HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2011; **26**: 51–57.
Published online 9 February 2011 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.1169

The comparison of aripiprazole and risperidone augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: a single-blind, randomised study

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Objective To investigate the comparative efficacy of aripiprazole and risperidone as augmenting agents in the treatment of obsessive-compulsive disorder (OCD) patients who did not show a ≥35% decrease in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) after 12-week monotherapy with selective serotonin reuptake inhibitors (SSRIs).
Methods The study consists of two different periods of treatment: a 12-week prospective period to determine resistance to SSRI treatment and an 8-week single-blind addition period for refractory patients only. Ninety patients were randomly assigned to receive one of the SSRI treatments. Sixty-nine patients (76.6%) completed the 12-week SSRI monotherapy period. Forty-one patients (59.4%) were considered refractory and were randomised to receive either risperidone (20 patients, 3 mgr daily) or aripiprazole (21 patients, 15 mgr daily) as augmentation to SSRI treatment. Sixteen patients (76.2%) in the aripiprazole group and 18 patients (84%) in the risperidone group completed the 8-week treatment period.
Results Eight patients (50%) in aripiprazole and 13 patients (72.2%) in risperidone group met response criteria of Y-BOCS decrease ≥35% at the end of the study. The risperidone group showed a significant improvement in Y-BOCS obsession scores compared with aripiprazole.
Conclusions The present findings suggest that risperidone may be more effective than aripiprazole. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS — obsessive-compulsive disorder; antipsychotic; treatment-refractory

INTRODUCTION

Serotonin reuptake inhibitors (SRIs) are considered the most effective and well-established pharmacotherapy for the treatment of obsessive-compulsive disorder (OCD). However, 40–60% of OCD patients do not respond adequately to SRI treatment (Bloch *et al.*, 2006; Fontenelle *et al.*, 2007) and these patients have significant disability and morbidity (Hollander *et al.*, 1996). In an adequate trial of an SRI, a less than 25–35% decrease in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score in patients with at least moderate obsessive compulsive symptom severity is usually considered partial response or non-response (Albert *et al.*, 2002; Bloch *et al.*, 2006; Denys, 2006; Pallanti and Quercioli, 2006). Since there is no operational definition for the concept of ''non-response'', the labels ''non-responder'', ''treatment-resistant'' and ''treatment refractory'' are often used idiosyncratically and synonymously (Pallanti and Quercioli, 2006).

Pharmacological options for SRI-refractory cases include increasing drug dose, changing to another SRI, or augmenting with lithium, clonazepam, buspirone and dopamine antagonists (Eisenberg and Asnis, 1985; Delgado *et al.*, 1990; Hewlett *et al.*, 1992; Pigott *et al.*, 1992; McDougle *et al.*, 1994). By reason of the acute and long-term side effects with conventional antipsychotics, second generation antipsychotics (SGAs) are preferred. Studies with olanzapine, quetiapine and risperidone have shown that SGAs reduce obsessive compulsive (OC) symptoms in patients with OCD (McDougle *et al.*, 2000; Atmaca *et al.*, 2002; Bystritsky *et al.*, 2004).

Although the specific mechanism of SGAs on OCD symptoms is unclear, it can be partially explained on the basis of dopamine (D2) and serotonin (5-HT2) receptor occupancy by SGAs (Ramasubbu *et al.*,

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Received 14 July 2010
Accepted 29 December 2010

2000). A study conducted with PET has tested the bidirectional effect of SGAs and showed that SGAs cause high levels of 5-HT2 antagonism at low doses, whereas relatively high doses are required to produce significant D2 antagonism (Kapur *et al.*, 1998). Given that 5-HT2 antagonism may induce or exacerbate OC symptoms, and that D2 antagonism may augment the anti-obsessional effect of 5-HT reuptake inhibitors, it might be expected that the anti-obsessional effect of SGAs may be more pronounced at higher doses (Ramasubbu *et al.*, 2000; Sareen *et al.*, 2004).

