Aripiprazole Augmentation in Patients with Resistant Obsessive Compulsive Disorder: a Pilot Study

Roberto Delle Chiaie*, Pierluigi Scarciglia, Massimo Pasquini, Maria Caredda and Massimo Biondi

Department of Psychiatry and Psychological Medicine, SAPIENZA University of Rome, Viale dell'Università, 30 - 00185 - Rome, Italy

Abstract: *Background:* Antipsychotic augmentation is an effective treatment intervention for Obsessive Compulsive Disorder (OCD) patients resistant to Selective Serotonin Reuptake Inhibitors (SSRI) agents. This pilot study was conducted to evaluate the effectiveness and tolerability of Aripiprazole for the augmentation of standard treatments in patients with resistant OCD.

Methods: Twenty patients diagnosed with OCD according to DSM-IV TR criteria and having a history of resistance to standard pharmacological treatment were included in the study. Aripiprazole was added to ongoing SSRI or clomipramine treatment with a starting dose of 5 mg/day and titrated up to a maximum of 20 mg/day (mean dose 12.62 mg ± 4.25). Efficacy was assessed with the Yale-Brown obsessive compulsive scale (Y-BOCS) and the Clinical Global Improvement-severity scale (CGI-S) at baseline and at week 12 of Aripiprazole augmentation. Side effects were monitored by the Udvalg for Kliniske Undersogelser (UKU) side effect rating scale.

Results: All 20 subjects enrolled in our study completed the full 12-week course of treatment. A significant improvement over the 12-week study period was observed (paired t-test for mean Y-BOCS total score at week 12 as compared with baseline – all patients: t = 13.146, d.f. = 19, p= 0.0001). Aripiprazole was generally well tolerated and no changes were observed in vital signs. The most commonly observed side effects after the introduction of the augmenting agent included: akathysia, nausea/vomiting, hyperkinesia, tension/inner unrest, tremors, asthenia/lassitude/increased fatiguability.

Conclusions: Although results of this pilot study are preliminary and require confirmation in randomized controlled trials, our experience suggested that Aripiprazole is effective and well-tolerated as an augmenting agent in patients with treatment resistant OCD.

Keywords: Aripiprazole, augmentation, treatment resistant OCD.

INTRODUCTION

Obsessive Compulsive Disorder (OCD) is a prevalent and disabling disorder with a lifespan prevalence approximately of 2,5% [1, 2]. The disorder follows a fluctuating course and only rarely resolves spontaneously [3].

Most of the patients favourably respond to psychopharmacological interventions with either selective serotonin reuptake inhibitors (SSRIs) or clomipramine. However, while these drugs are consistently superior to placebo, 40% to 60% of OCD patients fail to respond to an initial adequate trial and many times a substantial degree of residual symptomathology may persist [4].

There have been many attempts to enhance the effects of SSRIs or clomipramine using several psychotropic compounds as augmenting agents. Conventional antipsychotics have proved effective both in open and in double blind trials [5, 6]. Atypical antipsychotic have also been tested as add-on agents for treatment resistant OCD patients. Trials have been succesfully conducted with risperidone [7-10], olanzapine [11-13], amisulpride [14] and quietiapine [15, 16].

Among these new drugs aripiprazole is also considered of interest because of its properties: it is an atypical antipsychotic with partial agonist activity at the dopamine D2 and serotonin 5HT1A receptors and antagonistic activity at the 5HT2-A receptors [17, 18].

Clinical efficacy of aripiprazole was observed for the treatment of comorbid obsessive compulsive symptoms in bipolar patients [19], schizophrenics [20] or in children with Tic Disorders [21]. In OCD patients resistant to conventional treatments, aripiprazole's efficacy was first assessed as a monotherapy treatment in an open-label pilot trial [22]. However in these SSRI resistant OCD patients, the drug proved more effective as an augmenting strategy. This was observed in a series of case reports [23-26], and in two small open studies, one conducted on adult patients [27], and another on adolescents [28].

