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Comparison of the efficacy of Aripiprazole and Risperidone in improving the obsessive symptoms in bipolar disorder comorbid with obsessive-compulsive disorder

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ABSTRACT

Obsessive-compulsive disorder can be associated with bipolar disorder at the same time. Studies show that the relatively high synchronization of these two disorders throughout the life span is about 9-39%. Bipolar disorder comorbid OCD is still not well studied. Treatment for obsessive-compulsive disorder is a significant clinical problem, because antidepressants are effective for obsessive-compulsive disorder may lead to the Accelerated of mania or hypomania and mixed phase. In this double blind clinical trial, 60 patients bipolar disorder comorbid obsessive-compulsive disorder were evaluated according to DSM5 criteria. Patients were chosen at least 3 months of maintenance therapy and Yale-Brown score of 16 or more. In one group, aripiprazole was started at a dose of 2.5 mg and was given at a dose of 10 mg per day over a period of 15 days. In the other group, it started with 1 mg of risperidone and was given at a dose of 4 mg per day. In the 4th, 8th and 12th weeks, patients with Yale-Brown scale were evaluated. The Yale-Brown mean score in the aripiprazole group was 23.3 before the study and 12.3 after 12 weeks. The Yale-Brown mean score in the risperidone was 25.5 before the study and changed to 11.27 after 12 months of treatment. Moreover, according to ANCOVA analysis model, it was indicated that at week 12 of treatment, the Yale-Brown scale in the risperidone group was 1.47 units lower than that of the aripiprazole, demonstrating a significant difference ($P<.001$). It was revealed that both drugs (aripiprazole and risperidone) were effective on treating the therapeutic-resistant obsessive-compulsive disorder comorbid with bipolar disorder in the maintenance phase. Furthermore, it was found a slight difference between the Yale-Brown mean scores of the two groups, which showed the advantage of risperidone over aripiprazole.

Keywords: Obsessive-Compulsive Disorder, Bipolar Disorder, Aripiprazole, Risperidone, Yale-Brown Scale, Therapeutic-Resistant

1. INTRODUCTION

Obsessive-compulsive disorder can be in comorbidity with mood disorders including bipolar disorder. The literature indicates that the relatively high comorbidity of these two disorders throughout life is about 9-39% (Simon et al., 2004; McElroy et al., 2001; Tamam & zpoyraz, 2002; Koyuncu et al., 2010). Bipolar disorder, on the other hand, may often occur with other disorders such as anxiety disorder, eating disorder, and drug use (Pashinian et al., 2006). The patients with obsessive-compulsive disorder have similar symptoms to bipolar disorder with high recurrent cycles, longer depression periods, more suicide attempts, and multiple hospitalizations. The patients with comorbid bipolar disorder with obsessive-compulsive disorder have significant levels of sexual, religious, asymmetric, repetitive and compulsive disorders. A recent study reported that the patients with comorbid bipolar disorder with obsessive-compulsive disorder show high levels of social anxiety, avoidant personality disorder, and obsessive-compulsive disorder in first-degree relatives (Ozdemiroglu et al., 2015). There is little empirical research on comorbid obsessive-compulsive disorder with bipolar disorder as well as the effective treatment for these two (Sahraian et al., 2014). The comorbidity of these two disorders is associated with worse and more severe anti-manic response in chronic bipolar patients. Moreover, the treatment of the comorbid obsessive-compulsive-disorder is a clinically considerable problem since antidepressants that are effective for obsessive-compulsive disorder may accelerate the onset of mania or hypomania and the combination of these two (Joshi et al., 2010). Although serotonin reuptake inhibitors are considered as the first line of treatment for obsessive-compulsive disorder, they can lead to mood instability in the patients with comorbid bipolar disorder, especially in higher doses and longer-term periods (Amerio et al., 2014). One of the examined and documented strategies for treating therapeutic-resistant obsessive-compulsive disorder is adding antipsychotic to serotonin reuptake inhibitors. There is little empirical research on the use of aripiprazole for the patients with obsessive-compulsive disorder, who responded poorly to the serotonin reuptake inhibitors. Based on what has been discussed and reviewing the literature and considering the limited number of studies on the effective treatment of comorbid obsessive-compulsive disorder with bipolar disorder, this study aimed at comparing the effectiveness and improvement of obsessive-compulsive disorder symptoms in the patients with these disorders through using aripiprazole and risperidone. It is noteworthy that most patients in this study used lithium to control mood symptoms.

