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The Efficacy of Aripiprazole versus Risperidone as Augmentation Therapy in the Treatment of the Resistant Obsessive-Compulsive Disorder: A Double-Blind, Randomized 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: This study was aimed at comparing the efficacy of Risperidone and Aripiprazole as augmentation therapy in the resistant cases of obsessive-compulsive disorder.

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 12-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 $\pm$ 4.17 and 25.02 $\pm$ 4.46; respectively and had no significant difference (P = 0.79) at the beginning of the trial. At the end of the study (12^{th} week), it was changed for the Risperidone and Aripiprazole groups to 20.00 $\pm$ 4.45 and 16.24 $\pm$ 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 < 00.1).

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

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

1. Background

Obsessive-compulsive disorder (OCD) is the fourth common psychiatric disorder affecting 2-3% of the general population (1). 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 a 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 the 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 a 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 the 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 D_2 and serotonin receptor 5-HT1a, while Aripiprazole is a relative agonist of D_2 and 5-HT1a receptors and the 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 the pathophysiology of obsessive-compulsive disorder (19).

2. Objectives

This study 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, randomized clinical trial that was conducted at the Kashan University of Medical Sciences (KAUMS), Kashan, Iran, 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 existing 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:

$$n = \frac{\left(Z_{\frac{\alpha}{2}} Z_{\beta}\right)^2 2pq}{\Delta^2} \quad (1)$$

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 an expert psychiatrist. All patients signed the informed consent, and the study was approved by the Ethics Committee of KAUMS with the file number p/29/5/1/2056. The study was funded by the vice chancellor of research at KAUMS. All the ethical issues such as informed consent, plagiarism, duplication 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 were 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 an SSRI (2).

The exclusion criteria were breastfeeding and pregnancy, not using safe contraceptive methods, drugs and alcohol abuse during the last 6-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 the trial.

3.2. Study Design and Procedures

This study was a double-blind, randomized clinical trial on 100 patients with refractory OCD, who 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 the study (12^{th} week). On all the visits, the checklist for drug side effects was completed and in case of adverse reactions, either the dosage was decreased or other medications such as Propranolol, Lorazepam, and Biperidine was 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., Tehran, Iran) started with a 2.5 mg daily dose and was gradually increased to 10 mg daily by the end of the second week. Risperidone (Sobhan Darou Co., Tehran, Iran) initiated with a 1 mg daily dose and was gradually increased to 2 mg daily by the end of the 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 survey. The data regarding the history of the disease, received treatment and the side effects of medications were also recorded.

The Yale-brown obsessive-compulsive scale (Y-BOCS) was developed at the end of the 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 lie 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, the 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 $\pm$ 10.58 years and in the Aripiprazole group 40.06 $\pm$ 10.54 years with no significant difference (P = 0.09). As shown in Table 1, both groups were comparable for 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

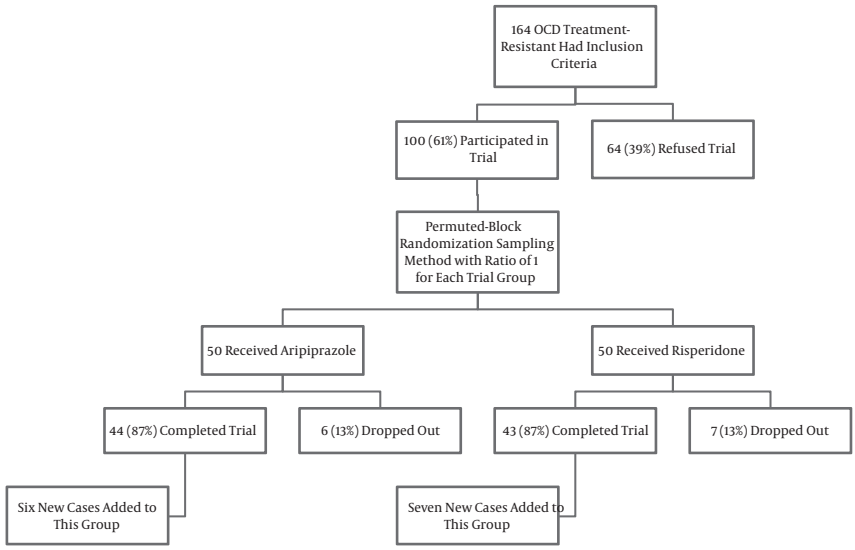

Figure 1. Sampling Flowchart of Treatment-resistant OCD Patients That Participated in the Aripiprazole vs. Risperidone Trial

Table 1. Demographic Characteristics of Study Population

Variable	Study Group			P Value[a]
	Risperidone	Aripiprazole	Total	
Sex, N. (%)				0.84
Male	22 (44)	21 (42)	43	
Female	28 (56)	29 (58)	57	
Age, Mean (SD)			-	0.26
Male	36 (10.2)	37.71 (10.74)		
Female	36.62 (11)	41.76 (10.29)		
Marital status, N. (%)				0.5
Single	14 (28)	9 (18)	23	
Married	35 (70)	40 (80)	75	
Divorced	1 (2)	1 (2)	2	

[a] $P < 0.05$ was considered significant.

