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Depressive Symptomatology:Comparative Evaluation of Typical Versus Atypical Antipsychotics in Schizophrenic Patients Using MADRS Scale

KEYWORDS: Olanzapine, risperidone, haloperidol, schizophrenia, depression, madrs.

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ABSTRACT ***OBJECTIVE:*** *To evaluate the efficacy among conventional antipsychotics Haloperidol, Thioridazine versus newer atypical antipsychotic agents Olanzapine, Risperidone on depressive symptomatology in Schizophrenic patients.*

MATERIAL AND METHODS: *An open label randomized prospective study was conducted in stable Schizophrenics for 12 weeks.A total no of 40 patients diagnosed according to DSM- IV criteria were divided into 4 groups. Group I(n=10) received haloperidol 5-20 mg/day. Group II(n=10) received thioridazine 50-800mg/day. Group III(n=10) received Olanzapine 5-20mg/day. Group IV(n=10) received Risperidone 1-12mg/day. Evaluation of changes on depressive symptomatology done by MADRS scores.*

RESULTS:

Intra group comparison showed significant reduction ($p<0.001$) that is, (31.6±1.14 to 22.2±1.01) and (29.2±1.37 to 23.1±0.60) in the haloperidol and thioridazine group at the end of study. Intragroup comparison showed significant reduction ($p<0.001$) that is (29.8±0.81 to 15.2±0.53) and (30±0.94 to 18.4±0.66) in the olanzapine and risperidone group at the end of study. Pronounced effects were observed from 3 weeks onwards with both the newer antipsychotics. Intergroup comparison between olanzapine, risperidone as against haloperidol and thioridazine was significant ($p<0.001$) at the end of 6 and 12 weeks and that between olanzapine and risperidone at the end of 6 weeks ($p<0.05$) and 12 weeks ($P<0.001$) respectively.

CONCLUSION:

Olanzapine and risperidone exhibited faster and greater improvement in depressive symptoms as compared to the conventional antipsychotics. Further, olanzapine is superior to risperidone in this scale.

INTRODUCTION

Schizophrenia is chronic debilitating major psychiatric disorder requiring lifelong treatment with various antipsychotic drugs. Schizophrenia is characterized by various ominous symptoms and behavioral dysfunctions. In addition to overt psychotic or "positive" symptoms, various deficits or "Negative" symptoms occur. Positive and negative symptoms vary in intensity over time and patient may have predominantly one type at any particular time. Depressive signs and symptoms are evident in 25 to 75 % of Schizophrenic patients that correlates with higher rates of morbidity, poor long term prognosis and more frequent rehospitalisation.

Olanzapine is a structural analogue of clozapine having similar pharmacological profile but lacking the serious haematalogical side effects of clozapine.It has affinity for D1 to D5 dopamine receptors, 5HT 2A, 5HT 2C and 5HT6 serotonin receptors and M1 muscarinic ,H1 histaminergic receptors and adrenergic receptors.[1] The advantage of newer drugs over conventional agents include a faster onset of antipsychotic action, lower incidence of extra pyramidal effects and superior efficacy against the negative symptoms of schizophrenia.[2,3]

Most of the clinical trials were conducted by comparing the conventional antipsychotic haloperidol with newer antipsychotic agents, olanzapine and risperidone .[1,4]These comparative studies have shown equal or superior efficacy of the newer atypical antipsychotics over the conventional ones .However, very few data exists as to the comparative effectiveness concerned with use of newer and conventional antipsychotics agents and their benefits on depressive symptomatology.

The present study was conducted to evaluate the efficacy among conventional antipsychotics Haloperidol,Thioridazine versus Newer atypical antipsychotic agents , Olanzapine, Risperidone on depressive symptomatology in schizophrenic patients.

MATERIAL AND METHODS

Setting

This open, label randomized study was conducted in the out patient Department of psychiatry, Himalayan Institute of Medical Sciences and Hospital, Dehradun, and collaborated with department of Psychiatry, Government Medical College , Haldwani, which is a tertiary care teaching institute. On first contact , patients were seen in the walk-in clinic by a psychiatrist who makes a diagnosis of Schizophrenia. Then the patients were allotted treatment in a randomised manner.

