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Velocity of response to atypical and typical antipsychotics in the treatment of acute psychosis

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ABSTRACT

Objective: Antipsychotic drugs are the first-line therapy of psychotic disorders. The aim of this study is to compare the response rapidity of the first and second generation antipsychotics in the treatment of acute psychosis.

Methods: In a randomized, double-blind, controlled clinical trial, thirty patients with acute psychosis were randomly allocated into three groups and treated with each of the three antipsychotics: Aripiprazole, risperidone, and perphenazine. The onset of response to each drug was assessed by the Positive and Negative Symptoms Scale.

Results: Initial response was seen in 66.6 % of subjects during two weeks of intervention. The mean time of response in the risperidone group was 9.6 days, in the aripiprazole group 11.1 days, and in the perphenazine group 11.3 days. Individuals who received risperidone reached the event sooner than the other two groups.

Conclusion: The result of this trial suggested that the response rate of the proposed three drugs was equal, but the onset of action of aripiprazole was slower than risperidone and perphenazine.

Keywords: Acute psychosis, antipsychotic, onset of action, response velocity

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INTRODUCTION

Acute psychosis can be a manifestation of many psychiatric and physical conditions, which is specified with delusion, hallucination, and bizarre behavior. Psychotic symptoms require immediate attention and treatment, and treatment in the acute phase focuses on reducing severe psychotic symptoms. Schizophrenia is a severe and debilitating psychiatric disease in which pharmacological interventions are carried out to reduce the symptoms, recurrence risk, and admission to hospital.[1-3]

Antipsychotic drugs are the first-line therapy of psychotic disorders. Using antipsychotic drugs begins in the first phase and may continue for years They are classified into two groups: typical (first generation of antipsychotic, FGA) and atypical (second generation of antipsychotic, SGA).Typical drugs are dopamine receptor antagonists such as perphenazine, haloperidol, and chlorpromazine, and atypical drugs (SGA) are dopamine-serotonin receptor antagonists such as risperidone, olanzapine, quetiapine, and aripiprazole.[2-9] There is much evidence that SGA drugs compared to FGA ones lead to more improvement in negative symptoms, better performance, and lower reoccurrence and cause fewer side effects . Therefore, these drugs are nowadays used by many psychiatrists as the first-line therapy for psychosis.[10-13]

Few strong studies have focused on the comparison of the effectiveness of antipsychotics in treating acute phase of psychosis, particularly studies in which two or more atypical antipsychotics were compared with typical antipsychotics. Recently, the initial episode of schizophrenia and other psychotic disorders have been studied in Europe.[14-17] In a study carried out in Peru, the effect of some atypical antipsychotic drugs in the first episode, and psychotic among teenagers was examined.[18]In short, most studies that have focused on this issue have shown that typical and atypical drugs have similar effectiveness in treating the initial acute phase of psychosis. However, the important issue here is the response speed of antipsychotic drugs.[14-22]

Clinically, it is observed that getting an appropriate response over the first two weeks after the therapy can predict the good effect of the drug over a long-term treatment period. Although the effect of the drug on the receptors is normally seen in the first hours after taking the drug, its effects of the disease symptoms during the first day are mostly due to the sedation caused by the drug, and improvement of other symptoms normally takes one to two weeks to appear.[18-29]

A few studies have focused on the comparison of the onset of action of different antipsychotics, and most of them focused on the initial episode of psychosis. In a controlled study on the comparison of olanzapine and risperidone, it was concluded that olanzapine group led to quicker remission.[23,24] The results of a retrospective study that was carried out to examine the effects of typical and atypical

antipsychotic drugs in the initial episode of schizophrenia indicated that the effect of typical drugs appeared sooner.[18] The results of another study showed that the effects of oral-extended-release paliperidone emerged in the first week.[19] In another study; however, no difference was seen between olanzapine and risperidone.[30]

In this study, we compared the velocity of response to the three different FGAs and SGAs in the treatment of acute psychosis

METHOD

The study cases were chosen from among the patients admitted in Psychiatric Ward, Golestan Hospital (Ahvaz, Iran).

All of them had the following inclusion criteria: 1) age of between 18-60 years; 2) the onset of psychotic symptoms delusion, hallucination, thought disorder, and bizarre behavior over the last thirty days; 3) current diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, psychotic disorder due to general medical condition or psychotic disorder non-otherwise specified, according to Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision criteria; 4) a score of equal to or above four on at least two items or equal to or above five on at least one positive item of Positive and Negative Symptoms Scale (PANSS) (p_1-p_6); 5) some degree of understanding and cooperation to be able to cooperate with the researcher in conducting treatment protocol and psychometric tests.

