ORIGINAL ARTICLE

Comparison the effectiveness of aripiprazole and risperidone for the treatment of acute bipolar mania

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Background: Second-generation antipsychotics, approved for the treatment of mania, are associated with adverse effects such as weight gain and metabolic disorders. Aripiprazole, a recently introduced second-generation antipsychotic, are thought to account for its low propensity for weight gain, metabolic disturbances and sedation. The purpose of this study was to investigate the effect of risperidone versus aripiprazole in the treatment of acute mania. **Materials and Methods:** Fifty patients with acute episodes of mania were enrolled in this study, and they were randomly assigned into a risperidone group of 24 cases and an aripiprazole group of 26 cases. In group A, aripiprazole with a dose of 5-30 mg/day and in group B, risperidone with a dose of 2-8 mg/day was given to patients. The average dose of aripiprazole was 27 mg/day, and the average dose of risperidone was 6 mg/day. The effects of each drug for the treatment of acute mania were assessed on the 1st day of admission and on days 2, 4, 6, 8 and at weeks 2, 4 and 6 after therapy using the young mania rating scale (YMRS) and at the baseline and on weeks 3 and 6 after admission using the clinical global impression (CGI) scale. **Results:** The mean age of the group of risperidone was 34 ± 8.6 years and in a group of aripiprazole it was 34 ± 9.1 years ($P = 0.83$). Comparison of YMRS scores over the period of 6 weeks revealed a statistically significant difference in both groups ($P < 0.0001$).There was also a statistically significant difference in YMRS scores between risperidone and aripiprazole at day 8 ($P = 0.026$) and weeks 2 ($P = 0.035$) and 4 ($P = 0.042$). There was also a statistically significant difference in CGI-Severity scale score at weeks 3 ($P = 0.003$) and 6 ($P = 0.000$) and in CGI-Improvement scale score at weeks 3 ($P = 0.005$) and 6 ($P = 0.002$). The most common side-effect observed in both groups was headache (0%15/4 in aripiprazole vs. %16/7 in risperidone) **Conclusion:** Aripiprazole that is readily available in our market, could be considered more effective than risperidone in the treatment of acute mania.

Key words: Aripiprazole, mania, risperidone

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INTRODUCTION

The global prevalence of bipolar spectrum disorders is believed to be 8%.[1] There are a number of factors such as: Delayed diagnosis, comorbidity with other mental illnesses, non-compliance with treatment and high rate of relapse that influence on treatment protocol and make the treatment of bipolar disorders difficult.[2] Due to unacceptably high relapse rate among patients with manic episodes and high mortality rate, Identifying effective treatment modalities is mandatory.[3,4] Lithium and Valproate have traditionally been used in the united states for the treatment of mania.[5] The atypical antipsychotics have been successfully used in the treatment of acute mania.[6] There is a special attention to the role of aripiprazole and risperidone in the treatment of manic episodes.[7-11] Aripiprazole is an atypical antipsychotic with partial agonist effects at dopamine 2 (D2) and 5-hydroxytryptamine 1A (5HT1A) receptors.[12-20] In a study that was performed on healthy individuals, aripiprazole with a dose of 0.5-30 mg/day could successfully suppress D2 receptor in 40-95% of participants.[19] Risperidone is an antagonist to D2 and serotonin (5HT2), adrenergic, and histamine (H1) receptors.[21] Both aripiprazole and risperidone are metabolized by cytochrome p450 enzymes.[22] The aripiprazole and risperidone have been recommended for the treatment of a variety of disorders, including: Tourette syndrome, autism spectrum, cocain or amphetamine dependence, schizophrenia and manic episodes of bipolar manic depressive illness.[7-11,23-26] In a study that was performed during the years 2000-2011 and it included 597 patients with bipolar disorders, there was an increased tendency towards the prescription of aripiprazole while the prescription of risperidone was decreased to half.[27] To determine what is the best drug

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treatment for acute mania and ultimately, to determine new guidelines for the treatment of manic episodes, comparison of the efficacy and tolerability between anti-manic drugs is mandatory. In a study, comparison of aripiprazole versus other second-generation antipsychotics for the treatment of manic episodes was performed in the pediatric population.[28]

Since aripiprazole is recently available in on our market, we decided to study the potential effectiveness of this drug for the treatment of acute mania and also we wanted to compare the effectiveness of this drug with risperidone that has been traditionally available in the market. To achieve this goal, we designed a study to investigate the effectiveness of aripiprazole versus risperidone in patients with acute bipolar mania.