Aripiprazole is the newest of a class SGAs and manifests a novel mechanism of action by serving as a partial agonist at both D2 and serotonergic 5-HT1A receptors and antagonism at the 5-HT2A receptors (Shapiro *et al.*, 2003). It is chemically different from other SGAs and is also believed to have unique pharmacological actions that set it apart from other atypical antipsychotic drugs.

Case reports have shown that combining SRIs and aripiprazole can significantly improve OC symptoms (Rocha and Correa, 2007; Storch *et al.*, 2008) and promising results have also been found in the studies evaluating the effect of aripiprazole on OC symptoms in patients with OCD. Although augmentation strategies with aripiprazole are quite often used by clinicians, relevant literature about aripipirazole in the treatment of OCD are generally limited to case reports or open label studies (Connor *et al.*, 2005; Pessina *et al.*, 2009).

The aim of the present study was to investigate the comparative efficacy of risperidone versus aripiprazole as augmenting agents in the treatment of selective SRI (SSRI)-refractory OCD patients.

METHODS

Participants

Patients were recruited from patients seeking psychiatric care to the Outpatient Clinic of Psychiatry Department, Yuzuncu Yil University, Hospital Van (Turkey), from January 2009 to December 2009. Inclusion criteria were: (1) age between 18 and 65 years; (2) diagnosis of OCD according to DSM-IV criteria and (3) being drug free for 2 weeks. Patients with present or previous diagnosis of psychotic disorder, substance use, mental retardation or an organic brain syndrome were not included in the study. The study was approved by the Ethics Committee of the Faculty of Medicine at Yuzuncu Yil University and all patients gave written informed consent.

Assessments

Diagnosis of patients was assessed by means of the Structured Clinical Interview for DSM-IV Clinical Version (SCID-I; First *et al.*, 1997). Demographic (age, gender and marital status) and social (occupation, working status and education) information, familial and a brief medical history, as well as other illness parameters (e.g. age of onset) were gathered by means of this instrument as a part of clinical interview. The severity and content of obsessions and compulsions were assessed using the Y-BOCS and its Symptom Checklist (Y-BOCS-SC; Goodman *et al.*, 1989). The Y-BOCS consists of two separate measures: a symptom checklist and a severity scale. The Y-BOCS-SC, a list of common obsessions and compulsions that the patient reports as currently having, having had in the past or having never experienced, is organised under 15 major symptom categories. The Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), a 17-item clinician-rated scale was used to assess the severity of depressive symptoms. Clinical changes were rated according to the Clinical Global Impression scale (CGI; Guy, 1987).

Study design

The present study consists of two different phases of treatment. First, a 12-week prospective period to determine resistance to SSRI treatment. Second, 8-week single-blind antipsychotic augmentation period for refractory patients only. All assessments were performed at the following time points: baseline (t_0), after 12 weeks of SSRI monotherapy (t_{12}), after 8 weeks of combined therapy (t_{20}). No patients were allowed to take concomitant psychotropic drugs during the study. Psychotherapy (i.e. cognitive–behavioural) interventions were also not allowed.

One hundred and two patients were screened for the inclusion criteria: of them 2 were excluded because of schizophrenia, 1 because of organic brain syndrome, 2 because of substance use, 3 female patients were excluded because of pregnancy, and 4 patients withdrew consent after the procedures were explained. Ninety patients entered the 12-week open-label phase. After completion of clinical assessments, 90 patients were randomly assigned to receive one of the SSRI (fluoxetine $n = 30$; sertraline $n = 30$; paroxetine $n = 30$).

The SSRIs were started at a dose of 50 mg/day for sertraline, or 20 mg/day for fluoxetine and paroxetine, and increased within the first 4 weeks to a maximum tolerated dose of 200 mg/day for sertraline, 60 mg/day