The study's exclusion criteria were: 1) taking any antipsychotic therapy for more than seven days over the last thirty days; 2) receiving any long-acting antipsychotic over at least three last months; 3) incidence of acute psychotic symptoms regarding mood disorder; 4) pregnancy or breastfeeding for women; 5) history of allergy or severe reactions to the drugs under investigation; 6) need for simultaneous use of anticonvulsants, antidepressant or mood-stabilizing drugs; 7) having any serious medical diseases that could interrupt the patients' safe participation in the study; 8) discontinuation of cooperation or consent with the study; 9) incidence of intolerable severe side effects despite a decrease in drug dose; 10) incidence of neuroleptic malignant symptom (NMS).

The present study was a randomized, double-blind, controlled, clinical trial including three drugs. It is approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. Moreover, informed consent was obtained from all of the participants or their qualified companion.

At the screening visit, after providing demographic data, eligible subjects were randomly assigned to risperidone, aripiprazole, and perphenazine groups. The allocation involved contacting the holder of the allocation schedule who was "off-site". These interventions were followed up during two weeks.

By taking into consideration the minimum effective dose of the treatment groups, risperidone, perphenazine, and aripiprazole was prescribed with doses of 4, 24, and 10 mg, respectively.[2,32,33]

The conventional dose of an anticholinergic like biperiden was prescribed for patients under 45 years with a history of extrapyramidal side effects or incidence of extrapyramidal side effects during the study.

The positive subscales of PANSS (p_1-p_6) including 1) delusion, 2) conceptual disorganization, 3) hallucinatory behavior, excitement, 5) grandiosity, and 6) suspiciousness/persecutory were employed to analyze the drugs' onset of action.

PANSS is a standard method to analyze symptoms of schizophrenia. Its reliability ranges from 0.73 to 0.83.[34] In order to check the validity of its Persian translation, translation and back translation method was used. In so doing, PANSS was translated into Persian by two psychiatrists and then translated back to its original language by two bilingual psychiatrists. And finally, the translations were evaluated by a translation team.[32,35]

The patients were assessed in two days intervals. Infrequent assessments, when all scores reached three or below it or a reduction of 30% is obtained in the total score of the subscales of PANSS (p_1 to p_6), it was considered as the drug's onset of action.[33, 36]

RESULTS

In this section, the results of the current study are presented. In the present randomized, clinical trial, there were thirty individuals who were randomly assigned into three groups each of which consisted of ten individuals. Each group received a drug and was followed up for fourteen days. At the beginning of the study, the individuals were given a psychological test, and after 30% reduction of the initial score or when all scores reached three or below it, their time was recorded. Since the study was a randomized one, the patients of the three groups were statistically compared to their age, gender, marital status, drug dose, and diagnosis status. In order to compare the qualitative variables in the three groups, Chi-square test was used, and Kruskal-Wallis test was run to compare the quantitative variables. The reason for employing these tests was to ensure that the groups were randomized and

Table 1 Comparison of gender in the intervention groups

		Drug				
		Risperidone	Aripiprazole	Perphenazine	Total	P-value
Gender	Female	4	9	4	17	
	Male	6	1	6	13	0.034
Total		10	10	10	30	

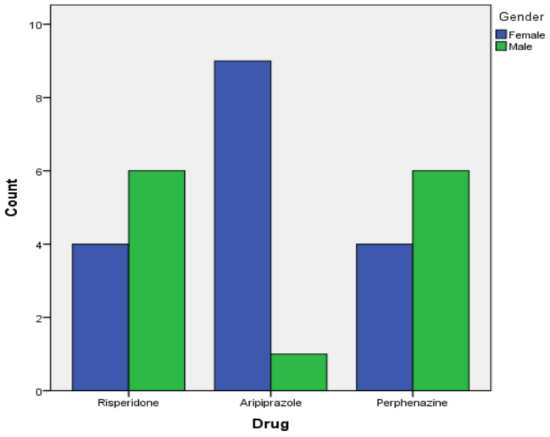
Table 2 Comparison of marital status in the intervention groups

		Drug				
		Risperidone	Aripiprazole	Perphenazine	Total	P-value
Marital status	Married	6	6	6	18	
	Single	4	4	4	12	0.999
Total		10	10	10	30	

equal to the mentioned variables. Whenever the groups were significantly different regarding a variable, that variable would be modified in a model that was fitted to compare the event time in the experiment. Kaplan-Meier tables and Cox regression were utilized to examine and compare the time of reaching the event which is 30% decrease in the initial score on the psychological test. The level of statistical significance was set at 0.05% for all tests. Data analysis was carried out using SPSS 23.0 Software.

