Augmentation of Serotonin Reuptake Inhibitors in Refractory Obsessive-Compulsive Disorder Using Adjunctive Olanzapine: A Placebo-Controlled Trial

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Background: The purpose of this study was to explore the efficacy of adding an atypical antipsychotic, olanzapine, to a serotonin reuptake inhibitor (SRI) in treatment-refractory obsessive-compulsive disorder (OCD).

Method: Twenty-six patients aged between 18 and 65 (mean = 41.2, SD = 11.9) years meeting DSM-IV criteria for OCD, who had not responded to SRIs, were treated for 6 weeks in a double-blind, placebo-controlled augmentation study with either olanzapine (up to 20 mg/day) or placebo. Severity of illness was assessed biweekly by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Analysis of covariance with baseline Y-BOCS score included as a covariate was used to compare improvement in Y-BOCS scores in the 2 groups. Response was defined as a 25% or greater improvement in Y-BOCS score. Data were collected between April 2001 and May 2003.

Results: Outcome was assessed for all patients using the last observation carried forward. Subjects in the olanzapine group had a mean decrease of 4.2 (SD = 7.9) in Y-BOCS score compared with a mean increase in score of 0.54 (SD = 1.31) for subjects in the placebo group ($F = 4.85$, $df = 2,23$; $p = .04$). Six (46%) of 13 subjects in the olanzapine group showed a 25% or greater improvement in Y-BOCS score compared with none in the placebo group. The final mean dose of olanzapine was 11.2 (SD = 6.5) mg/day. Medication was well tolerated. Only 2 (15%) of 13 subjects who received olanzapine discontinued because of side effects: sedation (N = 1) or weight gain (N = 1).

Conclusion: These results provide preliminary evidence that adding olanzapine to SRIs is potentially efficacious and well tolerated in the short-term treatment of patients with refractory OCD. Controlled studies with larger sample sizes are necessary to more definitively address this treatment strategy.

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Although serotonin reuptake inhibitors (SRIs) are the mainstay of pharmacologic treatment for obsessive-compulsive disorder (OCD), as many as 40% to 60% of patients have an inadequate response.[1] One approach to treating SRI-refractory patients has been to add other classes of medications to the SRI. While several agents have appeared promising in open trials, thus far only conventional neuroleptic medications[2] and risperidone[3] have been found effective in placebo-controlled augmentation studies. Older antipsychotics may have serious side effects and may not be recommended for nonpsychotic states.[4] Olanzapine, an atypical antipsychotic that blocks serotonin-2 ($5\text{-}HT_2$) receptors as well as dopamine receptors and has less severe extrapyramidal side effects than do older neuroleptics,[5] offers new treatment possibilities for patients with SRI-refractory OCD.

Several case reports and 3 open-label trials of olanzapine augmentation[6–9] have suggested that this strategy may reduce OCD symptoms in at least some patients with refractory OCD. Out of the total of 43 patients treated with adjunctive olanzapine in the 3 open trials published thus far,[6–9] 20 patients had decreases of 25% or more in their Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[10,11] scores, and 15 of those had ratings of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale (CGI-I).[12] The majority of subjects in these open trials had comorbid Axis I psychiatric disorders (the most common being major depressive disorder) that also improved, and therefore, it remains

unclear to what extent the improvement in OCD symptoms seen in those studies was related to improvement in the comorbid conditions.

We conducted a placebo-controlled trial of olanzapine augmentation in SRI-refractory OCD patients. Our goal was to more definitively test the efficacy of this treatment strategy on OCD symptoms among patients without significant comorbidity.