Sample

The study sample consist of forty Schizophrenic Patients who were diagnosed according to DSM –IV Criteria.[5]

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Prior to initiation of study , an informed written consent from the legal guardian of the patient was obtained after full explanation of the elements contained in the research protocol .The Total duration of trial was 12 weeks.

Inclusion criteria were:
- Age was more than 15 years.
- Both males and females were included in the study.
- Stabilized Schizophrenic Patients on conventional antipsychotics, Haloperidol were only included in this study.
- BPRS[6]- Initial severity of illness Scores on the BPRS had to be equal to or exceed 24.
- CGI- Clinical Global impression severity rating scale. The CGI score had to be moderate i.e more than or equal to 4.

Exclusion criteria were:
- Women of reproductive age group without adequate contraception.
- Pregnant or lactating mothers.
- Serious medical illness.
- History of Leucopenia without a clear etiology.
- History of severe allergies or multiple adverse drug reaction.
- Epileptic patient.
- Neurological or organic Syndrome.
- Abnormal ECG.
- History of drug abuse including alcohol.
- Liver and Kidney diseases.

A total of 46 patients consented to participate in the study. All patients were diagnosed for schizophrenia .Six patients did not come for follow up visits and had to be excluded. Hence, complete data for 40 schizophrenic patients were available and analysed.

Tools:
The following tools were used in this study-

Semi- structured sociodemographic proforma:
This proforma was used to record a detailed sociodemographic profile of the patients including age, sex, marital status, occupation, education, income, religion, type of schizophrenia and the duration of illness.

Structured Proforma for Schizophrenic Evaluation:
This proforma had the following**:**

Positive and Negative Symptoms Scale (PANSS).

Structured Proforma for evaluation of changes in depressive symptomatology.

Montgomery Asberg Depression Rating Scale.(MADRS).

PROCEDURE
Forty Schizophrenic Patients were randomly assigned to four treatment groups:

Group I- Consisted of 10 patients assigned to haloperidol treatment(5-20mg/day).

Group II-Consisted of 10patients assigned toThioridazine treatment(50-800mg/day.

Group III-Consisted of 10 patients assigned to Olanzapine treatment(5-20mg/day).

Group IV-Consisted of 10 patients assigned to Risperidone treatment(1-12mg/day).

Concomitant administration of Benzodiazepines, Anticholinergics, and Anti depressants were used during clinical trial of individual patients, which was duly recorded.

Efficacy variables included:
The BPRS [6] and PANSS [7] were used to measure drug efficacy. The BPRS included 18 items that address somatic concern, anxiety, emotional withdrawl, conceptual disorganization etc. The PANSS includes 30 items : 7 items make up the positive scale, next 7 items make up the negative scale, and 16 items make up the general psychopathology scale. The sum of the ratings of the particular psychometric evaluations were done on the first week that is, baseline at 0 week and repeated at 3,6 and 12 weeks intervals.

Evaluation of changes in depressive symptomatology:
The MADRS [8] was used to assess the effect of drugs on depressive symptoms. It is a 10 item check list which includes apparent sadness, feelings of guilt , suicidal thoughts, insomnia, work and activities, anxiety psychic, anxiety somatic, retardation or lassitude, loss of weight and insight. These items are rated on scale of 0-6. Total Scores on the MADRS range from 0 to 60. The following scores correlated with global severity measures : very severe 44; severe 31; moderate 25; mild 15 and recovered.[7]

Statistical Analysis
Stastical analysis was done using paired 't' test for intragroup comparison at 0 week versus 12 week. Intergroup comparison between the four treatment groups was done using unpaired 't' test. The value of $p< 0.05$, <0.001 was considered statistically significant.

Results
Table 1. The sociodemographic characteristics of the subjects are summarized. Total number of forty patients of stable schizophrenia with duration ranging from 1 to 20 years were included in this study. Out of these, 26 patients were in the age group of 16 to 30 years whereas 14 in the range of 31 t0 62 years and 28 were males and 12 females . Subcategories of Schizophrenia , as diagnosed by DSM-IV criteria revealed 26 patients were paranoid, 8 disorganised, 4 undifferentiated type and 2 of residual type.

