Olanzapine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder

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Background: Adding the atypical neuroleptic risperidone to a serotonin reuptake inhibitor (SRI) has benefited patients with treatment-refractory obsessive-compulsive disorder (OCD). Since olanzapine and risperidone have similar serotonergic and dopaminergic receptor binding profiles, we tested the hypothesis that olanzapine augmentation would be beneficial in treatment-unresponsive OCD.

Method: For this 8-week trial, we recruited 10 adult OCD patients (DSM-IV criteria) unresponsive to fluoxetine (≥ 60 mg/day) for ≥ 10 weeks, which was continued throughout the trial. Other psychotropic medications were discontinued. Subjects had OCD for ≥ 1 year, a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥ 18, and no organic, psychotic, or other primary Axis I disorder. Two weeks after olanzapine, 2.5 mg/day, was added, and in the absence of responder status (Y-BOCS score decrease ≥ 25%) and limiting side effects, we increased the dose to 5 mg/day, and after 2 more weeks, to 10 mg/day for 4 weeks.

Results: The subjects had failed a mean of 3.3 SRI trials (range, 1–5) and had a mean ± SD baseline Y-BOCS score of 29.0 ± 4.9. Nine patients completed the trial. The subjects' mean ± SD endpoint Y-BOCS score was 24.4 ± 8.0 (a 16% decrease). The 3 responders' Y-BOCS scores dropped 68%, 30%, and 29%, but only 1 patient was rated "much improved." He maintained this improvement during a 6-month follow-up period taking olanzapine, 5 mg/day. Improvement in OCD was independent of improvement in mood symptoms. Six patients (60%) experienced significant weight gain.

Conclusion: Olanzapine augmentation may benefit treatment-unresponsive OCD. Double-blind, placebo-controlled trials are warranted along with trials comparing risperidone and olanzapine augmentation.

(J Clin Psychiatry 2000;61:514–517)

Received July 13, 1999; accepted Dec. 30, 1999. From the Department of Psychiatry and Behavioral Sciences, Stanford Medical Center, Stanford, Calif.

Supported by Lilly Research Laboratories, which provided funding and study medication (Dr. Koran and Mr. Elliott).

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Many patients with obsessive-compulsive disorder (OCD) do not benefit from standard treatment with a serotonin reuptake inhibitor (SRI).[1–3] In several case series[4–6] and 2 small open-label trials,[7,8] such patients have benefited markedly from the addition of the atypical neuroleptic risperidone. The response rate in an open-label trial that used strict response criteria (including a decrease of ≥ 35% in Yale-Brown Obsessive Compulsive Scale [Y-BOCS] score to < 16) was 57% (8 of 14 patients).[8] The time to response, when reported, has been from days to within 4 weeks.[5,6,8]

The atypical neuroleptic olanzapine has a receptor binding profile that resembles risperidone's profile in many aspects: binding affinities to the dopamine-1 (D_1), D_2, D_4, serotonin-1D (5-HT_{1D}), 5-HT_{2A}, and 5-HT_{2C} receptors are all of the same magnitude,[9] and, as atypical neuroleptics, both drugs bind more strongly to the 5-HT_2 than to the D_2 receptor.[10] On the other hand, risperidone exhibits a higher affinity for the 5-HT_{1A} receptor, and olanzapine, a higher affinity for the 5-HT_3 receptor.[9] Although the 2 drugs have substantially differing binding affinities for the muscarinic, α_2, and histamine H_1 receptors,[9] these receptors, in contrast to serotonergic and possibly dopaminergic receptors, are not thought to be involved in the pathophysiology of OCD.[11,12] Because of the similarity of the serotonergic and dopaminergic receptor binding profiles of olanzapine and risperidone, we conducted an open-label trial to test the hypothesis that olanzapine augmentation will relieve OCD that has not responded to treatment with an SRI.