METHOD

Subjects were men and women aged between 18 and 65 (mean = 41.2, SD = 11.9) years who met DSM-IV criteria for OCD, diagnosed by clinical interview and the Mini-International Neuropsychiatric Interview (MINI).[13] All subjects received a comprehensive psychiatric evaluation by one of the study physicians (A.B. or R.M.R.). Exclusion criteria included any other concurrent major Axis I or Axis II disorder, any current active neurologic disorder, pregnancy, and any current major medical disorder that could destabilize the patient during the study. Subjects with current depressive symptoms were permitted into the study if their Hamilton Rating Scale for Depression (HAM-D)[14] scores did not exceed 21.[15] Subjects with strongly delusional OCD beliefs were included; however, patients with a history of psychosis with delusions that were either bizarre or not related to OCD were excluded. The protocol was approved by the University of California, Los Angeles (UCLA) Institutional Review Board. Written informed consent was obtained from all participants. Study physicians (A.B. or R.M.R) reviewed and agreed upon the diagnosis and eligibility of all patients.

None of the subjects had improved during the previous 12 weeks (or longer) in at least 2 trials of SRIs at an adequate dose and at least 1 trial of behavioral therapy. All behavioral therapy was administered at the UCLA Anxiety Disorders program or by clinicians affiliated with the program who were using the Foa approach.[15] Therapy included components of education, cognitive restructuring, and exposure and response prevention.

Subjects were taking an adequate dose of 1 of 3 SRI medications (fluoxetine, paroxetine, or sertraline) or clomipramine (with blood levels in the therapeutic range) for at least 12 weeks with a tolerable level of side effects. Most of the subjects were taking fluoxetine (N = 16: olanzapine, N = 8; placebo, N = 8) at a mean dose of 60 mg/day (range, 40–120 mg/day) or paroxetine (N = 7: olanzapine, N = 4; placebo, N = 3) at a mean dose of 80 mg/day (range, 60–100 mg/day). One subject in the placebo group was taking sertraline (200 mg) and 2 subjects (1 in each group) were taking clomipramine (200 mg and 250 mg with blood levels in the therapeutic range). Subjects were taking no other psychotropic medications for at least 2 weeks prior to randomization and during the 6-week olanzapine augmentation period.

Study Design

This study utilized a double-blind, randomized, placebo-controlled, parallel, flexible-dose design. A balanced randomization schedule was followed by the pharmacist. Twenty-six patients were randomly assigned to receive either olanzapine (N = 13) or placebo (N = 13) while continuing their SRI at a stable dose for 6 weeks. The starting dose of olanzapine was 2.5 mg administered at night. After 3 days, the dose was increased to 5 mg/day for the remainder of week 1. During the 6-week study, the dose was adjusted as indicated within a range of 5 to 20 mg/day. No subject received cognitive-behavioral therapy during the study period. Data were collected between April 2001 and May 2003. At the end of week 6, the patients were referred to the UCLA Anxiety Disorders Program for further treatment.

Assessments

We administered standardized rating scales to each subject upon entrance into the study and at 2-week intervals thereafter for 6 weeks. Assessment scales included the Y-BOCS,[10,11] HAM-D,[14] Hamilton Rating Scale for Anxiety (HAM-A),[16] and CGI.[12] In addition, subjects were monitored for the emergence of any adverse effects, including extrapyramidal side effects.

Statistical Analyses

The primary outcome measure was change in Y-BOCS score at the last visit. The difference between treatment groups, using the last visit carried forward, was assessed by analysis of covariance (ANCOVA) with baseline Y-BOCS scores included as a covariate. Effect size was calculated as the difference in Y-BOCS change scores divided by the pooled standard deviation (from Cohen[17]). The proportion of responders (i.e., subjects whose scores improved at least 25% on the Y-BOCS) was also calculated, as were the response risk difference representing the difference between the proportion of responders in the olanzapine and placebo groups, 95% confidence limits (CLs), and Fisher exact 2-sided p values. A p value of .05 or less was used to determine statistical significance. All reported p values are 2-sided.

