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Comparative Evaluation Of Olanzapine Versus Haloperidol on Depressive Symptoms Using Montgomery Asberg Depression Rating Scale (Madrs) in Stable Schizophrenic Patients

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

* Bhardwaj Reena	Bhardwaj Praveen	Dutta Shaktibala
Department of Pharmacology, Government Medical College, Haldwani	Department of Physiology, Government Medical College, Haldwani	Department of Psychiatry, epalgunj Medical College, Nepal.

Kaul Vijay	Dhasmana D.C
Department of Psychiatry, Nepalgunj Medical College, Nepal.	Department of Pharmacology ,SGRRIMHS and H.I.M.S5 Dehradun.

ABSTRACT *Objective : To evaluate the efficacy among newer atypical antipsychotic agent, olanzapine versus conventional antipsychotic, haloperidol on depressive symptomatology.*

Material and methods : An open label randomized prospective study was conducted in stable schizophrenics for 12 weeks. A total number of 20 patients diagnosed according to DSM-IV criteria were divided into two groups. Group I (n=10) received olanzapine (5-20mg/day) and Group II received haloperidol (5-20mg/day) orally in divided doses. Evaluation of changes on depressive signs and symptoms was done by MADRS scores.

Results: Intragroup comparison showed significant reduction (p<0.001) ie (29.8+ 0.81 to 15.2 + 0.53) and (31.6 + 1.14 to 22.2 + 1.01) in the olanzapine and haloperidol group at the end of study. More pronounced effects were observed from 3 weeks onwards with the newer antipsychotic, olanzapine. Intergroup comparison between olanzapine and haloperidol was significant at the end of 6 and 12 weeks (p<0.001) respectively.

Conclusion: Olanzapine exhibited faster and greater improvement in depressive symptoms. Further, olanzapine is superior to haloperidol in this scale.

Introduction

Schizophrenia is characterized by various ominous symptoms and behavioral dysfunction. In addition to the 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.

Olanzapine is a structural analogue of clozapine having similar pharmacologic profile but lacking the serious haematological side effects of clozapine. It has affinity for D1 to D5 dopamine receptors, 5HT 2A, 5HT 2 C and 5 HT 6 serotonin receptors and M1 muscarinic, H1 histaminergic and adrenergic receptors [1]. The advantage of newer drugs over conventional agents include a faster onset of antipsychotic action, lower incidence of extrapyramidal effects and superior efficacy against the negative symptoms of schizophrenia[1,2] .

Depressive signs and symptoms are also evident in 25 to 75 percent of schizophrenic patients [3] that correlated with higher rates of morbidity, poor long-term prognosis and more frequent rehospitalizations. Conventional antipsychotics are of limited benefit for depressive signs and symptoms, therefore antidepressants are often added as therapeutic adjuncts.

Most of the clinical trials were conducted by comparing the conventional antipsychotic haloperidol with the 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 antipsychotic agents and their benefits on depressive symptomatology. Therefore, the present study was undertaken to evaluate the therapeutic benefit of olanzapine and haloperidol on depressive symptoms in Indian schizophrenic patients.

Material And Methods

Setting

This open, label randomised 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 institution. 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 consisted of twenty schizophrenic patients who were diagnosed according to DSM - IV criteria. [5] Prior to the initiation of the 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 the trial was twelve weeks.

The inclusion criteria for this study were as follows:

- Patients of both sexes with age above 15 years
- Stabilized schizophrenia patients on conventional antipsychotic, haloperidol
- Brief Psychiatric Rating Scale (BPRS) scores more than or equal to 24.

The exclusion criteria included :

- Women of reproductive age group without adequate contraception.
- Pregnant or lactating mothers.
- Serious medical illnesses.
- History of leukopenia without a clear etiology.
- History of severe allergies or multiple adverse drug reaction.
- Epileptic patient.
- Neurological or organic syndrome.

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- Abnormal ECG.
- History of drug abuse including alcohol.
- Liver and kidney diseases.

A total of 24 patients consented to participate in the study. All patients were diagnosed for schizophrenia. Four patients did not come for follow-up visits and had to be excluded. Hence, complete data for twenty schizophrenic subjects were available and analysed.

Tools
The following tools were used in this study

1. 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.

2. Structured Proforma for Schizophrenia evaluation : This proforma had the following subcomponents :

- Brief Psychiatric Rating Scale (BPRS)
- Positive and Negative Symptoms Scale (PANSS)

3. Structured Proforma for Evaluation of changes in Depressive Symptomatology
- Montgomery Asberg Depression Rating Scale (MADRS).

Procedure
Twenty schizophrenic patients were randomly assigned to two treatment groups.

