ORIGINAL ARTICLE

Olanzapine has better efficacy compared to risperidone for treatment of negative symptoms in schizophrenia

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ABSTRACT

Objective: The safety and efficacy profile of risperidone and olanzapine were compared in a double-blind trial that used doses widely accepted in clinical practice.

Methods: Subjects ($n = 71$) who met Diagnostic and Statistical Manual of Mental Disorders-IV criteria for schizophrenia were randomly assigned to receive 2–8 mg/day of risperidone (mean modal dose = 5.5 mg/day) or 5–20 mg/day of olanzapine (mean modal dose = 14.4 mg/day) for 1 year.

Results: The two study groups were similar at baseline in all aspects. Seventy-four percent of the participants completed the trial, with no between-differences in the proportion of dropouts. Olanzapine group showed significantly greater improvement in negative symptoms in assessments at 3rd, 6th, 9th, and 12th months ($P = 0.05, 0.00, 0.00,$ and 0.00, respectively). Clinical global impression of severity (CGI-S) scores were consistently lower in the olanzapine group at 3rd, 6th, and 9th months ($P = 0.01, 0.03,$ and 0.05, respectively) as measured by positive and negative symptom scale (PANSS). Total scores on PANSS, positive symptoms, general psychopathology, and CGI improvement showed comparable improvement at 3rd, 6th, 9th, and 12th months of follow-up (all subjects, including dropouts). Severity of extrapyramidal symptoms was low in both groups, with no between-group differences. Mean change in body weight, fasting blood sugar, and fasting cholesterol was comparable in both groups. Risperidone group had significant hyperprolactinemia after one year ($P = 0.03$).

Conclusions: Both treatments were well-tolerated and efficacious. Greater reductions in severity of the illness and negative symptoms were seen with olanzapine consistently through 1 year. The frequency and severity of extrapyramidal symptoms were negligible and similar in the two treatment groups. Weight gain, hyperlipidemia, and hyperglycemia were comparable in both groups. Risperidone produced significant hyperprolactinemia.

Key words: Negative symptoms, olanzapine, positive symptoms, risperidone, schizophrenia

INTRODUCTION

Schizophrenia is a debilitating mental illness that afflicts about one percent of the population.[1] Antipsychotic medication is the mainstay of treatment for this condition, and there is a trend toward greater use of newer antipsychotics, especially risperidone and olanzapine.[2] Recent reports have shown that olanzapine and risperidone account for nearly half of all the antipsychotics prescribed and more than 90% of the atypical antipsychotics prescribed in the UK.[3] Olanzapine and risperidone along with haloperidol are the most common antipsychotics prescribed in India.[4]

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Access this article online	
Website: www.indianjpsychiatry.org	**Quick Response Code**
DOI: 10.4103/0019-5545.192016	

Olanzapine and risperidone are both second-generation antipsychotic agents. Even though they share same *in vitro* properties, they differ by virtue of their chemical structure, spectrum of receptor binding affinities, neuropharmacology, pharmacokinetics, and *in vivo* neuroimaging profile.[5] Risperidone is principally a dopamine-2 (D_2) and serotonin-2 (5-HT$_2$) receptor antagonist.[6] In addition to potent 5-HT$_{2A/2C}$, 5-HT$_3$, and 5-HT$_6$ receptor antagonism, olanzapine further exhibits affinity for dopamine D_1, D_2, D_3, and D_4 receptors and selective muscarinic-binding sites.[7]

In clinical practice, the choice of an atypical antipsychotic hinges mostly on the potential side effect profile of the drug rather than on differential therapeutic characteristics. To an extent, this was backed by a number of studies which showed that there is no definitive therapeutic superiority of either risperidone or olanzapine over the other.[8,9] However, some authors have pointed out that the lack of differences in efficacy may be due to limitations of the evidence base.[8]

In recent years, a number of studies have contested the idea that risperidone and olanzapine have identical clinical efficacy profile. Some studies do suggest that patients on olanzapine sustain a better treatment response in comparison to risperidone.[5] A meta-analysis of 212 randomized controlled trials to compare 15 antipsychotic drugs and placebo in the acute treatment of schizophrenia found that efficacy of olanzapine is marginally superior to that of risperidone.[10] In a 1 year naturalistic study, a significant number of patients who switched from risperidone to olanzapine experienced significant improvement in clinical and functional outcomes.[11] A Cochrane review concluded that olanzapine improved the general mental state (total positive and negative syndrome scale [PANSS] score) better than risperidone.[12]

At the same time, there are studies with contradictory results of clinical advantage with risperidone with greater reduction of positive and affective symptoms in comparison to olanzapine.[13]

To the best of our knowledge, studies from India comparing olanzapine and risperidone have typically focused on the tolerability and side effect profile, especially the metabolic side effects rather than on comparison of clinical efficacy.[14,15] We believe that the question of differential therapeutic characteristics of olanzapine and risperidone in schizophrenia is important as they are the most widely used atypical antipsychotics in India. Further information about the nature and magnitude of clinical improvement with these drugs would help in tailoring the treatment with the clinical profile of the patient.