METHOD

Eligible subjects were outpatients at least 18 years of age with a DSM-IV diagnosis of OCD of at least 1 year's duration established by the Structured Clinical Interview for DSM-IV Axis I Disorders,[13] with OCD the primary focus of treatment. Subjects must have failed an ongoing adequate trial of fluoxetine (≥ 12 weeks at 20 mg/day or the highest dose tolerated, whichever was greater) and have been willing to continue this dose throughout the trial. Failure to benefit was defined as a Clinical Global Impressions-Improvement (CGI-I)[14] scale score and a Patient Global Impressions-Improvement[14] scale score of no more than minimally improved and a Y-BOCS[15] score of ≥ 18.

Table 1. Olanzapine Augmentation of Fluoxetine: Patient Characteristics and Outcome[a]

Patient No.	Age (y)	Age at Diagnosis (y)	No. of Failed Trials	Y-BOCS Score		HAM-D-17 Score	
				Baseline	Endpoint	Baseline	Endpoint
1	24	16	3	27	19	10	2
2	40	30	1	33	33	7	5
3	41	30	5	40	34	15	5
4	35	31	5	32	32	6	0
5	39	29	4	28	28	12	10
6	50	40	4	27	22	7	7
7	27	16	2	23	23	17	7
8	33	5	3	24	17	17	8
9	32	21	4	28	27	15	16
10	29	22	2	28	9	2	0
Mean	35.0	24.0	3.3	29.0	24.4	10.8	6.0
SD	7.7	10.0	1.3	4.9	8.0	5.2	4.9
Range	24–50	5–40	1–5	23–40	9–34	2–17	0–16

[a]Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

We excluded patients with organic mental disorders, psychotic mental disorders (including OCD without insight), mental retardation or developmental disabilities, depressive disorders with current suicidal risk, substance or alcohol abuse or dependence within 6 months, a history of bipolar I or II disorder, personality disorders sufficiently severe to interfere with cooperation with the study, or Tourette's disorder, as well as women who were pregnant or nursing or were of childbearing potential and not using a medically acceptable contraceptive. We excluded patients with psychotic disorders because we wished to study treatment-unresponsive OCD patients without a comorbid condition for which olanzapine is effective. We also excluded patients who required psychotropic medications other than fluoxetine, were taking medications that may interact adversely with olanzapine, or had clinically significant abnormalities on prestudy physical examination, electrocardiogram (ECG), or laboratory tests (urinalysis, chemistry panel, complete blood count, and, for women of childbearing potential, a beta-hCG pregnancy test).

Because of the reported rapid response to added risperidone,[5,6,8] we designed an 8-week trial, with at least 4 weeks at the highest dose tolerated within the range of 2.5 to 10 mg/day. After screening, subjects were seen at baseline and at the end of weeks 1, 2, 3, 4, 5, and 8, at which times we evaluated adverse events and clinical response. The primary efficacy measure was the Y-BOCS. Responder status was defined prospectively as a ≥ 25% decrease in Y-BOCS score. In addition, at each visit we performed a CGI-I rating and rated depressive symptoms with the 17-item Hamilton Rating Scale for Depression (HAM-D).[16] We collected safety data at each visit by means of patients' spontaneous reports of adverse events, and by the Abnormal Involuntary Movement Scale[17] and Barnes Akathisia Scale.[18] Physical examination, ECG, and laboratory examinations were repeated at the last visit.

Subjects discontinued all psychotropic medications other than fluoxetine at least 1 week before beginning olanzapine augmentation. Open-label olanzapine was begun at 2.5 mg/day. In the absence of responder status and limiting side effects, the dose was increased after 2 weeks to 5 mg/day and again after 2 more weeks to 10 mg/day for the study's final 4 weeks.

RESULTS

We enrolled 10 adult subjects, 9 men and 1 woman (Table 1). The subjects' mean ± SD baseline Y-BOCS score was 29.0 ± 4.9, indicating severe OCD (see Table 1). Their major obsessional concerns included religion/morality (N = 5), aggression (N = 4), contamination (N = 4), symmetry/exactness (N = 4), fear of not saying just the right thing (N = 3), sexual themes (N = 1), and hoarding (N = 1). Their major compulsive rituals included rereading/rewriting (N = 6), cleaning/washing (N = 5), checking (N = 4), mental rituals (N = 4), need to ask or tell (N = 3), ordering (N = 2), and counting (N = 1). Two subjects (patients 5 and 7) had reduced, but not absent, insight.