Group I : Consisted of 10 patients assigned to olanzapine treatment (dose range 5-20 mg per day)
Group II : Consisted of 10 patients assigned to haloperidol treatment (dose range 5-20 mg per day)

Concomitant administration of benzodiazepines, anticholinergics and antidepressants 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 includes 18 items that address somatic concern, anxiety, emotional withdrawal, conceptual disorganization etc. The PANSS includes 30 items: 7 items makeup 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 scales BPRS or PANSS comprised the summary score and was the primary measure of symptoms control. 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 checklist 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 a 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
The change from baseline in the total BPRS, PANSS and MADRS were analysed using paired't' test. Intergroup comparison between the treatment groups were done using unpaired't' test. The value of $p<0.05$, <0.001 was considered statistically significant.

RESULTS

The sociodemographic characteristics of the subjects are summarized in Table 1. Total number of twenty patients of stable schizophrenia with duration of illness ranging from 1 to 20 years, were included in the study. Out of these, 13 patients were in the age group of 17 to 30 years whereas 7 were in the range of 31 to 62 years. Subcategories of schizophrenia, as diagnosed by DSM – IV criteria revealed 13 patients were paranoid, 4 disorganised, 1 undifferentiated type and 2 of residual type.

Table 2 shows that the antipsychotic drugs were administered in different dosage range. After 2 weeks of titration phase, mean daily doses were 11.5 mg of olanzapine and 17mg of haloperidol with dosage adjustments permissible in between also. At 12th week, daily maintenance doses were 13 mg of olanzapine and 18.5mg of haloperidol. All doses of antipsychotic medications were well within the therapeutic range. Concomitant medications like anticholinergics were prescribed to 9 patients in haloperidol group whereas in the olanzapine group, there was no requirement of anticholinergics.

Table 3 shows that antidepressants and anxiolytics were prescribed to more patients in the haloperidol group, which was however less in the olanzapine group.

Table 4 shows the evaluation of antipsychotic efficacy using the BPRS and PANSS scales. Both the groups were comparable in their baseline scores. A significant decrease in BPRS scores was observed in both groups at the end of 3, 6 and 12 weeks. Intergroup comparison showed that the decrease with olanzapine was significant ($p < 0.001$) than haloperidol at the end of 12 weeks. On the PANSS total scores, significant difference between olanzapine and haloperidol ($p < 0.001$) was also observed at the end of 6 and 12 weeks as depicted in figure 1.

Table 5 shows significant decrease in MADRS scores in both groups at the end of 3,6 and 12 weeks. Significant difference between olanzapine and haloperidol were observed at 6 and 12 weeks ($p<0.001$) respectively. Further, olanzapine was found to be superior to haloperidol in this scale based on an overall 48.99% change in depressive symptoms as against 29.75% change observed with haloperidol.

RESULTS
Table 1. Sociodemographic profile of the schizophrenic patients.(n=20)

Variable	Variants	Group 1 n=10 n(%)	Group 2 n=10 n (%)
Age(in years)	mean + SE Range	26.7 + 1.54 20 - 35	35.5 + 4.47 21-60
Sex	Male Female	6(60.0) 4(40.0)	10(100) 0
Marital Status	Single Married Others[1]	4(40.0) 4(40.0) 2(20.0)	6(60.0) 4(40.0) 0
Occupation	Professional Non-Professional Others[2]	3(30.0) 7(70.0) 0(0.0)	4(40.0) 5(50.0) 1(10.0)
Education	Literate Illiterate[3]	10(10.0) 0(0.0)	10(100.0) 0
Income	High Middle Low[4]	8(80.0) 2(20.0) 0(0.0)	7(70.0) 3(30.0) 0
Religion	Hindu Muslim Others[5]	9(90.0) 0(0.0) 1(10.0)	8(80.0) 1(10.0) 1(10.0)

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Type of Schizophrenia	Paranoid Disorganized Undifferentiated Residual	8(80.0) 1(10.0) 0(0.0) 1(10.0)	5(50.0) 3(30.0) 1(10.0) 1(10.0)
Duration of Illness [in years]	mean + SE Range	4.1 + 0.70 1 - 7	10.9 + 1.78 2 - 20

Note: Group1 patients received olanzapine treatment. Group 2 patients received haloperidol treatment.

1. Included divorced, remarried, separated.
2. Professional included engineer, teacher, computer professional. Non-professional included student, halwai, contractor, shop-keeper, others included housewife, unemployed.
3. Literate included one who could speak and write one language. Illiterate included one who could speak but not able to write.
4. High-income group included those who earn > Rs 5000per month, middle group in between Rs2000 - Rs5000 per month and low income was < Rs 2000per month.
5. Other religions included Christians, Sikhs.

Table 2. Dosages of Olanzapine and Haloperidol (mg/day) at various time intervals.