MATERIALS AND METHODS

This is a comparative study of efficacy of aripiprazole versus Risperidone for the treatment of acute mania. A randomized, double-blinded clinical trial was conducted. Both the patient and clinician were blinded to the type of drug use. The duration of the study was 6 weeks. From mid-March 2011 to early October 2012, 62 patients that were admitted to Ibn-e-Sina hospital (Mashhad, Iran) with a primary diagnosis of an acute episode of mania and who were fully met our inclusion criteria, were enrolled in this study. The patients were randomly assigned into two groups using a random-numbers table: A risperidone group of 31 cases and an aripiprazole group of 31 cases. Later in the study, seven patients in the group of risperidone and five patients in the group of aripiprazole were excluded from the study because of a diagnosis other than acute mania (e.g. Schizoaffective disorder) and ultimately, 26 cases in the group of aripiprazole and 24 cases in the group of risperidone were participated in this study [Figure 1]. The acute episode of mania was diagnosed by a psychiatrist using diagnostic and statistical manual of mental disorders, Fourth edition, text revision criteria.[29] Our Institutional Ethics Committee approved the research project, and Informed consent was obtained from patients or their surrogates.

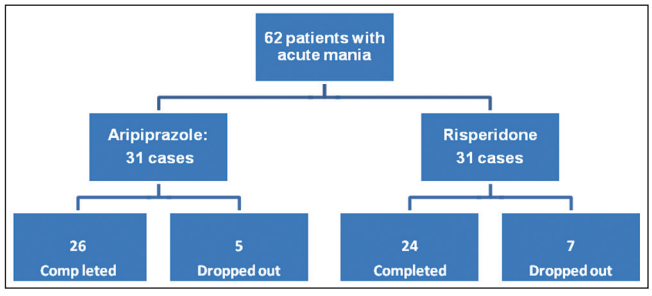

Figure 1: Consort diagram of participant flow

The inclusion criteria were as follows:

- Age between 18 and 50 years.
- Patients with a diagnosis of bipolar I disorder, current manic or mixed episodes according to the diagnostic and statistical manual of mental disorders IV-text revision criteria.
- Young mania rating scale (YMRS) score of ≥20.

Exclusion criteria were as follows:

- Patients with more than two manic episodes.
- Patients with a diagnosis of schizophrenia, schizoaffective disorder, personality disorder, becker muscular dystrophy II, delirium, dementia, history of seizure, history of substance abuse during the past 3 months and patients with a serious medical illness.
- Patients who were at risk for suicide or homicide.
- Female patients who were breastfeeding or had a positive beta-human chorionic gonadotropin test.
- Patients who were taking any medications during the 2 weeks before the study.
- Patients who were excluded from the study because of serious drug-induced side effects.
- Patients who refused to participate in this study.

The patients in group A, were treated initially with 5 mg/day aripiprazole (Sobhan Daru-Iran) then depending on the patient's symptoms and tolerance, the dose was increased by 5 mg/day at 2 days intervals up to 30 mg/day (based on previews studies, we determined the dose of aripiprazole).[30,31] In group B, patients received an initial dose of 2 mg/day risperidone (Sobhan Daru-Iran), followed by increasing up to 8 mg/day.[7,11] Lorazepam up to 4 mg/day for treatment of agitation, Biperidine 4 mg/day for treatment of extrapyramidal side effects and Propranolol up to 60 mg/day for treatment of akathisia or tremor were permitted. The patients had to be drug-free of any kind at least 8 h before each visit by the clinician.