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. 56% of patients in the Risperidone group and 46% in the 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 an interaction between time and administered drug ($P < 0.001$). As shown in Figure 1, the increasing trend of efficacy over time for Aripiprazole is superior to Risperidone.

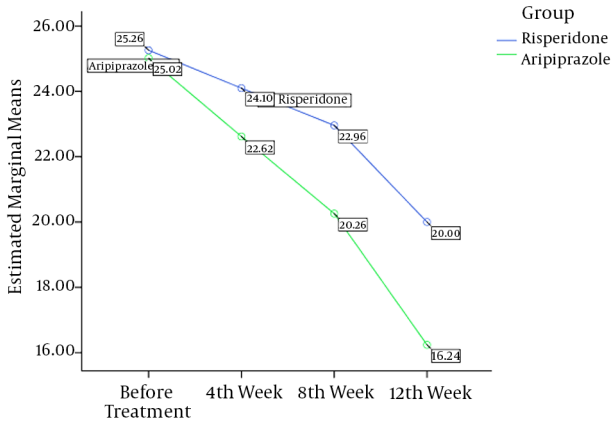

Figure 2. The Trend of Changes in Mean Y-BOCS Scores of Patients in Risperidone and Aripiprazole Groups Over Time

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

The Y-BOCS Score	Group		P Value[a]
	Risperidone	Aripiprazole	
Before treatment	4.17 ± 25.26	4.46 ± 25.02	0.79
4th week	4.11 ± 24.1	4.54 ± 22.62	0.09
8th week	4.21 ± 22.96	4.85 ± 20.26	0.004
12th week	4.45 ± 20.0	4.41 ±16.24	< 0.001
Total	4.16 ± 23.08	4.49 ± 21.03	0.02
P value	< 0.001	< 0.001	-

[a] P < 0.05 was considered significant.

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 results 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 to 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 an 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 SSRI 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 the study (29). Similar findings have been reported in other studies (30-38).

Risperidone has also proved quite effective in the 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 the 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 five 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 etiology of OCD, of which the role of serotonergic system has been well elucidated (46). However, other neurotransmitters like dopaminergic system are also probably in-

volved 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 anatomization, 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 a 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 the 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 Ghoreishi, and Mahboobeh Borna participated in the study concept and design; Mahboobeh Borna performed data collection and registration into SPSS software; Mohammadreza Razaghof performed the data analysis and Fatemeh Assarian and Ghoreishi performed interpretation and drafting of the manuscript.

