The Use of Aripiprazole in Obsessive-Compulsive Disorder: Preliminary Observations in 8 Patients

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Objective: To assess the effectiveness of aripiprazole, an atypical antipsychotic with dopamine- and serotonin-stabilizing properties, as monotherapy in treating obsessive-compulsive disorder (OCD).

Method: Adult subjects meeting DSM-IV criteria for OCD who were not currently receiving pharmacotherapy for the disorder were entered into an 8-week open-label trial of treatment with aripiprazole (10–30 mg/day). Efficacy assessments included the Yale-Brown Obsessive Compulsive Scale (YBOCS) and the Clinical Global Impressions-Improvement scale. Safety assessments included evaluation of vital signs, weight, and treatment-emergent side effects. Data were collected from June 2003 to August 2004.

Results: Eight subjects were enrolled, 7 of whom took at least 1 dose of study medication. Using the last observation carried forward, the mean total YBOCS score decreased from 23.9 at baseline to 17.6 at the final visit ($p = .06$). More pronounced improvement was observed in compulsive symptoms ($p < .05$) compared with obsessive symptoms ($p = .09$). Three subjects (43%) responded to treatment, showing a 30% or greater reduction in YBOCS total score. Two subjects discontinued treatment within 1 week due to side effects (akathisia, nausea). While no changes were noted in vital signs, a mean weight gain of 1.8 kg was observed.

Conclusion: Although from a small, open-label study, these results suggest that aripiprazole holds promise for treating OCD. Larger, controlled studies of aripiprazole as monotherapy and as augmentation in partial responders to selective serotonin reuptake inhibitors are needed.

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Obsessive-compulsive disorder (OCD) remains one of the most difficult conditions to treat successfully. While selective serotonin reuptake inhibitors (SSRIs) are consistently superior to placebo, there is usually a substantial degree of residual symptomatology.[1] For this reason, there have been many attempts to enhance the effects of an SSRI with augmentation by atypical antipsychotics, such as olanzapine, risperidone, and quetiapine.[2–13] This strategy is consistent with the fact that anxiolytic properties of atypical antipsychotics have been demonstrated in other anxiety disorders.[14,15]

Aripiprazole is the most recently approved antipsychotic drug in the United States, acting as a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} receptors. In addition, the drug serves as a serotonin 5-HT_{2A} receptor antagonist. These dopamine-serotonin–stabilizing properties might be of therapeutic value in OCD. Since we were unaware of any reports on aripiprazole in OCD, we conducted a small, open-label, pilot trial of the drug in 8 subjects, the results of which are described in this article.

METHOD

Study Sample

Subjects were recruited through advertising and clinical referral. Physically healthy adults aged 18 to 65 meeting DSM-IV criteria for OCD and scoring a minimum of 16 on the Yale-Brown Obsessive Compulsive Disorder Scale (YBOCS)[16,17] were eligible to participate. Key exclusion criteria were as follows: lifetime history of bipolar disorder, schizophrenia, or other psychotic disorder; recent history of substance abuse or dependence (last 6 months); suicidal behavior; clinically significant medical, laboratory, or electrocardiogram (ECG) abnormality; and need for concurrent psychotropic medications. All subjects gave written informed consent following full explanation of the study and of the availability of alternative, proven treatments for OCD. The study was approved by the Duke University Medical Center Institutional Review Board. Data were collected from June 2003 to August 2004.

Study Design

This was an 8-week, open-label, flexible-dose trial of monotherapy with aripiprazole. Subjects underwent an

Table 1. Efficacy Results for 7 Subjects With Obsessive-Compulsive Disorder Who Received Aripiprazole

	YBOCS Total Score			YBOCS Obsessive Subscale Score		YBOCS Compulsive Subscale Score		CGI-I Score
Subject	Baseline	Endpoint	Change (%)	Baseline	Endpoint	Baseline	Endpoint	Endpoint
1	19	11	42	10	6	9	5	2
2	25	19	24	15	12	10	7	3
3	24	24	0	9	12	15	12	4
4	24	24	0	13	12	11	12	4
5	23	21	9	14	13	9	8	4
6	26	6	77	12	2	14	4	1
7	26	18	31	13	9	13	9	3

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

initial screening evaluation that included medical and psychiatric assessment, including the Mini-International Neuropsychiatric Interview[18] and a clinical evaluation. Safety evaluation included vital sign and weight measurement, routine blood work (hematology, chemistry, thyroid function), urinalysis, ECG, and, in women of childbearing potential, a serum pregnancy test. Ratings performed included the clinician-administered YBOCS and Clinical Global Impressions-Improvement scale (CGI-I).[19]

Aripiprazole was started at 10 mg/day and increased to 30 mg/day at the clinician's discretion. Treatment outcome was measured by the YBOCS and CGI-I. Subjects returned for follow-up at 2-week intervals, at which time efficacy assessments were completed, vital signs and body weight were recorded, and side effects were evaluated using the Symptom Occurrence Scale.[20] Unused study medication and the completed medication log were collected and reviewed at each visit to assess treatment compliance.

