsessive-compulsive disorder (OCD) to serotonin reuptake inhibitors (SRIs) is often inadequate. Case series reporting successful augmentation with risperidone and olanzapine led us to investigate quetiapine in OCD that was resistant to SRI treatment.

Method: In this 8-week, 2-site (S1, S2), open-label trial, 30 adults (16 at S1 and 14 at S2) with a DSM-IV diagnosis of OCD, SRI-resistant, received augmentation with quetiapine, with the dose doubled every 2 weeks from 25 mg to 200 mg/day. Primary outcome was measured with the Yale-Brown Obsessive Compulsive Scale (YBOCS). A response was defined as a ≥ 25% decrease from the baseline YBOCS score.

Results: Significant differences between the sites in patient characteristics (7/14 at S2 were hoarders, i.e., more treatment resistant, vs. 1/16 at S1; p = .01) and in quetiapine treatment (mean ± SD dose of 116 ± 72 mg/day at S2 vs. 169 ± 57 mg/day at S1; p = .039) necessitated separate analysis of results. At S1, the mean ± SD YBOCS score fell significantly from 27.7 ± 7.0 to 23.3 ± 8.4 (t = 2.96, df = 15, p = .01), and the responder rate was 31% (5/16). At S2, the mean YBOCS score did not decrease significantly, and the responder rate was 14% (2/14). Most adverse medication events were mild or moderate. Two subjects (13%) at S1 and 3 (21%) at S2 withdrew due to adverse events.

Conclusion: The results at S1 resemble those reported with other atypical antipsychotics and suggest that quetiapine augmentation may benefit treatment-resistant OCD. The poorer results at S2 may reflect the large proportion of hoarders or the less intense treatment. Longer, higher dose, large, double-blind, placebo-controlled comparison trials of atypical antipsychotics are needed.

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Although serotonin reuptake inhibitors (SRIs) are often effective for the treatment of obsessive-compulsive disorder (OCD), an estimated 40% to 60% of patients experience very limited improvement in symptoms despite adequate trials.[1] This limited treatment response has stimulated the investigation of many augmentation strategies for SRI-resistant OCD.[2] By 1999, when we designed the current study, small case series reported rapid, marked benefit from adding risperidone in SRI-unresponsive OCD[3–5] and, in 1 case, olanzapine.[6] The reduction of OCD symptoms often brought about by SRIs clearly suggested that 1 or more of the serotonin (5-HT) receptors might be involved in the disorder's pathophysiology. We noted that quetiapine had a pattern of serotonergic receptor–binding affinities resembling that of risperidone: both drugs exhibit higher affinities for 5-HT_{2A} and 5-HT_{2C} receptors than for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors.[7] In that dopamine might also be involved in OCD pathophysiology, the similarity of the drugs' dopamine-binding profiles also provided a therapeutic rationale. Both drugs bind more strongly to the dopamine-2 (D_2) receptor than to the D_1 receptor.[7] Quetiapine's receptor-binding profile also resembles that of olanzapine: both drugs' binding affinities for the D_1, D_2, 5-HT_{2A}, and 5-HT_{2C} receptors are at least an order of magnitude greater than for the 5-HT_{1A} and 5-HT_{1B} receptors, where their binding affinities are of the same magnitude.[7] These pharmacologic similarities among quetiapine, risperidone, and olanzapine suggested to us that

Table 1. Trials of Atypical Antipsychotic Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder[a]

