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OLANZAPINE IN THE TREATMENT OF SCHIZOPHRENIA : AN OPEN LABEL COMPARATIVE CLINICAL TRIAL FROM NORTH INDIA

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ABSTRACT

The aim of the present study was to assess the efficacy and safety of olanzapine in the treatment of schizophrenic patients. 27 patients were randomly assigned to treatment with olanzapine or haloperidol over 12 weeks. The primary efficacy measure was the mean change from baseline to endpoint in total scores on the Brief Psychiatric Rating Scale (BPRS) and assessing treatment emergent adverse events. Secondary measures were positive symptoms, negative symptoms, general psychopathology, depression, anxiety and quality of life. Compared to haloperidol, olanzapine had equal effect in improving overall psychopathology, positive symptoms, and severity of schizophrenic illness. Olanzapine showed superior improvement on negative symptoms and secondary depressive features. Commonest side effects were weight gain, sleepiness and increased duration of sleep. Olanzapine is effective in improving overall psychopathology including positive symptoms, negative and secondary depressive features in Indian patients with schizophrenia and it is safe and well tolerated at dosage between 5 to 20 mg/day.

Key words : Olanzapine, schizophrenia, treatment

Schizophrenia is a hetrogeneous condition that includes positive, disorganized, dysphoric and negative symptoms. Evidence linking these symptoms to multiple brain regions is increasing suggesting the underlying disruption of one or more fundamental neural circuits (Andreason,1953). Furthermore, in contrast to earlier theories (e.g. one transmitter, one locus), broad ranges of neurotransmitters at multiple loci are now implicated (Carlsson,1995).

Conventional antipsychotic agents do not exert therapeutic effects against all domains of schizophrenic pathology e.g. negative or deficit features (Liberman,1993). Furthermore, neuroleptic induced adverse events contribute to rates of non-compliance approaching 50% (Kane,1987). Alternative approaches, implicating other neurotransmitter system have led to the development of novel antipsychotic drugs such as olanzapine polymorph (Meltzer,1991).

Olanzapine is an atypical antipsychotic with a broad binding and pharmacological profile (Bymaster et al.,1996). In vitro receptor binding studies showed a high affinity for dopamine D_2, D_3 and D_4 receptors; all 5-HT_2 receptor subtypes and the 5-HT_6 receptor; muscarinic receptors, especially the M_1 subtypes; and α1 - adrenergic receptors. In vivo studies showed that olanzapine had potent activity at D_2 and 5HT_{2A} receptors, but much less activity at D_1 and muscarinic receptors, and that it inhibited dopaminergic neurons in the A_{10} but not the A_9 tract, suggesting that this agent will not cause extrapyramidal side effects (EPS). Microdialysis studies showed that olanzapine increased the extracellular levels of norepinephrine and dopamine, but not 5-HT, in the prefrontal cortex, and increased extracellular dopamine levels in the neostriatum and neucleus accumbens, areas of the brain associated with scizophrenia. Studies of gene expression showed

that olanzapine 10 mg/kg also increased FOS expression in the prefrontal cortex, the dorsolateral striatum, and the nucleus accumbens These findings are consistent with the effectiveness of olanzapine on both negative and positive symptoms and suggest that, with careful dosing, olanzapine should not cause EPS (Bymaster et al.,1996).

In a series of double blind controlled trials in patients with schizophrenia and schizoaffective disorder, olanzapine appeared superior to conventional dopamine D_2 antagonist, haloperidol on measures of overall psychotic symptoms, negative symptoms, comorbid mood symptoms and quality of life (Tollefson et al.,1998; Beasley et al ,1997, Tollefson et al.,1997, Beasley et al.,1996). However, there is paucity of studies from India evaluating efficacy and safety of olanzapine. Transcultural including racial variations in psychopharmacological research in a nascent area, necessitating clinical trials of drugs in diverse populations

The present study was part of a multicentered clinical trial carried out at 7 centres to assess the safety and efficacy of olanzapine vs haloperidol in the treatment of schizophrenic patients in India. In this report, data from only one centre is being presented.