RESULTS

All subjects were aged between 18 and 65 years. The mean age was 44.5 (SD = 13.7) years in the olanzapine group and 38.3 (SD = 9.1) years in the placebo group. Thirteen patients (50%) were men: 7 in the olanzapine group and 6 in the placebo group. The 2 groups were similar with respect to age ($F = 1.86$, df = 1,24; $p = .19$), gender distribution (Pearson $\chi^2 = 0.15$, df = 1, $p = .70$), and distribution of concurrent SRI (Pearson $\chi^2 = 1.14$, df = 3, $p = .77$). Eleven subjects (85%) in the olanzapine group and 7 (54%) in the placebo group completed the 6-week

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Table 1. Clinical Characteristics of Patients With Obsessive-Compulsive Disorder Taking Serotonin Reuptake Inhibitors and Adjunctive Olanzapine at Baseline and at 6 Weeks

	Olanzapine (N = 13)		Placebo (N = 13)	
Variable	Baseline	6 Weeks	Baseline	6 Weeks
HAM-A score, mean (SD)[a]	16.2 (6.9)	14.4 (8.1)	22.1 (9.1)	20.2 (8.6)
HAM-D score, mean (SD)[b]	12.5 (5.6)	11.3 (6.9)	13.8 (5.0)	12.2 (6.1)
Y-BOCS score, mean (SD)[c]				
Obsessions subscale	13.2 (2.8)	10.6 (4.4)	12.6 (2.8)	12.7 (3.1)
Compulsions subscale	10.8 (2.2)	9.4 (3.7)	12.5 (2.0)	13.0 (2.1)
Total	24.2 (4.8)	20.0 (7.9)[d]	25.2 (4.2)	25.7 (4.7)[e]
Y-BOCS score ≥ 25%, N (%)	NA	6 (46)	NA	0 (0)

[a]No difference between the 2 groups in change in HAM-A score (F = 1.17, df = 2,23; p = .31).
[b]No difference between the 2 groups in change in HAM-D score (F = 2.01, df = 2,23; p = .19).
[c]ANCOVA from last observation carried forward with baseline Y-BOCS included as covariate: F = 4.83, df = 2,23; p = .04. ANCOVA for Y-BOCS change from 18 completers (olanzapine = 11, placebo = 7) with baseline Y-BOCS score included as covariate: F = 3.40, df = 2,15; p = .09.
[d]Mean change from baseline = –4.2 (SD = 7.9).
[e]Mean change from baseline = 0.54 (SD = 1.3).
Abbreviations: ANCOVA = analysis of covariance, CL = confidence limit, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, NA = not applicable, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

trial. At the end of the trial or at the last visit, the mean dose of olanzapine was 11.2 (SD = 6.5) mg/day (5 subjects were receiving 5 mg/day, 4 were receiving 10 mg/day, and 4 were receiving 20 mg/day). The final dose-equivalent of placebo was 16.9 (SD = 4.8) mg/day.

Outcome was assessed for all patients using the last observation carried forward. Table 1 summarizes the baseline and outcome data by treatment group. The subjects in the olanzapine group had a mean decrease of 4.2 (SD = 7.9) in Y-BOCS score compared with a mean increase in score of 0.54 (SD = 1.31) in the placebo group (F = 4.85, df = 2,23; p = .04). The effect size, i.e., the difference in Y-BOCS change scores divided by the pooled standard deviation, was 0.78. Improvements were also noted in the Y-BOCS obsession subscale (F = 7.64, df = 2,23; p = .003) and compulsion subscale (F = 14.10, df = 2,23; p = .0001) scores. Six subjects (46%) in the olanzapine group improved their scores by more than 25% on the Y-BOCS compared with none in the placebo group (response risk difference = 0.46, 95% CL = 0.19, 0.73; Fisher exact 2-sided p = .01). There were no differences between the 2 groups with respect to change in HAM-A (F = 1.17, df = 2,23; p = .31) or HAM-D (F = 2.01, df = 2,23; p = .19) scores. The final mean Y-BOCS score of the 6 responders was 13.2 (SD = 2.9; range, 10–17). The response-risk difference for 6 (of 11) completers in the olanzapine group compared with 0 (of 7) completers in the placebo group was 0.60 (95% CL = 0.30, 0.90; Fisher exact 2-sided p = .01).

