

## Original Article

### Onset of action of atypical and typical antipsychotics in the treatment of acute psychosis

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#### ABSTRACT

**Objective:** Antipsychotic medications are the frontline treatment for the most psychotic disorders. The aim of this study is to compare the onset of action of the first and second generation antipsychotics and the rate of their side-effects in the treatment of acute psychosis.

**Methods:** In a double-blind, controlled clinical trial, 40 acute psychotic patients were randomly allocated in four groups and treated with each of the four antipsychotics: olanzapine, risperidone, haloperidol or thiothixene. The onset of action of each drug was assessed by the Positive and Negative Symptoms Scale. The data were analyzed by Wilcoxon (Gehan) survival and Log Rank analysis, using SPSS version 20.0.

**Findings:** Initial response was observed in 97.5% ( $N = 39$ ) of subjects during 2 weeks of intervention. The mean time to the first response was  $6.15 \pm 2.9$  days and this was significantly shorter for risperidone than others. The most common side-effects were sedation and drug induced Parkinsonism.

**Conclusion:** Risperidone represented shorter onset of action for the treatment of acute psychotic symptoms compared with olanzapine, haloperidol and thiothixene.

**Keywords:** Acute psychosis; antipsychotic; onset of action; response; side effect

## INTRODUCTION

Acute psychosis could be a manifestation of many psychiatric and medical conditions. It is characterized by delusion, hallucination and bizarre behavior.<sup>[1]</sup> In the short term, treatment objectives consist of rapid control of symptoms and to minimize the mortality and morbidity rate.<sup>[2]</sup> Adequate pharmacotherapy during the acute stage could set the stage for subsequent long-term treatment. Antipsychotic

medications are the frontline treatment for the most psychotic disorders.<sup>[3-5]</sup>

Whatever antipsychotic is chosen by the physician during the initial period, it may be continued for many years and thus it is important to take into account the long-term safety profile of the chosen drug.<sup>[6-8]</sup> There is growing evidence that most of the new "atypical" or second-generation antipsychotics (SGAs), can offer some advantages over "typical" or the first generation antipsychotics (FGAs), such as greater improvement in negative symptoms, relapse prevention, functional capacity, along with fewer extrapyramidal symptoms (EPS).<sup>[9]</sup> Accordingly, many clinicians prescribe these new antipsychotics as the first-line agents.<sup>[10-13]</sup> However, these advantages, thus far, have been regarded as incremental and not necessarily substantial. In addition, concerns about side effects such as EPS

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have been replaced by other distressing side-effects, including weight gain, hyperglycemia and dyslipidemia. Studies specifically comparing the SGAs with the FGAs for first-episode schizophrenia have had mixed results, with small or limited advantages to secondary outcomes for SGAs.<sup>[14-19]</sup>

Few adequately powered studies have focused on the comparative effectiveness of antipsychotics in the treatment of acute psychosis. Especially informative about this issue are the large head-to-head trials of two or more atypicals with a typical antipsychotic comparator, similar to the recent Clinical Antipsychotic Trials of Intervention Effectiveness study, the European First Episode Schizophrenia Trial study, the Comparison of atypicals in First-Episode psychosis study and head-to-head comparisons of each atypical and typical antipsychotic drugs.<sup>[20-23]</sup> Briefly, these studies showed that atypicals appear to have similar effectiveness to typical.<sup>[20-23]</sup> However a central question is the speed of onset of the antipsychotic response. At a clinical level, the greatest rate of improvement is in the first 2 weeks of treatment that may predict the effectiveness of the drug for a given individual, in long term use.<sup>[24,25]</sup> The stable dopamine D2 receptor blockade can be achieved within hours after drug administration and the onset of the antipsychotic effect within the 1<sup>st</sup> day; but this effect is distinguishable from the behavioral sedation. Moreover, the other improvement of symptoms usually appears 1-2 weeks later.<sup>[24-27]</sup> Clinicians may not “see” the early treatment response during this period, because it does not cross their threshold of clinical noticeable improvement, although the same clinician may rates that improvement on a scale.<sup>[26]</sup>