MATERIAL AND METHOD

Patients were selected from those who were attending outpatient facility or admitted in the ward of Psychiatry Department of PGIMER, Chandigarh.

This was an open-label study of total 30 male/female inpatients and out patients between 18 to 65 years of age who met the DSM-IV criteria for schizophrenia (APA,1994) and had an initial score of atleast 3 on the CGI Severity Scale (Guy,1976) After describing various aspects of the study to the patients/guardians, informed consent was obtained

Study period I was the screening and washout period of the study. Study period II was the therapy period of the study and consisted of 12 weeks of open label therapy. At visit I (study period I) detailed history and psychiatric examination of the patients was done and clinical laboratory tests (all tests of clinical chemistry, hematology and hepatitis screen) were performed. Patients who were found to be positive for hepatitis surface antigen (HBs Ag), IgM fraction of the hepatitis core antibody (anti-HBc[IgM]) or had jaundice, current agranulocytosis (absolute neutrophil count <500 mm^3) were excluded from the study. Patients who qualified all the inclusion criteria at visit 2 were randomly assigned to the treatment group of either olanzapine or haloperidol. Either drug could be subsequently increased by 10 mg/day to 20 mg/day or decreased to a minimum of 5 mg/day as clinically warranted. Patients were assessed at 1 week interval from visit 2 to visit 6 and then after every 2 weeks from visit 6 to 10.

The primary efficacy measure was the mean change from baseline to end point on Brief Psychiatric Rating Scale's (BPRS) total score derived from Positive And Negative Syndrome Scale (PANSS Kay et al.,1986), Scale for the Assessment of Negative Symptoms (SANS) (Andreason,1983), Montgomery - Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg,1979), Hamilton-Anxiety Scale (HAM-A) (Hamilton,1959), Clinical Global Impression Scale (CGI) (Guy,1976), and Quality of Life Scale (QOL) (Heinrich et al ,1984).

Treatment emergent adverse events including extrapyramidal symptoms were assessed by UKU Side Effect Rating Scale (Lingjaerde et al.,1987), Simpson Angus Scale (Simpson and Angus,1970), Barnes Akathisia Rating Scale (Barnes,1989), and by changes in vital signs and laboratory tests.

RESULTS

A total of 30 patients were included in the study. Of those 30, 27 patients were randomized to treatment group. Two patients were excluded from the study as one patient was found to be positive for Anti-HBc (IgM) and the other patient

was positive on HBs Ag. The third patient was excluded from the study because she had tardive dystonia and she got randomized to haloperidol, so the physician decided against exposing the patient to this study drug.

10 patients were randomized to haloperidol and 17 patients were randomized to olanzapine. In haloperidol group 7 patients completed the protocol, 2 patients were lost to follow up and 1 patient was dropped from the study as he developed severe side effects. In olanzapine group 16 patients completed the trial as per protocol and 1 patient was lost to follow up. Thus, 23 patients completed the protocol, 7 in haloperidol group and 16 in olanzapine group.

Results revealed that improvements in mean scores from baseline to the endpoint of Brief Psychiatric Rating Scale (BPRS) total score extracted from Positive and Negative Syndrome Scale (PANSS) was significant in both the groups: olanzapine group (t-5.87 p<.01), as well as haloperidol group (t-2.49 p<.05). On BPRS positive score too both the groups have shown significant mean improvement from baseline to the endpoint. However, on BPRS - Negative and BPRS - Anxiety subscales, haloperidol group showed no significant mean improvement whereas olanzapine group had shown significant improvement on BPRS negative and BPRS anxiety subscales (Table 1 and 2).