Table 2. Shows that antipsychotic drugs were administered in different dosage range.After 2 weeks of titration phase, mean daily doses were 17mg of haloperidol, 350 mg of thioridazine, 11.5 mg of olanzapine and 48.5mg of risperidone with dosage adjustments permissible in between also. At 12th week, daily maintenance doses were 18.5 mg of haloperidol, 560 mg of thioridazine, 13mg of olanzapine and 5.6 mg of risperidone.All doses of antipsychotic medications were well within the therapeutic range, however higher doses of haloperidol and thioridazine were required for comparable effective control of symptoms than the olanzapine and risperidone.

Table 3. Shows the evaluation of antipsychotic efficacy using the PANSS scales. All the four groups were comparable in their baseline scores. The positive and negative symptoms scale was used for assessment of patients

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of all groups .The decrease in mean PANSS scores in all groups was significant at the end of 3, 6, 12 weeks. Intergroup comparison showed that the decreased in scores of olanzapine and Risperidone was significantly ($p<0.001$), greater than the conventional antipsychotics at the end of 6 and 12 weeks. Significant difference between olanzapine and risperidone ($p<0.001$). was also observed at the end of 12 weeks, as depicted in Fig. 1.

Table 4. Shows significant decrease in MADRS scores in all groups at the end of 3, 6 12 weeks.More pronounced effects were observed at 3 weeks with the newer antipsychotics as compared to the conventional ones. Intergroup comparison between olanzapine, risperidone, as against haloperidol and thioridazine was significant($p<0.001$) at the end of 6 weeks ($P<0.05$) and 12 weeks($p<0.001$) respectively.Thus olanzapine and risperidone exhibit faster and greater improvement in depressive symptoms as compared to the conventional antipsychotics.Further, olanzapine is superior to risperidone in this scale. Fig. 2

Table 5. Shows that antidepressants and anxiolytics were prescribed to fewer patients in olanzapine and risperidone group as compared to Haloperidol and thioridazine group.

Socio- demographic profile of schizophrenic patients of different groups

Table No 1: Socio- demographic profile of schizophrenic patients of different groups

Demographic parameters	Group I (Haloperidol) (n=10)	Group II (Thioridazine) (n=10)	Group III (Olanzapine) (n=10)	Group IV (Risperidone) (n=10)
Sex Ratio M:F*	10 : 0	6 : 4	6 : 4	6:4
Age(yrs) Mean±SE range	35.5 ± 4.47 21-60	28.7 ± 2.78 16-40	26.7 ± 1.54 20-35	29.9 ± 4.17 17-62
Occupation P:NP:N**	4:5:1	2:7:1	3:7:0	1:5:4
Education L:I X	10:0	8:2	10:0	8:2
Socioeconomic status(H:M:L) $	7:3:0	7:3:0	8:2:0	7:2:1
Marital status M:U:MS #	6:4:0	4:6:0	4:4:2	2:6:2
Religion H:M:O ^	8:1:1	8:2:0	9:0:1	8:1:1
Duration of illnes (yrs) Mean±SE	10.9 ± 1.78	3.8 ± 1.07	4.1 ± 0.70	6.6 ± 1.57
Types T P:D:U:R	5:3:1:1	6:2:2:0	8:1:0:1	7:2:1:0

*Sex ratio : male M : female F

**Occupation: P professional; NP non-professional; N= none

X Education: L literate; I illiterate

$ Socio-economic status: H high; M middle; L low income group.

Marital status: M married; U unmarried; M/S married and separated.

^ Religion: H hindus; M muslims; O others.

T Type of schizophrenia: P paranoid; D disorganized; U undifferentiated; R residual.

Table No 2 :Dosing schedule of Haloperidol(H), Thioridazine(T), Olanzapine(O), Risperidone(R) in mg per day at different time intervals

Time intervals in wks		Haloperidol (n=10)	Thioridazine (n=10)	Olanzapine (n=10)	Risperdone (n=10)
0	Mean daily dose ± SE Dosage range	8.5 ± 0.76 5-10	175 ± 8.33 150-200	6 ± 0.40 5-7.5	2.5 ± 0.16 2-3
3	Mean daily dose±SE Dosage range	17 ± 1.10 10-20	350 ± 14.91 300-400	11.5 ± 0.76 10-15	4.85 ± 0.18 4-6
6	Mean daily dose±SE Dosage range	18.5 ± 0.76 15-20	475 ± 15.38 400-550	13 ± 1.10 10-20	5.85 ± 0.14 5-6.5
12	Mean daily dose±SE Dosage	18.5 ± 0.76 15-20	560 ± 14.54 500-600	13 ± 1.10 10-20	5.6 ± 0.27 5-7.5