Few studies have compared the onset of antipsychotic effects of the different antipsychotics in the treatment of acute psychosis and the results are controversial. In a controlled study comparing olanzapine versus risperidone, a somehow shorter time were needed to reach the remission in olanzapine group.<sup>[28]</sup> In a controlled study comparing ziprasidone with risperidone, both agents equally improved psychotic symptom.<sup>[29]</sup> Another clinical trial compared haloperidol with olanzapine showed that two drugs didn't have statistically different level of improvement after 24 h of treatment.<sup>[30]</sup> An open-label trial, compared the ziprasidone with haloperidol, showed significantly more tolerability and effectiveness of ziprasidone in reducing the symptoms of acute psychosis.<sup>[31]</sup> Finally in another study onset of the action of antipsychotics was compared, which revealed that typical antipsychotics have faster onsets of action than atypical ones.<sup>[32]</sup>

In this study we compared the onset of action and the rate of side-effects of four different FGAs and SGAs in the treatment of acute psychotic episode.

## METHODS

Subjects were chosen from admitted patients in the psychiatric ward of Noor Hospital (Isfahan, Iran). All subjects met the following inclusion criteria: (1) 15-60 years aged; (2) Onset of psychotic symptoms (delusion, hallucination, thought disorder or bizarre behavior) during recent 30 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 at least four on at least two of the positive subscales, or at least five on at least one of the positive subscales (P1-P6) of the Positive and Negative Symptoms Scale (PANSS);<sup>[33]</sup> (5) Written informed consent. Subjects also met none of the following exclusion criteria: (1) Any serious medical condition that may interfere with safe study participation; (2) receiving any antipsychotic treatment for more than 7 days during the last 30 days; (3) receiving any long acting antipsychotic during last 3 months; (4) incidence of acute psychosis in the context of mood disorders; (5) pregnancy or nursing in women; (6) history of severe drug adverse reaction; (7) simultaneous use of anticonvulsants, antidepressants or mood stabilizer drugs.

This study is a randomized, double-blind, controlled clinical trial with four active medication conditions, carried out on year 2013 and has been registered on Iranian Registry of Clinical Trials with identifier Number IRCT201305177841N3. The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee of the Isfahan University of Medical Sciences. All the participants provided written informed consent. The eligible subjects were randomly assigned to olanzapine, risperidone, haloperidol and thiothixene groups. The intervention duration last 2 weeks and the drugs administrated with doses equivalent to 300 mg of drug chlorpromazine;<sup>[34]</sup> i.e., 4 mg of risperidone, 10 mg of olanzapine, 15 mg of thiothixene and 5 mg of haloperidol. Conventional dose of an anticholinergic drug (Biperiden) prescribed for subjects <45 years old, with previous extrapyramidal side effects, or incidence of extrapyramidal side effects (acute dystonia, Parkinsonism, akathisia) during study.

We used positive subscales of PANSS (P1-P6; Delusion, Conceptual disorganization, hallucinatory

behavior, excitement, grandiosity and suspiciousness/persecution) for assessing the onset of action of the drugs. PANSS is a standard measure for assessing symptoms of schizophrenia and its reliability is 0.73-0.83.<sup>[35]</sup> The translation and back-translation method was used to make the Persian translation of PANSS valid. PANSS was translated by two psychiatrists to Persian and then two other bilingual psychiatrists translated the same text to first language. Translated texts were evaluated by the translation team for final decision.<sup>[36]</sup> The subjects were assessed with 2 days intervals. In the subsequent assessments, score of at least three in all of positive subscales or decline of equal or more than 30% in total score of positive subscales (P1-P6) accounted as the determinant of the onset of action of the drugs.<sup>[15]</sup> The complete blood count, electrocardiography, aspartate transaminase, alanine transaminase, fasting blood sugar, blood pressure, body weight and body mass index of the subjects were assessed at the first screening and the last visits. In each subsequent visit, we also assessed drug side-effects, by using the Abnormal Involuntary Movement Scale-National Institute of Mental Health scale for EPS,<sup>[37]</sup> and checking for the other side-effects such as sedation, blurry vision, dry mouth, constipation, urine retention and rash.