The hypothesis of this study was that both olanzapine and risperidone are equally effective in the treatment of schizophrenia with similar side effect profile.

Aims

- To compare the efficacy of adequate dose of olanzapine versus adequate dose of risperidone in schizophrenia
- To compare the safety of adequate dose of olanzapine versus adequate doses of risperidone in schizophrenia.

METHODS

Study procedure

This trial was a randomized, double-blind, parallel-group comparison of risperidone and olanzapine in schizophrenia conducted at the Psychiatry Department of KMCT Medical College, Kozhikode, for 1 year.

A total 71 patients were included. They were divided into 2 groups, olanzapine ($n = 36$) and risperidone ($n = 35$) using random sampling technique.

Inclusion and exclusion criteria

Both inpatients and outpatients fulfilling a Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosis of schizophrenia aged 18–64 years were included. Patients with any other DSM-IV axis I diagnosis or a retrospective DSM-IV diagnosis of substance abuse in the 3 months before selection were excluded. Documented disease of the central nervous system, use of concomitant therapy such as mood stabilizers or antidepressants, prior exposure to olanzapine or risperidone were other reasons for exclusion.

Study design

The study was started after obtaining approval from the Institutional Ethics Committee. Informed consent was taken from the patient's relative in cases where the patient was not fit for giving consent. The screening evaluation included a diagnostic interview using Structured Clinical Interview for DSM-IV. Patients in maintenance phase were recruited for the study. During the week before the subject's assignment to one of the two treatment groups, all oral antipsychotics and anticholinergic medications currently taken by the subjects were gradually discontinued. Any depot antipsychotics were discontinued for at least one treatment cycle before the subject was assigned to a study group.

The 71 participants were then randomly assigned to receive risperidone (2–8 mg/day) or olanzapine (5–20 mg/day) for 48 weeks.

The investigators and the patients were blind to the medication. Olanzapine tablets were available in the dose ranges of 2.5, 5, 7.5, and 10 mg tablets (A1, A2, A3, and A4) and risperidone tablets were available in the dose ranges of 1, 2, 3, and 4 mg (B1, B2, B3, and B4). Both these tablets were identical in size, shape, and color. This was achieved by embedding the tablets in identical empty capsules.

The dose of these drugs was increased in identical fashion depending on the clinical response as well as side effects such as A1 bid for few days, then A2 bid for few days, A3 bid for few days, and A4 bid for few days, which was the maximum dose range.

The concomitant medications allowed were trihexyphenidyl, propranolol, and lorazepam. The number of pills taken was determined by pill counts, and use of concomitant or adjunctive medication was recorded at each study visit. The modal dose for each patient within a treatment group was the dose prescribed for that patient on the maximum number of days during the trial.

Study sample was recruited from patients on maintenance phase only for homogeneity. Only a small proportion of approached patients refused to give consent for the study. Both patients and investigators were blind to the medication allocation during assessments. Efforts were made to control for confounding variables such as adjunctive medications.

Assessment tools

- Structured Clinical Interview for DSM-IV (SCID)[16]
- PANSS[17]
- Clinical global impression of severity (CGI-S)[18]
- CGI of improvement[18]
- Simpson-angus scale[19]
- Barnes akathisia rating scale (BAS)[20]
- Abnormal involuntary movement scale (AIMS)[21]
- UKU side effect rating scale[22]

All the tools including standard laboratory tests and physical examination were performed at randomization visit and at weeks 4, 12, 24, 36, and 48 (or withdrawal). The primary efficacy variable, defined *a priori*, was the mean change in PANSS score at different time points (3rd, 6th, 9th, and 12th months). Efficacy parameters were assessed by Dr. Suresh. Patients were monitored for the occurrence of side effects at each visit using the concerned scales. Adverse events scales were administered by Dr. Anish. Weight was recorded at each visit. Vital signs (blood pressure and pulse were taken in the supine position (after the patient has been resting for 5 min) and standing (after the patient had been standing for 2 min) positions.

Fasting blood glucose, fasting total cholesterol, and prolactin were assessed at baseline and at the end of study (or withdrawal). Fasting was defined as no caloric consumption for eight or more hours prior to the blood draw. Serological analysis was quantitatively estimated by glucose oxidase-peroxidase method using semi autoanalyser, TRANSASIA, ERBA, and CHEM-5-PLUS.[23]

Statistical analysis

Statistical tests on all data were performed at the 5% two-tailed significance level. Baseline measures of demographic and clinical characteristics were compared for categorical variables and continuous variables using Student's *t*-test and Chi-square test, respectively. ANOVA was administered for the repeatedly measured values using the baseline scores as a covariate. Mean change from baseline to different time points was calculated using last observation-carried-forward methodology for efficacy and adverse events and compared between two groups to ascertain whether there were any significant differences between two groups.