Study	Study Type	Sample Size, N[b]	Medication	Mean Final Dose, mg/d	Final Dose Range, mg/d	Responders N/N	Responders %
Atmaca et al (2002)[23]	SB-PC	14	Quetiapine	91	50–200	10/14	71
Sevincok and Topuz (2003)[25]	Open	8	Quetiapine	150	150	2/8	25
Denys et al (2002)[24]	Open	10	Quetiapine	200	200	7/10	70
Mohr et al (2002)[22]	Chart review	7	Quetiapine	118	25–300	4/7	57
Hollander et al (2003)[39]	DB-PC	10	Risperidone	2.3	Not available	4/10	40
McDougle et al (2000)[26]	DB-PC	20	Risperidone	2.2	1–4	11/20	55
McDougle et al (2000)[26]	Open	14	Risperidone	Not available	Not available	7/14	50
Pfanner et al (2000)[30]	Open	20	Risperidone	3	3	15/20	75
Saxena et al (1996)[40]	Open	21	Risperidone	2.75	0.5–8	14/21[c]	67
Ravizza et al (1996)[31]	Open	17	Risperidone	3	3	7/17	41
Jacobsen (1995)[41]	Open	5	Risperidone	3.6	3–6	5/5	100
Stein et al (1997)[3]	Chart review	8	Risperidone	1.25	1–2	3/8	38
Bystritsky et al (2004)[42]	DB-PC	13	Olanzapine	11.2	5–20	6/13	46
Shapira et al (2004)[21]	DB-PC	22	Olanzapine	6.1	5–10	= placebo	41
D'Amico et al (2003)[28]	Open	21	Olanzapine	10	10	7/21	33
Francobandiera (2001)[29]	Open	9	Olanzapine	4.4	2.5–5	6/9	67
Bogetto et al (2000)[27]	Open	23	Olanzapine	5	5	10/23	43
Koran et al (2000)[43]	Open	10	Olanzapine	8.25	5–10	3/10	30
Weiss et al (1999)[32]	Open	10	Olanzapine	7.3	1.25–20	7/10	70

[a]Responder is defined as ≥ 25% improvement of Yale-Brown Obsessive Compulsive Scale score from baseline to endpoint.
[b]Number of subjects treated with active drug.
[c]Yale-Brown Obsessive Compulsive Scale score unavailable. Instead, Saxena et al.[40(p304)] report "substantial reductions in obsessive-compulsive symptoms."
Abbreviations: DB-PC = double-blind–placebo-controlled, SB-PC = single-blind–placebo-controlled.

quetiapine might be an effective augmenting drug in resistant OCD. In addition, in our clinical practice we noted that some OCD patients did not benefit from risperidone or olanzapine augmentation and some were unable to tolerate these medications. For these reasons, we designed the current study to test the safety and effectiveness of quetiapine for SRI-resistant OCD. While this study was in progress, other investigators also pursued these treatment avenues (Table 1).

METHOD

This was a 2-site, 8-week, open-label trial in adults with a DSM-IV[8]–defined diagnosis of OCD, who were treatment resistant to at least 1 adequate SRI trial. All diagnoses were established by psychiatric interview, supported by the Mini-International Neuropsychiatric Interview.[9,10] The 2 sites are designated S1 (Stanford University Medical Center, Stanford, Calif.) and S2 (UCLA Medical Center, Los Angeles, Calif.). Adults with a primary diagnosis of OCD of at least 1 year duration were recruited between October 2000 and November 2003 through radio and newspaper advertisements and via referrals from our OCD clinics and other psychiatrists.

Eligible subjects had failed at least 1 adequate trial of an SRI (≥ 10 weeks at the highest dose tolerated, which had to equal or exceed the effective dose demonstrated in double-blind trials) and were willing to continue their SRI at the current dose. Failure was defined as a less than 35% decrease in the Yale-Brown Obsessive Compulsive Scale (YBOCS)[11] score. In judging subjects' responses to prior trials for which no baseline and endpoint YBOCS scores were available, we utilized clinical interview and review of medical records to establish that the Clinical Global Impressions-Improvement scale (CGI-I)[12] score for that trial was no better than a score of 3 (minimally improved), meaning "failure to benefit substantially." Adequate SRI doses were defined as citalopram (≥ 20 mg/day), clomipramine (≥ 150 mg/day), fluoxetine (≥ 20 mg/day), fluvoxamine (≥ 100 mg/day), paroxetine (≥ 40 mg/day), sertraline (≥ 50 mg/day), and venlafaxine (≥ 225 mg/day). Adequate antipsychotic augmentation trials were defined as ≥ 2 weeks of olanzapine (≥ 5 mg/day) or risperidone (≥ 1 mg/day). Failure to benefit from an augmentation trial was defined just as for an SRI trial.