Randomization was generated by a third party physician using tables of random numbers. Care providers and physician assessing outcomes were blinded for each other works and results.

We used Wilcoxon (Gehan) survival analysis and Log Rank analysis for comparing mean time to first response in four treatment groups. Paired-samples *t*-test was used for measuring decline in score of PANSS and Pair wise comparison with Fisher exact test was performed for comparing the rate of different side-effects. All analyzes were performed using Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA) and a *P* < 0.05 was considered as statistically significant for all analyses.

## RESULTS

A total of 68 patients screened and 41 met all inclusion and no exclusion criteria, which allocated randomly into the four intervention groups [Figure 1]. The mean age of participants was 31.65 years (range, 22-43 years). The demographic and clinical features of the sample are tabulated in Table 1. There were no statistically significant differences on demographics or disorders type between intervention groups. All of the participants received anticholinergic drug (Biperiden 2 mg 3 times/daily).

Clinical response was observed in 97.5% (*N* = 39) of subjects within 2-weeks study and only one subject (in olanzapine group) did not respond after 14 days. The total mean time to first response was 6.15 ± 2.9 days. The mean time to first response was significantly different between four groups (*P* < 0.003) [Figure 2 and Table 2]. Log Rank analysis showed that the mean time to first response in risperidone group was significantly <3 other groups; although was not significantly different between these three groups [Table 3].

Paired *t*-test showed significant decline in score of PANSS subscales (P1-P6) in four groups. The comparison of mean percentage of decline was not significantly different in P1 (Delusion), P2 (Conceptual Disorganization), P3 (Hallucinatory Behavior), P5 (Grandiosity), and P6 (Suspiciousness/Persecution) between four groups. In P4 (Excitement), the mean percentage of decline in risperidone group was less than haloperidol and thiothixene groups significantly (*P* = 0.02).

The most frequent side effects were sedation (9 cases) and drug induced Parkinsonism (8 cases). Patients with EPS (Parkinsonism, Akathisia, Acute dystonia). Side-effects that were elicited at any time during the trial in all subjects are listed in Table 4. Between-group

**Table 1: Demographics and clinical characteristics of the studied subjects (n=40)**

Characteristics	Olanzapine N=10	Risperidone N=10	Haloperidol N=10	Thiothixene N=10	<i>P</i>
Sex					0.849
Male	6 (60)	5 (50)	5 (50)	4 (40)	
Female	4 (40)	5 (50)	5 (50)	6 (60)	
Mean (SD) of age (years)	31.70 (4.9)	30.30 (4.0)	34.50 (6.7)	30.10 (6.0)	0.272
Disease type					0.496
Schizophrenia	7 (70)	3 (30)	3 (30)	4 (40)	
Substance induced psychotic disorder	2 (20)	2 (20)	1 (10)	2 (20)	
Schizoaffective	1 (10)	3 (30)	4 (40)	2 (20)	
Psychotic disorder NOS	0 (0)	2 (20)	2 (20)	2 (20)	

All variables are presented as number (%), unless otherwise indicated. SD=Standard deviation, NOS=Not otherwise specified