2. MATERIAL AND METHODS

This study is a double-blind clinical trial. The patients in this study were diagnosed, according to DSM-5 criteria, with bipolar disorder in the maintenance phase, which was in comorbidity with obsessive-compulsive disorder, and were under treatment in outpatient or inpatient clinics of Kashan University of Medical Sciences. The samples were selected by using the simple sampling method. To determine the number of subjects needed to evaluate and compare the effectiveness of risperidone and aripiprazole in

the patients with bipolar disorder and due to the absence of a similar study, a pilot study (in two groups of ten) was conducted to evaluate the applicability of the intervention and calculate the required sample size. The Yale-Brown mean score in the risperidone group was 25 (SD: 1.97) and 23.3 (SD: 1.97) in the aripiprazole group before the intervention. After 12 weeks of treatment, they changed to 10.2 (SD: .793) and 12.2 (SD: .793), respectively. The difference before and after intervention in the risperidone group was 11.1 (3.72) and in the other group was 15.3 (5.29). Thus, the sample size was calculated as to be 30 with the accuracy of at least 95% and error of type II for at most 20% and error rate of d=0.6.

The inclusion criteria included 1) a definitive diagnosis of comorbid bipolar disorder with obsessive-compulsive disorder based on DSM-5 criteria; 2) ages 18 to 65 years old; 3) be in the maintenance phase for a minimum of 3 months; 4) knowledge and enough education to answer (diploma and higher), and 5) obtaining Yale-Brown scale score of 16 or higher. The exclusion criteria included 1) diagnosing acute and severe physical illness during the study; 2) failure to follow up for 4 weeks; 3) severe drug complications; 4) uncertain contraceptive methods in women at reproductive age; 5) pregnant or breast-feeding women; 6) abuse of alcohol and drug within 6 months prior to the study; 7) comorbidity with psychotic disorder, severe depression, mental retardation or other mental disorders, and 8) receiving psychotherapy during the study.

The Implementation Method

This double-blind trial was conducted for 12 weeks in 2017. The subjects were selected through psychiatric diagnosis and in accordance with DSM-5 criteria of comorbid bipolar disorder with obsessive-compulsive disorder, who referred to psychiatric clinics affiliated to Kashan University of Medical Sciences. The subjects were under treatment for at least three months to control periods of mania, hypomania, and depression and were in the maintenance phase at the time. In addition, they had signs and symptoms of obsessive-compulsive disorder that were not treated despite the improvement of mood periods of bipolar disorder. Before the intervention, the Yale-Brown scale score was measured by one of the project researchers. Those obtained a score above 16 were referred to the project psychiatrist. Then, considering the inclusion and exclusion criteria, the eligible subjects were selected. Demographic characteristics and information about other confounders including the age at onset of obsessive-compulsive disorder, duration of disease, type of drug or the mood stabilizing drugs and associated psychiatric disorders were collected. The patients who took any type of drugs and their mood periods were treated were selected and the patients who took antipsychotic medication were prescribed to gradually reduce the medication taking and then stop, and, at the same time, use aripiprazole and risperidone. The treatment was randomly assigned. The patients were divided into two groups. Due to the gradual referral of the patients and the maintenance of balance in the groups, the permuted block randomization method was used. In this method, the patients and the researcher were blind to it. The double blindness of the study is as follows:

The subjects in this study were taken the two selected medications, i.e. risperidone and aripiprazole for 3 months. They were not told about this in order to prevent them from taking a specific medication. The medications as alternative mood stabilizers were taken to the patients by a person other than the researcher of the study. The researcher evaluated the patients by Yale-Brown scale as well as examining the medications side effects. Aripiprazole 2.5mg was taken to the subjects of one group, and gradually increased to a dose of 2.5mg every five days and finally after 15 days increased to 10mg a day. Risperidone was taken to the patients initially at a dose of 1mg and gradually increased to 4mg a day by the end of the second week. All the subjects were visited by the psychiatrist for 8 times. The first visit was administered for randomization and receiving the medications, the second was at the end of the first week, the third was at the end of the second week, and then every two weeks till the end of the study, i.e. week 12, the visits were continued. The checklist of medication side effects was completed at all visits. In the case of any complication, dose reduction and gradual initiation of medication or prescription other medications (propranolol, lorazepam, and biperiden) were administered to control risperidone or aripiprazole side effects. At visits four, eight, and twelve, the Y-BOCS scale score was measured for all subjects through referring them to a psychiatrist. Response to treatment was determined by changing the Y-BOCS scale score from the baseline to the end of the study and comparing the two medications.