We excluded subjects with organic mental disorders, psychosis, mental retardation or developmental disabilities, depressive disorders with current suicidal risk, substance abuse or dependence within the last 6 months (excluding alcohol), personality disorders sufficiently severe to interfere with cooperation with the study, a history of bipolar I or II disorder, or a serious medical disorder. We also excluded pregnant or nursing women and women of childbearing potential not using a medically acceptable contraceptive method.

Subjects who required psychotropic medications other than an SRI or a medication that could interact adversely with quetiapine, or had clinically significant abnormalities on prestudy physical examinations, electrocardiogram readings, or laboratory tests were excluded. After receiving a full explanation of the study and of possible

risks, all participants gave written informed consent by signing forms approved by the sites' institutional review boards.

Quetiapine 25 mg/day was added to the subjects' current medication regimen, and, in the absence of marked response or limiting side effects, the dose was doubled every 2 weeks to a maximum of 200 mg/day. Ratings, including YBOCS, Montgomery-Asberg Depression Rating Scale (MADRS),[13] CGI-Severity (CGI-S),[12] CGI-I, and Patient Global Impression of Improvement (PGI),[12] were obtained at baseline and each study visit (end of weeks 1, 2, 4, 6, and 8). We also noted any spontaneously reported adverse effects of quetiapine and their severity. Extrapyramidal symptoms were elicited with the Abnormal Involuntary Movement Scale (AIMS)[14] and the Barnes Akathisia Scale.[15]

Continuous variables were analyzed within sites by means of the (parametric) Student t test for paired samples, 1-tailed with $p \leq .05$ for significance, and across sites with 2-sample Student t tests, assuming unequal variance, 2-tailed with $p \leq .05$ for significance. Because of the relatively small sample sizes, these results were checked with the nonparametric Mann-Whitney U test. In all cases, the results of the nonparametric and parametric tests were consistent. Correlations between variables were examined with parametric (Pearson) correlation coefficients with $p \leq .05$ for significance and were corroborated by calculating nonparametric (Spearman) correlation coefficients utilizing the same p value. In all cases, the results of the nonparametric and parametric correlation tests were consistent. Categorical variables were analyzed using the Fisher exact probability test with $p \leq .05$ for significance. All analyses were performed in the intent-to-treat samples, with the last observation carried forward.

The primary outcome measure was change in YBOCS score from baseline to endpoint. Secondary outcome measures were percent change in YBOCS score, percent responders, CGI-I score, and change in CGI-S and MADRS scores. An OCD responder was defined prospectively as a subject having a ≥ 25% decrease from baseline in YBOCS score. We also report "responder" rates using criteria utilized by other investigators, i.e., a ≥ 35% decrease in YBOCS score, and criteria combining these percentage decreases with achieving CGI-I scores of 1 (very much improved) or 2 (much improved). A mood disorder responder was defined prospectively as a subject with a baseline MADRS score of ≥ 16 and an endpoint decrease of ≥ 50% from baseline.

RESULTS

We recruited 30 subjects, 16 at S1 and 14 at S2. At the completion of the trial, analysis revealed 1 statistically significant, clinically important baseline difference between subjects at the 2 sites. Significantly more S2 subjects had hoarding as their primary OCD symptom (7/14 vs. 1/16, Fisher exact probability test, $p = .01$, 2-tailed). OCD hoarding is well recognized as less responsive to pharmacotherapy than other forms of OCD.[16–19] Subjects at the 2 sites did not differ significantly, however, in demographic characteristics or in baseline measures of OCD severity such as mean YBOCS or CGI-S scores, or in the measure of mood symptoms, the MADRS. Post-study analysis also revealed that subjects at S2 had received significantly less intensive treatment; the mean ± SD quetiapine dose achieved at S2 was significantly lower (116 ± 72 mg/day vs. 169 ± 57 mg/day, $t = 2.19$, $df = 24.7$, $p = .039$) (Tables 2 and 3). For example, 12 (75%) of 16 subjects at S1 received 200 mg/day versus only 5 (36%) of 14 at S2. The significant differences between S1 and S2 in the proportion of subjects with a more treatment-resistant form of OCD (hoarding) and in the intensity of treatment received preclude combining the data from the 2 sites for analysis. A combined analysis of subjects with differing disease prognosis and differing treatment would lack validity and be misleading.