RESULTS

Out of 71 patients, 36 were enrolled in olanzapine group and 35 in risperidone group. The mean modal doses received by the participants during the trial were 5.8 mg/day (standard deviation [SD] =1.2) of risperidone and 14.4 mg/day (SD = 4.6) of olanzapine. Similar proportions of participants in the two treatment groups completed the study (74.8% [*n* = 27] in the olanzapine group and (74.3% [*n* = 26] in the risperidone group). There was no significant difference in socio-demographic characteristics, mean duration of illness, and mean duration of treatment between the two treatment groups [Table 1]. Mean dose and number of patients received concomitant medications such as trihexyphenidyl and lorazepam were comparable [Table 2].

Efficacy

Mean baseline PANSS total score was 65 (SD = 18.3) in the olanzapine group and 61.9 (SD = 16.7) in the risperidone group, mean baseline negative symptoms score was

Table 1: Sociodemographic characteristics

	Olanzapine (*n*=36) (%)	Risperidone (*n*=35) (%)	χ^2/t	P
Age (years)	41.5±9.6	39.8±09.5	0.8	0.46
Male	25 (69.4)	11 (30.6)		
Female	23 (65.7)	12 (34.3)	0.1	0.74
Married	14 (38.9)	13 (37.1)	0.0	0.88
Education (years)	06.3±04.1	07.7±03.8	1.5	0.13
Employed	28 (77.8)	20 (57.1)	3.5	0.06
Family history of psychiatric illness	12 (33.3)	17 (48.6)	1.7	0.19
Medical illness	4 (11.1)	1 (2.9)	1.9	0.17
Duration of illness (months)	157.8±119.6	166.2±119.6	0.3	0.74
Duration of treatment (months)	136.0±101.1	150.1±143.1	0.5	0.63

Table 2: Adjuvant medications

	Olanzapine (*n*=36)	Risperidone (*n*=35)	χ^2/t	P
Total dose of trihexyphenidyl (mg)	188.1±195.8	228.1±173.0	0.5	0.63
Number of patients who received trihexyphenidyl	7	15	0.0	0.03
Total dose of lorazepam (mg)	70.2±74.9	46.3±47.2	1.3	0.19
Number of patients who received lorazepam	22	27	0.1	0.09

17.1 (SD = 6.6) in the olanzapine group and 17.5 (SD = 9.2) in the risperidone group, mean baseline CGI score was 2.1 (SD = 0.84) in the olanzapine group and 2.1 (SD = 1.1) in the risperidone group, and mean baseline CGI severity score was 4.3 (SD = 1.1) in the olanzapine group and 3.9 (SD = 1.0) in the risperidone group, which were comparable. Improvements in PANSS negative subscale were significantly higher in olanzapine group at 3rd, 6th, 9th, and 12th months of follow-up (P = 0.05, 0.00, 0.00, and 0.00, respectively). Mean CGI severity scale showed a consistently significant difference at 3rd, 6th. and 9th months of follow-up in favor of olanzapine (P = 0.01, 0.03, and 0.05, respectively). Comparison of mean change in the score of CGI improvement from baseline to 3rd, 6th, 9th, and 12th months of follow-up showed comparable improvement in both groups [Table 3].

Adverse events

Serious adverse events were experienced by none of the participants. Comparison of mean change in score from baseline to different time points of assessment in the simpson angus scale, BAS, AIMS [Table 4], and UKU side effects scale [Table 5] were comparable in both groups.

Metabolic parameters

The baseline mean value of fasting blood sugar (olanzapine vs. risperidone; 100.7 vs. 93.4; P = 0.48), mean baseline total cholesterol values (olanzapine vs. risperidone; 163.4 mg/ml vs. 176 mg/ml; P = 0.13), and mean baseline prolactin levels (olanzapine vs. risperidone; 18.7 vs. 11.7; P = 0.08) were comparable. Mean change in prolactin level from baseline to the end of study (20.8 vs. 44.4; P = 0.03) was significantly higher in the risperidone group [Table 6].

DISCUSSION

In this prospective study of risperidone and olanzapine in clinically relevant doses, both antipsychotic drugs were generally safe and efficacious in treating schizophrenia. Both the groups were comparable in terms of socio-demographic characteristics, mean duration of illness, and treatment. In addition, dropouts were comparable in both the groups.