DOI: 10.1002/hup

for fluoxetine, and 60 mg/day for paroxetine. After 4 weeks, patients were adequately treated with maximum tolerated dose of SSRIs (fluoxetine 60 mg/day, sertralin 200 mg/day, paroxetine 60 mgr/day) during 8 weeks (March *et al.*, 1997). Average doses of SSRIs within 12 weeks were as follows: fluoxetine 55 mg/day; sertraline 170 mg/day, paroxetine 55 mg/day. All the adverse effects were recorded at every 2 weeks by means of the UKU Side Effect Rating Scale (Lingjaerde *et al.*, 1987). Twenty-one patients did not complete the study. Nine patients dropped out because of side effects (nausea–vomiting, erectile dysfunction, headache, vertigo), 5 patients were excluded due to lack of communication and 4 patients were excludud because of irregular use of medication. Three patients changed their mind about participating in the study. Sixty-nine patients completed the 12-week SSRI monotherapy period. In the light of relevant literature (Albert *et al.*, 2002; Denys, 2006), at the end of the 12-week SSRI treatment, patients who showed a reduction of less than 35% in the initial Y-BOCS scores were regarded as refractory. Twenty-eight patients (40.6%) responded to the SSRI monotherapy and were not accepted to the second period of the study (Figure 1).

Statistical analysis

2×3 factorial design ANOVA with repeated measures were performed for the Y-BOCS-Obsessions, the Y-BOCS-Compulsions, the Y-BOCS Total and the HDS scores at three time points in order to assess the time–drug interaction and the main effects. Tukey Multiple Comparison Test was utilised in *post hoc* analyses. Differences between two drugs in terms of OC and depressive symptoms at three time points separately were evaluated by using independent t-tests. Finally, $\geq$35% decrease in the Y-BOCS total scores was also used as an indicator of recovery after drug treatment. Logistic regression analysis was performed to assess differences in effectiveness of aripiprazole and risperidone, additionally. The minimal alpha for statistical significance was set at $p < 0.05$.

RESULTS

Forty-one patients (59.4%) were considered SSRI-refractory and were randomised to receive either risperidone (20 patients, 3 mgr daily) or aripiprazole (21 patients, 15 mgr daily) for augmentation to high-

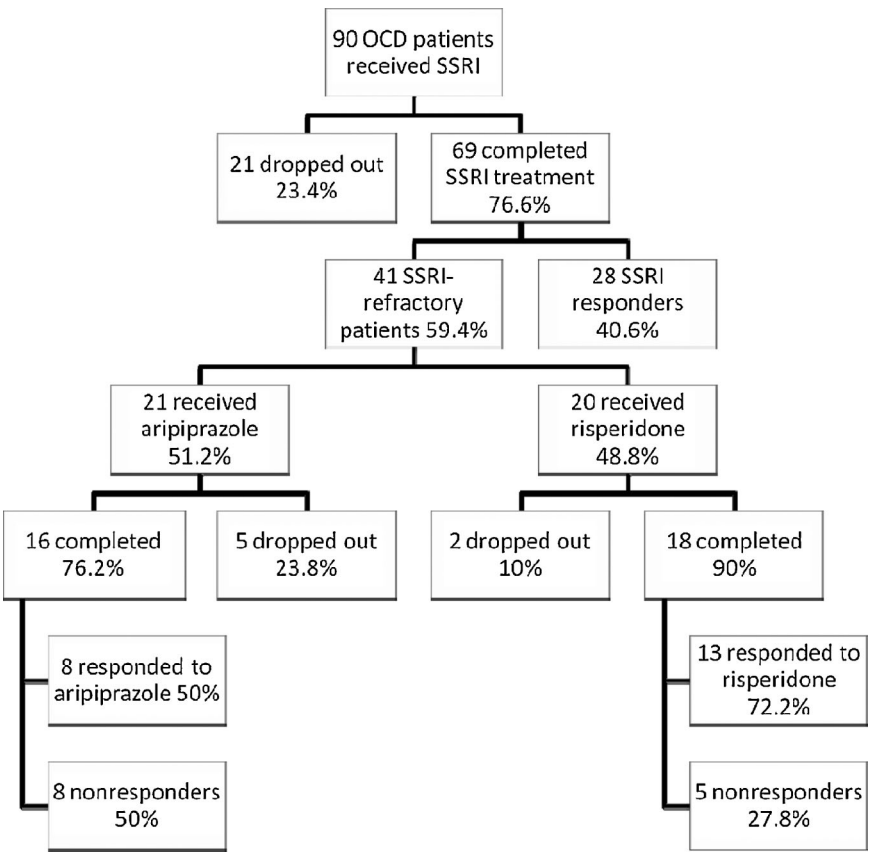


Figure 1. The summary of the study according to the response to treatment.