On positive symptoms, negative symptoms and general psychopathology subscales of Positive and Negative Syndrome Scale (PANSS) both the groups i.e. olanzapine group and haloperidol group had shown significant mean improvement from baseline to the endpoint (Table 1 and 2). On overall psychopathology, based on the CGI Severity Scale, both the groups have shown significant improvement (OLZt=5.96 p<0.01, HALt=3.87 p<0.05).

On Montgomery - Asberg Depression Rating Scale (MADRS) and Hamilton - Anxiety Scales (HAM-A), haloperidol group showed no significant mean improvement from baseline to endpoint, whereas, olanzapine group showed significant improvement on both MADRS and HAM-A. There was no significant improvement on Global Rating of Affective

TABLE 1
BASELINE TO END-POINT SCORES OF RATINGS SCALES IN OLANZAPINE GROUP

	Olanzapine group (n=16)				
	Base line		End point		
	M	SD	M	SD	t-ratio
BPRS-total	23.31	9.94	9.50	7.06	5.87**
BPRS-positive	9.12	5.35	3.75	4.25	4.87**
BPRS-negative	5.06	4.14	3.12	3.42	2.64**
BPRS-anxiety	4.19	2.20	1.31	1.66	5.49**
PANSS-positive	19.37	7.06	11.44	4.11	4.06**
PANSS-negative	21.87	7.69	15.62	7.93	4.52**
PANSS-GenPsyPath	36.56	9.46	25.12	5.25	4.83**
MADRS	9.12	5.15	3.00	2.42	5.68**
HAM-A	8.31	5.13	2.31	2.47	4.67**
CGI-severity	4.68	0.89	3.19	0.98	5.96**
Affecting flattening	1.69	1.54	1.19	1.28	1.96
Alogia	1.37	1.26	1.06	1.12	1.31
Avoilition	2.31	1.45	1.50	1.32	2.55**
Anhedonia	2.87	1.31	1.81	1.38	3.88**
Attention	1.68	1.63	0.94	1.12	2.27*
SANS total score	32.94	19.69	21.87	19.47	2.95*
Barnes akathisia	0.44	1.09	0.00	0.00	1.60
Simpson-Angus	1.37	1.71	0.75	1.39	1.40
Quality of Life (total score)	47.0	24.64	51.19	23.38	1.03

* Significant at 0.05 level
** Significant at 0.01 level

TABLE 2
BASELINE TO END-POINT SCORES OF RATINGS SCALES IN HALOPERIDOL GROUP

	Haloperidol group (n=7)				
	Base line		End point		
	M	SD	M	SD	t-ratio
BPRS-total	25.00	4.56	12.57	13.39	2.49*
BPRS-positive	7.43	5.53	3.00	5.51	2.46*
BPRS-negative	5.29	2.50	3.57	2.37	1.58
BPRS-anxiety	4.86	2.34	2.71	2.87	1.73
PANSS-positive	19.29	10.86	10.86	8.49	2.95*
PANSS-negative	23 29	8.37	16.86	8.71	2.54*
PANSS-GenPsyPath	38.29	9.45	26.57	8.73	2.87*
MADRS	10.29	4.61	5.00	4.58	2.29
HAM-A	9.71	3.80	4.57	4.72	1.91
CGI-severity	4.29	1.11	2.86	1.57	3.87*
Affecting flattening	2.14	1.21	1.57	0.97	1.37
Alogia	2.14	0.90	1.14	1.21	2.29
Avoilition	2.57	0.98	1.57	1.27	1.73
Anhedonia	2.71	0.76	2.57	1 72	0.33
Attention	2.43	0.98	1.71	1.70	1 07
SANS total score	39.71	12.05	27.43	19.48	2 07
Barnes akathisia	0.43	0.79	0.29	0 49	0 55
Simpson-Angus	1.43	2.57	0.86	1.86	0.43
Quality of Life (total score)	38.29	31.74	49.14	33.88	1.82

* Significant at 0.05 level
** Significant at 0.01 level

Flattening or Blunting and Alogia subscales of scale for the Assessment of Negative Symptoms (SANS) in both the groups. On global rating of avolition - apathy, anhedonia and attention subscales of SANS as well as on SANS total score, only olanzapine group had shown significant mean change from baseline to endpoint, as compared to haloperidol group.

