The Efficacy of Aripiprazole versus Risperidone as Augmentation Therapy in Treatment-Resistant Obsessive-Compulsive Disorder: A Double Blind Clinical Trial

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Abstract

Background: Obsessive-compulsive disorder (OCD) is the fourth common psychiatric disorder. Among the anxiety disorders, OCD has the least therapeutic response and 40-60% of OCD patients do not satisfactorily respond to the first-line standard treatment known as treatment-resistant OCD. One of the best therapeutic strategies is the augmentation therapy, which is adding antipsychotics to the standard treatment (SSRIs).

Objectives: In this study, the efficacy of risperidone and aripiprazole was compared as an augmentation therapy.

Methods: In this double blind randomized clinical trial, 100 patients with treatment-resistant OCD were diagnosed based on the DSM-IV-TR and were followed for twelve weeks. The patients were randomly divided into two groups of aripiprazole and risperidone and received an average daily dose of 5 mg and 1.5 mg for twelve weeks, respectively. The efficacy of treatment was measured and compared by the Yale-brown obsessive compulsive scale (Y-BOCS) at 4, 8 and 12 weeks.

Results: The mean Y-BOCS score of patients in risperidone and aripiprazole groups were 25.26 ± 4.17 and 25.02 ± 4.46; respectively and had no significant difference (P = 0.79) at the beginning of the trial. At the end of the study (12th week) it was changed for the risperidone and aripiprazole groups to 20.00 ± 4.45 and 16.24 ± 4.41, respectively (P < 0.001). Furthermore, there was a significant decreasing trend of Y-BOCS scores in both groups, which was demonstrated by the repeated measurement analysis (P < 0.001).

Conclusions: It was found that both aripiprazole and risperidone could be effective in treatment of treatment-resistant OCD patients. However, aripiprazole showed a higher efficacy compared to risperidone.

Keywords: Treatment-Resistant, Obsessive-Compulsive Disorder, Risperidone, Aripiprazole

1. Background

Obsessive-compulsive disorder (OCD) is the fourth common psychiatric disorder affecting 2-3% of the general population (4). It is one of the chronic anxiety disorders in which the patient suffers from obsessions or compulsions. According to the DSM-IV-TR criteria, the obsessions are defined as persistent thoughts, urges and images that are disturbing for the patient and cause anxiety or distress. The compulsions are repetitive thoughts or behaviors to cope with the anxiety caused by obsessions (2). It is amongst the most disabling psychiatric disorders (3). OCD patients experience a variety of chronic symptoms which affect their quality of life and interfere with social, occupational and marital functions (4). According to the last study about the prevalence of psychiatric disorders in Kashan, Iran, the prevalence of OCD was an estimated 6.8% and the third most common disorder after major depressive disorder (MDD) and generalized anxiety disorder (GAD) (5), which is three times more than its prevalence in Iran (1.8%) (6). Therefore, providing novel treatment for these patients is one of the priorities for mental health programs in the city.

The first and standard treatment of OCD is selective serotonin reuptake inhibitors (SSRIs), namely; fluoxetine, citalopram, fluvoxamine, and sertraline. This disorder has the least therapeutic response rate amongst the anxiety disorders. Forty to sixty percent of OCD patients do not satisfactorily respond to the first-line standard treatment (2, 7-9). The treatment-resistant OCD is defined as no response to the maximum and tolerable dosage of standard treatment after three months (2). These patients are highly prone to the disability and complications caused by OCD.
in addition, there is a positive correlation between the severity of OCD and the worsening of patient’s quality of life (10, 11). Therefore, it is necessary to investigate more effective treatment modalities (2, 7-10) recently used by clinicians (12).

