DOES OLanzapine HAVE ADVANTAGE OVER Iloperidone IN EARLY AMELIORATION OF SYMPTOMS IN SCHIZOPHRENIA? A RANDOMISED PARALLEL GROUP TRIAL

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BACKGROUND
The development of more effective and safer drugs for the optimal treatment of schizophrenia has become quite essential in the present era. We find limited literature directly comparing the efficacy of the two ‘atypical’ antipsychotics, i.e. olanzapine and iloperidone.

MATERIALS AND METHODS
The study participants were persons diagnosed with schizophrenia between the age of 18-65 years who were randomised to treatment with olanzapine or iloperidone and analysed for symptoms on the basis of Positive and Negative Symptom Scores (PANSS) at 4 and 8 weeks. Statistical Analysis- Mean changes in the PANSS were analysed by paired and independent t-tests.

RESULTS
There was statistically significant and similar reduction in clinical symptoms at eight weeks in both olanzapine (PANSS score of 92.22 (±17.03) at baseline to 78.63 (±15.30) at 8 weeks; p<0.001) and iloperidone (PANSS score of 93.75 (±19.70) at baseline to 74.88 (±30.52) at 8 weeks; p<0.001) groups (p<0.001). Olanzapine showed significantly higher reduction (p<0.01) in PANSS as compared to iloperidone at four weeks particularly in the PANSS negative symptom score. The two groups did not differ in the treatment completion rates.

CONCLUSION
Though both the study drugs significantly improve the symptoms in schizophrenia, but olanzapine seems to cause an early amelioration of negative symptoms as compared to iloperidone.

KEYWORDS
Olanzapine, Negative Symptoms, Iloperidone, Schizophrenia.


BACKGROUND
Antipsychotics, both old and new, are clearly effective and have been a boon to the treatment of schizophrenia.¹ The first-generation agents that were antagonists at the dopamine type 2 (D₂) offered little benefit in controlling negative symptoms or cognitive deficits and could result in Extrapyramidal Symptoms (EPS) and a progressively increasing risk of tardive dyskinesia.²,³ The introduction of second generation antipsychotic drugs promises enhanced efficacy and safety.⁴ The second generation or the atypical agents differ pharmacologically from the previous antipsychotic agents in their lower affinity for dopaminergic D₂ receptors and greater affinities for other neuroreceptors like serotonergic (5-HT₁₅, 5-HT₂a, etc.) and adrenergic (α₁ and α₂) receptors.⁵ The new or atypical agents are thought to have efficacy in reducing both positive and negative symptoms. Among these agents, variations are seen as regards their efficacy, safety and tolerability owing to the differences in their dynamic profile.²,⁶

Olanzapine is an atypical agent, which has proved high as well as broad spectrum of efficacy when compared with the typical antipsychotics.⁷ Iloperidone too is a second-generation antipsychotic, which represents another treatment option for the management of schizophrenia. Structurally related to risperidone,⁸ it has shown efficacy and safety in treatment of schizophrenia on both short and long-term basis.⁹,¹⁰
The receptor binding profiles of both the study drugs being similar in showing higher affinity for serotonin receptor 5-HT1A than dopamine receptor D2, have certain important differences. While olanzapine binds with high affinity to histamine receptor H1, iloperidone displays low affinity for the same. Comparing their affinities at adrenergic receptor α2C, iloperidone with moderate affinity supersedes olanzapine, which has low affinity for these receptors. A major difference in their pharmacodynamic profile is the anticholinergic action of olanzapine at muscarinic receptors (M1, M2 and M3), which is not seen with iloperidone. Yet another contrast between the two drugs is created by their differing affinities for the norepinephrine transporter being high in case of olanzapine and negligible in case of iloperidone.5,11,12

Both the drugs, i.e. olanzapine and iloperidone have shown their own unique pharmacodynamic profile. However, to the best of our knowledge, we do not find much of literature regarding head to head comparison of efficacy of these two drugs. Hence, in our quest to find better treatment options, the present study was conducted to observe as to how the variation in their receptor profiles would translate into difference, if any, in the efficacy of the two drugs in patients suffering from schizophrenia in the north Indian population.

Aim- To compare the efficacy of olanzapine and iloperidone in patients of schizophrenia.

Settings- Tertiary care hospital-based study conducted in patients attending Psychiatry OPD of IGMC, Shimla.

Study Design- Two-arm, randomised, prospective and comparative parallel clinical trial.

MATERIALS AND METHODS

It was a tertiary care hospital-based study conducted in patients attending Psychiatry OPD of Indira Gandhi Medical College, Shimla.