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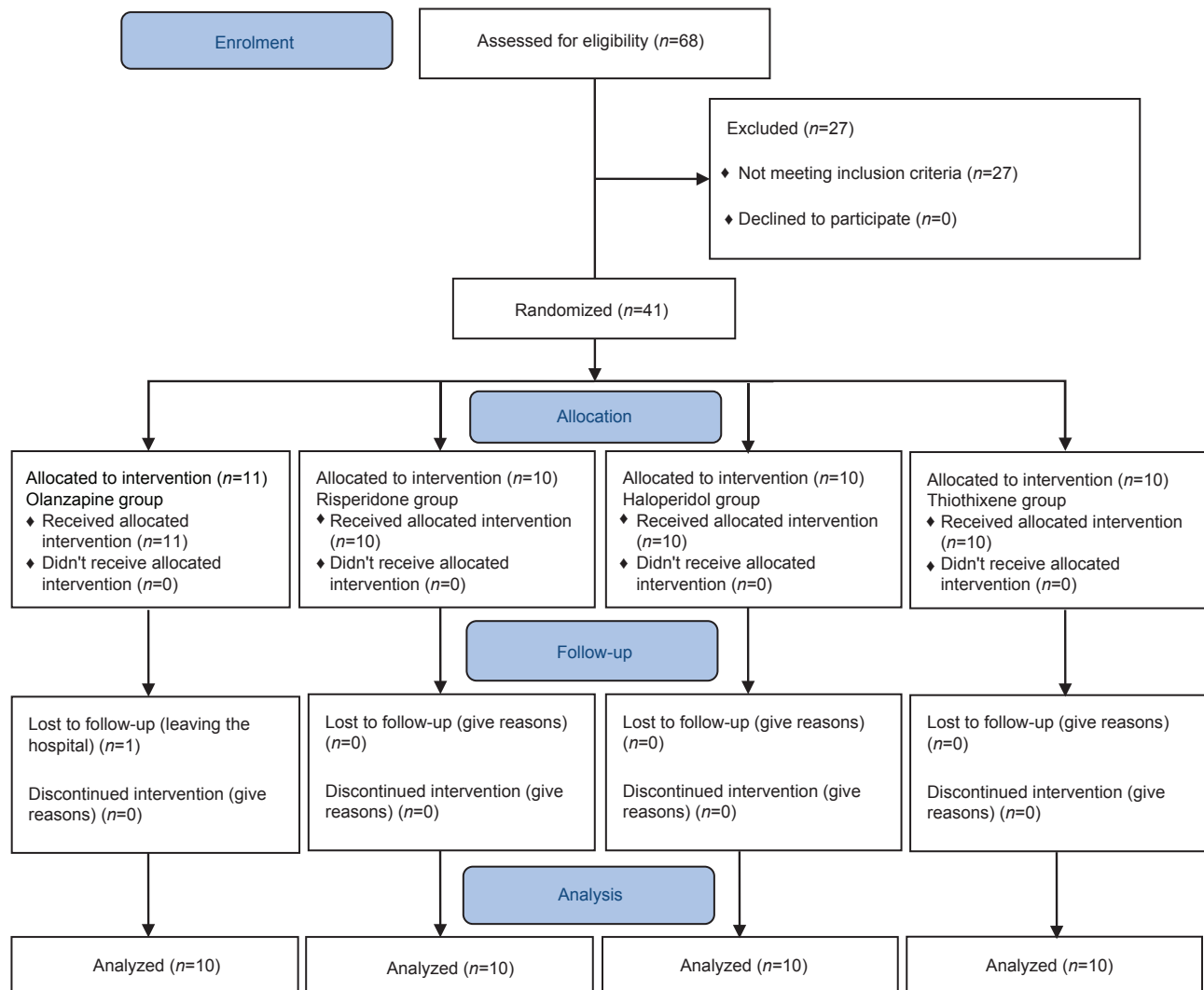


Figure 1: Study design flow chart

Table 2: Wilcoxon (Gehan) survival analysis to compare mean of time to first response in four groups

Groups	Mean±SD (day)	Min, Max (day)	P
Olanzapine	8.44±2.2	6, 12	
Risperidone	3.60±1.9	2, 6	
Haloperidol	6.60±2.5	2, 10	
Thiothixene	6.20±2.9	2, 10	
Total	6.15±2.9	2, 12	<0.003

SD=Standard deviation

comparisons of maximal EPS demonstrated more frequent symptoms in the haloperidol group ( $P = 0.001$ ). Furthermore in risperidone group, EPS were significantly more than olanzapine and thiothixene groups ( $P = 0.04$ ).