The subjects' ages ranged from 19 to 50 years (mean ± SD age = 35.6 ± 9.9) at S1 and from 26 to 60 years (mean ± SD age = 40.6 ± 10.9) at S2. The ethnic distribution of the patients was white (13 at S1, 11 at S2), Asian/Pacific Islander (1 at each site), black (1 at each site), and Hispanic (1 at each site). All subjects had failed at least 1 adequate SRI trial, and 13 subjects (S1) and 7 subjects (S2) had failed 2 or more adequate trials. Subjects at S1 had failed a mean ± SD number of 2.2 ± 0.9 SRI trials (range, 1–4) and those at S2, a mean ± SD number of 2.1 ± 1.3 (range, 1–4). The participants' then current SRIs and doses are shown in Tables 2 and 3. In addition, 6 subjects (S1) and 3 subjects (S2) had failed 1 adequate atypical antipsychotic augmentation trial, while 2 subjects (S1) and no subject (S2) had failed 2 such trials. Most participants at both sites had current comorbid conditions (Tables 2 and 3).

Efficacy Endpoints

At S1, the subjects' mean ± SD YBOCS score decreased significantly from 27.7 ± 7.0 (range, 13 [obsessions only]–39) at baseline to 23.3 ± 8.4 (range, 6–36) at endpoint ($t = 2.96$, $df = 15$, $p = .01$) (Table 2). The change at S2 was not significant, from a mean of 27.1 ± 4.3 (range, 19–33) to 25.5 ± 4.7 (range, 15–31) (Table 3). The mean ± SD percent change in YBOCS score was a decrease of 16.3% ± 22.7% at S1 and of 5.6% ± 11.8% at S2. At S1, the mean baseline CGI-S score was 5.1 ± 1.0 (range, 4–7) and improved to 4.5 ± 1.2 (range, 2–6) at study end. At S2, the mean scores were unchanged, 5.4 ± 0.6 (range, 4–6) at baseline and 5.4 ± 0.7 (range, 4–6) at endpoint. The distributions of endpoint CGI-I scores confirm that much less benefit was experienced

Table 2. Characteristics and Outcomes at Site 1 of 16 Serotonin Reuptake Inhibitor (SRI)–Resistant Obsessive-Compulsive Disorder Subjects Who Received Quetiapine Augmentation

Subject	Sex	Comorbid Diagnosis	SRI and Dose, mg/d	Quetiapine Dose, mg/d	Baseline YBOCS Score	Endpoint YBOCS Score
1	Male	Major depressive episode, generalized anxiety disorder, alcohol dependence	Fluvoxamine, 100	200	25	28
2	Female	Major depressive episode, generalized anxiety disorder	Fluoxetine, 60; clomipramine, 50	200	22	22
3	Female	None	Fluvoxamine, 300	100	28	25
4[a]	Male	None	Fluoxetine, 20	200	20	10
5[a]	Female	Dysthymia	Citalopram, 60	200	38	23
6	Male	Panic disorder with agoraphobia	Citalopram, 60; clomipramine, 150	50	33	30
7	Female	None	Citalopram, 120	200	32	32
8	Male	Major depressive episode	Sertraline, 300	200	28	27
9	Male	Dysthymia, panic disorder without agoraphobia, generalized anxiety disorder	Clomipramine, 125	200	36	36
10	Female	None	Fluvoxamine, 400	200	22	21
11	Female	Dysthymia	Fluvoxamine, 300	200	30	30
12[b]	Male	Major depressive episode	Fluoxetine, 40	100	13	11
13[a]	Male	Major depressive episode	Fluoxetine, 60	200	27	18
14[a,b]	Female	Social phobia	Fluvoxamine, 250	50	39	29
15	Male	None	Citalopram, 60	200	27	25
16[a]	Female	Dysthymia, social phobia, generalized anxiety disorder, bulimia nervosa	Fluoxetine, 40	200	23	6