Study Population

All consecutive patients of schizophrenia attending Psychiatry OPD of IGMC, Shimla from May 2012 to March 2013 were screened for enrolment in the study. Out of the total of 487 patients screened, 64 met the inclusion and exclusion criteria and hence were included in the study. Study approval was obtained from the institution’s ethical committee and a written informed consent was obtained from participants or their close family members prior to the initiation of study procedures. The patients enrolled were randomised to receive either of the two study drugs, i.e. olanzapine or iloperidone.

Inclusion Criteria

1. Age 18-65 years.
2. Diagnosis of schizophrenia according to the criteria of Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Text Revision (DSM-IV TR).13
3. Consenting patient or family member.

Exclusion Criteria

1. Current DSM-IV TR Axis I diagnosis other than schizophrenia.
2. Substance dependence/abuse.
3. Clinically significant/unstable medical illness.
4. Pregnant/nursing women.
5. Suicidal risk too serious to be included in the study.
6. Requirement of treatment with anticonvulsants (except as allowed for agitation control of extrapyramidal signs) antidepressants, psychostimulants or other antipsychotic drugs concurrently with study medications beyond those permitted as concomitant treatments.
7. Treatment with ECT within one month before study entry.
8. Treatment with oral neuroleptic one week or earlier before study entry.
9. Drug treatment for more than 16 cumulative weeks, treatment with clozapine at any time in their lifetime, or treatment with injectable depot neuroleptic within less than 3 dosing intervals before study entry.
10. History of refractoriness to the study drugs.

Study Treatments

Olanzapine was started at a dose of 5 mg/day and increased by 5 mg every five days till a dose of 20 mg/day was reached. Patients receiving iloperidone were given a dose of 2 mg on first day, 4 mg on second day, 8 mg on third day and from the fourth day onwards a dose of 12 mg/day was continued through the study period. In patients experiencing the adverse effect of Extrapyramidal Symptoms (EPS), trihexyphenidyl in a dose of 2 mg/day was added.

Assessment

After informed consent was signed, a detailed medical and psychiatric history was obtained. Examination included detailed Mental Status Examination (MSE) besides routine physical examination. Routine laboratory investigations were carried out and additional tests were conducted as per the need.

PANSS was administered to assess the severity of positive and negative symptoms at each visit. PANSS is a rating scale, which has consistency in scoring individual patients overtime and illness course. The PANSS is a 30-item scale divided into positive, negative and general psychopathology subscales.14 This is typically administered by endorsing 1 of 7 options (weights) numbered 1 through 7.11 Abnormal Involuntary Movement Scale (AIMS) was administered during follow-ups for the assessment of extrapyramidal side effects. The reassessment was done at 4 weeks and the final assessment was done at the end of 8 weeks.

Computer generated randomised list was used for the purpose of randomisation of the participants into the two study groups.
Statistical Analysis
Mean changes in the PANSS were analysed by paired and independent T-tests. To analyse discrete variables (sex, patients with positive family history), the Wilcoxon and Chi-square tests were used. A two-tailed significance with p<0.05 was taken as statistically significant. The data were entered, verified, validated and analysed using SPSS Statistical Software Package (SPSS version 17). The analyses were carried out on the basis of ‘intention to treat.’ Statistical analyses were performed following the LOCF (last observation carried forward) approach for all time points except in those cases in which patients switched from any of the groups to other antipsychotics. Data for patients who were switched to a different antipsychotic were analysed up until the point at which medication was switched.

RESULTS
Of the 64 patients enrolled, there were 32 in the olanzapine group and 32 in the iloperidone group (Figure 1). During the course of study, 5 patients were lost to follow-up. The reasons included financial constraints, social stigma and residence in distant hard areas. The demographic and clinical profile of the patients is depicted in Table 1. The two study groups did not differ significantly in positive subscale, negative subscale, general psychopathology subscale or total PANSS score as assessed at the baseline.

On comparison at four weeks, the decrease in the PANSS-T score was significantly higher for olanzapine than iloperidone. On examining the subscale scores (PANSS-N), we found that the difference arose from the significantly higher reduction of the negative symptoms such as blunted affect, emotional and social withdrawal by olanzapine as compared to iloperidone. At eight weeks, PANSS-T scores significantly improved further in both the groups, but there was no between-group significant difference showing that iloperidone had reached almost identical level of improvement as that seen in the olanzapine group (Table 2). EPS and treatment completion rates did not differ between the olanzapine and iloperidone group.