On Barnes Akathisia Scale and Simpson Angus Scale both groups showed no significant change from baseline to endpoint. The same was true for Quality of Life. Nearly the same trends are noticed upon comparing the mean change in scores from baseline to endpoint and percentage reduction of scores on various rating scales in the two study groups, but for Alogia subscale of SANS, Barnes Akathisia and QOL (Table 3).

TABLE 3
COMPARISON OF MEAN CHANGE AND PERCENTAGE REDUCTION OF SCORES

	Olanzapine group		Haloperidol group	
	Mean change	% reduction	Mean change	% reduction
BPRS-total	13.81	59.2	12.43	49.7
BPRS-positive	5.37	58.9	4.43	59.6
BPRS-negative	1.94	38 3	1.71	32.4
BPRS-anxiety	2.87	68.7	2.14	44.1
PANSS-positive	7.94	41.4	8.43	43.7
PANSS-negative	6 25	28.6	6.43	27.6
PANSS-GenPsyPath	11.44	31.3	11.71	30.6
MADRS	6.12	67.1	5.30	51.4
HAM-A	6 00	72.2	5 14	52.9
CGI-severity	1.50	32.0	1.43	33.3
Affecting flattening	0.50	29.6	0.57	26.6
Alogia	0.31	22.7	1.00	46.7
Avoilition	0.81	35.1	1.00	38.9
Anhedonia	1.06	37.0	0.14	5 3
Attention	0.75	44.4	0.71	29.2
SANS total score	11.06	33.6	12.29	30.9
Barnes akathisia	0.44	100.0	0.14	33 4
Simpson-Angus	0.62	45.4	0.57	39.9
Quality of Life (total score)	4.18	8.9	10 86	28.4

Side effects Patients receiving olanzapine did not report epileptic seizures, EPS or any side effects related to CVS, GIT, dermatology, sexual and reproductive functioning. Treatment emergent side effects i.e. possibly drug-related undesirable effects or increase in severity of baseline experiences unrelated to the diagnosis under study, after the initiation of the study - drug revealed that weight gain was the commonest side effect with olanzapine.

Sleepiness, increased duration of sleep and asthenia was observed in more number of patients in olanzapine group than haloperidol group.

Pstients receiving haloperidol also did not report epileptic seizures or any side effects related to CVS, GIR, dermatology and sexual functioning. EPS like rigidity and tremors were reported in more number of patients in haloperidol group than olanzapine group. Tension/inner unrest was also reported more in haloperidol group.

TABLE 4
COMPARISON OFTREATMENT EMERGENT SIDE-EFFECT

	Olanzapine group (N=16)		Haloperidol group (N=7)	
	N	%	N	%
Asthenia	7	43.7	3	42.9
Sleepiness	8	50.0	2	28.6
Tension	-	-	4	57.1
Increase duration of sleep	7	43.7	2	28.6
Dystonia	-	-	1	14.3
Rigidity	1	6.2	5	71.4
Hypokinesia	1	6.2	2	28.6
Tremor	5	31.2	4	57.1
Akathesia	1	6.2	2	28.6
Accomodation disturbance	-	-	2	28.6
Increased salivation	3	18.7	-	-
Reduced salivation	4	25.0	-	-
Constipation	5	31.2	-	-
Micturition disturbances	1	6.2	2	28.6
Weight gain	13	81.2	2	28.6
Others*	5	31.2	7	100

*Others : Polyuria, orthostatic dizziness, papitations, nausea, increased sweating and menstrual disturbances

DISCUSSION

Results of the study indicate that when compared to haloperidol, olanzapine had equal effect in improving overall psychology, positive symptoms and severity of schizophrenic illness. In clinical studies conducted in its development, olanzapine has shown therapeutic efficacy that is at least comparable (and in some instances superior) to that of conventional antipsychotic drugs (Beasley et al, 1996, 1996a, 1997; Tollefson

et al, 1997; Tran et al, 1997).

