

Haloperidol Versus Risperidone: A Comparison of Beneficial Effect on Cognitive Function of Patients With Chronic Schizophrenia

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Objective: The current study was performed to evaluate the cognitive improvements of the chronic schizophrenic patients treated with risperidone in comparison with those treated with haloperidol according to Wisconsin Card Sorting Test (WCST).

Methods: In a double blind clinical trial, 65 patients with a diagnosis of chronic schizophrenia were randomly allocated into two groups. They received a 7 days washout and then during an eight weeks period one group was treated with risperidone 4-8 mg daily while patients in the other group received haloperidol 10-15 mg daily. Patients of the two groups were assessed by positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Patients' cognitive abilities were assessed by WCST. Treatment side effects were also evaluated in both groups.

Results: The overall PANSS score, the scores of the positive and negative subscales and BPRS scores revealed that risperidone was significantly superior to haloperidol in the treatment of psychotic symptoms ($p < 0.001$). Risperidone caused less marked dyskinetic side effects in comparison with haloperidol ($p < 0.001$). Haloperidol produced more symptoms of parkinsonism and tardive dyskinesia than risperidone. The positive cognitive effect of risperidone was significantly better than haloperidol at 4th ($p < 0.001$) and 8th ($p < 0.001$) weeks.

Conclusion: Apart from being more effective in improving positive and negative symptoms of psychotic disorders, risperidone is also more beneficial in reducing the symptoms of cognitive impairment in chronic and long standing form of schizophrenia. It also seems to be better tolerated than haloperidol.

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Introduction

Schizophrenia is a severe, incapacitating and often chronic psychiatric disorder that accounts for 20% of all chronic medical disabilities. It affects 1 % of the population worldwide, and occurs with equal frequency in men and women. The disease usually develops in early adulthood, and lasts for at least several decades in 75% of patients, at huge economic cost to society. In the UK, the total direct healthcare costs attributable to schizophrenia in 1994 were £ 397 million, 1.6% of the total healthcare budget (1), whilst total costs are around £ 2.6 billion (2). Compared with other functional psychoses,

schizophrenia still has the poorest outcome and is often used as a proxy for more severe and enduring form of psychotic illnesses.

Schizophrenia manifests itself as a diverse range of severe psychosocial symptoms; these can be divided into positive symptoms, which include hallucinations, delusions and thought disorder, and negative symptoms, which include blunted emotions, social withdrawal and a reduction in spontaneous behavior. Together these symptoms often result in serious suicidal tendencies. Indeed, 10-15 % of patients with schizophrenia die by suicide (3). Conventional antipsychotics, such as haloperidol, are generally effective in controlling positive symptoms of schizophrenia, but have minimal efficacy against negative symptoms. These antipsychotics have the added disadvantage of causing a range of severe side effects, most notably extrapyramidal symptoms (EPS), which makes many patients unwilling to take these medications for any

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length of time. Haloperidol might be the most widely used conventional antipsychotic worldwide that is more effective on positive symptoms than negative ones such as the cognitive impairments (4).

Since the introduction of Clozapine, several atypical antipsychotics, including olanzapine, risperidone and sertindole, have been developed. These drugs provide improved efficacy against both the positive and negative symptoms of schizophrenia and carry a much lower risk of causing the severe and unpleasant side effects associated with conventional antipsychotic agents. The superior efficacy and safety profiles of the atypical antipsychotic drugs compared with conventional agents stem from differences in their receptor binding affinities (5-8).

As a new class of antipsychotics, the atypical agents are frequently grouped together, with efficacy and safety being reported for the group as a whole. It can certainly be said that the atypical antipsychotics as a class of drugs improve the quality of life of schizophrenic patients, and offer substantial advantages over conventional treatments (9). In USA, risperidone is a Food and Drug Administration (FDA) approved atypical antipsychotic that is a benzisoxazole derivative with potent serotonin-5HT₂ antagonistic activity. It has affinity for the D₂, Alpha-1 and Alpha-2 adrenergic, and H-1 receptors. Risperidone appears to have a favorable effect on both positive and negative symptoms (10-12) and induces less extrapyramidal symptoms in comparison with Haloperidol at therapeutic dosage (12, 13).

This study was carried out to compare the cognitive improvements of the chronic schizophrenic patients treated with risperidone with those treated with haloperidol.