Table no 3 :Effect of Haloperidol, Thioridazine, Olanzapine, Risperidone on changes in PANSS scores (mean ± SE) used for evaluating schizophrenia symptomatology at different time intervals

Time intervals in weeks	PANSS			
	Haloperidol	Thioridazine	Olanzapine	Risperdone
0	75.1 ± 0.74	75.1 ± 0.91	77.1 ± 0.69	75.4 ± 1.25
3	66 ± 4.5**	66.8 ± 0.88**	65.7 ± 0.72**	64.5 ± 1.06**
6	62.1 ± 0.53**	63.2 ± 0.85**	58.1 ± 0.41**£	58.8 ± 0.95**ł
12	60.1 ± 0.57**	60.5 ± 0.69**	51.6 ± 0.31**£ƒ	55.4 ± 0.89**ł

*p value < 0.05
**p value < 6.001 versus 0 week value
£ p value < 0.001 versus corresponding Halopeirdol & Thioridazine values at 6 and 12 weeks.
ƒ p value < 0.001 versus values at 12 weeks.
ł p value < 0.001 versus H & T values at 6 and 12 weeks.

Table No 4 :Effect of Haloperidol, thioridazine, Olanzapine and Risperidone on depressive symptoms using MADRS Scores (Mean ± SE) at different time intervals.

Time in interval in weeks	MADRS			
	Haloperidol n=10	Thioridazine n=10	Olanzapine n=10	Risperidone n=10
0	31.6 ± 1.14	29.2 ± 1.37	29.8 ± 0.81	30 ± 0.94
3	28.4 ± 1.10*	26.6 ± 1.12*	23.4 ± 0.67*	25.2 ± 0.74**
6	24.8 ± 0.95**	24.3 ± 0.73**	18.6 ± 0.79**£ƒ	20.8 ± 0.61**ǂ
12 % Change	22.2 ± 1.01** 29.75	23.1 ± 0.60** 20.89	15.2 ± 0.53£µ 48.99	18.4 ± 0.66**ǂ 38.67

P value <0.05 ** p value <0.001 versus 0 week values
£ ; p <0.001 versus Haloperidol and Thioridazine group values at 6 and 12 weeks
ǂ; p <0.001 versus Haloperidol and Thioridazine group values at 6 and 12 weeks
ƒ; p <0.05 versus Risperidone group values at 6 weeks
µ ; p <0.001 versus Risperidone group values at 12 weeks.

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Table No 5: Use of concomitant antidepressant and anxiolytic medications by schizophrenic patients on Haloperidol, Thioridazine, Olanzapine, Risperidone at different time intervals

Time intervals in weeks	Concomitant antidepressant & anxiolytics	Haloperidol (n=10)	Thioridazine (n=10)	Olanzapine (n=10)	Risperidone (n=10)
0	Antidepressant Anxiolytics	-	-	-	-
3	Antidepressant Anxiolytics	4 1	5 1	-	--
6	Antidepressant Anxiolytics	5 2	5 3	- 1	2 -
12	Antidepressant Anxiolytics	6 2	6 3	1 -	- 1

Figure- 1. Effect of haloperidol, thioridazine, olanzapine and risperidone on mean PANSS scores at different time intervals

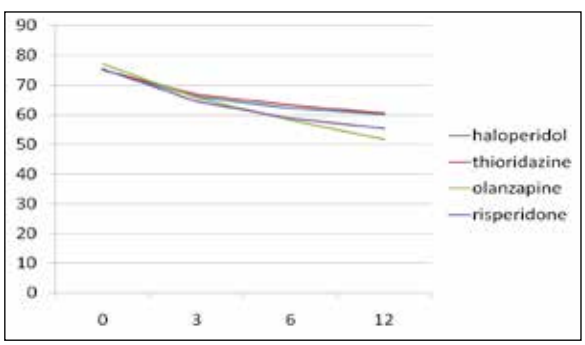
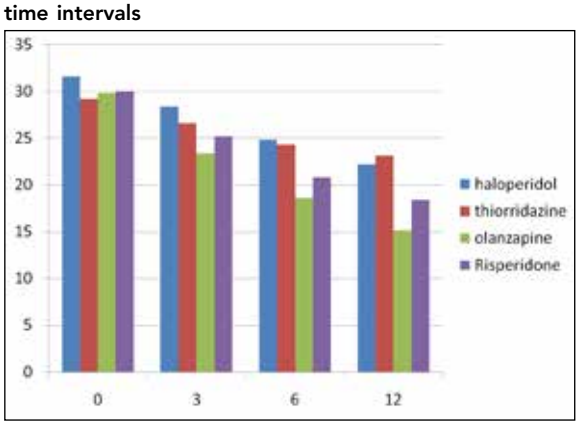