The aim of this study was to provide confirmatory evidence for aripiprazole as a potential augmentation agent in the treatment of a larger sample of refractory OCD adult patients. For this reason we performed an open-label add-on

*Address correspondence to this author at the SAPIENZA University of Rome Viale dell'Università, 30 00185-Roma, Italy; Tel: +390639742364; Fax: +390639038466; E-mail: r.dellechiaie@centrokahlbaum.it

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study conducted in OCD patients with severe symptoms resistant to standard pharmacological treatments.

MATHERIALS AND METHODS

Subjects

The study was carried out at the Outpatient Center of the Department of Psychiatric Science and Psychological Medicine of the SAPIENZA University of Rome during the period February 2007 through October 2009. During this period 28 consecutive patients who had received a diagnosis of OCD according to DSM-IV TR [29] criteria showed to be resistant to standard treatments. Of these 28 patients invited to participate, 20 (70%) were enrolled in the study. The most frequent reason reported by the 8 patients that refused to be enrolled in the study, was their concern for the potential adverse effects of the treatment, due to the off-label use of aripiprazole. The key criterion for inclusion was treatment resistance to SSRIs or clomipramine, defined as no or inadequate response to previous treatment with at least two SSRIs or clomipramine, at an adequate dose and time (at least 12 weeks) [30]. The second inclusion criterion was the severity of the obsessive-compulsive symptomatology as measured on the Y-BOCS [31]. Despite ongoing drug treatment, scores at baseline were of at least 16 or greater. In order to avoid possible methodological drawbacks, all diagnostic procedures were carried out by three senior members of the research team (RDC, MP, MC) with several years of practice and experience in clinical research.

Key criteria for exclusion were the presence of a lifetime history of Bipolar Disorder, Schizophrenia, delirium or other psychotic disorders, personality disorders, a recent history of substance abuse or dependence, suicidal attempts, clinically significant medical disorder, laboratory abnormalities (endocrine, metabolic or ECG) and need for concurrent psychotropic medications other than SSRI*s*, clomipramine or benzodiazepines at bedtime for sleep induction (if necessary).

PROCEDURE AND ASSESSMENT

Before entering, all subjects gave a written informed consent, according to the procedures approved by the Hospital Committee, following full explanation of the aims of the study, of the off-label use of aripiprazole and of the availability of alternative, proven treatments for OCD.

Treatment outcome was measured by the Y-BOCS total score and the Clinical Global Impressions Severity (CGI-S) [32]. Response was assessed by change in Y-BOCS total score from baseline to endpoint visit and the response criteria were set as follows: "full response" 35% or greater reduction of Y-BOCS score, "partial response" greater than 25% but less than 35% Y-BOCS reduction, "non response" less than 25% Y-BOCS reduction".

Side effects were monitored with the UKU side effect rating scale [33]. Scales were administred at the end of the first visit (baseline evaluation). Subjects then returned for further follow-up visits, which were set at 3 weeks intervals. At the end of the 4^{th} visit (12^{th} week: endpoint) scales were newly administred. Vital signs and body weight were recorded both at baseline and at endpoint. All raters received specific training in the use of the study instruments.

Unused study medication and the completed medication log were collected and reviewed at each visit to assess treatment compliance.

Aripiprazole, was administered in the morning and was added to ongoing SSRI or clomipramine with a starting dose of 5 mg/day in the morning. This dose was titrated up to a maximum of 20 mg/day, according to the patients clinical response and tolerability. Maximum dose reached was 20 mg/day (mean dose 12,62 mg ± 4,25).

Statistical Analysis

We used a descriptive analysis to study the frequency distribution of all variables of interest, and the paired t-test to examine differences in scores on outcome measures at baseline and follow-up assessments. SPSS for Windows, version 13.0 was used for all analyses.

RESULTS

All of 20 subjects enrolled in our study completed the full 12-weeks course of treatment. The sample was composed of 13 men and 7 female patients, all Caucasian and all yet treated for their OCD with a conventional therapy. Their ages ranged from 24 to 49 years (mean age 32,40 ± 6,38) with a mean duration of disorder of 12,5 years (± 6,72). All patients were on a standard anti OCD therapy: 14 patients were on clomipramine (mean dose 153,57 mg ± 33,40), 5 patients were on paroxetine (mean dose 52 mg ± 8,36) and 1 patient was on fluvoxamine (daily dose 300 mg). Sociodemographic and clinical characteristics of the twenty patients are shown in Table **1**.