Various strategies have been proposed to increase the therapeutic response of treatment-resistant OCD (11). One of the most common strategies is the augmentation therapy by adding antipsychotics to the standard treatment (2, 7-13). The priority of antipsychotics as augmentation therapy over placebo has been supported in different meta-analyses (7-9, 14-16). For instance, Bloch et al. (2006), in a systematic review of nine studies, compared antipsychotics (quetiapine, olanzapine, haloperidol and risperidone) with placebo and found that haloperidol and risperidone were more effective than other agents in augmentation therapy of treatment-resistant OCD (7). However, the question in most of these studies is whether all the antipsychotics, as the augmentation therapy, have the same therapeutic response (7, 14, 15). The different results in these studies could be due to the differences in inclusion criteria, study design, the severity of disorder, the duration of treatment with SSRI and comorbid conditions. Therefore, it would be necessary to compare antipsychotic agents after demonstrating the priority of antipsychotics over placebo. To our knowledge, this has been investigated in few studies (17).

Maina et al. (18), in a single-blinded study in 2008, compared the efficacy and tolerance of risperidone and olanzapine as the augmentation therapy in treatment-resistant OCD patients during eight weeks and did not find any significant differences between them. In another study in Turkey in 2011, Selvi compared the therapeutic response of risperidone and aripiprazole amongst treatment-resistant OCD patients that showed risperidone is superior to aripiprazole in augmentation therapy (19).

Risperidone has been studied in several studies and appears to have more evidence of it compared to other second-generation antipsychotics, like quetiapine and olanzapine (7). In a meta-analysis, Dold et al. (9), in subgroup analysis, showed that amongst different antipsychotics, only the efficacy of risperidone is significant.

On the other hand, the efficacy of aripiprazole as augmentation therapy of treatment-resistant OCD has been supported in several recent studies (20-22). To our knowledge, in Iran, only two studies have been conducted in this regard, none of which had a head-to-head design. In a study by Sayyah et al. (17), it was shown that aripiprazole is superior to placebo. In another study, Shabani et al. (23), found no evidence regarding the efficacy of olanzapine compared with placebo in treatment-resistant OCD.

Aripiprazole as the last second-generation antipsychotics has a different chemical structure and showed unique pharmacologic features (19). It is noted that risperidone is pharmacodynamically the antagonist of dopamine receptor D2 and serotonin receptor 5-HT1a, while aripiprazole is a relative agonist of D2 and 5-HT1a receptors and antagonist of serotonin receptor 5-HT2a (2). Therefore, comparing the efficacy of risperidone, one of the first second-generation antipsychotics, with aripiprazole and having a slightly different pharmacologic structure could provide an opportunity to verify the theories regarding pathophysiology of obsessive-compulsive disorder (19).

2. Objectives

Thus, this study was designed to compare the efficacy of risperidone and aripiprazole in augmentation therapy of patients with treatment-resistant OCD in Kashan, Iran.

3. Methods

3.1. Subjects

This is a double blind simple randomized clinical trial that was conducted at the Kashan University of Medical Sciences (KAUMS) in 2015. The convenient sampling method was used. The patients were selected from the outpatient clinic of Kargarnejad hospital, which is the only governmental psychiatric referral hospital of KAUMS with 100 active beds.

The sample size for each group was an estimated 50 patients with a confidence interval of 95%, type II error of 20%, and a minimum of 20% difference between the size of two groups according to below Formula 1:

\[ n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times 2pq}{\Delta^2} \]  \hspace{1cm} (1)

The patients were assessed by a checklist designed based on the study protocol. For easy access to the patients, all of them were selected from referred patients in the area covered by KAUMS, i.e. Kashan and Aran & Bidgol. The patients were recruited only after the goals of the study and its stages were explained for them by expert psychiatrist. The informed consent formula approved by the ethical board of KAUMS was signed by all the patients. The study was approved by the Ethic Committee of KAUMS with letter number p/29/5/1/2056 and was funded by the vice chancellor of research at KAUMS. All the ethical issues such as informed consent, plagiarism, double publication and/or submission were considered. The respondents were anonymous and participated willingly in this study. The study protocol was registered in Iranian registry
of clinical trials (IRCT) portal with "IRCT2015110424882N1" code.

The inclusion criteria for this study was OCD patients aged 18 and above with the Yale-brown obsessive compulsive scale (Y-BOCS) score of 16 or more and after at least three months of therapy with a maximum and tolerable dose of any SSRI (2).