[a]Responder.
[b]Early discontinuation.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 3. Characteristics and Outcomes at Site 2 of 14 Serotonin Reuptake Inhibitor (SRI)–Resistant Obsessive-Compulsive Disorder Subjects Who Received Quetiapine Augmentation

Subject	Sex	Comorbid Diagnosis	SRI and Dose, mg/d	Quetiapine Dose, mg/d	Baseline YBOCS Score	Endpoint YBOCS Score
1[a]	Female	None	Fluvoxamine, 200	25	19	21
2[a]	Female	None	Fluvoxamine, 400	25	33	31
3	Female	None	Fluvoxamine, 200	100	32	31
4	Female	None	Fluvoxamine, 400	50	21	20
5[a,b]	Male	Major depressive episode, panic disorder with agoraphobia, social anxiety disorder	Citalopram, 40	100	32	24
6	Female	Major depressive episode	Citalopram, 100	150	28	28
7	Male	Posttraumatic stress disorder	Fluvoxamine, 200	200	25	23
8[b]	Male	Panic disorder, generalized anxiety disorder	Paroxetine, 40	200	23	15
9	Male	None	Paroxetine, 40	50	30	29
10	Female	Major depressive episode	Fluvoxamine, 300	200	27	28
11[a]	Male	Major depressive episode	Citalopram, 60	50	28	25
12	Male	Major depressive episode	Clomipramine, 250	200	27	28
13	Male	None	Fluvoxamine, 200	75	24	24
14	Female	Major depressive episode, generalized anxiety disorder	Sertraline, 50	200	30	30

[a]Early discontinuation.
[b]Responder.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

at S2. These scores (S1,S2) were very much improved (2,0), much improved (3,1), minimally improved (6,5), no change (4,7), minimally worse (0,1), and much worse (1,0). Similar results were reported on the PGI.

The mean ± SD MADRS score at S1 improved from 18.5 ± 9.9 (range, 2–33) at baseline to 14.9 ± 8.2 (range, 0–28) at endpoint. At S2, these mean scores were 13.2 ± 5.8 (range, 0–22) at baseline and 13.5 ± 5.2 (range, 3–26) at endpoint. The percent changes in YBOCS and MADRS scores were not significantly correlated at either site: at S1, r = –.16, p = .55; at S2, r = .25, p = .42.

Responder Analyses

The predefined responder rates (≥ 25% decrease in YBOCS score from baseline) were 31% (5/16) at S1 and 14% (2/14) at S2. The comorbidity burden among responders and nonresponders at S1 was similar (Table 2); at S2, both responders had comorbid conditions (Table 3), as did half of the nonresponders. Two of the 5 OCD responders at S1 had a mood disorder (dysthymia) at baseline, but neither achieved the criterion for MADRS response. The responder at S2 with a mood disorder also failed to achieve the MADRS criterion, but this subject

left the study after week 4 by moving out of the area. The 1 hoarder at S1 did not respond, and only 1 of the 7 hoarders at S2 was a responder.

The mean ± SD percent change in YBOCS scores for responders at S1 was a decrease of 45% ± 19% (range, –74% to –26%) compared with a mean decrease of 3% ± 8% (range, –15% to 12%) for nonresponders. At S2, the responders' YBOCS scores decreased by 25% and 35%. The nonresponders showed essentially no mean ± SD decrease (2% ± 6%).

At S1, the responders had failed 1 (N = 2) or 2 (N = 3) SRI trials, whereas nonresponders had failed from 1 (N = 1) to 4 (N = 2) SRI trials. Two of the 5 responders had failed 1 atypical antipsychotic augmentation trial. Of the 11 nonresponders, 5 had never failed such a trial, 4 had failed 1, and 2 had failed 2. At S2, both responders had failed 1 SRI trial. One had also failed an atypical antipsychotic augmentation trial, as had 2 of the 12 nonresponders.

"Responder" rates utilizing the criterion of a ≥ 35% decrease in YBOCS score were 19% (3/16) at S1 and 7% (1/14) at S2, as were the rates utilizing the criterion of a ≥ 35% decrease and a CGI-I score of 1 or 2. Responder rates utilizing the criterion of a ≥ 25% but < 35% decrease in YBOCS score and a CGI-I score of 1 or 2 were 13% (2/16) at S1 and 0% (0/14) at S2.