Data Analysis

Data were analyzed by SPSS 19. Descriptive statistics and Chi square and T tests were used in this study. The results were reported as mean and standard deviation, P value less than 5% was considered as to be significant.

3. RESULTS

In the present study, 60 patients with comorbid bipolar disorder with therapeutic resistant obsessive-compulsive disorder in two groups were under treatment by aripiprazole and risperidone. The mean age in the aripiprazole-treated group was 36.37 years old and, in the risperidone-treated group was 37.27 years old. The patients were randomly divided in the two groups. However, the

duration of disease in the risperidone-treated group was significantly shorter than that of the other group. The frequency percent of comorbid anxiety disorder in the group under treatment by risperidone was 3.53% and 7.46% in the other group. This difference is not statistically significant. Moreover, the frequency percentage of the comorbid hypercholesterolemia in the group under treatment by risperidone was 46.7% and 50% in the other group, which was not statistically significant. There could be found no significant difference between the two groups in terms of practical obsession. There was no significant difference between the two groups on mental obsession.

Table 1 Comparison of the Yale-Brown mean scores before the intervention and after week four

Time	Group				Diff (95%CI)	Independent T-test
	Aripiprazole		Risperidone			
	Average	Standard deviation	Average	Standard deviation	2.2 (-5.31,0.91)	0.163
Before study	23.3	5.00	25.5	6.90		
Forth Week	19.00	4.55	20.4	6.11	-1.4 (-4.18,1.38)	0.318
Difference	4.3	0.65	5.10	1.73		
Paired t test	<0.001		<0.001			

According to Table 1-3 & figure 1 - 4, Yale-Brown scale mean score in the group under treatment by aripiprazole was 23.3 before the intervention and after week four, it changed to 19. In the group under treatment by risperidone, it was 25.5 initially and changed to 20.4 after week four. The difference of means in the group was 2.20 before the intervention and changed to 1.4 after week four. The differences of the Yale-Brown mean score after 4 weeks of the intervention in the group under treatment by aripiprazole reduced 4.3 units and 5.1 units in the other group, demonstrating a significant difference. The difference between the two groups before the interventions was not significant but the changes of the Yale-Brown scale in the two groups after week 4 of the intervention was significant (P<.001).

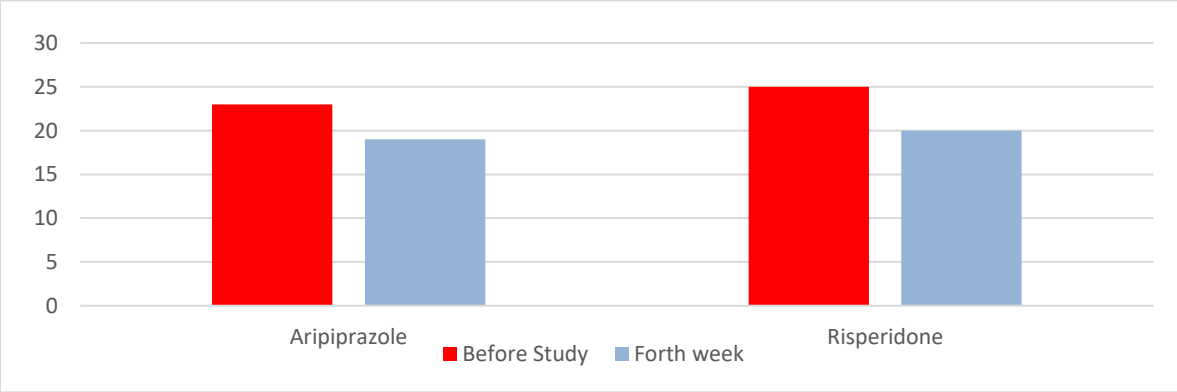

Figure 1 Comparison of the Yale-Brown mean scores before the intervention and after week four

Table 2 Comparison of the Yale-Brown scale mean score before the intervention and eight weeks after the intervention

