Aripiprazole in Schizophrenia Patients With Comorbid Obsessive-Compulsive Symptoms: An Open-Label Study of 15 Patients

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Background: Approximately 15% of patients with schizophrenia also meet DSM-IV criteria for obsessive-compulsive disorder (OCD) at some point in their illness, a rate considerably higher than in the general population. This study examined aripiprazole treatment of patients with comorbid schizophrenia and obsessive-compulsive symptoms (OCS) that did not meet full criteria for OCD.

Method: Physically healthy adults aged 18 to 65 years with DSM-IV schizophrenia and a minimum score of 16 on the Yale-Brown Obsessive Compulsive Scale (YBOCS) were eligible to participate in this 6-week, open-label, flexible-dose trial of aripiprazole monotherapy. Patients currently taking another antipsychotic medication were concurrently down-titrated from their current antipsychotic and up-titrated with aripiprazole, starting with 15 mg/day. Coadministration of the 2 medications lasted from 7 to 14 days, until a stable therapeutic dose of 10 to 30 mg/day was reached. Subjects were recruited into the study, which was conducted at the Schizophrenia Clinic of Stanford University School of Medicine, between January 2005 and December 2006.

Results: Of 15 eligible patients, 7 completed the trial. All 7 had at least minimal improvement on the YBOCS, the Clinical Global Impressions (CGI) scale, and the Positive and Negative Syndrome Scale (PANSS). At week 6, the mean CGI-Improvement scale score was 2.3 (much improved). Mean PANSS scores decreased from 75 to 56, a mean decrease of 21%, ($p < .05$). On the YBOCS, 6 of 7 completers showed a change of greater than 35% from baseline to week 6.

Conclusion: These results suggest that aripiprazole monotherapy can modestly improve the outcome for some schizophrenia patients with obsessive-compulsive symptoms. Further studies with aripiprazole under controlled conditions are indicated for this population of patients. Overall, even modest improvement in global functioning due to an improvement in an OCS component may be clinically meaningful for this difficult-to-treat subset of schizophrenia patients.

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Approximately 15% of patients with schizophrenia also meet DSM-IV criteria for obsessive-compulsive disorder (OCD) at some point in their illness.[1–3] When obsessive-compulsive symptoms (OCS) that do not meet full DSM criteria for OCD are also assessed, an even higher rate of comorbidity (up to 49%) is observed.[4] This rate of OCD is considerably higher than that in the general population (1.2%–2.4%),[5] suggesting a possible pathophysiological linkage between the 2 disorders. Schizophrenia patients with OCD or OCS comorbidity are generally characterized by lower levels of social functioning, longer duration of hospitalization, and more neurocognitive deficits. (For review, see Poyurovsky et al.[3]) Furthermore, there is a general consensus that the schizo-obsessive subgroup is characterized by apparent therapeutic resistance. To date, studies evaluating possible effective therapeutic approaches in this difficult-to-treat patient population are limited. This is also a very difficult group to enroll and maintain in studies because of (1) thought disorder inherent in schizophrenia, as well as (2) hallucinations, (3) prominent negative symptoms, (4) obsessional doubts, and (5) the anxiety about risks of treatment associated with OCS.

Emergence de novo of or the exacerbation of preexisting OCS/OCD has been reported in schizophrenia

patients treated with clozapine, olanzapine, risperidone, and quetiapine.[3] However, preliminary observations indicate that clozapine and olanzapine, either alone or in combination with selective serotonin reuptake inhibitors, may be efficacious in alleviating both schizophrenia and OCS in some schizo-obsessive patients.[6–9] The major limitations of olanzapine and clozapine monotherapy, however, are metabolic side effects and weight gain, which appear to be strongly associated with nonadherence to pharmacotherapy.[10]