The exclusion criteria was breastfeeding and pregnancy, not using safe contraceptive methods, drugs and alcohol abuse during the last six months, receiving psychotherapy during the study, any known disorder in DSM-IV-TR axis I and II such as major depressive disorder (MDD), personality disorder or mental retardation, any physical disease impeding the use of risperidone or aripiprazole, severe adverse effects to administered drugs and dropped out for more than four weeks during trial.

3.2. Study Design and Procedures

This study was a double-blinded randomized clinical trial on 100 patients with refractory OCD, whom were followed for 12 weeks. The patients filled a demographic questionnaire and then went through a clinical interview. The diagnosis of OCD and comorbid conditions were based on the structured clinical interview for DSM-IV-TR axis I disorders, clinical trials version (SCID-CT) and structured clinical interview for DSM-IV-TR axis II personality disorders (SCID-II) (24, 25). There were eight visits for each patient during the study. The first visit was for randomization and receiving the treatment, the second at the end of the first week, the third at the end of the second week, and then every two weeks until the end of study (12th week). On all the visits, the checklist for drug side effects were completed and in case of adverse reactions, either the dosage was decreased or other medications such as propranolol, lorazepam, and biperidine were used to control it. On the fourth, eighth, and 12th visits, Y-BOCS score was measured by the colleague psychiatrist.

To randomize the treatment allocation the permuted block randomization method was used. Both the treatments were provided in identical covers, so that the patients and the physician were not aware of it. Aripiprazole (Sobhan Darou Co.) started with a 2.5 mg daily dose and was gradually increased to 10 mg daily by the end of second week. Risperidone (Sobhan Darou Co.) started with a 2.5 mg daily dose and was gradually increased to 10 mg daily by the end of second week. The dosing was on the basis of previous studies (18, 22).

In this study, the questionnaires used were Yale-brown obsessive compulsive scale and a demographic questionnaire. The data regarding the history of disease, received treatment and the side effects of medications were also recorded.

Three months of therapy with a maximum and tolerable dose of any SSRI (2).

The Yale-brown obsessive compulsive scale (Y-BOCS) was developed at the end of 1980s to quantify the severity of OCD symptoms. It consists of ten questions with the first five on obsessions and the remainder on compulsions. Each question has a score of 0 to 4, so that the total score would range between 0 and 40. The usual score of OCD patients lies between 16 and 30 and a score of 16 is an appropriate threshold for beginning medical treatment. In this study the Persian version of Y-BOCS was used, which has shown good validity and reliability. In a study of 140 OCD patients and 30 controls, the test-retest reliability and the internal consistency score of this scale was reported to be 0.99 and 0.95, respectively (26).

3.3. Statistical Analysis

To examine the efficacy of drugs over time and to compare it between two mutually exclusive assigned drugs, the repeated measure analysis was used. This method has the advantages of reducing type I error, requiring smaller sample size and the ability to both compare the efficacy between the two groups and examine it within each group over time.

4. Results

Among the referred patients, 61% (100 patients) agreed to participate in this RCT, which were assigned to two equal groups (n = 50).

The rate of dropout in every group was 13%. In the aripiprazole group, three cases were excluded because of akathisia and three cases left the trial because of non-compliance without any reason. In the risperidone group, three cases were excluded because of the sedation side effects, two cases because of tremor and two cases left the trial because of non-compliance without any reason.

According to the study protocol, severe side effects were considered as the exclusion criteria and were substituted with new cases. In this study, per-protocol analysis was used. There was no significant difference found between the two groups in this regard.

The sampling processes are presented in Figure 1.

The mean age in the risperidone group was 36.42 ± 10.58 years and in the aripiprazole group 40.06 ± 10.54 years with no significant difference (P = 0.09). As shown in Table 1, both groups were comparable with respect to sex, age and marital status.

There was no significant difference between the Y-BOCS score of the two groups at the baseline. It is presented in Table 2.