Pair wise comparison of groups for side-effects was carried out using Fisher exact test with adjusting of  $P$  value. The incidence of sedation in olanzapine

Table 3: Log rank pair wise analysis of mean time to first response comparisons in four groups

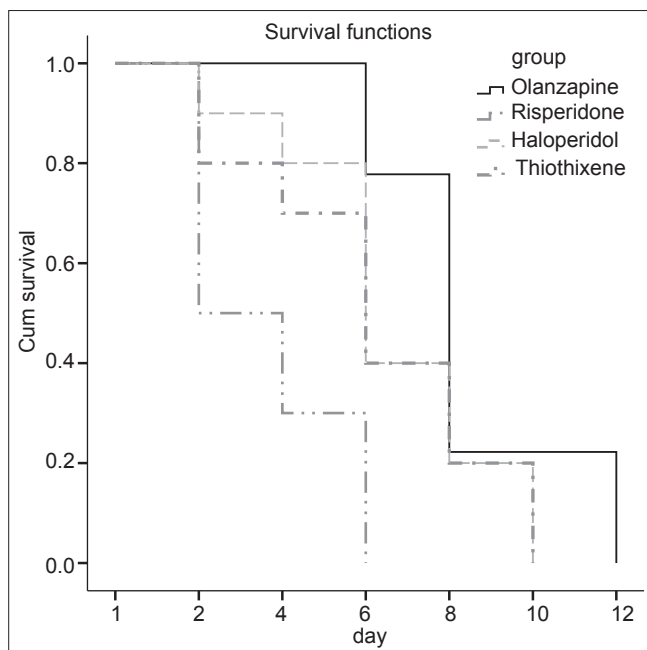
Groups	P
Risperidone versus olanzapine	<0.001
Risperidone versus haloperidol	0.007
Risperidone versus thiothixene	0.021
Olanzapine versus haloperidol	0.100
Olanzapine versus thiothixene	0.089
Haloperidol versus thiothixene	0.859

group was significantly more than haloperidol group ( $P = 0.04$ ). The weight gain in olanzapine group was significantly more than haloperidol and thiothixene groups ( $P = 0.04$ ); Also it was more in atypical group (Olanzapine, Risperidone) than typical group (Haloperidol, Thiothixene), significantly ( $P = 0.035$ ). Other side-effects were acute dystonia, akathisia, blurred vision, dry mouth, constipation and rash which did not differ significantly between groups.

**Table 4: Elicited side effects of treatment**

Side effects	Olanzapine N=10	Risperidone N=10	Haloperidol N=10	Thiothixene N=10
Sedation	4 (40)	2 (20)	1 (10)	2 (20)
Parkinsonism	1 (10)	2 (20)	4 (40)	1 (10)
Weight gain	3 (30)	1 (10)	0 (0)	0 (0)
Akathisia	0 (0)	2 (20)	2 (20)	0 (0)
Constipation	1 (10)	1 (10)	0 (0)	1 (10)
Blurry vision	1 (10)	1 (10)	0 (0)	0 (0)
Dry mouth	1 (10)	0 (0)	0 (0)	1 (10)
Rash	0 (0)	0 (0)	1 (10)	0 (0)
Acute dystonia	0 (0)	0 (0)	1 (10)	0 (0)

All variables are presented as number (%)