Aripiprazole is an atypical antipsychotic agent with a unique pharmacologic profile, characterized by a partial agonism at the dopamine D_2 receptor, as well as interaction with various serotonin receptors (5-HT_{1A}, 5-HT_{2A}, and 5-HT_7).[11] Complex interplay between serotonergic and dopaminergic systems appears to be significant in the pathogenesis and treatment of both schizophrenia and OCD.[12] Aripiprazole's unique receptor pharmacology[11,13] suggests that it may be effective in schizophrenia patients with associated OCS without potentially inducing or exacerbating symptoms. Aripiprazole is effective in treating both positive and negative symptoms and in preventing relapse in schizophrenia patients.[14,15] Preliminary evidence indicates that aripiprazole may also be efficacious for some patients with "pure" OCD.[16] In schizophrenia patients, treatment with aripiprazole was safe and well-tolerated and exhibited low potential for inducing side effects, including short-term weight gain, extrapyramidal side effects (EPS), and prolactinemia.[17]

This study examined aripiprazole treatment of patients with comorbid schizophrenia and obsessive-compulsive symptoms who did not meet full criteria for OCD.

METHOD

Study Sample

This study was conducted at the Schizophrenia Clinic of Stanford University School of Medicine, Stanford, California. Subjects were recruited between January 2005 and December 2006 through advertising and clinical referral. Physically healthy adults aged 18 to 65, meeting DSM-IV criteria for schizophrenia and having OCS with a minimum score of 16 on the Yale-Brown Obsessive Compulsive Scale (YBOCS) were eligible.[18] Those who qualified were white males, aged between 18 and 37 years (Table 1). Most were single, with restricted social lives, and most were not working. Subjects had been in treatment for at least 5 years, tried numerous first- and second-generation antipsychotics, and achieved partial response. Some of the patients were taking other agents like mood stabilizers or lorazepam because of partial response to antipsychotic agents. None had other comorbid disorders, such as bipolar or anxiety disorders. The patients described the presence of OCS only after very careful questioning and reported that these symptoms had never been targeted for treatment.

Table 1. Baseline Characteristics of Study Completers With Schizophrenia and Obsessive-Compulsive Symptoms (N = 7)

Characteristic	Subjects, N (%)
Sex	
Male	6 (86)
Female	1 (14)
Race/ethnicity	
White	5 (71)
Other	2 (29)
Marital status	
Never married	6 (86)
Divorced	1 (14)
Education	
High school graduate	2 (29)
Some college	3 (43)
Bachelor's degree	1 (14)
Some graduate school	1 (14)
Occupational status	
Unemployed	4 (57)
Student or part-time employment	3 (43)

Key exclusion criteria were a recent history of substance abuse or dependence (past 6 months); suicidal behavior; clinically significant medical, laboratory, or electrocardiogram (ECG) abnormality; and need for concurrent psychotropic medications (except for mood stabilizers or lorazepam). All subjects gave written informed consent following full explanation of the study and of the availability of alternative treatments for schizophrenia with comorbid OCS. The study was approved by the Institutional Review Board of Stanford University School of Medicine.

Study Design

This was a 6-week, open-label, flexible-dose trial of monotherapy with aripiprazole. Subjects underwent an initial screening evaluation that included medical and psychiatric assessment. Safety evaluations included measurements of vital signs and weight, routine blood work (hematology, chemistry, and thyroid function), urinalysis, electrocardiogram, and a serum pregnancy test in women of childbearing potential. Ratings included the YBOCS, the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales,[19] the Positive and Negative Syndrome Scale (PANSS),[20] and the Calgary Depression Rating Scale (CDRS),[21] administered at baseline and at the end of week 6.

Patients with prior exposure to either first- or second-generation antipsychotics (for a minimum of 3 months) were concurrently down-titrated from their current antipsychotic medication and up-titrated with aripiprazole, beginning with 15 mg/day. Coadministration lasted 7 to 14 days, until the patient achieved a stable therapeutic dose of aripiprazole (10–30 mg/day).