Time	Group				Diff (95%CI)	Independent T-test
	Aripiprazole		Risperidone			
	Average	Standard deviation	Average	Standard deviation	2.2 (-5.31,0.91)	0.163
Before study	23.3	5.00	25.5	6.90		
Eighth week	15.5	3.29	15.12	3.94	-0.38 (1.49,2.25)	0.684
Difference	7.8	2.17	10.38	3.14		
Paired t test	<0.001		<0.001			

In the group under treatment by aripiprazole, the difference between the two groups before the intervention and after 8 weeks of interventions was 7.8 units. In the other group, this difference was 10.38 units, indicating a significant difference in both groups (P<.001).

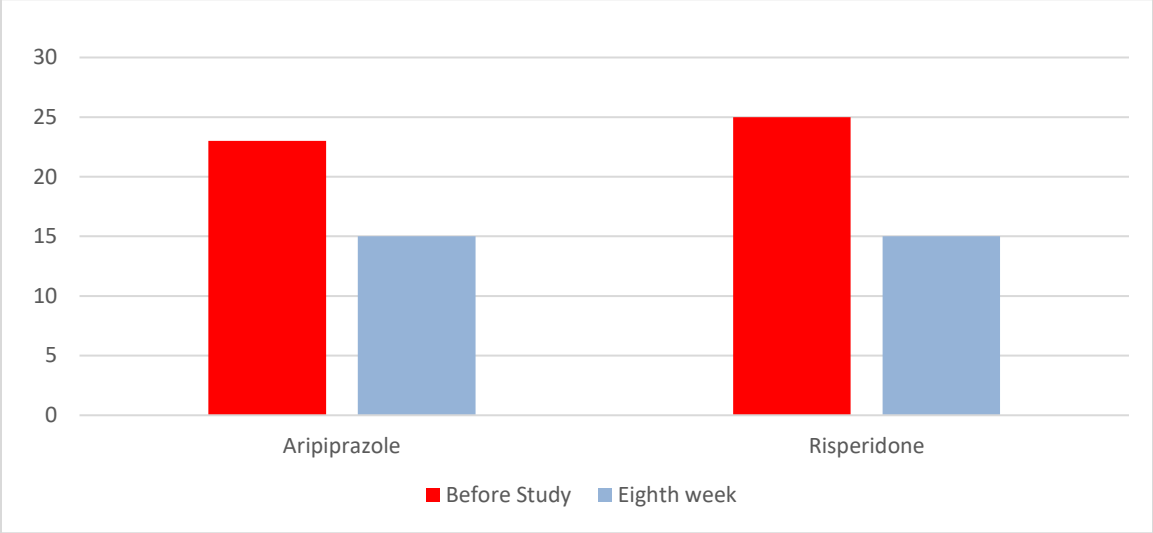

Figure 2 Comparison of the Yale-Brown scale mean score before the intervention and eight weeks after the intervention

Table 3 Comparison of the Yale-Brown scale mean score before the intervention and after 12 weeks of intervention

Time	Group				Diff(95%CI)	Independent T-test
	Aripiprazole		Risperidone			
	Average	Standard deviation	Average	Standard deviation	2.2 (-5.32,0.91)	0.163
Before study	23.3	5.00	25.5	6.90		
Twelfth week	12.3	2.32	11.27	1.23	1.03 (0.07,1.99)	0.037
Difference	11.00	3.69	14.23	6.07		
Paired t test	<0.001		<0.001			