Analysis

Analyses were performed on data from subjects who took at least 1 dose of study medication and returned for at least 1 postbaseline assessment. Using the last observation carried forward, response was assessed by change in YBOCS score from baseline to final visit, and those subjects classified as responders met the following criteria: (1) a 30% or greater drop in YBOCS score from baseline and (2) a CGI-I score of 1 or 2. Analyses of efficacy measures and safety parameters were performed using the Wilcoxon signed rank test, with statistical significance achieved at $p < .05$.

RESULTS

Of 13 subjects screened, 8 subjects were eligible for participation and were given study medication. Of these 8, 7 took at least 1 dose of study medication, while 1 subject changed his mind about participating in the study once he left the clinic and did not take any medication. Two subjects discontinued treatment early due to side effects, 1 after 4 days due to akathisia and 1 after 1 week due to severe nausea. The remaining 5 subjects completed the full 8-week course of treatment.

The sample was composed entirely of men, including 5 white subjects, 2 black subjects, and 1 Hispanic subject. Half of the sample (N = 4) were married, and the mean (SD) age was 39.8 (9.6) years. Five subjects had never received pharmacotherapy for OCD. Three subjects had been previously treated with an SSRI, 2 of whom responded to treatment and 1 of whom failed to respond fully to 2 previous trials of SSRIs; of note, the adequacy of dosing and duration of the trials could not be verified.

Scores for the individual subjects are presented in Table 1. Mean (SD) total YBOCS scores at baseline and the final visit were 23.9 (2.4) and 17.6 (6.8), respectively ($p = .06$). On the obsessive subscale of the YBOCS, mean (SD) baseline and final visit scores were 12.3 (2.1) and 9.4 (4.1) ($p = .09$), respectively, while mean (SD) scores on the compulsive subscale were 11.6 (2.4) and 8.1 (3.1), respectively ($p < .05$). Three subjects (42.9%) met the YBOCS response criterion, based on a ≥ 30% reduction in YBOCS score from baseline. On the CGI-I, 2 subjects (28.6%) were judged to be responders at their final visit.

The following adverse events were observed: drowsiness (N = 3) and dry mouth, nausea, thirst, tingling, tremor, akathisia, and unsteadiness (N = 1 each). Final doses of aripiprazole were as follows: 10 mg (N = 3), 20 mg (N = 2), and 30 mg (N = 2). The 2 subjects who remained on 30 mg complained of mild akathisia and sleepiness throughout (N = 1) or fatigue at the final visit only (N = 1). Other subjects either could not tolerate higher doses or had responded sufficiently well at lower doses so that an increase was not required. No changes were observed in vital signs; however, a mean 1.8-kg increase in body weight was observed, from 95.0 to 96.8 kg ($p < .05$).

DISCUSSION

Although from a small and open-label study, our results suggest that aripiprazole holds promise for treating OCD. Inasmuch as this was a study of monotherapy, it even suggests the possibility that the drug could prove efficacious alone in some patients with OCD. Two subjects showed a very robust response, with final total

YBOCS scores of 11 and 6. There did not appear to be any association between response and past treatment, as the 3 subjects with the greatest responses (Table 1) were treatment naive, had been responsive to an SSRI in the past, or had failed to respond to an SSRI. Effects of the drug were slightly more pronounced on compulsive symptoms, where improvement was statistically significant; however, a trend was noted on obsessive symptoms as well, which might have been significant with a larger sample.

It was our impression that the doses chosen were higher than might be ideal for OCD. A starting dose of 5 mg would perhaps have been more acceptable, as the initial 10-mg dose may have produced side effects that could have been avoided at a starting dose of 5 mg or lower. Such a dosing strategy might have enabled us to retain the 2 early dropouts. We also found that a number of potential subjects were alarmed at the side effect profile described in the consent form, and there may have been unnecessary anxiety about the feared dangers of the drug. As a result, many otherwise suitable subjects decided not to participate in the study.

While atypical antipsychotics may hold a useful role in treatment of OCD, we should remain aware of the body of evidence concerning their adverse events with regard to weight, blood sugar regulation, and development of the metabolic syndrome.[21] Clinically significant weight gain may be considered an increase of ≥ 7% of total body weight. In this 8-week study, body weight increased by an average of 2%. While this may not be considered clinically significant, it was a statistically significant change, and it is possible that further gains could be noted over a longer treatment period. Also, while the risk of extrapyramidal side effects is low with atypical antipsychotics, it is present.[22] The debate about comparative risks among the various atypical antipsychotics continues, and it may take some time until we understand where this class of drug will fall in the management of OCD. Based on our findings, larger and well-designed studies of aripiprazole as monotherapy and as augmentation in SSRI partial responders are well justified.

Drug names: aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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