One patient in olanzapine group and two in iloperidone group experienced Extrapyramidal Symptoms (EPS). The patients with EPS responded to trihexyphenidyl. None of the patients required discontinuation of study drugs due to EPS and the two groups did not differ significantly from each other in this regard.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olanzapine (Mean Change from Baseline)</th>
<th>Iloperidone (Mean Change from Baseline)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS-T</td>
<td>-7.03 (±3.19)</td>
<td>-5.19 (±2.35)</td>
<td>.01</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>-2.53 (±1.24)</td>
<td>-2.03 (±0.97)</td>
<td>.08</td>
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<tr>
<td>PANSS-N</td>
<td>-1.19 (±1)</td>
<td>-0.63 (±0.66)</td>
<td>.01</td>
</tr>
<tr>
<td>PANSS-GP</td>
<td>-3.31 (±1.96)</td>
<td>-2.53 (±1.34)</td>
<td>.07</td>
</tr>
<tr>
<td>PANSS-T</td>
<td>-13.59 (±5.09)</td>
<td>-11.47 (±4.83)</td>
<td>.09</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>-4.81 (±2.28)</td>
<td>-4.22 (±2.15)</td>
<td>.29</td>
</tr>
<tr>
<td>PANSS-N</td>
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<td>-2.28 (±1.14)</td>
<td>.29</td>
</tr>
<tr>
<td>PANSS-GP</td>
<td>-6.16 (±2.74)</td>
<td>-4.97 (±2.40)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Table 2. Comparison of Effects of Olanzapine and Iloperidone on Symptoms in the Study Population at 4 Weeks and 8 Weeks
DISCUSSION

Despite the progress made in developing therapy for schizophrenia, there still remains an unmet need for more effective and safer drugs. Olanzapine and iloperidone were both found to be effective in treating symptoms of schizophrenia in this randomised study (Table 2). Similar efficacy results with olanzapine have also been demonstrated earlier by Conley RR and Mahmoud R who showed a decrease of 14.5 in PANSS-T in their eight-week study. The efficacy of iloperidone assessed by PANSS at eight weeks was also consistent with the study of Potkin SG and co-workers who also reported decreases of 9.9, 11.1 and 11 respectively in PANSS-T scores in their analysis of three separate studies.

We noted that olanzapine caused an earlier amelioration of negative symptoms than iloperidone. These findings were consistent with the results shown by its comparison with other drugs in earlier studies. This effect may be attributed to a range of activities shown by olanzapine at various receptors.

Muscarinic overactivity has been seen to be associated with causation of negative symptoms in patients of schizophrenia. The appearance of similar symptoms in normal subjects on IV infusion of physostigmine and the reduction of negative symptoms on administration of trihexyphenidyl further supports the implication of this system in the pathogenesis of negative symptoms.

The anticholinergic action of olanzapine on the predominant cholinergic receptors in the brain (M₁, M₂ and M₄) could be the mechanism underlying the difference in the results of negative symptoms between the two study drugs at four weeks.

In the aetio-pathogenesis of schizophrenia, relation between norepinephrine and negative symptoms has been described in earlier studies. Furthermore, among the most pronounced biochemical findings in patients of schizophrenia is decrease in the level of norepinephrine activity. Adding to the evidence is the recent study demonstrating reduction of negative symptoms by reboxetine, a norepinephrine reuptake inhibitor. In this regard, olanzapine’s higher affinity for norepinephrine transporter in comparison to that of iloperidone (negligible affinity) may have acted as added advantage in the control of negative symptoms in our study.

Hypoglutamatergic neurotransmission has been seen to be involved in the pathogenesis of negative symptoms of schizophrenia and its enhancement by using agonist drugs is seen to improve these symptoms. Interestingly, in this context, recent evidence points towards rapid onset facilitatory effects of olanzapine on glutamatergic transmission in medial prefrontal cortex similar to that seen with ketamine.

Negative symptoms are indeed important symptoms in schizophrenia because the severity of negative symptoms...
predicts long-term debility better than the positive or disorganisation symptoms. Negative symptoms may also be the most significant indicator of social function.27,28 The greater severity of negative symptoms adversely affects compliance as well in these patients.29,30 The earlier response to negative symptoms hence may have additional benefits favouring the use of olanzapine over iloperidone in the treatment of schizophrenia. However, in the long run, the two drugs appear to have almost similar efficacy as suggested by the results of the present study.

The study completion rates of patients in the olanzapine and iloperidone group were higher (93.75% and 90.62%, respectively) as compared to the observations in the earlier studies from the West wherein the completion rates range from 52% to 68%.7,9,16,31 In our country, most patients of schizophrenia live with their families.32 In this regard, even in an unwilling patient, family persuasion may have resulted in the higher success rate of completion of treatment. Our study, in this context, further substantiates the impact of caregivers on the treatment of schizophrenia.

The findings of our study must be interpreted in the light of its limitations such as relatively small sample size and limited duration of observation.

CONCLUSION
The results of this randomised, prospective, comparative study showed that both olanzapine and iloperidone are effective in treatment of schizophrenia. There was an earlier improvement in symptoms especially the negative ones as compared to iloperidone. However, over long-term use, efficacy of iloperidone seems to be similar to that of olanzapine.

REFERENCES