Though fluvoxamine raises serum levels of quetiapine, only 1 of the 5 subjects receiving fluvoxamine and quetiapine at S1 showed significant improvement in OCD symptoms, with a decrease of 26% in YBOCS score. Of the 7 subjects at S2 who received this combination, none was a responder.

Adverse Events

All subjects at both sites experienced at least 1 adverse event, but most were mild. In the intent-to-treat sample (N = 30), the following adverse events were reported by 10% or more of subjects: sedation (N = 20, 67%), fatigue (N = 12, 40%), forgetfulness or feeling "spacey" (N = 6, 20%), increased appetite (N = 5, 17%), dry mouth (N = 5, 17%), and transient akathisia or restless legs (N = 3, 10%) noted on the Barnes Akathisia Scale. No abnormal motor signs were elicited with the AIMS. In many cases, the severity of sedation and fatigue remained mild or decreased from moderate to mild over time despite increasing doses of quetiapine.

Five subjects discontinued the study because of adverse effects of medication, 2 (13%) at S1 and 3 (21%) at S2. In addition, 1 subject (7%) at S2 discontinued by moving out of the area after week 4. Thus, 14 (88%) of 16 subjects completed the study at S1 and 10 (71%) of 14 subjects at S2. At S1, 1 subject withdrew at week 2, reporting moderate fatigue, mild tremor, mild lightheadedness, and mild muscle ache; the other withdrew at week 4 due to mild forgetfulness and mild-to-moderate fatigue. At S2, 3 subjects withdrew due to drowsiness, 1 at week 1 and 2 at week 2.

DISCUSSION

The results of this study at S1 resemble those seen with other atypical antipsychotics[3,28,31,39,43] and suggest that quetiapine is effective as an augmenting agent for SRI-resistant OCD, even in patients who have failed an augmentation trial with another atypical antipsychotic medication. The responder rate (31%) at S1 is within the range observed in other atypical antipsychotic augmentation trials (30%–100%) (Table 1). The results at S2, however, are quite different. The responder rate (14%) at this site is lower than those reported with other atypical antipsychotics, and the 14 subjects did not exhibit a significant mean decrease in YBOCS score. One possible explanation for the difference in results at the 2 sites is the large proportion (50%) of hoarders at S2. OCD hoarders are less responsive to pharmacotherapy than nonhoarders[16–19] and may suffer from a different pathophysiology: the abnormality in their pattern of cerebral glucose metabolism differs from that of nonhoarder OCD patients.[20] In support of this explanation for the difference in the 2 sites' results, only 1 (12.5%) of 8 hoarders was a responder versus 6 (27.3%) of 22 nonhoarders, although this difference is not statistically significant (Fisher exact probability test, p = .64, 1-tailed). Alternatively, the difference in results may be due to the significantly lower mean quetiapine dose reached at S2. The results at both sites, however, suggest that the improvement of OCD symptoms is independent of improvement in comorbid mood disorders, if present.

This study is limited not only by baseline and treatment differences between the 2 sites, but also by a small sample size, lack of randomization, open-label design, nonblinded ratings, and the limited doses of quetiapine utilized.

Most published trials of atypical antipsychotic augmentation for SRI-resistant OCD report a 40% to 70% responder rate (Table 1). The failure of olanzapine augmentation to separate from placebo in a recent double-blind trial[21] can reasonably be attributed to beginning augmentation after only 8 weeks of SRI treatment. As the authors note, subjects in both the olanzapine and placebo groups may well have experienced growing benefit from longer exposure to the SRI, thus obscuring the olanzapine effect.[21] Studies of quetiapine augmentation in OCD (published after our trial was well underway) report rates of 57% to 71% (Table 1).[22–24] Unfortunately, we cannot confidently compare our responder rates at S1 or at S2 to those observed in these studies because of differences in both the subjects' clinical characteristics and study design. For example, most of our subjects (13/16 at S1 and 7/14 at S2) had also failed at least 2 adequate SRI trials, and many (8/16 at S1 and 3/14 at S2) had failed at least 1 atypical