Materials and Methods

In a double blind clinical trial, 65 consenting male patients, aged 23 to 65, with a DSM-IV diagnosis of chronic schizophrenia, who were admitted to Ebne-Sina psychiatric hospital of Mashhad University of Medical Sciences, were

selected. None had a diagnosis of mental retardation. They all had normal neurological examination, routine laboratory test results and normal ECG. In order to go through a washout period, their previous medication was stopped one week prior the trial. They were then randomly allocated into two groups of 30 and 35 patients; the first group received haloperidol and the second received risperidone for a period of eight weeks. They did not receive any other antipsychotic. Neither did they receive a depot antipsychotic. Some patients only received a benzodiazepine for sedation as needed. Anticholinergic medications were administered for parkinsonian symptoms or acute dystonic reaction.

Patients in risperidone group received an initial dose of 2 mg daily and titrated up to 4 mg daily after 2-3 days. Since there were two brands of risperidone available, 20 patients received the brand that was produced in Iran (2 mg tablets, Bakhtar Shimi brand) and the others received the brand that was imported from abroad as Risperdal. Since some patients did not respond properly to dose of 4 mg, after two weeks the dose was increased to 6 mg daily, and in some to 8 mg daily. Patients in the haloperidol group received the starting dose of 5 mg daily that was increased by another 5 mg daily every other day and reached the final dose of 10-15 mg daily.

For evaluation of the improvement of positive and negative symptoms of the patients, Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) were used in the beginning and after 8 weeks of treatment. Patients were also assessed by Wisconsin Card Sorting Test (WCST) for the evaluation of any improvement in cognitive ability in the beginning of the study, at 4th and 8th weeks of the treatment.

Tardive dyskinesia was assessed by completing Abnormal Involuntary Movement Scale (AIMS) in every patient before starting the study and at 8th week. Other side effects such as agitation, anxiety, insomnia, nausea, headache and extrapyramidal symptoms were also evaluated in all patients. The data were then analyzed using Chi square and ANOVA test by SPSS 11.00 statistical software.

Results

The age of the onset of the disease in patients was between 15 to 30 years, and the age of the first hospitalization was between 17 to 35 years. Most patients belonged to age group of 33 to 42 years (24 patients, 40.3%). Twenty three patients (39%) were 43 to 52 years old. Most of the patients were the first born child of the family (25 people, 42%). Most of the patients (38 people, 58.5%) were single and 57 (87.7%) had no occupation. Most of the patients had left education after finishing primary school (18 people, 27.7%).

The number of previous hospitalizations was between 5 to 35 times and the duration of hospitalizations was between 1 to 20 years. All of the patients were men and all had the DSM-IV criteria for a diagnosis of chronic schizophrenia; 41 (63%) with a diagnosis of paranoid type, 13 (20%) undifferentiated and 8 (12%) disorganized. Three people (5%) had a diagnosis of residual schizophrenia. There were no statistically significant differences between the two groups regarding the basic and demographic data ($p=0.05$).

Average total PANSS score in the beginning of the study was 92.8 and 95.4 in risperidone and haloperidol groups respectively. Total PANSS score in the beginning of the study had no statistical association with age, marital situation, and level of education ($p=0.05$).

There was no statistical difference between the two groups with regard to the side effects of agitation ($P=0.332$) and anxiety ($P=0.290$). There was also no difference between the two groups regarding the side effects of headache, nausea, and insomnia. As regards the extrapyramidal side effects (EPS), the symptoms were observed in fewer number of patients in risperidone group (4 people, 6.2%) than haloperidol group (12 people, 18.5%) ($p=0.007$) (Table 1). Based on total AIMS scores, tardive dyskinesia was also observed more in those treated with haloperidol than those treated with risperidone (1.6 for haloperidol, 0.36 for Risperdal, and 0.75 for Iranian brand risperidone) (Table 1).

Based on WCST, at 4th week there was significantly higher Preservation Error (PE) mean score for haloperidol group than

risperidone one ($p<0.001$) (Table 2). There was also an obvious difference between the two groups in WCST at 8th week ($p<0.001$); as PE mean score for haloperidol group was about two times higher than the same mean score in risperidone group (Table 2). In risperidone group, neither at 4th week nor at 8th week, there was no statistically significant difference between the PE mean scores of those treated with Iranian brand risperidone and those treated with the brand coming from abroad (Risperdal).