References

1. Sadock BJ. *Sadock, and P. Ruiz, Kaplan and Sadock's Synopsis of Psychiatry*. Wolters Kluwer Health; 2014.
2. Sadock BJ. *Kaplan & Sadock's comprehensive textbook of psychiatry*. **2**. Philadelphia: Williams & wilkinslippincott; 2009.
3. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*. 1997;**349**(9063):1436–42. doi: 10.1016/S0140-6736(96)07495-8. [PubMed: 9164317].
4. Koran LM. Quality of life in obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2000;**23**(3):509–17. [PubMed: 10986724].
5. Ahmadvand A. Prevalence of mental disorders in general population of Kashan City. *Iranian J Epidemiol*. 2010;**6**(2):16–24.
6. Mohammadi MR, Ghanizadeh A, Rahgozar M, Noorbala AA, Davidian H, Afzali HM, et al. Prevalence of obsessive-compulsive disorder in Iran. *BMC Psychiatry*. 2004;**4**:2. doi: 10.1186/1471-244X-4-2. [PubMed: 15018627].
7. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;**11**(7):622–32. doi: 10.1038/sj.mp.4001823. [PubMed: 16585942].
8. Pallanti S, Quercioli L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;**30**(3):400–12. doi: 10.1016/j.pnpbp.2005.11.028. [PubMed: 16503369].
9. Dold M, Aigner M, Lanzenberger R, Kasper S. [Efficacy of antipsychotic augmentation therapy in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomised, placebo-controlled trials]. *Fortschr Neurol Psychiatr*. 2011;**79**(8):453–66. doi: 10.1055/s-0031-1273397. [PubMed: 21809258].
10. Hollander E. Obsessive-compulsive and spectrum disorders: Overview and quality of life issues. *J clin psychiatr*. 1996.
11. Decloedt EH, Stein DJ. Current trends in drug treatment of obsessive-compulsive disorder. *Neuropsychiatr Dis Treat*. 2010;**6**:233–42. [PubMed: 20520787].
12. Afshar H, Roohafza H, Mohammad-Beigi H, Haghighi M, Jahangard L, Shokouh P, et al. N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2012;**32**(6):797–803. doi: 10.1097/JCP.0b013e318272677d. [PubMed: 23131885].
13. Carey PD. Quetiapine augmentation of serotonin reuptake inhibitors in treatment-refractory obsessive-compulsive disorder: is response to treatment predictable? *Int Clini Psychopharmacol*. 2012;**27**(6):321–5. doi: 10.1097/yic.0b013e3283576881.
14. Dhansay Y, Ipser J, Stein DJ. *Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders*. The Cochrane Library; 2005.
15. Skapinakis P, Papatheodorou T, Mavreas V. Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: a meta-analysis of the randomized controlled trials. *Eur Neuropsychopharmacol*. 2007;**17**(2):79–93. doi: 10.1016/j.euroneuro.2006.07.002. [PubMed: 16904298].
16. Vulink NC, Figee M, Denys D. Review of atypical antipsychotics in anxiety. *Eur Neuropsychopharmacol*. 2011;**21**(6):429–49. doi: 10.1016/j.euroneuro.2010.12.007. [PubMed: 21345655].
17. Sayyah M, Sayyah M, Boostani H, Ghaffari SM, Hoseini A. Effects of aripiprazole augmentation in treatment-resistant obsessive-compulsive disorder (a double blind clinical trial). *Depress Anxiety*. 2012;**29**(10):850–4. doi: 10.1002/da.21996. [PubMed: 22933237].