antipsychotic augmentation trial. The chart review quetiapine study of Mohr et al.,[22] for example, does not report data regarding failed SRI or augmentation trials. The subjects studied by Atmaca et al.[23] had failed at least 2 adequate SRI trials, and those reported by Denys et al.[24] had failed at least 3, but none had failed an atypical antipsychotic trial. Moreover, subjects in the latter trial received 200 mg/day of quetiapine for 4 weeks in contrast to the maximum of 2 weeks in our study. Finally, the subjects of Sevincok and Topuz[25] were treated with a lower dose, 150 mg/day, but for a longer period, 9 weeks.

The literature is unclear as to whether the number of failed SRI trials is a useful predictor of response to augmentation with an atypical antipsychotic medication. In a double-blind risperidone augmentation trial,[26] 67% of subjects (6/9) who had failed 1 SRI trial responded, compared with 45% (5/11) who had failed 2 or more. These rates contrast with the 70% response rate observed by Denys et al.[24] in subjects who had failed at least 3 SRI trials. Many studies do not unambiguously report these data.[27–32]

An additional problem in attempting comparisons is the large confidence interval that surrounds responder rates observed in studies with small study group sizes. For example, the 90% confidence interval for the responder rate at S1, calculated by the modified Wald method,[33] extends from 16% to 52%. Moreover, a χ^2 goodness of fit test (continuity corrected) shows that if we assume that the "true" responder rate is 50% in a group such as ours at S1, then the chance of observing our responder rate of 31% in a group of 16 subjects (5/16), or a smaller rate, is 21% (i.e., $\chi^2 = 1.56$, df = 1, p = .21).[34]

Finally, differences among atypical antipsychotic medications in the likelihood of inducing various side effects, and thereby differences in tolerability in individual patients, may be associated with differences in particular patients' outcomes as well as in intent-to-treat responder rates. For example, quetiapine is less likely to cause extrapyramidal symptoms requiring treatment than is risperidone,[35] and is less likely than olanzapine, but more likely than ziprasidone, to cause weight gain.[36] Thus, the choice of an atypical antipsychotic medication for a given patient must still be made clinically rather than by algorithm.

The antipsychotic effectiveness of atypical antipsychotics is generally agreed to be the result of their blockade of D_2 receptors.[37] Whether blockade of D_2 receptors, blockade of 5-HT_{2A} receptors,[37] or some other property is critical for the effectiveness of atypical antipsychotics as augmentors in SRI-resistant OCD is unknown. Conceivably, differences in responder rates and in the likelihood that an individual patient will respond to a specific atypical antipsychotic may be related to potency differences for D_2 and/or 5-HT_{2A} receptor occupancy,[37] or to dissociation constants from the D_2 receptor.[38]

Work is still needed in OCD augmentation trials to establish the best dosing strategies for each atypical antipsychotic, the most reasonable duration of a therapeutic trial, and how to match a specific drug to individual patient characteristics in order to optimize treatment outcome. Only large-scale, double-blind, placebo-controlled, head-to-head comparisons can produce these clinically important data. Unfortunately, funding for such studies is unlikely to be forthcoming from either the pharmaceutical industry or the National Institute of Mental Health. As a result, clinicians' decisions will of necessity rely on imperfect comparisons of the results of small-scale studies. We hope that the data we have generated and those presented in Table 1 will contribute to informing these decisions.

Drug names: citalopram (Celexa), clomipramine (Anafranil and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor), ziprasidone (Geodon).