Table 1. Side effects of risperidone and haloperidol

Side effect	Risperedon	Haloperidol	P
Agitation	3	5	0.32
Anxiety	2	4	0.29
Headache	3	5	0.33
Nausea	5	7	0.54
Insomnia	13	17	0.14
Extrapyramidal Effects	4	12	0.0077
AIMS Tardive dyskinesia	0.55	1.6	0.015

Table 2. PE[†] mean scores in WCST[‡] at different stages of the study

	Risperidone	Haloperidol	P
Baseline	48.8 ± 11.4	50.1 ± 13.1	NSS§
4 th week	30.7 ± 7.6	48.3 ± 9.3	0.014
8 th week	21.7 ± 6.7	43.9 ± 8.9	0.000

† Preservation Error

‡ Wisconsin Card Sorting Test

§ Not Significant

The improvement in BPRS scores from baseline was also better in risperidone group in comparison with haloperidol one ($p<0.001$) (Figure 1). The mean changes of the total PANSS score from the baseline were much higher for risperidone group in comparison with haloperidol group ($p<0.001$) (Table 3).

Table 3. PANSS[†] scores at different stages of the study

	Haloperidol mean±SD	Risperidone mean±SD	t	P
Baseline:				
Total	95.3	95.6	0.98	NS
Positive	25.3	24.8	1.1	NS
Negative	25	24.8	0.101	NS
GPS [‡]	45.5	45.8	0.86	NS
8th Week:				
Total	86.1	71.3	4.52	0.000
Positive	21.3	18.2	3.04	0.000
Negative	22.1	19.2	3.43	0.000
GPS	41.7	34.5	4.76	0.000

†Positive and negative syndrome scale

‡ General Psychopathology Scales

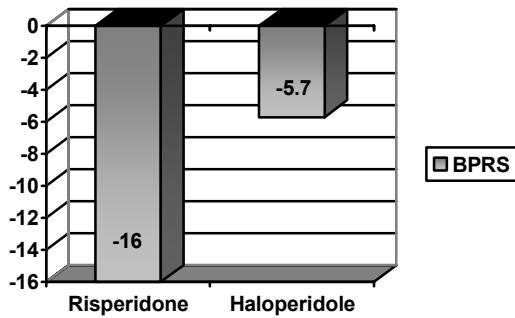


Figure 1. Change in BPRS mean scores from the baseline in the two groups of risperidone and haloperidol.

There was also no statistical association between the total PANSS at 8th week and age, marital status, and level of education of the patients. Neither was there any association between the positive subscales score and age, marital status, and level of education of the patients in the beginning of the study and in 8th week. Also there was a significant decrease in positive symptoms in the married patients in comparison with the singles ones. This indicates a better prognosis and response to treatment in married people. Positive subscale also showed more reduction in risperidone group (average score: 18.2) in comparison with haloperidol group (average score: 21.3) ($p < 0.001$) (Table 3).

There was also a statistically significant difference in the negative subscale scores between the two groups of risperidone and haloperidol at the end of study; the average score was 19.2 for risperidone and 22.1 for haloperidol group ($p < 0.001$) (Table 3).

There was no association between the negative subscale scores and age or marital status but it was higher in people with lower education level at the beginning of the study ($p < 0.00$). This finding might be attributed to the deteriorative effects of negative symptoms on educational progress.

No association was found between the General Psychopathology Scales (GPS) score and the age, marital status, and educational level of the patients in both the beginning and end of the study. Nonetheless, there was a clear and significant difference between the two groups in GPS score at 8th week; the average score was 34.5 for risperidone and

41.7 for haloperidol group ($p < 0.001$).