The prevalence of depression in the risperidone and aripiprazole group was 12% and 8%, respectively (P = 0.50).
The prevalence of anxiety was 10% and 5% in risperidone and aripiprazole groups, respectively, with no significant difference (P = 0.46). The most common type of obsession in patients of both groups was contamination and the most common type of compulsion was washing. There was no significant difference between the two groups in terms of the type of OCD. Fifty-six percent of patients in the risperidone group and 46% in aripiprazole group received fluoxetine with the rest receiving fluvoxamine in each group. The two groups were statistically the same with regards to the SSRI agents used (P = 0.32).

To perform the repeated measure analysis, the equality of covariance as the required assumption was checked with Box’s test. Then to examine within the subjects effects, the compound symmetry assumption was checked with Mauchly’s test. Due to the significant result of this test and rejection of the compound symmetry, multivariate results were considered. It showed different effects among the times (with respect to Pillai’s Trace test, P < 0.001). Therefore, the efficacy of both administered drugs changed significantly over time (see Figure 1). When the mean Y-BOCS scores were compared between the two groups it was found to be more evident for aripiprazole than risperidone. In addition, there was interaction between time and administered drug (P < 0.001). As shown in Figure 1, the increasing trend of efficacy over time for aripiprazole is su-
perior to risperidone.

Figure 2. The Trend of Changes in Mean Y-BOCS Scores of Patients in Risperidone and Aripiprazole Groups Over Time

### Table 2. The Efficacy of Treatment Measured by Yale-Brown Obsessive Compulsive Scale (Y-BOCS) Score Before Treatment, at the End of 4, 8, and 12 Weeks

<table>
<thead>
<tr>
<th>The Y-BOCS Score</th>
<th>Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risperidone</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Before treatment</td>
<td>4.17 ± 25.26</td>
<td>4.46 ± 25.02</td>
</tr>
<tr>
<td>4th week</td>
<td>4.31 ± 24.1</td>
<td>4.54 ± 22.62</td>
</tr>
<tr>
<td>8th week</td>
<td>4.21 ± 22.96</td>
<td>4.85 ± 20.26</td>
</tr>
<tr>
<td>12th week</td>
<td>4.45 ± 20.0</td>
<td>4.41 ± 16.24</td>
</tr>
<tr>
<td>Total</td>
<td>4.16 ± 21.08</td>
<td>4.82 ± 21.03</td>
</tr>
<tr>
<td>P value</td>
<td>0.001 &gt;</td>
<td>0.001 &gt;</td>
</tr>
</tbody>
</table>

### 5. Discussion

In this study, the efficacy of adding aripiprazole or risperidone to the standard treatment of treatment-resistant OCD was studied in 100 patients. It was demonstrated that aripiprazole and risperidone lead to a significant decrease in the Y-BOCS score of patients, which was more prominent in the aripiprazole group.

This finding is consistent with the findings of other studies. In a pilot study of Delle et al. (27) in 2009, the studied efficacy of adding aripiprazole with a dose of 5-20 mg per day to the standard treatment (SSRIs) in 20 OCD patients showed a significant decrease in the severity of OCD. In a case series study conducted by Higuma et al. (28) in 2012 on 13 patients with treatment-resistant OCD, combination therapy with aripiprazole (3-12 mg/day) and a SSRI caused a significant decrease in the Y-BOCS score of the patients. In a double-blind study, Sayyah et al. (17) in 2012 followed 39 OCD patients in two groups receiving placebo and aripiprazole (10 mg/day) for 12 weeks. It was shown that aripiprazole led to a significant decrease in Y-BOCS score compared with placebo. Pessina et al. (20) in an open-label study added a 5-20 mg daily dose of aripiprazole to SSRIs in 12 patients with treatment-resistant OCD and after 12 weeks observed a significant decrease in the Y-BOCS score of the patients. Another open-label study in 2005 by Connor et al. on 18 OCD patients treated with a daily dose of 10-30 mg aripiprazole for eight weeks showed 43% of patients had at least 30% decrease in their Y-BOCS score at the end of study (29). Similar findings have been reported in other studies (30-38).