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. Koran LM. Obsessive-Compulsive and Related Disorders in Adults: A Comprehensive Clinical Guide. New York, NY: Cambridge University Press; 1999:62–70
3. 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
4. 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
5. Berigan TR, Harazin JS. Response to risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases [letter]. J Clin Psychiatry 1996;57:594–595
6. Potenza MN, Wasylink S, Longhurst JG, et al. Olanzapine augmentation of fluoxetine in the treatment of refractory obsessive-compulsive disorder [letter]. J Clin Psychopharmacol 1998;18:423–424
7. Bymaster FP, Calligaro DO, Facone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996;14:87–96
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association Press; 1994:417–423
9. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, et al. Reliability and validity of the Mini-International Neuropsychiatric Interview (MINI): according to the SCID-P. Eur Psychiatry 1997;12:232–241
10. Lecrubier Y, Sheehan D, Weiller E, et al. The Mini-International Neuropsychiatric Interview (MINI): a short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry 1997;12:224–231
11. Goodman WK, Price L, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 1: development, use and reliability. Arch Gen Psychiatry 1989;46:1006–1011
12. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-388. Rockville, Md: National Institute of Mental Health; 1976:218–222
13. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
14. Munetz MR, Benjamin S. How to examine patients using the Abnormal Involuntary Movement Scale. Hosp Community Psychiatry 1988;39:1172–1177
15. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
16. Saxena S, Maidment KM, Vapnik T, et al. Obsessive-compulsive hoarding: symptom severity and response to multimodal treatment. J Clin Psychiatry 2002;63:21–27

17. Winsberg ME, Cassic KS, Koran LM. Hoarding in obsessive-compulsive disorder: report of 20 cases. J Clin Psychiatry 1999;60:591–597
18. Black DW, Monahan P, Gable J, et al. Hoarding and treatment response in 38 nondepressed subjects with obsessive-compulsive disorder. J Clin Psychiatry 1998;59:420–425
19. Mataix-Cols D, Rauch SL, Manzo PA, et al. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. Am J Psychiatry 1999;156:1409–1416
20. Saxena S, Brody AL, Maidment KM, et al. Cerebral glucose metabolism in obsessive-compulsive hoarding. Am J Psychiatry 2004;161:1038–1048
21. Shapira NA, Ward HE, Mandoki M, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. Biol Psychiatry 2004;55:553–555
22. Mohr N, Vythilingum B, Emsley RA, et al. Quetiapine augmentation of serotonin reuptake inhibitors in obsessive-compulsive disorder. Int Clin Psychopharmacol 2002;17:37–40
23. Atmaca M, Kuloglu M, Tezcan E, et al. Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study. Int Clin Psychopharmacol 2002;17:115–119
24. Denys D, van Megen H, Westenberg H. Quetiapine addition to serotonin reuptake inhibitor treatment in patients with treatment-refractory obsessive-compulsive disorder: an open-label study. J Clin Psychiatry 2002;63:700–703
25. Sevincok L, Topuz A. Lack of efficacy of low doses of quetiapine addition in refractory obsessive-compulsive disorder. J Clin Psychopharmacol 2003;5:448–450
26. 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
27. 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
28. D'Amico G, Cedro C, Muscatello MR, et al. Olanzapine augmentation of paroxetine-refractory obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:619–623
29. Francobandiera G. Olanzapine augmentation of serotonin uptake inhibitors in obsessive-compulsive disorder: an open study. Can J Psychiatry 2001;46:356–358
30. 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
31. Ravizza L, Barzega G, Bellino S, et al. Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). Psychopharmacol Bull 1996;32:677–682
32. 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
33. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998;52:199–126
34. Vassar Stats. Available at: http://faculty.vassar.edu/lowry/csfit.html. Accessed Dec 12, 2002
35. Sussman N. Choosing an atypical antipsychotic. Int Clin Psychopharmacol 2002;17(suppl 3):S29–S33
36. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601
37. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry 1999;60(suppl 10):5–14
38. Kapur S, Seeman P. Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics? a new hypothesis. Am J Psychiatry 2001;158:360–369
39. Hollander E, Rossi NB, Sood E, et al. Risperidone augmentation in SRI-resistant obsessive compulsive disorder: a preliminary double-blind, placebo-controlled study. Int J Neuropsychopharmacol 2003;6:397–401
40. 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
41. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. J Clin Psychiatry 1995;56:423–429
42. Bystritsky A, Ackerman DL, Rosen RM, et al. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. J Clin Psychiatry 2004; 65:565–568
43. Koran LM, Ringold AL, Elliott MA. Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry 2000;61:514–517