Scales

The effects of each drug for the treatment of acute mania, were assessed on the first day of admission and on days 2, 4, 6, 8 and at weeks 2, 4 and 6 after admission using the YMRS and on the 1st day of admission and on weeks 3 and 6 after admission using the Clinical Global Impression (CGI) scale.[32,33] Evaluation of the effectiveness was done by a psychiatrist without knowing the specific drug that had been used. Patients were weekly visited by clinician for any potential drug side-effects. For this purpose, a check-list was prepared by a psychiatrist based on textbooks and the patients were rated from 0 to 3 for each potential side-effect where 0 was no complaint and 3 was apparent complaint plus impaired function. If the side-effect were rated as 1, the patient would be visited again in a few days, and if the side-effect were still exist, the patient would be treated with

the above-mentioned drugs. If the side-effect was rated as 2, the dose of aripiprazole or risperidone would be decreased. If the side-effect were rated as 3, the treatment would be stopped. The primary efficacy measure was defined as a reduction in total mean YMRS score from baseline to study end point. Secondary efficacy measures are defined as ≥50% decrease in total YMRS scores.[32]

Statistical analysis

Statistical calculations were performed using IBM SPSS statistics version 20.0 (SPSS Inc, Chicago, Illinois, USA) For data analysis, we used Kolmogorov-Smirnov test for determining normality distribution of quantitative variables, analysis of variance (ANOVA) with repeated measures, Student's *t*-test and Bonferroni multiple pair-wise comparison test, Tukey test, and Chi-square test.

RESULTS

Sixty-two patients were initially included in this study and they were randomly assigned into two groups, but five patients in the group of aripiprazole and seven patients in the group of risperidone were then dropped out from the study because of a diagnosis other than acute mania (e.g. Schizoaffective disorder) and ultimately, 50 patients completed the study [Figure 1] including: A risperidone group of 24 cases consisting of 12 males and 12 females and an aripiprazole group of 26 cases consisting of 13 males and 13 females.

The normal distribution of age in two groups was confirmed using Kolmogorov-Smirnov test ($P > 0.05$). Mean (±Standard deviation (SD)) age of the group of risperidone was 34 ± 8.6 years and in a group of aripiprazole it was 34 ± 9.1 years ($P = 0.83$).

In both groups, the gender distribution was equal (K-S test, $P > 0.05$). According to the Chi-square test, gender was not significantly different between two groups. In group of risperidone, Mean (±SD) duration of disease was 4.1 ± 3.6 years and in the group of aripiprazole, it was 2.5 ± 2.9 years ($P > 0/05$) 12 patients in group of risperidone and 15 patients in the group of aripiprazole had more than 1 episode of mania. There is not any significant differences in the number of mania episodes between two groups ($P > 0.05$).

The effects of each drug for the treatment of acute mania were assessed on the 1st day of admission and days 2, 4, 6, 8 and at weeks 2, 4 and 6 after admission using the YMRS. In the group of aripiprazole and risperidone, Mean YMRS scores at baseline were 39.4 ± 10 and 39.7 ± 10.0, respectively. The *t*-test showed no significant difference between baseline YMRS scores in two groups. According to the ANOVA with repeated measures test, there was a statistically significant difference in YMRS scores in both groups ($P < 0.0001$). The Bonferroni multiple pairwise comparison test showed that in both groups, As it has shown in Tables 1 and 2, there was a statistically significant difference between YMRS scores at baseline compared to other time points ($P < 0.0001$) that demonstrates the effectiveness of both drugs in the treatment of acute mania. In group of risperidone, there was also a significant difference in YMRS scores at days 2, 4 compared with other time points and at day 6 with all other time points except day 8. YMRS scores were significantly decreased at day 8 compared with weeks 2, 6 and 8. These are summarized in Table 1. In group of aripiprazole, there was a significant decrease in YMRS scores at day 2 compared with days 6 and 8 and weeks 2, 4 and 6, at day 4 compared with day 8 and weeks 2, 4, and 6 and at days 6 and 8 compared with weeks 2, 4 and 6 [Table 1].

As it is illustrated in Table 1, comparison of mean YMRS score between two groups of the above time points was done using the Tukey test that demonstrated that risperidone group had significantly higher YMRS scores compared with aripiprazole at day 8 ($P = 0.026$) and weeks 2 ($P = 0.035$) and 4 ($P = 0.042$).

