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RESEARCH ARTICLE

COMPARING THE EFFECTIVENESS OF ARIPIPRAZOL VS RISPERIDONE ADJUNCTIVE TO LITHIUM IN PATIENTS WITH ACUTE MANIA WITH PSYCHOTIC FEATURES. A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL

Romina Hamzehpour[1]., Fetemeh Sheikhmoonesi[2]., Narjes Hendoiee[3] and Seyed Mohammad Moosavi[4]

[1]Department of Psychiatry, Yahyanejad Hospital, Babol University of Medical Sciences, Babol, Iran
[2]Psychiatry and Behavioral Sciences Reasearch Center, Adiction Institute, Mazandaran University
[3]Department of Pharmacotherapy, Faculty of Pharmacy and Psychiatry and Behavioral Scences Research Center, Addiction Instiutte, Mazandaran University of Medical Science Sari, Iran
[4] Department of Psychiatry, Mazandaran University of Medical Sciences, Sari, Iran

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ABSTRACT

Introduction: Research suggests that both aripiprazole and risperidone are effective in treating acute mania in combination with mood stabilizers. The present study was conducted to determine the relative merits of these two medications.
Materials and Methods: The present double-blind randomized clinical trial was performed on 60 patients who suffer from acute mania with psychotic features. Block randomization was used to assign the patients to two groups, one receiving aripiprazole plus lithium and the other risperidone plus lithium. Clinical evaluations were conducted and the side effects were assessed based on the Young Mania Rating Scale (YMRS), the Brief Psychiatric Rating Scale (BPRS), the Simpson Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Rating Scale (BARS).
Findings: Based on the YMRS and BPRS scores, the timeline of the response to treatment was significant in both groups (P<0.0001), suggesting no significant differences between the two groups (P=0.47 and 0.66). The mean AIMS score associated with both medicines showed a significant reduction over the course of time (P<0.0001), although they had no significant differences in terms of complications (P=0.13).
Conclusion: No significant differences were observed between aripiprazole and risperidone in terms of their effect on improving the symptoms of acute manic phase and their side effects

INTRODUCTION

Mood disorders are the most common psychiatric disorders [1]. The prevalence of bipolar I disorder is about 1% and type II about 5% [2]. Moreover, psychosis is common in depressed and manic patients with bipolar disorder. Over 20% of patients with bipolar disorder experience psychotic symptoms throughout their lifetime [3]. Bipolar disorder can become highly debilitating unless proper long-term treatments are used [4].As an adjunctive therapy, antipsychotics have been widely used in combination with lithium as the first choice of treatment to tackle bipolar disorder [5]. Second-generation antipsychotics or atypical antipsychotics, including risperidone and aripiprazole, have been approved for treating acute manic episodes of the illness [6]. A combination of mood stabilizers and atypical antipsychotics constitutes the first-line therapy formanic episodes with psychotic features[6]. Different studies suggest that atypical antipsychotics such as aripiprazole affect the treatment of acute manic episodes and have been well tolerated by the patients [7-8]. They were also shown to cause better responses and tolerance compared to haloperidol [9]. According to the data obtained from the YMRS, aripiprazole is preferred to placebo in improving symptoms of the acute manic phase, as a higher percentage of the patients recovered from these symptoms when they underwent aripiprazole treatment compared to taking placebo [10]. Few double-blind studies have so far evaluated the effectiveness of a combination of mood stabilizers and atypicalantipsychotic such as risperidone; nevertheless, some studies confirmed the superiority of a combination of risperidone and mood stabilizers over placebo [11]. Research suggests that manic patients experience relatively higher degrees and rates of recovery when they take a combination of risperidone and a

mood stabilizer such as lithium or valproate [12]. Studies show that either aripiprazole or risperidone affects the treatment of acute mania in combination with mood stabilizers; however, the prevalence of metabolic complications caused by these medicines should also be monitored in patients with bipolar disorder. The present study therefore selected aripiprazole owing to its fewer metabolic complications and compared it with risperidone, which causes many metabolic complications [2]. The main purpose was to determine whether the effectiveness of aripiprazole is as high as risperidone, since bipolar disorder causes a significant dropin the occupational and social performance of the patients. Identifying the most effective medicine with the fewest complications can therefore be a great help to these patients and their families.