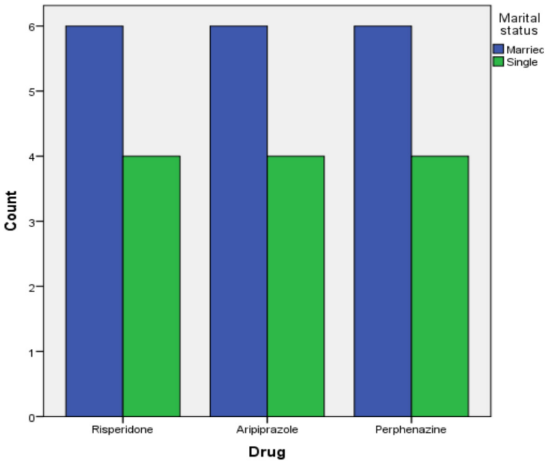
Comparison of gender in the intervention groups:

According to Table 1, out of the thirty participants in the present study, seventeen were women, and thirteen were men. In groups that received risperidone and perphenazine, out of ten patients in each group, four were women, and six were men. In the group that received aripiprazole; however, 90% of the individuals were women (n=9), and only ten percent were men (n=1). This difference led to a significant statistical difference at a level of 5%.



Comparison of marital status in the intervention groups:

According to the results presented in Table 2, out of the ten participants in all of the groups that received the drugs, six were married, and four were single, which indicates that the intervention groups were similar to their marital status. In other words, there was no significant difference among the groups regarding their marital status.



Comparison of the status of disease diagnosis in the intervention groups

As seen in Table 3, the diagnosis status was compared in the three groups that received the drugs. As seen, all of the intervention groups had paranoid schizophrenia, and there was no significant difference among the groups regarding the type of diagnosis (p>0.05).

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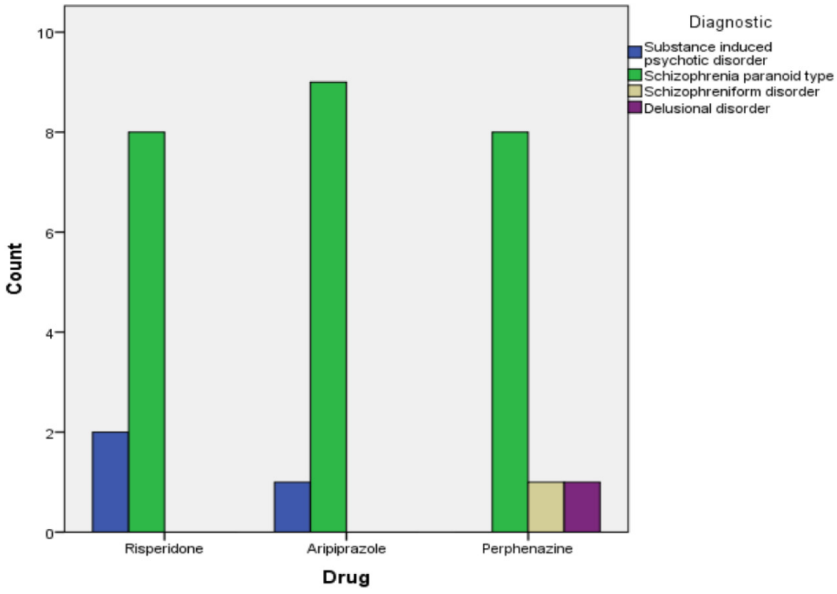
Table 3 The status of disease diagnosis in the intervention groups

		Drug			Total	P-value
		Risperidone	Aripiprazole	Perphenazine		
Diagnostic	Substance-induced psychotic disorder	2	1	0	3	0.414
	Schizophrenia paranoid type	8	9	8	25	
	Schizophreniform disorder	0	0	1	1	
	Delusional disorder	0	0	1	1	
Total		10	10	10	30	

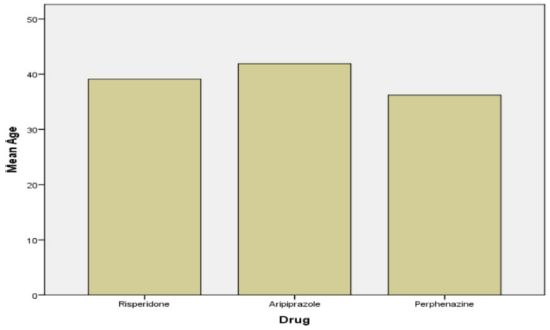
Table 4 Comparison of the participants' age in the intervention groups