Risperidone has also proved quite effective in treatment of OCD symptoms. In a study by Maina et al. (18), in a single-blind study in 2008, 96 treatment-resistant OCD patients were treated with a daily dose of 1-3 mg risperidone combined with SSRIs for eight weeks. There was a significant decrease in the Y-BOCS scores of the patients. Erzegovesi et al. (39) in a double-blind placebo-control study in 2005 studied the efficacy of low doses of risperidone added to the SSRI regimen (fluvoxamine) in 45 patients with treatment-resistant OCD. It was demonstrated that even very low doses of risperidone (0.5 mg/day) for six weeks can improve OCD symptoms. In Li et al. (40) crossover study in 2005 on 12 OCD patients observed that the nine-week treatment with a daily dose of 1-3 mg risperidone, besides its positive effect on OCD, improves the depressive mood of patients. Similar findings to our study and aforementioned studies have been reported in literature (10, 41-45).

Despite differences in treatment duration, therapeutic response and the Y-BOCS baseline score between previous studies and this study, their results were consistent. However, it was also found in our study that treatment-resistant OCD patients under treatment of aripiprazole had a greater decrease in their Y-BOCS score than risperidone. To our knowledge, there was only one study regarding the comparison between risperidone and aripiprazole as the augmentation therapy of treatment-resistant OCD patients, which is inconsistent with our findings. In a single-blind randomized study by Selvi et al. (19), in 2011, 41 patients with treatment-resistant OCD were treated with aripiprazole (15 mg/day) or risperidone (3 mg/day) for eight weeks. It was found that patients treated with risperidone had a greater decrease in their Y-BOCS score. This difference could be due to a difference in doses, 1.5 versus 3 mg per day for risperidone and 5 versus 15 mg per day for aripiprazole. Furthermore, it could also emanate from the fact that different doses can cause different effects of used
drugs on serotonin and dopamine receptors.

Different neurotransmitter systems are involved in the aetiology of OCD, of which the role of serotonergic system has been well elucidated (46). However, other neurotransmitters like dopaminergic system are also probably involved in OCD pathogenesis, so that antagonistic effects of antipsychotics increase the efficacy of SSRIs in treatment-resistant OCD (27). In PET (Positron Emission Tomography) studies, it has been observed that low doses of antipsychotics cause high levels of 5-HT2 receptor anatominization, while it is only with high doses of antipsychotics that remarkable dopaminergic antagonistic effects have been seen (47). Therefore, it appears that the role of serotonergic system is more dominant in this study.

Another justification for the inconsistency seen between the results of our study and Selvi et al. study (19) is that there was a higher dropout rate in the Selvi study amongst the aripiprazole group compared to risperidone, while it was identical in our study. Compared to previous studies, low doses of the drugs was a limitation of this study. It was because lower doses are associated with a lower rate of adverse effects and better compliance. There are also limitations due to volunteer bias. As mentioned before, 39% of patients refused to participate in this trial that could cause selection bias. The sampling area of this study was restricted to only two cities in Iran with high homogeneity of cultural and social factors. This might limit the generalization of findings to other study populations. However, the results of this study can be notable in the evaluation of different neurotransmitter systems roles in the treatment of treatment-resistant OCD.

The strengths of this study were the double-blind design, adequate sample size and the comparison between two antipsychotic drugs in a head-to-head design for the first time in Iran.

5.1. Conclusion

In this study, it was found that both aripiprazole and risperidone could be effective in treatment of treatment-resistant OCD. It was also demonstrated that aripiprazole has a higher efficacy in treating treatment-resistant OCD.

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Footnote

Authors’ Contribution: Fatemeh Assarian, Fatemeh Sadat Ghereishi, and Mahboobeh Borna participated in study concept and design; Mahboobeh Borna performed data collection and registration into SPSS software; Mohammadvaz Raghafoz performed the data analysis and Fatemeh Assarian and Ghereishi performed interpretation and drafting of the manuscript.

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