DOI: 10.1002/hup

dose SSRI treatment. Doses were adjusted according to the average maintenance antipsychotic efficiency doses in accordance with similar studies (Maina *et al.*, 2008; Pessina *et al.*, 2009).

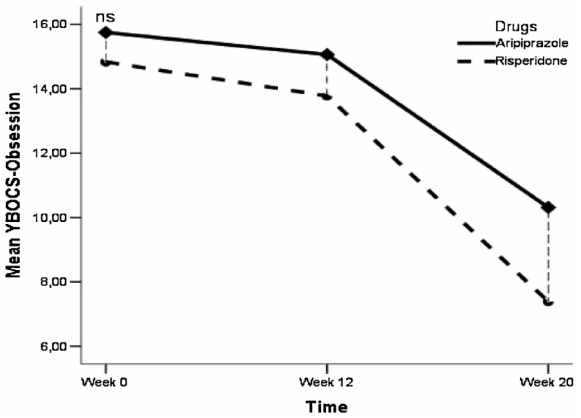
Seven patients dropped out from the study. In the aripiprazole group: 4 patients dropped out because of adverse effects (unrest and insomnia) and 1 patient dropped out because of lack of communication. In the risperidone group: 2 patients dropped out because of adverse effects (tension, nausea–vomiting). Finally, 34 patients [16 (76.2%) in the aripiprazole group and 18 (84%) in the risperidone group] completed the 8-week antipsychotic augmentation period and we considered responders who had an improvement $\geq$35% at the Y-BOCS with respect to beginning of the antipsychotic treatment (Figure 1). There were no significant differences between the aripiprazole and risperidone groups for the demographic or clinical characteristics in the beginning of the antipsychotic treatment (Table 1).

2×3 factorial design ANOVA with repeated measures were performed for the Y-BOCS and the HDRS scores at three time points in order to assess the time–drug interaction and the main effects, as given in Table 2. Measurements were obtained at three time points when at the initial interview, 12 and 20 weeks after the first interview. Time–drug interactions were not significant for the Y-BOCS and the HDRS scores. However, OCD patients in both aripiprazole and risperidone group revealed marked decline in severity of OC symptoms over 20-week time period during the study. The Y-BOCS-Obsession, the Y-BOCS-Compulsion, and the Y-BOCS total scores were significantly lower after 12 weeks' time passed [F (2, 64) = 117.501 for obsessions ($p < 0.01$); F (2, 64) = 84.550 for compulsions ($p < 0.01$) and F (2, 64) = 138.288 for Y-BOCS total scores ($p < 0.01$)]. In addition, mean differences for the HDRS scores between three time points was significant that depression scores of the patients were significantly lower after 20-week drug medication as well [F (2, 64) = 32.382, $p < 0.01$]. The Tukey multiple comparison test was utilised in *post hoc* comparisons between three time points. The Y-BOCS-Obsession, the Y-BOCS-Compulsion, the Y-BOCS total and the HDRS scores of the OCD patients were significantly lower at week 20 compared to measurements at previous time points ($p < 0.05$).

Table 1. Demographic and clinical characteristics of the patients administering antipsychotics

	Aripiprazole ($n = 16$)		Risperidone ($n = 18$)			
Variables	$\overline{X}$	SD	$\overline{X}$	SD	t (32)	p-Value
Age	29.44	11.26	32.61	8.32	−0942	0.353
Age at onset	20.88	6.83	23.44	9.49	−0.895	0.377
	n	(%)	n	(%)		
Gender						
Male	6	17.65	7	20.59	$\chi(1) = 0.007$;	
Female	10	29.41	11	32.35	$p = 0.934$	
Status						
Single	10	29.41	7	20.59	$\chi(1) = 1.889$;	
Married	6	17.65	11	32.35	$p = 0.169$	
Type of onset						
Abrupt	6	17.65	4	11.76	$\chi(1) = 0.952$;	
Insidious	10	29.41	14	41.8	$p = 0.329$	

Table 2. Two-way ANOVA with repeated-measures analysis



*$p < 0.05$.
**$p < 0.01$.
‡*Post hoc* comparisons between groups were performed by using Tukey multiple comparison test and significant differences illustrated with capital letters ($p < 0.05$).