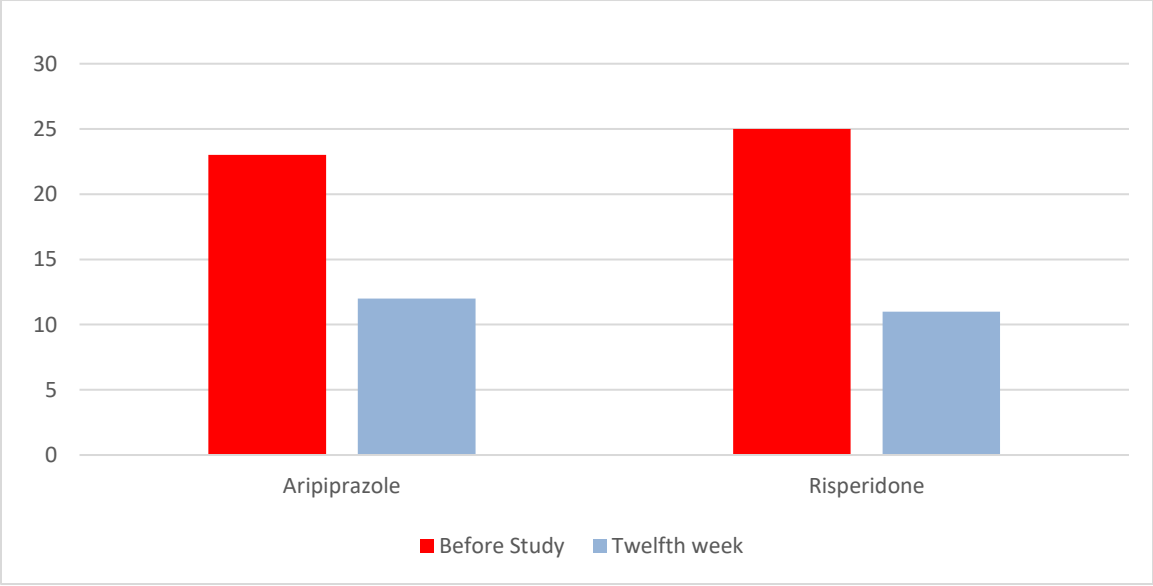

Figure 3 Comparison of the Yale-Brown scale mean score before the intervention and after 12 weeks of intervention

The difference between the two groups, in the group under treatment by aripiprazole, before the intervention and after 12 weeks of intervention was 11 units. This difference in the other group was 14.23 units. This difference was significant in both groups.

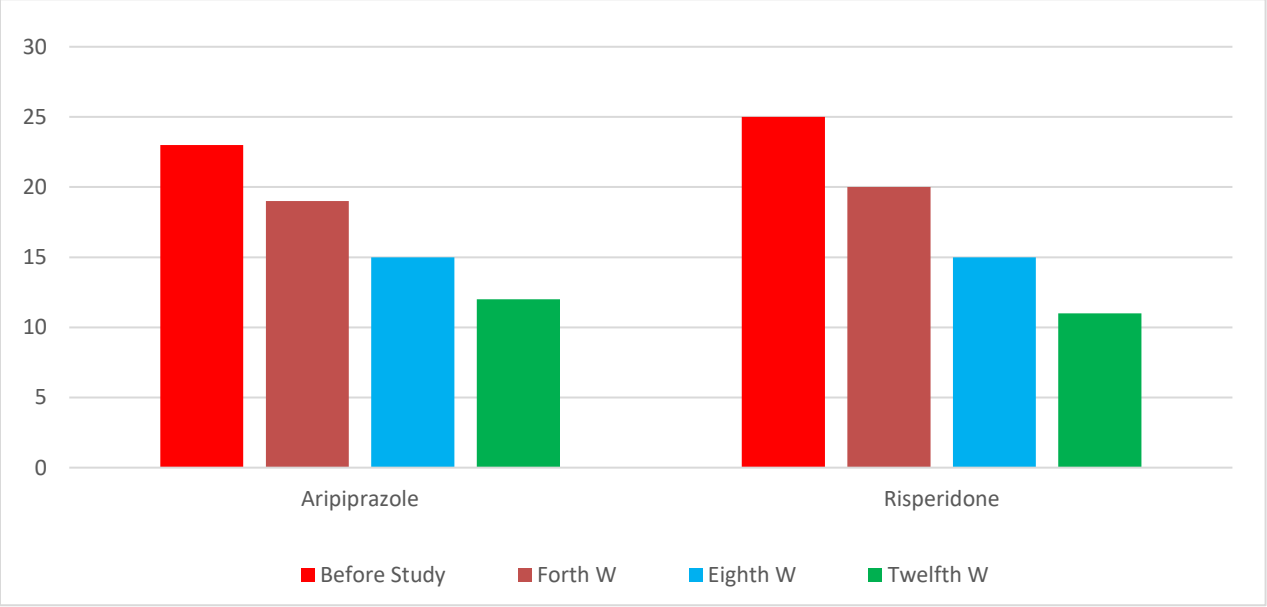

Figure 4 Comparison of the Yale-Brown scale mean score before the intervention and after 4,8,12 weeks of intervention

4. DISCUSSION

This study investigated the effectiveness of risperidone and aripiprazole in 60 patients with obsessive-compulsive disorder in comorbidity with bipolar disorder in maintenance phase. It was revealed that aripiprazole and risperidone can reduce the Yale-Brown scale scores. Nevertheless, it was found that risperidone was more effective. The following studies reported the effectiveness of aripiprazole on the patients with therapeutic-resistant obsessive-compulsive disorder or comorbidities of obsession.