Discussion

Our study shows that, although both haloperidol and risperidone can improve active symptoms of schizophrenia, the rate of improvement with haloperidol is significantly lower than risperidone. In recent years studies on effectiveness of atypical antipsychotic drugs have been quite popular, although their outcomes have yielded different results. Some studies were similar to our study and showed better effect of atypical antipsychotic drugs on schizophrenic patients (14-16). Some other studies showed that haloperidol had the same effect as atypical antipsychotic drugs (17-22). However, atypical antipsychotic drugs have been shown to have other beneficial effects. For instance, in one study, although the rate of recurrence of psychosis in patients was similar in both groups of typical and atypical antipsychotics, symptoms recurred earlier in patients treated with typical antipsychotic drugs (17). Another study showed that recurrence rate is higher with haloperidol than risperidone (20). Some studies were also concerned with the speed in which the drug treated and controlled the symptoms. These studies showed an earlier patients response to risperidone than to conventional antipsychotic drugs (23). In our study, review of drug side effects showed that extra pyramidal side effects were more common in haloperidol treated patients than those treated with risperidone. Other studies have shown the same result; that side effects occur less frequently with atypical antipsychotic drugs than haloperidol. These studies revealed that atypical drugs were better tolerated than the typical antipsychotics in long-term (14-16, 18-21, 24-25).

Cognitive impairment in schizophrenia is very important and has a relationship with drug compliance and rehabilitation programs (26). Our research, similar to previous studies (26-31), shows that risperidone is more effective in improving cognitive symptoms of schizophrenia than haloperidol. In a recent study, cognitive abilities of 95 healthy individuals were compared with 68

schizophrenic patients (28). The cognitive status was worse in schizophrenic patients. This study showed that overall improvement in cognitive symptoms was better when patients were treated with risperidone rather than haloperidol (28).

Another study showed that risperidone causes functional improvement in episodic memory, verbal fluency, vigilance, executive functioning, and visio-motor speed, but haloperidol could only improve the function of episodic memory, vigilance, and visio-motor speed (30). It appeared that risperidone had a wider beneficial effect on cognitive dysfunction than haloperidol. However a recent study did not confirm the preferentiality of risperidone vs. haloperidol on cognitive symptoms based on mini mental status examination (32).

The findings of our study are limited due to a relatively small sample size, and selection of only male and seriously ill patients (hospitalized patients). Our study also compared only one area of the cognitive impairment (PE) in patients with schizophrenia.

Conclusion

Our study confirms the findings of the previous research projects in showing that, apart from being more effective in improving positive and negative symptoms of psychotic disorders, atypical antipsychotic (risperidone) is also more beneficial in reducing the symptoms of cognitive impairment in chronic and long standing form of schizophrenia. It also seems to be better tolerated than typical antipsychotic (haloperidol) by the patients.

References

1. Davies LM, Drummond MF. Economics and schizophrenia: the real cost. *Br J Psychiatry* 1994; 25 suppl 1: 18-21.
2. Knapp M. Cost of schizophrenia. *Br J Psychiatry* 1997; 171: 509-18.
3. Kaplan HI, Sadock BJ, editors. *Synopsis of Psychiatry, Behavioral Sciences/Clinical Psychiatry*. Philadelphia:

- Lippincott Williams and Wilkins; 1998. p. 457-89.
4. Buchanan RW, Carpenter WT. Concept of Schizophrenia. In: Sadock BJ, MD and Sadock VA, MD editors. *Kaplan and Sadock's Comprehensive textbook of psychiatry*. Philadelphia: Lippincott Williams and Wilkins; 2005. Vol. 2. p. 1329-45.
5. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D1, D2 and serotonin pKi values. *J Pharmacol Exp Ther* 1989; 251: 238-46.
6. Nyberg S, Nordström A-L, Halldin C, Farde L. Positron emission tomography studies on D2 dopamine receptor occupancy and anti-psychotic drug plasma levels in man. *Int Clin Psychopharmacology* 1995; 10 suppl 3: 81-5.
7. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. *Neuropsychopharmacology* 1998; 18(2): 63-101.
8. Kasper S, Tauscher J, Kufferle B, Barnas C, Hesselmann B, Asenbaum S, et al. Sertindole and dopamine D2 receptor occupancy in comparison to risperidone, clozapine and haloperidol: a 123 I-IBZM SPECT study. *Psychopharmacology* 1998; 136: 367-73.
9. Kasper S. How much do novel antipsychotics benefit the patients? *Int Clin Psychopharmacol* 1998; 13 Suppl 3: S71-7.
10. Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, et al. A Canadian multi center placebo controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J. Clin. Psychopharmacol* 1993; 13: 25-40.
11. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994; 151: 825-35.
12. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind,