MATERIALS AND METHODS

The present double-blind randomized clinical trial was registered in the Iranian Registry of Clinical Trials (IRCT 201409176691 N_2). The eligible candidates comprised 60 patients with acute mania with psychotic features according to DSM_IV_TR who were being treated with lithium and hospitalized in Zare Hospital in Sari, Iran in 2014Diagnosis was made by a psychiatrist. The present research was performed based on the Declaration of Helsinki, and informed consent was obtained from all the patients. The study was examined and approved by the Ethics Committee of Mazandaran University of Medical Sciences with the code of 1390-03-10

Inclusion and Exclusion Criteria

The inclusion criteria consisted of diagnosis of manic phase of bipolar disorder with psychotic features based on the DSM-IV-TR criteria, age of over 18, receiving lithium, having a serum lithium level of 0.8-1.2 meq/L and receiving a YMRS baseline score of at least 20. The exclusion criteria comprised experiencing at least ten manic episodes over the previous year, mood disorders caused by drug abuse or physical illnesses, mental retardation, pregnancy, breastfeeding, a history of sensitivity to aripiprazole and other atypical antipsychotics, the patient's willingness to withdraw from the study, chronic medical diseases, a history of seizures, delirium, dementia, a need for treatment with other mood stabilizers such as carbamazepine and sodium valproate, using drugs or other stimulants, being at a high risk for suicide., a history of neuroleptic malignant syndrome (NMS) and recently receiving long-acting antipsychotics.

Medicinal Regimen

Block randomization was used to assign the patients to two groups, one receiving 15 mg of aripiprazole and the other 6 mg of risperidone over 3 weeks.

Clinical Evaluation

Clinical evaluations were performed using the YMRS and BPRS and the disease complications were assessed using the SAS, the AIMS and the BARS. A psychiatry resident completed the YMRS and the BPRS and recorded their changes in the beginning of the study and on the 7^{th}, 14^{th} and 21^{st} day. To assess the side effects, the psychiatry resident completed the SAS, the BARS and the AIMS on the 2^{nd}, 4^{th}, 7^{th} and 10^{th} day followed by a once-a-week schedule up to the end of the study.

YMRS

The 11-item YMRS is a rating scale used to evaluate manic symptoms at baseline and over time in individuals with mania. This20-30-minute evaluation was performed as clinical observations. Different studies confirmed the reliability and validity of this scale [13]. The test reliability was reported to be 0.643 after standardizing the translation conditions [14]. This scale evaluates the main manic symptoms, namely 1-elevated mood, 2-increased motor activity/energy, 3-sexual interest, 4-sleep, 5-irritability, 6-speech (rate and amount), 7-language/thought disorder, 8-thought content (disorders), 9-disruptive/aggressive behavior, 10-appearance and 11-insight.. The item scores were added up to give a total YMRS score of 0-60 [2].

BPRS

The 18-item BPRS measures the variation and degree of a wide range of psychotic symptoms in inpatients, including thought disorders and emotional symptoms, including anxiety and depression, and also aggression and suspiciousness. These items were scored on a seven-point scale of 0-6, and the total score was 0-108. This 20-30-minute test included the examination of patients.

SAS

The 10-item SAS was developed to investigate the effects of antipsychotics, and focuses on the Parkinson's disease symptoms, especially rigidity [2].

AIMS

The AIMS is a clinical examination and a rating scale that is used to measure motor disorder symptoms in patients taking antipsychotics [2].

BARS

The BARS was designed to evaluate the neuroleptic-induced akathisia [2].

Statistical Methods

The patients' qualitative data were reported as frequency and relative frequency and their quantitative information as mean values. The data collected were analyzed in SPSS-22 using statistical tests, including the chi-squared, the t-test, the Mann–Whitney U test, repeated measures and the Friedman. To examine the normality of the data, the Kolmogorov-Smirnov test was used. $P<0.05$ was set as the level of statistical significance.

Findings

The present study initially selected 60 patients in two groups. Group A (n=30) received risperidone and group B (n=30) aripiprazole. Table 1 presents the patients' basic and demographic information.