In a study, aripiprazole was added as an adjunct to serotonin reuptake inhibitors for 12 weeks, initiated at a dose of 5mg and increased to a maximum dose of 20mg a day. The Yale-Brown scale scores were significantly reduced after 12 weeks of intervention (Pessina et al., 2009). In A study, aripiprazole 10 to 30 mg was taken to 18 patients with obsessive-compulsive disorder for 8 weeks. The Yale-Brown scale score was decreased at least 30% for 43% of the patients (Connor et al., 2005). Other studies previously explained reported similar results. In a study on 44 patients with Tic, among whom 15 patients suffered from OCD, 16 patients with comorbid ADHD, 14 patients with comorbid depression, and 15 patients suffered from comorbid anxiety were under treatment by aripiprazole at an average dose of 10mg. The results showed that 1) aripiprazole significantly reduced Tic symptoms but did not affect premonitory urge; 2) aripiprazole significantly improved OCD and was shown to be effective on other comorbid disorders including depression, anxiety, and ADHD. But its effectiveness on severity and quality of life of patients with Tic was not significant (Gerasch et al., 2016). In another study, a 51-year-old man with schizophrenia who suffered ablutomania. The patient was treating by clozapine 100mg. Increasing the dose to 150 mg exacerbated his obsession. He was prescribed aripiprazole 10 mg that was increased to a dose of 30mg a day, resulting in reduction in the PANSS and Y-BOCS scores at the end of week six (Eryilmaz et al., 2013).

Also, a study was conducted in two review groups on patients with refractory obsessive-compulsive disorder. One group took second-generation antipsychotic medications added to the main treatment and placebo was added to the main treatment of the other group. The inclusion criteria were treatment with adequate doses of SSRI or Clomipramine for eight weeks and resistance to such treatment. The information sources were all valid medical websites since September 2013. The short-term effectiveness of aripiprazole and risperidone in two studies were generally proved. However, no evidence of effectiveness of quetiapine or Olanzapine as compared to placebo was found (Veale et al., 2014). Regarding the above cases, all the evidence indicated the effectiveness of aripiprazole in combination with other medications and only in the patients with resistant obsessive-compulsive disorder or the patients with obsession in comorbidity with other psychological disorders. Contradictory results have been also found in studies:

In a study, one of two subjects of the study was an 18-year-old female with psychotic bipolar disorder, who was under treatment by aripiprazole at a dose of 15m a day. After two weeks of treatment, the subject showed the symptoms of obsession disorder despite improved symptoms of the primary disorder. Reducing the dose of aripiprazole to 10mg was not effective on improving the symptoms of obsession. The symptoms were completely eliminated after treatment by Carbamazepine. The onset of disease, in the

second subject, was started after taking aripiprazole, and improved after stopping that (Desarker et al., 2007). In one study, eating disorder and OCD were reported in the 27-year-old patients with schizophrenia, who was under treatment by Clozapine for 4 years. Due to abrupt discontinuation of the medication, the patient took aripiprazole as an alternative medication at a dose of 10mg. after 2 weeks; the symptoms of obsession were exacerbated. The severity of OCD decreased after discontinuation and replacement with risperidone (Mouaffak et al., 2007).

Considering the controlled clinical trials and numerous studies on the positive effects of Aripiprazole on obsessive-compulsive disorder, aripiprazole appears to have beneficial effects in the treatment of obsessive-compulsive disorder alone or occurring with other psychiatric disorders. There have been also numerous studies on the effectiveness of risperidone. In a study, reported a subject with schizophrenia in comorbidity with obsession disorder, who was treated by risperidone at a dose of 4mg a day (Chiou et al., 2015). In another case study, the subject was a young person with severe obsession disorder, who refrained from eating food, beverage, and medications because of contamination phobia. He was also resistant to cognitive behavioral psychotherapy (CBT). He took risperidone on admission and after several times, he could attend the psychotherapy sessions and Sertraline was prescribed for him (Nguyen et al., 2012).