Group	N	Mean	Std. Error	P-value
Risperidone	10	39.10	4.932	0.635
Aripiprazole	10	41.90	4.503	
Perphenazine	10	36.20	2.851	
Total	30	39.07	2.375	



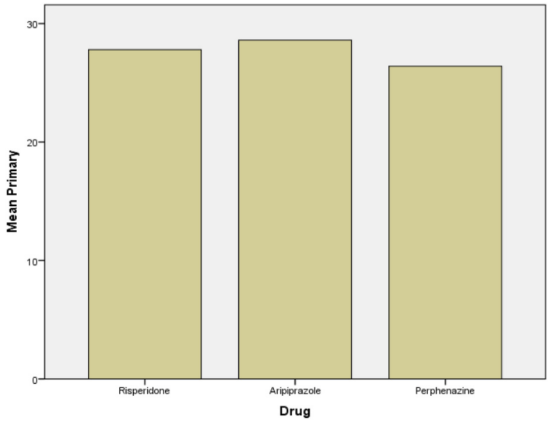
Comparison of the age of the participants in the intervention groups:

The results of the comparison of the participants' age in the three intervention groups showed that there was no significant difference among the groups in that regard (p>0.05). Although there was no difference between the three groups to their age, those that received aripiprazole had the highest mean age of almost 42 years, and those who received perphenazine had the lowest mean age of 36 years. These differences; however, were not statistically significant.



Comparison of the scores of the initial test in the intervention groups

According to the results presented in Table 6, the three intervention groups were similar regarding their scores on the initial test. On average, the individuals of the three groups had a mean score of 28, and they were not significantly different in this regard.



The effect of pharmacological intervention on the time needed for 30% reduction in the individuals' score

In the beginning, the descriptive data including the number and percentage of the individuals who did not experience the event until the end of the study (censored) and those that experienced the event were presented in a table.

According to the results presented in Table 7, in each group, ten individuals received the drugs. As seen, in the risperidone group, out of ten individuals, eight experienced a decrease of 30% in their test scores, and two did not experience it until the end of the study. In the aripiprazole group, half of the individuals did not experience the event while the other half did. And in perphenazine group, seven individuals' initial scores dropped by 30%, and three did not experience that decrease of 30%. The highest percentage of censor was 50% which was related to the aripiprazole group, and the lowest to the risperidone with 20% censor. The individuals in the perphenazine group experienced 30% censor. In total, out of the thirty participants, twenty experienced the event, and ten did not.

In this section, since there was a statistically significant difference among the three groups regarding their gender, its effect on the event time will be modified in Cox regression fitting model. Afterward, Kaplan-Meier tables and Cox regression will be employed to compare the three groups in terms of their time to reach the event, i.e. experiencing a decrease of 30% in their scores on the initial test.

According to Table 8, the mean time of 30% decrease in the individuals' score in the risperidone group was 9.6 days, in the aripiprazole group 11.1 days, and in the perphenazine group 11.3 days. Individuals who received risperidone drug reached the event sooner than the other two groups.

The participating individuals' median, i.e. the time required for at least 50% (half) of the individuals to experience the event or 30% decrease in their test scores, in the risperidone group was nine days, while it was eleven days for the other two groups.

Then, by fitting Cox regression and modifying two variables of gender which were significantly different in the groups, the event time was compared in the groups.

According to the results presented in Table 9, there was no significant difference among the groups in terms of the time required for 30% decrease in their initial scores ($p>0.05$).

Although the drugs had no significant effect on the event time, the aripiprazole group's chance was 1.7 times more than that of the perphenazine group, and the risperidone group's chance was 0.940 times more than that of the perphenazine group. The

Table 6 Comparison of the scores of the initial test in the intervention groups

Group	N	Mean	Std. Error	P-value
Risperidone	10	27.80	1.937	
Aripiprazole	10	28.60	1.470	0.683
Perphenazine	10	26.40	1.928	
Total	30	27.60	1.012	

Table 7 Case processing summary

			Censored	
Drug	Total N	N of events	N	Percent
Risperidone	10	8	2	20.0%
Aripiprazole	10	5	5	50.0%
Perphenazine	10	7	3	30.0%
Total	30	20	10	33.3%