Patients generally tolerated the treatment well. In fact, more dropouts (i.e., discontinued treatment before the sixth week) occurred in the placebo group rather than in the olanzapine group (6 vs. 2). All dropouts in the placebo group stopped treatment because of "lack of effect." One patient in the olanzapine group stopped treatment because of lack of effect and sedation, and another discontinued because of weight gain. The response risk difference for 6 (of 11) completers in the olanzapine group compared with 0 (of 7) completers in the placebo group was 0.60 (95% CL = 0.30, 0.90; Fisher exact 2-sided p = .01).

DISCUSSION

This is the first placebo-controlled study of olanzapine augmentation of SRIs for refractory OCD reported thus far. Six (46%) of 13 subjects who had shown no response during at least 12 weeks of successive trials with a single SRI responded to olanzapine augmentation, compared with no responders (0%) to placebo. Mean Y-BOCS scores improved 16% in the 13 subjects who received olanzapine; whereas, there was no improvement with placebo. The 0.78 effect size reflects this difference. The 46% response rate in this study is consistent with the 50% response rate found with risperidone versus placebo augmentation for SRI-refractory OCD.[3] It differs from the results of a larger placebo-controlled trial of olanzapine augmentation of fluoxetine in refractory OCD that found no difference between drug and placebo.[18] In our study, 4 of 6 responders were also taking fluoxetine. The subjects in our study had no significant comorbid psychiatric or medical conditions. Thus, the effect of olanzapine on reducing OCD symptoms was not secondary to its antipsychotic or mood-stabilizing effects.

The mechanism of action of olanzapine's effect on OCD symptoms is unclear. One possibility is that, like risperidone augmentation, olanzapine augmentation of SRI treatment may increase extracellular concentrations of 5-HT in the prefrontal cortex.[19] The ability of olanzapine to block dopamine receptors, as well as 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors, may also play a role in suppressing OCD symptoms.

Medication was well tolerated. Only 2 (15%) of 13 subjects discontinued because of side effects: sedation (N = 1) and weight gain (N = 1). We observed no extrapyramidal side effects. This observation agrees with the recent finding of Shelton et al.[20] that the combination of fluoxetine and olanzapine is safe and effective in managing patients with treatment-resistant depression.

Our findings are limited by the small sample and the short duration of the trial. With only 26 subjects, our power was too low to demonstrate unequivocally the efficacy of olanzapine augmentation. If more people in the placebo group had continued for the full 6 weeks, we may have seen more improvement in that group. The low incidence of side effects we observed, particularly weight

gain, may have been due to the short duration of the trial and our reliance on self-reports. Although blood levels of clomipramine were in the therapeutic range, blood levels of SRIs were not obtained. Because a structured interview was not used to assess Axis II disorders, it is possible that some patients with Axis II comorbidity were included. None of the subjects had any obvious tics; however, no specific assessment of tics was performed.

A mean improvement of 16% on the Y-BOCS may not be clinically important; however, 6 subjects improved more than 25%. Clearly some people who had not improved during the previous 12 or more weeks did improve during the 6 weeks they received olanzapine. No one in the placebo group improved.

Controlled studies with larger numbers of subjects will be required to evaluate the influence of symptom subtype and other clinical and demographic characteristics on response to olanzapine. Studies with a longer duration and more rigorous assessment of diagnosis, treatment-emergent side effects, and functional status changes are needed to establish the true value of adding novel neuroleptics to SRIs in treatment-refractory OCD.

CONCLUSION

Despite a small sample size, our study further confirms previous knowledge that adding novel neuroleptics such as olanzapine can improve symptoms in some treatment-refractory OCD patients.[21–23] The majority of subjects in the open trials conducted to date had comorbid Axis I disorders (most common was major depressive disorder) that also improved. We excluded subjects with significant comorbidity and found improvement in OCD symptoms.

Further work investigating the efficacy and mechanisms of action of olanzapine and other atypical antipsychotics will be of great value in broadening the options for treatment-refractory OCD.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac and others), olanzapine (Zyprexa), paroxetine (Paxil and others), risperidone (Risperdal), sertraline (Zoloft).

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