Table 1 The basic and demographic information of the patients in two groups

Variable	Group A	Group B	P
Gender			
Male	22 (73.3%)	20 (66.7%)	0.77
Female	8 (26.7%)	10 (33.3%)	
Age Group (year)			
20-30	10 (33.3%)	14 (46.7%)	
31-40	14 (46.7%)	11 (36.7%)	0.36
41-50	5 (16.7%)	2 (6.7%)	
51-60	1 (3.3%)	3 (10%)	
Marital Status			
Single	11 (36.7%)	19 (63.3%)	0.07
Married	19 (63.3%)	11 (36.7%)	

Level of Education			
Illiterate	1 (3.3%)	1 (3.3%)	0.44
Below high school diploma	10 (33.3%)	15 (50.0%)	
At least high school diploma	19 (63.4%)	14 (46.7%)	
Occupation Status			
Unemployed	16 (53.3%)	11 (36.7%)	0.29
Employed	14 (46.7%)	19 (63.3%)	
Reason for Presenting Aggression	17 (56.7%)	15 (50.0%)	
Talkativeness	6 (20.0%)	5 (16.7%)	0.12
Suspiciousness	1 (12.5%)	7 (23.3%)	
Abnormal behavior	6 (20.0%)	3 (10.0%)	

Table 2 shows the YMRS scores in the two groups in different time points and suggests a significant timeline of response to treatment in both groups (P<0.0001). Given that the mean YMRS score reduced over the course of time in both groups, no significant differences were observed between these groups (P=0.66). In other words, the data obtained from the YMRS indicated the effectiveness of both risperidone and aripiprazole, and showed a similar response to treatments in the two groups. Furthermore, the mean BPRS score significantly dropped over the course of time in both groups (P<0.0001), and no significant differences were observed between these groups (P=0.47), suggesting the similarity of response to treatment.

Table 2 The mean scores obtained from the YMRS and BPRS in the risperidone group and aripiprazole group at four-time points

		Beginning	7th day	14th day	21st day	P*
YMRS	Group A	51.10±3.68	37.37±7.59	57.27±5.96	20.43±4.51	<0.0001
	Group B	50.84±0.14	36.33±7.28	27.4±5.24	20.67±4.25	<0.001
	P**	0.76	0.59	0.90	0.83	
BPRS	Group A	67.00±3.21	52.70±5.35	70.39±6.03	26.97±4.64	<0.0001
	Group B	67.87±3.98	51.83±6.98	38.90±5.93	26.53±3.98	<0.0001
	P**	0.35	0.59	0.60	0.69	

*: Using repeated measured in different time intervals
**: Using the independent t-test in different time intervals

Different side effects were examined in the two groups and no significant differences were observed (Table 3).

Table 3 Side effects in groups A and B

Side Effect (yes)	Group A	Group B	P
Tremor	10 (47.6%)	11 (52.4%)	0.99
Dystonia	-	1 (100%)	0.99
Parkinsonism	18 (62.1%)	11 (37.9%)	0.12
Akathisia	20 (51.3%)	19 (48.7%)	0.99
Insomnia	10 (41.7%)	14 (58.3%)	0.43
Weight Loss	2 (66.7%)	1 (33.3%)	0.99
Restlessness	8 (66.7%)	4 (33.3%)	0.333
Nausea	-	-	-
Vertigo	-	-	-

The AIMS, SAS and BARS were used to investigate the side effects on the 2nd, 4th, 7th, 10th and 21st day. The mean AIMS scores of both medicines exhibited significant reductions over the course of time (P<0.0001) (Table 3). Both aripiprazole and risperidone similarly caused extrapyramidal complications, suggesting no significant differences (P=0.13). As shown in Table 5, although the SAS score significantly decreased in both groups during the course of the five-time points (P<0.0001), the two groups showed statistically significant differences observed (P=0.003), meaning that aripiprazole causes fewer parkinsonism symptoms compared to risperidone.

Table 4 The mean AIMS and SAS scores on the 2nd, 4th, 7th, 10th and 21st day in the two groups

		2nd day	4th day	7th day	10th day	21st day	P*
AIMS	Group A	-	0.47±0.77	0.73±0.69	0.67±0.75	-	<0.0001
	Group B	-	0.03±0.18	0.50±0.86	0.43±0.77	-	<0.0001
	P	-	0.004***	0.25**	0.24**	-	
SAS	GroupA	-	1.23±1.35	1.47±1.27	0.83±0.79	0.07±0.25	<0.0001
	Group B	-	0.30±0.59	0.87±1.27	0.57±1.00	0.13±0.43	<0.0001
	P	-	0.001***	0.07**	0.25**	0.47**	

*: Using repeated measured at different time points within a group
**: Using the independent t-test at different time points between the two groups
***: Using the Mann-Whitney U Test at different time points between the two groups

The BARS was used to measure the frequency of akathisia in both groups. Significant differences were observed in each group over the course of time (P<0.0001) (Table 5). The frequency of this complication was also the same in the group receiving either of the medicines (P=0.45).