18. Maina G, Pessina E, Albert U, Bogetto F. 8-week, single-blind, randomized trial comparing risperidone versus olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 2008;**18**(5):364–72. doi: 10.1016/j.euroneuro.2008.01.001. [PubMed: 18280710].
19. Selvi Y, Atli A, Aydin A, Besiroglu L, Ozdemir P, Ozdemir O. The comparison of aripiprazole and risperidone augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: a single-blind, randomised study. *Hum Psychopharmacol*. 2011;**26**(1):51–7. doi: 10.1002/hup.1169. [PubMed: 21308781].
20. Pessina E, Albert U, Bogetto F, Maina G. Aripiprazole augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a 12-week open-label preliminary study. *Int Clin Psychopharmacol*. 2009;**24**(5):265–9. doi: 10.1097/YIC.0b013e32832e9b91. [PubMed: 19629012].
21. Kim SW, Dysken MW, Katz R. Rating scales for obsessive compulsive disorder. *Psychiatr Ann*. 1989;**19**(2):74–9. doi: 10.3928/0048-5713-19890201-07.
22. Rajezi Esfahani S. Reliability and Validity of the Persian version of the Yale-Brown Obsessive-Compulsive scale (Y-BOCS). *Iran J Psychiatr Clin Psychol*. 2012;**17**(4):297–303.
23. Shabani M, Ghoreishi S. Olanzapine Augmentation Therapy in Patients with the Obsessive-Compulsive Disorder Resistant to Treatment. *Zanjan Uni Med ASci J*. 2009;**17**(66):21–8.
24. First MB. *User's guide for the Structured clinical interview for DSM-IV axis I disorders SCID-I: clinician version*. USA: American Psychiatric Pub; 1997.
25. First MB. *User's guide for the structured clinical interview for DSM-IV axis II personality disorders: SCID-II*. USA: American Psychiatric Pub; 1997.
26. Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;**46**(11):1006–11. [PubMed: 2684084].
27. Delle Chiaie R, Scarciglia P, Pasquini M, Caredda M, Biondi M. Aripiprazole augmentation in patients with resistant obsessive compulsive disorder: a pilot study. *Clin Pract Epidemiol Ment Health*. 2011;**7**:107–11. doi: 10.2174/1745017901107010107. [PubMed: 21686322].
28. Higuma H, Kanehisa M, Maruyama Y, Ishitobi Y, Tanaka Y, Tsuru J, et al. Aripiprazole augmentation in 13 patients with refractory obsessive-compulsive disorder: a case series. *World J Biol Psychiatry*. 2012;**13**(1):14–21. doi: 10.3109/15622975.2010.551667. [PubMed: 22256827].
29. Connor KM, Payne VM, Gadde KM, Zhang W, Davidson JR. The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. *J Clin Psychiatry*. 2005;**66**(1):49–51. [PubMed: 15669888].
30. Ashton AK. Aripiprazole augmentation of combination escitalopram and sertraline in the treatment of refractory obsessive-compulsive disorder. *Psychiatr (Edgmont)*. 2005;**2**(1):18.
31. da Rocha FF, Correa H. Successful augmentation with aripiprazole in clomipramine-refractory obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;**31**(7):1550–1. doi: 10.1016/j.pnpbp.2007.07.008. [PubMed: 17692447].
32. Friedman S, Abdallah TA, Oumaya M, Rouillon F, Guelfi JD. Aripiprazole augmentation of clomipramine-refractory obsessive-compulsive disorder. *J Clin Psychiatry*. 2007;**68**(6):972–3. [PubMed: 17592930].
33. Masi G, Pfanner C, Millepiedi S, Berloffa S. Aripiprazole augmentation in 39 adolescents with medication-resistant obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2010;**30**(6):688–93. [PubMed: 21105283].
34. Matsunaga H, Hayashida K, Maebayashi K, Mito H, Kiriike N. A case series of aripiprazole augmentation of selective serotonin reuptake inhibitors in treatment-refractory obsessive compulsive disorder. *Int J Psychiatry Clin Pract*. 2011;**15**(4):263–9. doi: 10.3109/13651501.2011.605958. [PubMed: 22121999].
35. Muscatello MR, Bruno A, Pandolfo G, Mico U, Scimeca G, Romeo VM, et al. Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2011;**31**(2):174–9. doi: 10.1097/JCP.0b013e31820e3db6. [PubMed: 21346614].
36. Ozturk M, Coskun M. Successful aripiprazole augmentation in a child with drug-resistant obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2009;**29**(6):607–9. doi: 10.1097/JCP.0b013e3181bfe068. [PubMed: 19910732].
37. Sarkar R, Klein J, Kruger S. Aripiprazole augmentation in treatment-refractory obsessive-compulsive disorder. *Psychopharmacology (Berl)*. 2008;**197**(4):687–8. doi: 10.1007/s00213-008-1091-1. [PubMed: 18264798].
38. Storch EA, Lehmkuhl H, Geffken GR, Touchton A, Murphy TK. Aripiprazole augmentation of incomplete treatment response in an adolescent male with obsessive-compulsive disorder. *Depress Anxiety*. 2008;**25**(2):172–4. doi: 10.1002/da.20303. [PubMed: 17340610].
39. Erzegovesi S, Guglielmo E, Siliprandi F, Bellodi L. Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Eur Neuropsychopharmacol*. 2005;**15**(1):69–74. doi: 10.1016/j.euroneuro.2004.04.004. [PubMed: 15572275].
40. Li X, May RS, Tolbert LC, Jackson WT, Flournoy JM, Baxter LR. Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study. *J Clin Psychiatry*. 2005;**66**(6):736–43. [PubMed: 15960567].
41. Arias HF. Effectiveness and tolerability of addition of risperidone in obsessive-compulsive disorder with poor response to serotonin reuptake inhibitors. *Actas Espa-Olas De Psiquiatría*. 2005;**34**(3):147–52.
42. Sun TF, Lin PY, Wu CK. Risperidone augmentation of specific serotonin reuptake inhibitors in the treatment of refractory obsessive-compulsive disorder: report of two cases. *Chang Gung Med J*. 2001;**24**(9):587–92. [PubMed: 11725630].
43. Yoshimura R, Kaneko S, Shinkai K, Nakamura J. Successful treatment for obsessive-compulsive disorder with addition of low-dose risperidone to fluvoxamine: implications for plasma levels of catecholamine metabolites and serum brain-derived neurotrophic factor levels. *Psychiatry Clin Neurosci*. 2006;**60**(3):389–93. doi: 10.1111/j.1440-1819.2006.01519.x. [PubMed: 16732759].
44. McDougle CJALHP. Antiobsessional effect of risperidone add-on treatment in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder may be dose-dependent. *Arch General Psychiatr*. 2002;**59**(5):472–3. doi: 10.1001/archpsyc.59.5.472.
45. Boricevic Marsanic, V . Misdiagnosis and exacerbation of unusual obsessive-compulsive disorder presentation with Risperidone and Clozapine in an adolescent girl-a case report. *Collegium Antropologicum*. 2011;**35**(1):293–6.
46. Stein DJ. Obsessive-compulsive disorder. *Lancet*. 2002;**360**(9330):397–405. doi: 10.1016/S0140-6736(02)09620-4. [PubMed: 12241794].
47. Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA, et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. *Am J Psychiatry*. 1998;**155**(7):921–8. doi: 10.1176/ajp.155.7.921. [PubMed: 9659858].