Seven subjects had comorbid conditions: major depression in partial remission (N = 4), dysthymia (N = 1), social phobia (N = 1), avoidant personality disorder (N = 1), and schizotypal personality disorder along with tics (N = 1, patient 2). The subjects had failed a mean of 3.3 adequate prior SRI trials (defined as ≥ 10 weeks at the following minimum doses: clomipramine, 150 mg/day; fluoxetine, 20 mg/day; fluvoxamine, 150 mg/day; paroxetine, 40 mg/day; or sertraline, 50 mg/day). Seven subjects had failed ≥ 3 adequate trials (see Table 1). At baseline, subjects had taken fluoxetine, 60 mg/day (N = 4) or 80 mg/day (N = 6), for at least 12 weeks (7 patients for at least 6 months) and continued these doses throughout the trial.

Nine subjects completed the trial; 1 patient (patient 8) dropped out after 3 weeks because of fears of developing a movement disorder (without any objective signs). Three subjects, including the dropout, were responders, with Y-BOCS score decreases of 30% (patient 1), 29% (patient 8), and 68% (patient 10; see Table 1). Only 1 (patient 10), however, had a corroborative CGI-I score (very much improved). He responded after 1 week to olanzapine, 2.5 mg/day, and improved further after his dose was increased to 5 mg/day at the end of week 2. His religious obsessions decreased from "constant" to less than 1 hour per day, and his mental rituals from about 11 hours to less than 1 hour per day. His distress fell from severe to mild, and his ability to resist obsessions rose from none to nearly 90% of the time.

The other 2 responders had CGI-I scores of minimally improved. The obsessions of patient 1 decreased from 4 to 1 hour per day, and his distress from severe to mild.

Nonetheless, his rereading rituals continued to interfere markedly with his ability to complete school work, and he experienced no improvement in ability to resist compulsions. His symptoms seemed to fluctuate with changes in work and school stress. Patient 8 experienced a marked decrease in obsessions about contamination, getting ill, and being possibly responsible for bad events from "constant" to 2–4 hours per day; resistance increased from about 50% to about 90%, but the success rate remained moderate. Compulsions continued to occupy about 2 hours per day, with moderate distress, definite interference with social functioning, and only moderate control.

Two other patients had Y-BOCS score decreases of 5 (patient 6) and 6 (patient 3) points without a ≥ 25% decrease or a CGI-I score of much improved. The obsessions of patient 3 decreased from "constant" to about 80% of the day and he could eat 2 rather than 1 meal per day and wash and groom daily instead of every third day. He increased resistance to compulsions from 2%–3% to 65%–70%, but succeeded only 15% of the time for behavioral rituals and "never" for mental rituals. He remained unable to work, substantially impaired in social and family roles, and severely distressed. Patient 6 decreased compulsion time from 3–5 hours per day to 1.5–3 hours per day (by, for example, not always changing "contaminated" clothes) and increased her success from little to moderate; her distress levels fell from severe to moderate, and OCD interference decreased from substantial to moderate. She continued to obsess about contamination 7 to 8 hours per day, with no change in her moderate resistance or success rates. She felt "only a little better." All 7 nonresponders took olanzapine, 10 mg/day, for the final 4 weeks of the study.

Among the 4 patients with comorbid major depression, 1 patient's mood symptoms markedly improved (patient 3), but he did not become an OCD responder; the patient with dysthymia and OCD (patient 8) experienced rapid improvement in both. Although the subjects' mean HAM-D scores decreased significantly from baseline to endpoint (paired 2-tailed t test; $t = 3.56$, $df = 9$, $p = .006$), as did their mean Y-BOCS scores (paired 2-tailed t test; $t = 2.42$, $df = 9$, $p = .04$) (see Table 1), the baseline-to-endpoint percent changes in these 2 scores were not significantly correlated (Spearman rank correlation; $r = 0.27$, NS).