It should be noted that in the previous study, the effectiveness of risperidone was investigated while in another study, the effectiveness of risperidone and exposure therapy and response prevention (EX/RP was compared in the patients with therapeutic-resistant obsession. The results indicated the advantage of exposure therapy over taking risperidone (Foa et al., 2015), also, investigated the effect of low doses of risperidone combined with SSRIs on the treatment of 45 patients who were resistant to standard treatment with Fluvoxamine. It was found that even low doses of this medication (at dose 0.5mg a day) could improve the symptoms of obsessive-compulsive disorder after 6 weeks of intervention (Erzegovesi et al., 2005). In the following two studies, the potentiation of aripiprazole and risperidone as adjunctive therapies for patients with bipolar disorder is examined.

In a double-blind study, Vieta et al. added aripiprazole to Lithium and Valproate for one group and placebo for the other group of patients with bipolar disorder. They reported aripiprazole as a safe and effective treatment to be added to the primary treatment of patients with bipolar disorder (Vieta et al., 2010). In a meta-analysis on the potentiation of second-generation antipsychotics in the treatment of patients with bipolar disorder, the following results were indicated: treatment with quetiapine, aripiprazole, and ziprasidone reduces the risk of relapse in patients in the maintenance phase. However, quetiapine was the only effective medication at both phases of mania and depression that reduced the risk of relapse. As monotherapy, olanzapine, quetiapine, and risperidone had advantages over placebo in decreasing the risk of relapse (Lindstrom et al., 2017). The results of the two studies that showed the effectiveness of the two medications on patients with obsession disorder resistant to standard therapies are as follows: In a study on 41 patients with obsessive-compulsive disorder resistant to standard treatment, the patients took Aripiprazole at a dose of 15mg a day or risperidone at a dose of 3mg a day for 8 weeks. It was found that patients who took risperidone showed a greater decrease in the obtained Yale-Brown scale score rather than the subjects in the other group (Selvi et al., 2011).

In another study on 100 patients with obsessive-compulsive disorder resistant to standard therapies, the patients were divided in two groups of 50. One group took aripiprazole and the other group took risperidone for 12 weeks. The Yale-Brown scale mean score in the aripiprazole group had a greater decrease as compared to that of the other group (Assarian et al., 2013). Though the studies discussed above were not in line with the present study in terms of the type of disease and the selected medications, the similar results showed that despite the differences between others studies and the present study in terms of the type of comorbid disorders, duration of treatment, medication dosage and the inclusion and exclusion criteria, the effectiveness of aripiprazole and risperidone was clearly evident in the treatment of comorbid obsessive-compulsive disorder with bipolar disorder. In the present study, it was revealed that these two medications reduced the Yale-Brown scale and the Yale-Brown scale mean score of the group took risperidone was 1.4 lower than the other group.

One of the major limitations of the present study was this fact that in order to include patients with bipolar disorder in the maintenance phase and to consider the ethical dimension of the study, the researchers had to consider the patients' mood-stabilizing medications according to the instructions of their respective physicians. This study was performed on the selected patients for a limited period (12 weeks). It is suggested for further studies in alonger period. Finally, it is suggested to conduct further studies in the future, taking into account the ethical aspects and obtaining the informed consent forms to change the alter stabilizers and medication-composition (stabilizer-antipsychotic) to achieve better results.

5. CONCLUSION

In this study, it was found that both drugs (aripiprazole and risperidone) were effective in treating obsessive-compulsive disorder, which was comorbid with bipolar disorder and was in the maintenance phase. There was also a small difference between the Yale Brown averages of both groups, which reported Risperidone's superiority.

Funding
This research received no external funding.

Conflicts of Interest
The authors declare no conflict of interest.

Informed consent
The implementation method was explained in details and the written consent forms were obtained from all the selected subjects.

Ethical Considerations
All ethical principles were considered in this study. Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/ or submission, redundancy, etc.) were completely observed by the authors. (Ethical approval no.1396.23)

Future studies
If we correlate & analyze efficacy olanzapine, haloperidol and paliperidone on OCD-BD; or with combination of Aripiprazole and Risperidone may be the improved version.

Data and materials availability
All data associated with this study are present in the paper.

Peer-review
External peer-review was done through double-blind method.

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