Response to aripiprazole was defined as clinical improvement in the OCS component (2 or more [much

Table 2. Outcomes for Study Completers With Schizophrenia and Obsessive-Compulsive Symptoms (N = 7)

	CGI Scores									
	Severity of Illness			Improvement	PANSS Total Score			YBOCS Total Score		
Subject Number	Baseline	End of Week 6	Change	End of Week 6	Baseline	End of Week 6	Change in Total Score	Baseline	End of Week 6	Change in Total Score
1	6	5	1	2	117	79	38	28	14	14
2	3	2	1	2	50	44	6	16	9	7
3	5	4	1	2	80	66	14	25	4	21
4	6	4	2	2	124	66	58	27	17	10
5	4	3	1	2	56	46	10	30	14	16
6	4	3	1	3	57	54	3	28	22	6
7	3	2	1	1	44	36	8	24	7	17

Abbreviations: CGI = Clinical Global Impressions scale, PANSS = Positive and Negative Syndrome Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 3. Mean Outcome Scores for Study Completers With Schizophrenia and Obsessive-Compulsive Symptoms (N = 7)

Scale	Baseline, Mean (SD)	End of Week 6, Mean (SD)	Percentage Change, Mean (SD)
CGI			
Severity of Illness	4.4 (1.3)	3.3 (1.1)	26.7 (7.9)
Improvement	…	2.3 (0.9)	…
PANSS*	75.4 (32.8)	55.9 (15.1)	21.4 (13.9)
YBOCS**	25.4 (4.6)	12.4 (6.2)	51.5 (20.9)

*$p \leq .05$.
**$p \leq .01$.
Abbreviations: CGI = Clinical Global Impressions scale, PANSS = Positive and Negative Syndrome Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.
Symbol: … = not applicable.

improved] on the CGI) or ≥ 35% decrease in total YBOCS score.

Analysis

Descriptive statistics with a significant p value set at ≤ .05 were used.

RESULTS

Fifteen patients provided written informed consent to participate. Two patients were screen failures, and 2 withdrew consent before starting aripiprazole (they changed their minds about beginning a study). During the first 2 weeks of the cross-titration, 2 more withdrew due to what they perceived as mild worsening of their schizophrenia symptoms (they felt more "stimulated"), and 2 dropped out because of mild akathisia in one case and an increase in pre-existing tardive dyskinesia in the second. All of these patients expressed troubling, mixed feelings about participating in research or switching from their current antipsychotic medication.

Seven participants completed all 6 weeks of aripiprazole treatment. Table 2 shows their scores on the CGI-S and CGI-I scales, the PANSS, and the YBOCS. All 7 had at least minimal improvement on all 3 scales. Table 3 shows that the mean CGI-S score changed by 1 point from baseline (moderately ill) to week 6 (mildly ill). At week 6, the mean CGI-I score was 2.3 points (much improved). Mean PANSS scores decreased from 75 to 56, a mean score decrease of 21% ($p < .05$). On the YBOCS, 6 of 7 completers showed an improvement of greater than 35% from baseline to week 6.

There were minimal side effects reported or observed among the aripiprazole completers. One patient developed mild akathisia during the last week of the study.

DISCUSSION

This small pilot study suggests that aripiprazole monotherapy can modestly improve the outcome for some schizophrenia patients with OCS. Whether the improvement is secondary to overall improvement in psychosis after switching to a different second-generation antipsychotic or to specific effects on OCS exerted by aripiprazole is yet to be clarified. Without a placebo control group, we do not know whether similar improvement would have been observed had the patients continued treatment with their original antipsychotic agent. This possibility seems unlikely, since the study participants were mostly partial responders (with regard to their schizophrenia symptoms) with comorbid OCS for many years. Finally, it is possible that some of the study participants experienced OCS while receiving other antipsychotic agents and that their discontinuation and switch to aripiprazole might account for our findings.[22] Unfortunately, our patients and families were unable to accurately recall the duration of the OCS and treatments they were receiving when the OCS emerged or whether the symptoms had been present prior to the onset of schizophrenia.

Finally, aripiprazole has been recently reported to be associated with the emergence of OCD, although not in patients with schizophrenia.[23] In this context, none of the dropouts in our study experienced worsening of their OCS.

Further studies with aripiprazole under controlled conditions are indicated for schizo-obsessive patients.[3]

Overall, even modest improvement in global functioning due to an improvement in an OCS component may be clinically meaningful for this difficult-to-treat subset of schizophrenia patients.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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