The most common adverse events were weight gain (affecting all 10 patients), drowsiness, dry mouth, and increased appetite (Table 2). Patients gained from 5 to 32 lb (median = 17 lb, mean ± SD = 17 ± 10 lb); 6 patients (60%) gained ≥ 7% of baseline weight. With the exception of weight gain, adverse events were mild to moderate; no patient discontinued the study because of them. No patient exhibited abnormal involuntary movements or akathisia.

Table 2. Adverse Events Associated With Olanzapine Augmentation in Obsessive-Compulsive Disorder (total N = 10)

Adverse Event	N
Weight gain	10
Drowsiness	6
Dry mouth	4
Increased appetite	4
Indigestion	3
Constipation	3
Flatulence	3
Feeling disoriented	3
Acid reflux	2
Decreased appetite	1
Increased anxiety	1
Restlessness	1
Increased belching	1
Decreased sleep	1
Headache	1
Frequent urination	1
Frequent bowel movement	1
Sensitive skin	1
Tremor	1

DISCUSSION

Only 1 subject (patient 10) had a dramatic response to olanzapine augmentation; his religious obsessions and mental rituals rapidly and persistently diminished, with improvement maintained on olanzapine, 5 mg/day, over a 6-month follow-up period. Four other patients experienced partial improvement (2 of whom met our response criterion of ≥ 25% decrease in Y-BOCS score). Our 30% formal response rate is low compared with the 50% response rate seen in small open-label trials of risperidone augmentation.[7,8] However, our results, together with positive results a case series[19] and a report[20] published after we completed our trial, suggest that olanzapine augmentation may benefit many patients with treatment-unresponsive OCD even in the absence of comorbid tic disorders or schizotypal personality disorder. In both our trial and the recent case series of 10 patients,[19] improvement in OCD was independent of the response of comorbid mood disorders.

Our patients gained weight more often (100%) and more substantially (median = 17 lb) than would be expected,[19,21] and we have no explanation for this. Since weight gain is common with olanzapine treatment,[21] studies of counteractive strategies are indicated. In general, olanzapine was well tolerated in our trial, and adverse events were rated only mild to moderate. The patient who dropped out did so because of fears of developing a movement disorder (his grandmother had developed parkinsonian symptoms from haloperidol), not because of drug side effects.

Our modest response rate may have been a result of our dosing strategy or the trial's limited length. A dose ratio of 1:4 for risperidone to olanzapine gives equal occupancy

of D_2 receptors.[22] Our maximum olanzapine dose (10 mg/day) may not, however, have achieved the same degree of receptor occupancy at the (as yet unknown) critical receptors for OCD response as does risperidone, 1 to 3 mg/day, the effective dose range in most treatment-refractory OCD cases. In 1 treatment-refractory OCD case,[19] an olanzapine dose of 20 mg/day was effective. In contrast, we believe that our trial's duration was adequate. The vast majority of treatment-refractory OCD patients who respond to risperidone do so within a few days to 4 weeks.[4-6,8,19]

Although we did not measure plasma levels of either drug, pharmacokinetic interactions are unlikely to explain response or lack thereof. Improvement in OCD is not related to plasma levels of fluoxetine or norfluoxetine,[23] and these compounds do not enhance the hepatic metabolism of olanzapine.

CONCLUSION

Despite its small sample size, open-label design, and limited dose range, our trial suggests that olanzapine augmentation may benefit some patients with treatment-refractory OCD. Larger, double-blind, placebo-controlled trials are needed to further test this hypothesis as well as to identify useful predictors of response. Double-blind, placebo-controlled comparisons of risperidone and olanzapine augmentation in treatment-refractory OCD are needed to establish their comparative safety, tolerability, and effectiveness.

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

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