In the analysis of variance it was found that differences between two medication groups were significant for the Y-BOCS-Obsessions subscale and the Y-BOCS total scores [F (2, 32) = 6.782, $p < 0.05$; F (2, 32) = 6.311, $p < 0.05$, respectively). In order to make a thorough evaluation considering treatment response, changes through weeks 12 to 20 for mean Y-BOCS-Obsession and mean Y-BOCS total scores were compared between aripiprazole and risperidone groups by using t-test.

OCD patients in the risperidone group showed a significant improvement compared with aripiprazole group in Y-BOCS-Obsessions subscale. Independent t-tests for mean Y-BOCS-Obsession scores between two groups at weeks 12 and 20 were significant in favour of risperidone medication ($t(32) = 2.417, p < 0.05$; $t(32) = 2.630$, $p < 0.05$; Figure 2).

Independent t-tests for mean Y-BOCS total scores between two groups at weeks 12 and 20 were significant in favour of risperidone medication

DOI: 10.1002/hup

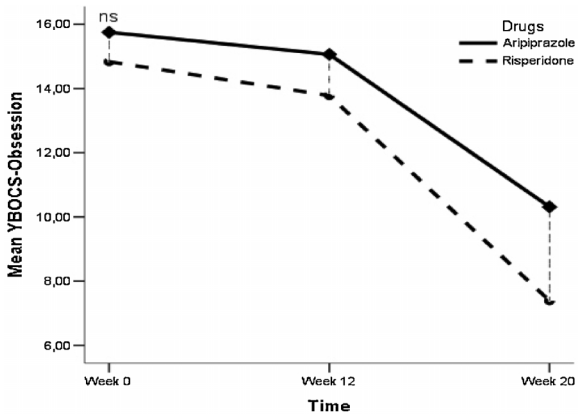


Figure 2. Changes in Y-BOCS obsession scores.

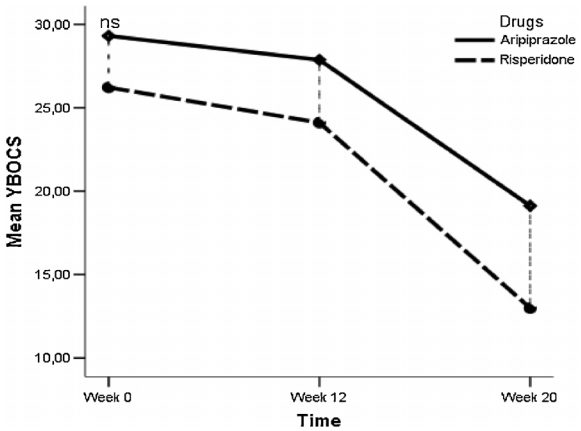


Figure 3. Changes in Y-BOCS total scores.

[$t(32) = 2.115$, $p < 0.05$; $t(32) = 2.675$, $p < 0.05$; Figure 3]. Differences between two groups at three time points in neither the Y-BOCS-Compulsions subscale nor the HDRS were significant ($p < 0.05$).

A decrease $\geq$35% in the Y-BOCS scores was also used to make an extensive analysis of drug effectiveness. Logistic regression analysis was run to assess the efficacy of drug type in positive outcomes. No significant difference was detected between two groups in positive improvement percentages ($\beta = 0.956$; Wald $= 1.733$; $p = 0.188$). Additionally, 8 patients (50%) in aripiprazole group and 13 patients (72.2%) in risperidone group met response criteria of $\geq$35% improvement in Y-BOCS at the end of the study.