**Figure 2:** Time to the first response in four treatment groups

## DISCUSSION

This study compared the FGAs and SGAs about the onset of action and the frequency of side-effects in the treatment of acute psychotic episode. The first clinical response was achieved in almost all of the patients within 2 weeks, which is consistent with many of the current opinions that the different typical and atypical antipsychotics have similar effectiveness.<sup>[20-23]</sup> In this study, the mean time for reaching the first response was nearly like the Zedkova findings, i.e. 6.9 ( $\pm 4.2$ ) days for the atypical antipsychotics and 5.8 ( $\pm 3.5$ ) days for the typical antipsychotic;<sup>[32]</sup> and consistent with previous studies, which showed that substantial improvement is usually seen 1-2 weeks after using the antipsychotic.<sup>[24,25]</sup>

The results provide preliminary evidence that the mean time to first response was significantly shorter

for risperidone, comparing to the three other drugs. The Zedkova study showed although the differences among drugs were not significant, but the typical antipsychotics have somehow faster onsets of action than atypical antipsychotic drugs.<sup>[32]</sup> Our study performed on 15-60-year-old patients and only on 2 weeks, however Zedkova studied only adolescent patients. Lambert, in study of comparing risperidone with olanzapine in the treatment of the first episode of the affective psychosis showed somehow shorter time to reach the treatment response with olanzapine.<sup>[28]</sup> This study was open and retrospective and the difference was not significant. Hence, we think our study showed a new significant finding in the velocity of action of the risperidone compared with the other antipsychotics and this must be trialed in future studies, more.

Our study showed that in risperidone group the mean percentage of decline in PANSS P4 (Excitement) component was lower than haloperidol and thiothixene groups, but in a study for treatment of acute psychotic agitation, Lim concluded that there was not any significant group difference between risperidone and haloperidol groups.<sup>[38]</sup>

The sedation and drug induced Parkinsonism were the most frequent side effects. The EPS were more frequent in the haloperidol group, as in the Sikich study.<sup>[39]</sup> Moller also found that there is a significantly higher prevalence of EPS with haloperidol than with risperidone.<sup>[40]</sup> The weight gain was significantly more with atypical antipsychotics (Olanzapine, Risperidone) than with typicals (Haloperidol, Thiothixene) in our study. However, Sikich found the sedation and EPS as the primary side effects with risperidone, olanzapine and haloperidol.<sup>[39]</sup> This difference may relate to the different study populations, i.e. Sikich study was on 8-19-year-old children. There were not significant differences between the frequency of each EPS (Parkinsonism, Akathisia, Acute dystonia) with haloperidol, and risperidone, but when comparing all the EPS as a single variable, the prevalence was

significantly higher in haloperidol group. Likewise, McEvoy did not find any significant difference between olanzapine, quetiapine and risperidone in the treatment of early psychosis.<sup>[22]</sup>

Our study had some limitations, which must be considered before generalizing the findings. We compared only four antipsychotics in our study, although these are the most commonly used in our country and most of the other related studies compared less than these in one randomized controlled trial. The second limitation was in scoring the symptoms and response; we did these by only one scale. Comparing only ten patients in each group may somehow be considered as another limitation.

Briefly, we found that the mean time for reaching the first response in the treatment of psychosis with each of the typical or atypical antipsychotics is about 1 week and this was shorter with risperidone than with others. Considering side effects, the atypical antipsychotics caused more sedation and weight gain while in typicals haloperidol caused more EPS than others. Future trials with more antipsychotic, more patients, more scales and in other settings may guide the practitioners to more reliable conclusion.

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## AUTHORS' CONTRIBUTION

Dr. Mousavi contributed in concepts, design and definition of intellectual content, literature search, data acquisition, manuscript preparation and review. Dr. Rostami contributed in concepts, design, definition of intellectual content, and data acquisition. Dr. Sharbafchi contributed in concepts, design and definition of intellectual content, literature search, manuscript preparation, and correspondence. Dr. Saeidi boroujeni contributed in concepts, design, definition of intellectual content and literature search. Dr. Mahaki contributed in concepts, design and definition of intellectual content, data analysis and statistical analysis.

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