Figure- 2 Effect of haloperidol, thioridazine, olanzapine and risperidone on mean MADRS scores at different time intervals



DISCUSSION

Schizophrenia is characterized by various ominous symptoms and behavioural dysfunction. In addition to the overt psychotic or "positive" symptoms, various deficit or "negative" symptoms occur. Positive and negative symptoms vary in intensity over time and patient may have predominantly one type at any particular time.[9] An overall treatment response is composed of changes in three elements: positive , negative and general psychopathology symptoms. In total PANSS Scores , improvement with Olanzapine and Risperidone was more favourable than the conventional antipsychotics haloperidol and Thioridazine.[10]

Faster effects on depressive symptoms was evident in the olanzapine and risperidone group from 3 weeks onwards and persisted upto 12 weeks of study period.[11] This is also evident indirectly as the requirement of concomitant antidepressant drugs were more in the haloperidol and Thioridazine group as compared to the newer atypical antipsychotics.

Olanzapine was also found to alleviate depressive symptoms better as compared to risperidone, an interesting finding to note such difference between the two newer antipsychotics not reported earlier. As the density of 5HT2A receptors have been reported to be increased among patients with major depression , Olanzapine as a potent 5HT2A antagonist may have acted at these sites and produce action similar to an antidepressant drug like nefazadone.[12]

In our study both Olanzapine and Risperidone exhibited pronounced effects on depressive symptoms as compared to conventional agents, which is in consonance with earlier works.

REFERENCES

1. Tollefson GD. Olanzapine versus haloperidol in the treatment of schizophrenia, of schizoaffectve and schizophreniform disorders; result of an collaborative trial. Am.J.Psychiatry.1997;154: 457-465.
2. Grant S, Kitton A.Risperidone: a review of its pharmacology and therapeutic potential in treatment of schizophrenia.Drugs.1994;48(2): 253-273.
3. Siris SG depression and schizophrenia, in schizophrenia.Edited by Hirsch SR, Weinberger DR.Oxford, England,Blackwell Science,1995;128-145.
4. Csernansky JG, Mahmoud R, Brenner R.The Risperidone-USA-79 Study Group: A comparision of risperidone and Haloperidol for the prevention of relapse in patients with Schizophrenia**.** N Engl J Med. 2002;346(1):16-22.
5. American Psychiatric Association(1994) : Diagnostic and Statistical Manual of mental disorders 4th ed, Washington.
6. Hedlund JL, vieweg B.W. The Brief Psychiatrioc Rating Scale(BPRS): a comprehensive review. Journal of operational Psychiatry.1980; 11:48-65.
7. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale(PANSS) for Schizophrenia. Schizophur Bull 1987;13:261-276.
8. Montogomery SA, Asberg M.A new depression scale designed to be sensitive to change. Br.J Psychiatry. 1979;134:382-389.
9. Davis JM et al.The effects of olanzapine on the 5 dimensions of Schizophrenia derived by factor analysis: combined results of the North American and International Trials. J clin Psychiatry 2001;62:757-71.
10. Gomez JC et al. Superior efficacy of olanzapine over haloperidol:analysis of patient with Schizophrenia from a multicentre international trial. J Clin Psychiatry 2001;62:6-11.
11. Peuskens J. et al. Risperidone in the treatment of Patients with chronic Schizophrenia: a multi- national, multicenter, double- blind, parallel group study versus Haloperidol. Br J. Psychiatry 1995; 166: 712-26.
12. Nemrick-Luecke Sk et al.Evaluation of Nefazodone as a serotonin uptake inhibhitor and a serotonin antagonist in vivo. Life Sci 1994;55:479-483.