Table 5 The mean BARS score in both groups at specific time points

	2nd day	4th day	7th day	10th day	21st day	P*
Group A	-	0.50±0.82	0.60±0.89	0.33±0.47	-	<0.0001
Group B	0.17±0.37	0.50±0.57	0.83±0.95	0.53±0.68	0.23±0.43	<0.0001
P	0.02**	0.99**	0.33**	0.19**	0.006**	

*: Using the Friedman test at different time points within a group
**: Using the Mann-Whitney U test at different time points between the two groups

DISCUSSION

Based on the search carried out in the accessible databases, no studies have so far compared the effectiveness of atypical antipsychotics in treating acute mania with psychotic features. The present research was therefore the first clinical trial conducted on the effect and safety of risperidone and aripiprazole.

The main goal of treating acute mania is to quickly and safely alleviate the patient's symptoms. This disease is mainly treated using mood stabilizers, particularly lithium carbonate; nevertheless, given that there is a 4-15-day delay for these medications to begin affecting, and also due to the aggression, restlessness and sometimes psychotic symptoms in the patient, antipsychotics may also be used in these patients [1].

The effectiveness of aripiprazole has been compared with risperidone in different diseases, including hyperactivity in children, schizophrenia and methamphetamine-associated psychosis. Many studies have also been conducted on the effect of risperidone and aripiprazole on treating bipolar disorder andmanic/mixed episode and preventing recurrences, both individually or in combination with other medicines. All these studies confirmed the effectiveness and safety of administrating these medicines.

The article presented by Razjoyan *et al*. in the sixth international conference on pediatric and adult psychology, suggested no significant differences between aripiprazole and risperidone in terms of their efficacy in treating attention deficit hyperactivity disorder in children under the age of 6 [15]. The comparative study conducted by Hatta *et al*. in 2009 using the positive and negative symptoms questionnaire showed that a combination of risperidone and olanzapine is more effective than a combination of quetiapine and aripiprazole in treating schizophrenia patients with acute psychosis [16]. A recently-conducted study by Wang *et al*. in 2016 showed both risperidone and aripiprazole are effective in treating methamphetamine-associated psychosis, suggesting no significant differences [17]. Carlson *et al*., 2012, investigated

the effect of aripiprazole in combination with lamotrigine on the long-term treatment of patients with bipolar I disorder. They observed no unpredictable complications and found this combination to delay the time to manic/mixed relapse, which was, however, statistically insignificant [18]. Moreover, Marcus *et al*., 2011, compared the effectiveness and safety of placebo againstaripiprazole as the adjunctive therapy to lithium or sodium valproate. They reported that combining aripiprazole to mood stabilizers prolongs the time to the next relapse [19]. Keck *et al*., 2006, conducted a study on the safety and effectiveness of aripiprazole in preventing relapses in patients with bipolar disorder. They concluded that 15-30 mg/day of aripiprazole is significantly superior to placebo in preventing relapses [8].

Double-blind studies have demonstrated the higher effectiveness of risperidone in treating acute mania compared to placebo. Macfadden *et al*. conducted a study in 2011 on the effectiveness of risperidone as an adjunctive therapy in patients with bipolar disorder who frequently relapsed. They concluded that using risperidone for at least 3 months can alleviate the symptoms and recurrence of bipolar disorder [20]. Vieta *et al*., 2012, found risperidone to be highly safe and to significantly delay the recurrence of manic episodes [21]. Similarly, Quiroz *et al*., 2010, reported that risperidone can delay the time to recurrence of mood episodes and found it to be tolerable and highly safe [22].

Although the relative merits of risperidone and aripiprazole simply appear to be the same, a review of literature suggests a lack of comparative studies on these medicines in terms of treating acute manic episodes. It is worth noting that metabolic complications caused by patient sensitivity and the increasing weight caused by mood stabilizers constitute the major complaints of patients with the acute manic episode of bipolar disorder [2]. To help the patients and their families, further studies are recommended to compare different atypical antipsychotics and possibly find the most effective medications with the minimum side effects.

CONCLUSION

Aripiprazole or risperidone monotherapy was found to improve the symptoms of acute mania phase, while neither aripiprazole nor risperidone was found superior to the other. Moreover, aripiprazole causes fewer parkinsonism symptoms compared to risperidone.

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