Overall, a significant improvement in OCD symptoms was observed (Tables **2**-**3**). On the basis of the Y-BOCS scores reduction response criterion, after the aripiprazole add-on 16 (80%) patients showed full response, 2 (10%) patients showed partial response and 2 (10%) patients were non responders. A significant reduction from baseline to endpoint was also showed by CGI-S scores.

Aripiprazole was generally well tolerated and no changes were observed in vital signs. Baseline UKU scale scores were significantly reduced at endpoint (BL: 8,25±4,96, EP: 6.25±4,65; $p<.001$).

The most commonly observed side effects after the introduction of the augmenting agent included akathysia (25%), nausea/vomiting (15%), hyperkinesia (15%), Tension/Inner unrest (10%), tremors and asthenia/lassitude/increased fatiguability (10%). These symptoms never reached a score of 3 on the UKU scale. Among other adverse effects, mainly observed in patients under clomipramine, were dry mouth (35%), constipation (35%), erectile and ejaculative dysfunctions (20%). None of these required drug discontinuation.

DISCUSSION

In this open-label study was considered a larger sample than previous studies conducted till now. Our results confirm that aripiprazole augmentation may be effective and well tolerated in patients with OCD refractory to standard treatments.

Table 1. Sociodemographic and Clinical Characteristics

Patient	Sex	Age	Duration of OCD	AD Drug	AD Dose (mg/day)	Aripiprazole (mg/day)
1	F	41	5	Clomipramine	150	10
2	F	34	8	Clomipramine	112,5	10
3	M	37	15	Clomipramine	150	20
4	M	39	19	Clomipramine	225	15
5	M	35	15	Clomipramine	150	10
6	M	30	14	Paroxetine	50	10
7	M	27	6	Paroxetine	50	10
8	M	31	10	Clomipramine	150	15
9	F	30	10	Clomipramine	112,5	10
10	M	30	16	Clomipramine	150	20
11	F	24	3	Paroxetine	40	5
12	M	38	18	Paroxetine	60	15
13	M	38	25	Clomipramine	150	20
14	F	26	3	Fluvoxamine	300	10
15	M	49	22	Clomipramine	150	10
16	F	32	13	Clomipramine	125	10
17	M	37	24	Clomipramine	150	7,5
18	M	27	8	Clomipramine	150	15
19	M	24	6	Paroxetine	60	15
20	F	29	10	Clomipramine	225	15

A full response was observed in 80% of the 20 patients treated in this study. Such rate of responders is higher than the rates observed by Connor [22] and Pessina [27]. Some methodological differences might account for this discrepancy. With respect to the Connor study, since it was an aripiprazole monotherapy trial, higher response rates obtained in our add-on study could depend upon this difference. In the Pessina study, only 8 out 12 of the enrolled patients completed the 12 weeks trial, while all of our 20 subjects were completers. These differences could have influenced the higher rate of responders found in our study.

However, even if some of these differences could partially explain our better results, our data are interesting, because we set the response threshold at a level of 35% reduction of the Y-BOCS score from baseline to endpoint to define a "full response", while in the previous two studies this level was set at 30% and at 25% respectively. We cannot rule out anyhow the possibility that our pattern of findings may differ from previous studies depending on different OCD subtypes observed.

High response rates however, have been reported also in several other studies when other antipsychotics were added as augmenting agents to standard treatments in patients with refractory OCD, such as 65% for haloperidol [5], 50%–71.4% for quetiapine [15, 16], 50%–85% for risperidone [9,10] and 43.5%–70% for olanzapine [12, 13]. The highest response rate among these augmentation trials was observed in the amisulpride study (90%)[14]. Although the study designs, definitions of resistance and response criteria were different, an explanation for the high rate of response to aripiprazole augmentation might lie in its pharmacodynamic profile.