The severity of illness was evaluated at three-time points, at baseline and weeks 3 and 6, using the CGI scale. The improvement assessment was done using the CGI-I Scale with a comparison of mean CGI-I scores at baseline and weeks 3 and 6. In group of aripiprazole, the mean CGI-S score on the day of admission was 6.06 ± 0.27 and for group of risperidone the mean CGI-S score was 6.00 ± 0.00. The

Table 1: Comparison mean ± SD YMRS scores in study population

Mean YMRS Score	Aripiprazole	Risperidone	*P*
Day 0	39.4±6.8	39.7±9.9	0.900
Day 2	31.1±8.6	34.9±9.5	0.140
Day 4	28.4±8.4	31.2±8.7	0.240
Day 6	25.0±7.4	27.3±7.2	0.270
Day 8	21.8±6.8	26.1±6.5	0.026
Week 2	17.1±4.6	20.3±5.7	0.035
Week 4	15.4±3.5	18.0±5.1	0.042
Week 6	14.8±4.2	16.3±5.1	0.250
P	<0.0001	<0.0001	

YMRS = Young mania rating scale; SD = Standard deviation

Table 2: Comparison mean ± SD CGI scores in study population

Mean CGI Scores	Aripiprazole	Risperidone	*P*
Mean CGI-S score at baseline	6.07±0.27	6.00±0.01	0.172
Mean CGI-S score at week 3	2.92±0.27	3.25±0.44	0.003
Mean CGI-S score at week 6	1.76±0.43	2.33±0.48	0.000
Mean CGI-I score at week 3	2.46±0.51	2.83±0.38	0.005
Mean CGI-I score at week 6	1.73±0.45	2.08±0.28	0.002
P	<0.0001	<0.0001	

CGI-S = Clinical global impression-severity; CGI-I = Clinical global impression-improvement; SD = Standard deviation

t-test showed no significant difference between baseline CGI-S scores in two groups. According to the Tukey test, Greater reduction in CGI-S scores after 3 weeks ($P = 0.003$) and 6 weeks ($P = 0.000$) of therapy and greater reduction in CGI-I scores after 3 weeks ($P = 0.005$) and 6 weeks ($P = 0.002$) of therapy, occurred with aripiprazole compared with risperidone [Table 2].

The primary efficacy measure was defined as a reduction in total mean YMRS score from baseline to study end point. Both drugs showed significant improvement on the primary efficacy measures. Secondary efficacy measures are defined as ≥50% decrease in total YMRS scores. After 4 weeks of therapy, in a group of aripiprazole, secondary efficacy was observed in 88.5% (23 out of 26) of patients. The number of patients was increased to 24 cases or 92.3% at the end of week 6 of treatment. In the group of risperidone, secondary efficacy was observed in 18 cases out of 24 (75%) after 4 weeks of therapy and the number of patients who effectively responded to treatment remained unchanged at the end of week 6 of treatment.

The observed side effects in the group of aripiprazole were one case of sedation and two cases of headache and for the group of risperidone, the observed side effects were one case of headache and one case of sedation. All observed side-effects were rated as one, and no interventions were needed and no patient was received mood stabilizers of medications other than aripiprazole and risperidone during the study period. There was no significance between two groups on using Lorazepam and Propranolol.

DISCUSSION

In this study, the effectiveness of aripiprazole versus risperidone was evaluated. Evaluation of mean YMRS scores in two groups indicated that both drugs are effective in the treatment of acute mania, but aripiprazole was significantly more effective than risperidone at day 8, at weeks 2 and 4 of treatment, but there was no statistically significant difference in mean YMRS scores at days 2, 4, 6 and at week 6 of admission. The mean difference in YMRS scores at baseline compared with days 2, 4, 6, 8 and weeks 2, 4, 6 was significant in both groups that demonstrate that both drugs are effective in the treatment of acute mania but aripiprazole has advantages over risperidone in terms of efficacy and rapid response onset. The primary efficacy measures are defined as a reduction in total mean YMRS scores from baseline to study end point. Both drugs showed significant improvement on the primary efficacy measures