On negative symptoms, haloperidol group showed significant mean improvement only on PANSS - negative subscale and there was no significant improvement shown by haloperidol group on BPRS - negative, SANS - total, SANS-subscales. Though there was greater difference in mean change of Alogia subscale of SANS in haloperidol group than olanzapine group, but it did not emerge significant.

Olanzapine group showed significant improvement on BPRS-Negative, PANSS - Negative Scale, SANS-total and Avolition-apathy, Anhedonia and Attention subscales of SANS. There was no significant improvement on Affective Flattening and Alogia Sub-scales of SANS. Significant superior treatment benefits of olanzapine relative to haloperidol for negative symptoms among patients with schizophrenia have been previously reported (Beasley et al.,1997; Tollefson et al.,1997; Tollefson and Sanger,1997).

Tollefson and Sanger (1997) demonstrated that high dose olanzapine had significantly greater direct effect than placebo on all SANS dimension except anhedonia-asociality. Olanzapine also demonstrated a significantly greated direct effect than haloperidol on negative symptoms especially on the dimentions of affective-flattening and avolition-apathy. In our study, olanzapine group showed significant improvement on avolition-apathy but not on dimension of affective flattening.

Conventional neuroleptics reportedly fail to provide a sustained reduction in primary or deficit negative symptoms for the majority of patients (Kane and Mayeroff,1989; Liberman,1993). Negative symptoms impose great suffering on patients by impending their rehabilitation and psychosocial functioning (Breier et al.,1991). A superior negative symptom outcome is a principal objective in novel antipsychotic drug development (Kirkpatrick & Carpenter, 1995). Meltzer (1995) commented that a pleotrophic pharmacology (similar to that of olanzapine) may convey a therapeutic advantage in the treatment of negative symptoms.

Olanzapine group showed significant improvement on MADRS and HAM-A scales whereas haloperidol group did not show any significant mean improvement on both MADRS and HAM-A Scales. Secondary depression, which is common in schizophrenia, is predictive of a poorer prognosis, including greater difficulty reintegrating into society and a higher risk of suicide. It has been suggested in the literature (Harrow et al, 1994) that neuroleptic drugs may actually induce dysphoria. Tollefson et al (1998) reported data from a double blind, controlled, multicentre trial of treatment of exacerbations of schizophrenia or schizo-affective disorder with olanzapine versus haloperidol and found significant greater improvement in depressive symptoms with olanzapine.

The broad receptor profile of olanzapine may contribute to this treatment differeence. The density of 5-HT_{2A} receptors, for example, has been reported to be increased among patients with major depression. Accordingly, olanzapine as a potent 5-HT_{2A} antagonist, may act at these sites, similar to the action of the recently approved antidepressant nefazodone (Nemrick Luecke et al, 1994). The importance of these mood related findings is clinically relevant regardless of whether they are primary or secondary therapeutic effects (Tollefson et al, 1997).

Studies have also reported that patients treated with olanzapine show greater improvement in quality of life as compared to patients treated with haloperidol (Beasley et al, 1996; Tollefson et al, 1997; Tollefson and Sanger, 1997; Beasley et al, 1997). However, in the present study olanzapine group did not show significant improvement in quality of life.

The most common side effects related to olanzapine was weight gain, sleepiness and increased duration of sleep. Our results reaffirm earlier assertions that compared with traditional antipsychotics, olanzapine has a vastly improved extra-pyramidal side-effect profile (Casey 1996).

In conclusion, the analysis indicate that olanzapine is effective in the improvement of overall psychopathology including positive symptoms, negative symptoms and secondary depressive

features and it is safe and well tolerated at dosage between 5 to 20 mg/day. However, small sample size and open-label trial are major limitations for any definitive assertions.

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