Table 8 Means and medians for survival time

	Mean				Median			
			95% confidence interval				95% confidence interval	
Drug	Estimate	Std. error	Lower bound	Upper bound	Estimate	Std. error	Lower bound	Upper bound
Risperidone	9.600	.839	7.955	11.245	9.000	1.549	5.964	12.036
Aripiprazole	11.100	1.024	9.093	13.107	11.000			
Perphenazine	11.300	.788	9.755	12.845	11.000	2.108	6.868	15.132
Total	10.667	.532	9.624	11.709	11.000	.976	9.088	12.912

Table 9

					95.0% CI for Exp(B)	
Variables	B	SE	Sig.	Exp(B)	Lower	Upper
Risperidone	Reference group		.484			
Aripiprazole	.531	0.535	.321	1.700	.596	4.852
Perphenazine	-.062	.638	.923	.940	.269	3.282
Male into female	.409	.491	.405	1.505	.575	3.940

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perphenazine group was considered as the reference group, and the other two groups were compared with it. In other words, the results of the present study proved no difference between the three drugs to 30% decrease in the initial scores obtained by the individuals. The observed differences indicated that individuals who took aripiprazole needed to spend 1.7 more times to reach the response than those who received perphenazine. Individuals who received risperidone and perphenazine had almost chance to reach equal response.

The variable of gender had no significant effect on reaching the event; however, the men's chance in the decrease of 30% in their scores on the initial test was 1.5 times more than those of the women.

The survival diagram of the three groups that received the drugs

In the end, it can be concluded that despite modifying confounding variables, pharmacological interventions had no different effect on the 30% decrease in the scores of the initial test. In other words, the drugs were not statistically significantly different regarding the response time, but there were clinical differences among the drugs, and the results were presented in Cox regression section.

DISCUSSION

In the present study, the onset of action of atypical antipsychotics like risperidone and aripiprazole was compared to a typical antipsychotic like perphenazine in the treatment of acute episode of psychosis.

The results of previous studies showed that improvement normally began within the first two weeks after the start of antipsychotics.[22,23,32] The results of the present study indicated that the first response was significantly shorter for the risperidone group compared to the other two groups.

The results of Mousavi's study in which risperidone was compared with three antipsychotics like olanzapine and thiothixene also showed that response to risperidone was faster than the other drugs.[32]

In the study carried out by Zedkova; however, typical antipsychotics had a faster onset of action although the the difference between the drugs was not significant.[18] In our study, the mean time to reach response was 9.6 days for risperidone, 11.1 days for aripiprazole, and 11.3 days in the perphenazine group and consistent with previous studies, which showed that substantial improvement is usually seen during two weeks after using the antipsychotic.[25,26] In Mousavi's study, the time to reach response was 3.6±1.9 days for risperidone, 8.4±2.2 days for olanzapine, 6.6±2.5 days for haloperidol, and 6.2±2.9 days for thiothixene.[32] In Zedkova's study, the time to reach response was 7.1±4.1 days for risperidone and 5.9±3.8 days for perphenazine.[18] The present study was carried out on patients with an age range of 18-60 years over two weeks, and Mousavi's study focused on patients of 15-60 years over the same period of time, but Zedkova's study examined adolescents.[18]

In a study, Lambert compared risperidone and olanzapine in the initial episode of affective psychosis and showed that the latter led to a shorter response time.[24]

The study conducted by McEvoy on 400 patients with an initial episode of psychosis showed that the total decrease in PANSS scale in the three groups of quetiapine, risperidone, and olanzapine over 52 weeks was equal. However, decrease in subscales of positive symptoms was better during weeks 12 and 52 for olanzapine and week 12 for risperidone in comparison to other groups.[16]

In the present study, there was no significant difference among the three groups in terms of their response to the drugs. Moreover, in the study carried out by Kahn, there was no difference among low dose haloperidol and amisulpride, olanzapine, quetiapine, and ziprasidone to reaching the required response, and a one-year follow-up indicated a decrease of 60% in the symptoms.[37]

However, despite equal chance to reach treatment response, in our study when perphenazine was taken as the reference drug, the response time for risperidone was 0.94 times more than that of perphenazine, while this time was 1.7 times more for aripiprazole.

CONCLUSION

Analysis of the data collected in the present study showed that the response rate of the proposed three drugs was equal, but the onset of action of aripiprazole was slower than risperidone and perphenazine.

Our study had some limitations, which must be considered before generalizing the findings. We compared only three antipsychotics in our study. The small sample size was another limitation of this trial. The third limitation was in scoring the symptoms and response; we did these by only one scale. Therefore, it is recommended that samples of larger sizes, more antipsychotic and more scales should be selected in future studies.

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