The Secondary efficacy measures are defined as ≥50% decrease in baseline YMRS scores. After 4 weeks of therapy, in the group of aripiprazole, secondary efficacy was observed in 88.5% of patients. The number of patients was increased to 92.3% at the end of week 6 of treatment. In the group of risperidone, secondary efficacy was observed in (75%) after 4 weeks of therapy and the number of patients who effectively responded to treatment remained unchanged at the end of week 6 of treatment. Mean CGI-I and CGI-S scores improved over the course of treatment in both the aripiprazole group and the risperidone group. Greater reduction in CGI-S scores after 3 weeks and 6 weeks of therapy and greater reduction in CGI-I scores after 3 weeks and 6 weeks of therapy, occurred with aripiprazole compared with risperidone. Our findings are similar to those reported by Fountoulakis and Vieta.[30] In our study, the patients in the group of Aripiprazole were treated with 5 mg/day up to 30 mg/day aripiprazole with an average dose of 27 mg/day and all patients tolerated the course of therapy and completed the study. The average dose of risperidone was 6 mg. Keck *et al*., have shown that aripiprazole with a dose of 27.9 mg/day up to 30 mg/day is well-tolerated in 31% of patients with acute mania. aripiprazole group showed significantly higher improvement on the total mean YMRS score compared with placebo. After 3 weeks of therapy, the mean reduction in YMRS scores was 8.2 in patients treated with aripiprazole and 3.4 in the placebo.[31] In our study, the mean reduction in YMRS score after 2, 4 and 6 weeks of therapy were 22.26, 23.13 and 24.57 respectively. These differences may partially be due to the fact that we did not measure the mean differences in YMRS scores after 3 weeks of therapy, or they may be due to higher clinical response rate to aripiprazole in Iranian population. In another study, aripiprazole was successfully used for treatment of acute mania or mixed episode. The mean reduction in YMRS score after a course of 3 weeks of aripiprazole therapy was 12.5.[34] Fountoulakis *et al*., have shown that aripiprazole is an effective and well-tolerated therapy for acute mania.[35] In another study, aripiprazole was compared with lithium and placebo for the treatment of acute mania. aripiprazole had significantly more improvement in mean YMRS total score compared with placebo.[36] Similar findings have been reported by Young *et al*.[37] The above studies demonstrate the effectiveness of aripiprazole in the treatment of acute mania. In some studies, Response to therapy started as early as days 2-4.[30] In our study, mean total YMRS score at baseline and day 2 were 39.4 ± 6.8 and 31.1 ± 8.6 respectively that demonstrates the rapid onset of drug effect. In the present study, severity of illness was evaluated at three time points, at baseline and at weeks 3 and 6, using the CGI scale. In both groups, the mean CGI-S score progressively decreased that confirms the effectiveness of both drugs in the treatment of acute mania. These findings are compatible with that found by evaluation of mean YMRS scores. Greater reduction in CGI-S scores after 3 weeks and 6 weeks of therapy and in CGI-I scores after 3 weeks and 6 weeks of therapy occurred with aripiprazole compared

with risperidone. Similar findings have been reported by Sachs *et al*. and Keck *et al*. In their studies, aripiprazole significantly reduced the CGI score for mania.[31,34]

Collectively, the purpose of this study was to investigate the effect of risperidone versus aripiprazole in the treatment of acute mania. A 6-weeks randomized, double-blinded clinical trial was conducted. There was a statistically significant difference in YMRS scores between risperidone and aripiprazole. There was also a statistically significant difference in CGI-Severity scale score and in CGI-Improvement scale score.

Our findings suggest that the aripiprazole, which is readily available in our market could be considered more effective than risperidone in the treatment of acute mania. By considering the limitations of our study include the small sample size and the relatively short length of study duration, more studies needs to be done to clarify the effectiveness of aripiprazole compared with risperidone in the treatment of acute mania.

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AUTHORS' CONTRIBUTION

AAR, conducting the study and agreed for all aspects of the work. PH contributed in the conception of the work, design the study and agreed for all aspects of the work (adviser Postdoctoral Dissertation). FB, conducting the study,revising the draft approval of the final version of the manuscript and agreed for all aspects of the work (Supervisor Postdoctoral Dissertation). MS conducting the study, and agreed for all aspects of the work. MNM analyzing data, and agreed for all aspects of the work.

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