- parallel-group study versus haloperidol. *Br J Psychiatry* 1995; 166: 712-26.
13. Heck AH, Haffmans PM, de Groot IW, Hoencamp E. Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: a double blind, multi center trial. *Shizophrenia Research* 2000; 46: 97-105.
 14. Hunter RH, Joy CB, Kennedy E, Gilbody SM, Song F. Risperidone versus typical antipsychotic medication for schizophrenia. *Cochrane Database Syst Rev* 2003; (2): CD000440.
 15. Dossenbach M, Erol A, el Mahfoud KM, Shaheen MO, Sunbol MM, Boland J, et al. Effectiveness of antipsychotic treatments for schizophrenia: interim 6-month analysis from a prospective observational study (IC-SOHO) comparing olanzapine, quetiapine, risperidone, and haloperidol. *J Clin Psychiatry* 2004; 65(3):312-21.
 16. Yen YC, Lung FW, Chong MY. Adverse effects of risperidone and haloperidol treatment in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28(2): 285-90.
 17. de Sena EP, Santos-Jesus R, Miranda-Scippa A, Quarantini LC, Oliveira IR. [Relapse in patients with schizophrenia: a comparison between risperidone and haloperidol.] *Rev Bras Psiquiatr* 2003; 25(4): 220-3. Portuguese.
 18. Marder SR, Glynn SM, Wirshing WC, Wirshing DA, Ross D, Widmark C, et al. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *Am J Psychiatry* 2003; 160(8):1405-12.
 19. Gothelf D, Apter A, Reidman J, Brand-Gothelf A, Bloch Y, Gal G, et al. Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. *J Neural Transm* 2003; 110(5): 545-60.
 20. Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, Kopala L, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. *Am J Psychiatry* 2005; 162(5): 947-53.
 21. Crespo-Facorro B, Perez-Iglesias R, Ramirez-Bonilla M, Martinez-Garcia O, Llorca J, Luis Vazquez-Barquero J. A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. *J Clin Psychiatry* 2006; 67(10): 1511-21.
 22. McCue RE, Waheed R, Urcuyo L, Orendain G, Joseph MD, Charles R, et al. Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia. *Br J Psychiatry* 2006; 189: 433-40.
 23. Glick ID, Shkedy Z, Schreiner A. Differential early onset of therapeutic response with risperidone vs. conventional antipsychotics in patients with chronic schizophrenia. *Int Clin Psychopharmacol* 2006; 21(5): 261-6.
 24. Scher-Svanum H, Zhu B, Faries D, Landbloom R, Swartz M, Swanson J. Time to discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. *BMC Psychiatry* 2006; 6: 8.
 25. Gareri P, De FP, Stilo M, Ferreri G, De SG. Conventional and atypical antipsychotics in the elderly: a review. *Clin Drug Investig* 2003; 23(5): 287-322.
 26. Stip E. [Cognition, schizophrenia and the effect of antipsychotics.] *Encephale* 2006; 32(3 Pt 1): 341-50. French.
 27. Fakra E, Salgado-Pineda P, Besnier N, Azorin JM, Blin O. Risperidone versus haloperidol for facial affect recognition in schizophrenia: Findings from a randomized study. *World J Biol Psychiatry* 2007; 10:1-10.
 28. Lee SM, Chou YH, Li MH, Wan FJ, Yen MH. Effects of antipsychotics on cognitive performance in drug-naive schizophrenic patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31(5):1101-7.
 29. Terry AV Jr., Gearhart DA, Warner SE, Zhang G, Bartlett MG, Middlemore ML, et al. Oral haloperidol or risperidone treatment in rats: temporal effects on nerve growth factor receptors, cholinergic

- neurons, and memory performance. *Neuroscience* 2007; 146(3): 1316-32.
30. Harvey PD, Rabinowitz J, Eerdeken M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry* 2005; 162(10): 1888-95.
31. Keefe RS, Young CA, Rock SL, Purdon SE, Gold JM, Breier A. One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. *Schizophr Res* 2006; 81(1): 1-15.
32. Daneshmand R, Mazinani R, Fadaei F. [The effect of risperidone on cognitive symptoms of schizophrenia: a comparison with haloperidol.] *Journal of Mazandaran University of Medical Sciences* 2007; 17(59): 1-10. Persian.