DISCUSSION

This is the first study comparing aripiprazole and risperidone addition to the ongoing SSRI treatment in treatment-refractory OCD patients. This study has also the largest sample size of OCD patients which evaluating the effectiveness of aripiprazole augmentation.

We found that aripiprazole augmentation is an effective treatment option for OCD patients who failed to exhibit a 35% or greater reduction in Y-BOCS total score after an adequate duration—at least 12 weeks—of maximum recommended dose SSRI treatment. Half of treatment-refractory OCD patients exhibit a treatment response to aripiprazole augmentation. However, significantly higher response rate was found with risperidone compared to aripiprazole.

One type of augmentation strategy is the addition of atypical antipsychotics to SSRI medications (Keuneman *et al.*, 2005; Skapinakis *et al.*, 2007). Most studies have demonstrated dopamine antagonists to be the most effective agent for alleviating OC symptoms, with the atypical antipsychotic including quetiapine (Atmaca *et al.*, 2002), risperidone (McDougle *et al.*, 2000), olanzapine (Bogetto *et al.*, 2000; Crocq *et al.*, 2002). However, there are little data regarding the effectiveness of aripiprazole in OCD patients. Pessina *et al.* (2009) have demonstrated in a 12-week open label study with limited sample size OCD patients that aripiprazole augmentation at an average dose of 11.2 ± 5.2 mg/day led to significant improvement in Y-BOCS scores. Connor *et al.* (2005) have also investigated the use of aripiprazole as monotherapy in an 8-week, open-label, flexible dose (10–30 mg/day) pilot trial. Seven patients took at least one dose of aripiprazole; at the end of the study period, 3 patients (42.85%) responded to treatment. showing a 30% or greater reduction in the Y-BOCS total score. In addition, some case reports showed that aripiprazole in combination with SSRIs or clomipramine implicated a sufficient improvement of OCD symptoms (Rocha and Correa, 2007; Storch *et al.*, 2008).

These findings raise an important question: what is the pharmacological mechanism of successful aripiprazole augmentation in the treatment of OCD? Aripiprazole acts as a partial agonist at dopamine D2 receptors, with the potential to exert either antagonistic or agonistic effects and it has also both 5-HT2A antagonistic and 5-HT1A agonistic pharmacological characteristics. Thus, it is likely that the anti-OC symptoms of aripiprazole are mediated by the combination of potent 5-HT2A antagonism, 5HT1A agonism with a weak D2 blockade. This idea supports the pathogenesis of OCD could be related to a dysbalance between the serotonergic and the dopaminergic system (Sarkar *et al.*, 2008).

Another important result of our study was that the risperidone was more likely to be effective in the

DOI: 10.1002/hup

augmentation treatment of OCD than aripiprazole. This may be ascribed to the fact that risperidone exerts more antidopaminergic effect than aripiprazole, a D2 partial agonist that maintains a moderate dopaminergic-mediated neurotransmission (Tamminga, 2002). Kim *et al.* (2003) showed that OCD patients have higher dopamine transporter densities and lower dopamine D2 binding ratios, and Skapinakis *et al.* (2007) noted that these results are indirect evidences of increased dopaminergic activity in OCD. These findings point to the role of dopamine in the aetiology of OCD, while it also refers to importance of antidopaminergic efficiency in the antipsychotic augmentation strategies. Our findings are consistent with the knowledge that implied the improvement in OC symptoms occur at high-doses antipsychotics due to high-D2 antagonistic effect (Ramasubbu *et al.*, 2000; Denys *et al.*, 2004).

This study has several limitations, including its single-blind design, relatively small number of patients. This study also does not point the long-term effects of treatment with aripiprazole and risperidone. Despite these limitations, this study may present an opportunity to test indirectly the validity of serotonine-dopamine hypothesis for the pathophysiology of OCD. However, further double-blind studies in larger populations are needed to identify possible correlations between clinical characteristics and response to antipsychotics and to distinguish which antypsychotic augmentation strategies are most effective in OCD patients who do not respond to SSRI treatment.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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DOI: 10.1002/hup