Time Intervals	Baseline	3 Weeks	6 Weeks	12 Weeks
Mean Daily Dose ± SE O	6.0 ± 0.40	11.5 ± 0.76	13.00 ± 1.10	13 ± 1.10
H	8.5 ± 0.76	17 ± 1.10	18.5 ± 0.76	18.5 ± 0.76
Dosage Range O	5 – 7.5	10 – 15	10 – 20	10 – 20
H	5 – 10	10 – 20	15 – 20	15 – 20

O = olanzapine, H = haloperidol

Table 3. Use of concomitant antidepressant and anxiolytic medications by schizophrenic patients on olanzapine and haloperidol at different time intervals.

Time intervals in weeks	Concomitant antidepressant and anxiolytics	Olanzapine n =10	Haloperidol n =10
0	Antidepressant Anxiolytics	¾	¾
3	Antidepressant Anxiolytics	¾	4 1
6	Antidepressant Anxiolytics	¾ 1	5 2
12	Antidepressant Anxiolytics	1 ¾	6 2

Table 4. Evaluation of Olanzapine and Haloperidol on changes in BPRS and PANSS scores (mean + S.E.) in schizophrenic patients.

Time Intervals in weeks	Psychometric scales	OLANZAPINE	HALOPERIDOL
0	BPRS PANSS	43.2 ± 0.68 77.1 ± 0.69	42.5 ± 0.58 75.1 ± 0.74
3	BPRS PANSS	37.4 ± 0.56** 65.7 ± 0.72**	39 ± 0.44 ** 66 ± 0.45 **
6	BPRS PANSS	34.3 ± 0.51** 58.1 ± 0.41**ff	36.8 ± 0.49** 62.1± 0.53**
12	BPRS PANSS	31.6 ± 0.52**f 51.6 ± 0.31**ff	35.5 ± 0.52 ** 60.1 ± 0.57 **

BPRS stands for Brief Psychiatric Rating Scale.

PANSS stands for total scores on the positive and negative symptoms scale.

** - p value < 0.001 versus 0 week values.

f - p value <0.001 versus corresponding haloperidol values at 12 weeks.

ff - p value <0.001 versus haloperidol values at 6 and 12 weeks.

Figure 1. Effect of olanzapine and haloperidol on PANSS scores at different time intervals

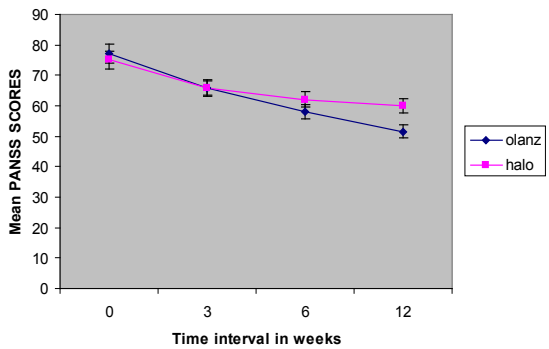

Table 5. Effect of Olanzapine and Haloperidol on depressive symptoms using MADRS Scores (mean + SE) at different time intervals

Time intervals in Weeks	MADRS	
	Olanzapine n=10	Haloperidol n = 10
0	29.8 ± 0.81	31.6 ± 1.14
3	23.4 ± 0.67 **	28.4 ± 1.10 *
6	18.6 ± 0.79 **$	24.8 ± 0.95**
12	15.2 ± 0.53 ** $	22.2 ± 1.01 **
% change	48.99	29.75

* p value <0.05 versus 0 week values

** p value < 0.001 versus 0 week values

$ p value < 0.001 versus haloperidol group values at 6 and 12 weeks.

DISCUSSION

The findings of this prospective study would definitely have an important implications on the therapy of schizophrenia. Olanzapine was found to be more effective than haloperidol on the basis of greater change in BPRS scores. Further, in total PANSS scores, the improvement with olanzapine and haloperidol was favourable. The improvement tended to occur speedily and was evident as early as 3 weeks and sustained through weeks 6 and 12.

MADRS is a rating scale used for assessment of depression. In our study olanzapine exhibited pronounced effects on depressive symptoms which was evident as early as 3 weeks and persisted upto 12 weeks of study period. The requirement of concomitant antidepressant drugs was also less with this atypical antipsychotic agent. Further, olanzapine was also found to alleviate depressive symptoms better as compared tohaloperidol. These features are more likely to be associ-

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ated with olanzapine's pleotrophic pharmacology, which includes dopaminergic, serotonergic, muscarinic and adrenergic activities. As the density of $5HT_{2A}$ receptors have been reported to be increased among patients with major depression [1] , olanzapine as a potent $5HT_{2A}$ antagonist may have acted at these sites and produce action similar to an antidepressant drug like nefazodone [9] . The importance of these mood-related findings is clinically relevant to distinguish a novel antipsychotic agent that is capable of producing better additional benefits on depressive symptoms.

Thus, on the basis of present study , it is concluded that the newer antipsychotic olanzapine as monotherapy is efficacious, olanzapine being superior than haloperidol in treatment of depressive symptoms in schizophrenia. However , since present study was done in a small number of patients, therefore future studies involving a larger group of patients may further substantiate these findings.

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