The role of the serotonergic system in the aetiology of OCD is well known, but not sufficiently to understand the disorder thoroughly. Indeed, a range of other neurochemical systems may be implicated in OCD, and the dopamine system has been a particular focus of attention [34]. On the other hand, the increased dopaminergic activity may play a role in the pathophysiology of OCD and seems to point out that, among the properties of antipsychotic drugs, dopamine antagonism may contribute to enhance the efficacy of SSRIs in treatment resistant OCD patients.

According to Positron Emission Tomography studies, atypical antipsychotics cause high levels of 5HT2 antagonism at low doses, whereas relatively high doses are required to produce significant dopamine D2 antagonism [35].

In all the studies in which atypical antipsychotics were found to be effective augmenting agents for treatment resistant OCD patients, significant results were reported at lower doses than those currently recommended for treatment of psychotic disorders [36]. This may indicate that the augmentation of the ongoing anti OCD treatment obtained when these compounds are added, is mainly based on a modulation of the serotonin transmission rather than on a functional antagonism on the dopamine system. Moreover, since low

Table 2. Outcome Measures

Patient	BL Y-BOCS	EP Y-BOCS	Response	BL CGI-S	EP CGI-S	BL UKU Scale	EP UKU Scale
1	26	12	Full response	4	2	7	3
2	24	16	Partial response	5	2	4	7
3	24	9	Full response	5	2	8	5
4	30	16	Full response	6	3	14	10
5	32	18	Full response	6	2	9	4
6	23	14	Full response	4	2	4	2
7	28	10	Full response	5	3	0	2
8	30	18	Full response	6	2	9	4
9	24	10	Full response	4	2	5	2
10	32	10	Full response	5	2	12	7
11	27	14	Full response	5	2	0	0
12	29	16	Full response	5	3	3	5
13	34	18	Full response	6	2	11	7
14	32	12	Full response	5	3	5	3
15	26	18	Partial response	4	3	10	4
16	28	22	Non Response	5	2	8	5
17	38	32	Non Response	6	5	15	18
18	31	10	Full response	6	3	18	15
19	28	10	Full response	5	3	8	10
20	32	18	Full response	5	3	15	12

CGI-S: Clinical Global Impression-Severity Scale; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; BL: Baseline, EP: Endpoint.

Table 3. Outcome Measures

Y-BOCS BL	Y-BOCS EP	*t*	*df*	*p*
28,99(±3,84)	15,55(±5,47)	13,146	19	.0001
CGI-S BL	CGI-S EP			
5,1 (±0,71)	2,55(±0,75)	12,856	19	.0001

Note. Paired t-tests are used for differences of means. P=by the two-tailed *t*-test. CGI-S: Clinical Global Impression-Severity Scale; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; BL: Baseline, EP: Endpoint.

doses of antipsychotics mainly antagonize dopamine presynaptic autoreceptor, this mechanism is more likely to increase or modulate, rather than antagonize dopaminergic transmission.

Furthermore, the high response rates we observed could depend on other pharmacologic properties of aripiprazole, such as its partial agonism at 5HT1a receptors. In fact the increase in synaptic 5HT caused by SSRIs activates feedback mechanisms mediated by 5HT-1a (cell body) and 5HT1b (terminal) autoreceptors, wich, respectively, reduce the firing in 5HT neurons and decrease the amount of 5HT released per action potential, resulting in attenuated 5HT neurotransmission [37]. Partial agonism of aripiprazole at serotonin 5HT-1 autoreceptors could modulate or reduce this mechanism, resulting in an enhanced anti OCD efficacy of SSRIs.

For these reasons, the unique pharmacological profile of aripiprazole based on its partial agonistic properties on dopamine transmission, could bring an advantage over other atypical antipsychotics in the treatment of refractory OCD and partially explain the results of our study.

The present study has some limitations First, the lack of a placebo-controlled group which might mean that the results may reflect a natural improvement in OCD or a placebo effect. Second, the use of different antidepressants for standard treatment. Third, the small sample size and the open design of the study. As such the results are preliminary and require confirmation in a randomized controlled trial.

To conclude, this study suggests that, as an augmenting agent, aripiprazole is effective and well tolerated in patients with treatment resistant OCD.

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