The mean modal doses of risperidone (5.8 mg/day) and olanzapine (14.4 mg/day) received by the participants in this study are similar to those used in current clinical practice (4.5 mg/day of risperidone and 12.7 mg/day of olanzapine) (National dosing data for schizophrenia).[24] Optimal dosing is important to study interpretation. In addition to reducing tolerability, excessive doses may actually reduce efficacy, perhaps because of the loss of an optimal receptor occupancy (e.g., D_2) range, or because of an optimal binding pattern across different receptors (e.g., across 5-HT, D_2, and α_2).[25,26]

With respect to efficacy, mean change in PANSS negative symptoms and overall severity of illness showed significantly

Table 3: Score of positive and negative symptom scale total, positive and negative, clinical global index severity and clinical global index-improvement at baseline and change from baseline at (3rd, 6th, 9th, and 12th month)

	Mean±SD		P
	Olanzapine (*n*=36)	Risperidone (*n*=35)	
PANSS total score			
Baseline	65.0±18.3	61.9±16.7	0.46
3rd month	41.2±10.8	39.4±9.9	0.19
6th month	41.6±8.6	41.1±11.9	0.74
9th month	40.5±8.8	40.7±10.0	0.77
12th month	39.2±9.0	38.0±7.4	0.54
PANSS positive			
Baseline	17.1±6.6	17.5±6.8	0.77
3rd month	9.1±3.5	9.2±2.4	0.99
6th month	9.0±3.5	9.6±3.3	0.73
9th month	9.1±3.4	10.3±5.02	0.30
12th month	8.7±2	93.5	0.34
PANSS negative			
Baseline	16.8±6.3	18.9±7.9	0.23
3rd month	10.9±3.7	11.7±4.4	0.05*
6th month	12.1±4.2	12.2±3.7	0.00*
9th month	10.8±4.1	11.5±4.3	0.00*
12th month	9.5±3.7	10.7±4.5	0.00*
CGI improvement			
3rd month	2.1±0.84	2.1±1.1	0.89
6th month	1.5±0.80	1.8±1.1	0.56
9th month	1.7±0.80	1.6±0.8	0.19
12th month	1.7±0.80	1.70.7	0.41
CGI severity			
Baseline	4.3±1.1	3.9±1.0	0.19
3rd month	3.0±0.80	2.9±0.8	0.01*
6th month	2.8±0.8	3.0±0.6	0.03*
9th month	3.0±0.9	2.9±0.8	0.05*
12th month	3.01.01	2.9±0.8	0.08

*Significant. PANSS – Positive and negative symptom scale; CGI – Clinical global index; SD – Standard deviation

Table 4: Scores of Simpson Angus scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale score at baseline and change from baseline to 3rd, 6th, 9th, and 12th months

	Mean±SD		P
	Olanzapine (*n*=36)	Risperidone (*n*=35)	
Simpson Angus scale			
Baseline	0.9±2.4	0.5±1.2	0.38
3rd month	1.0±2.8	1.7±3.4	0.30
6th month	1.1±3.3	1.6±2.6	0.48
9th month	0.9±2.0	0.4±0.8	0.35
12th month	0.8±2.5	0.1±0.4	0.29
Barnes Akathisia Scale			
Baseline	0.2±0.9	0.02±0.2	0.23
3rd month	0.2±0.9	0.03±0.2	0.39
6th month	0±0	0.1±0.5	0.30
9th month	0±0	0.06±0.3	0.30
12th month	0.2±0.6	0±0	0.37
AIMS score			
Baseline	0.2±0.4	0.2±0.5	0.61
3rd month	0.2±0.4	0.2±0.4	0.91
6th month	0.2±0.4	0.2±0.4	0.51
9th month	0.1±0.3	0.2±0.4	0.94
12th month	0.2±0.4	0.3±0.6	0.94

AIMS – Abnormal Involuntary Movement Scale

Table 5: Scores of Udvalg for Kliniske Undersøgelser side effects at baseline and change from baseline to 3rd, 6th, 9th, and 12th months

| | UKU side effects scale | | P |
| | Mean±SD | | |
	Olanzapine (*n*=36)	Risperidone (*n*=35)	
Psychological			
Baseline	1.7±1.7	1.6±2.1	0.83
3rd month	1.8±1.3	2.3±2.6	0.52
6th month	1.9±1.5	1.7±1.6	0.39
9th month	1.6±1.2	1.4±1.2	0.17
12th month	1.8±1.5	1.31.0	0.07
Neurological			
Baseline	0.4±1.0	0.6±0.9	0.45
3rd month	0.6±1.4	0.8±1.5	0.89
6th month	0.3±0.7	0.8±1.5	0.30
9th month	0.2±0.4	0.2±0.4	0.61
12th month	0.30.8	0.10.3	0.12
Autonomic			
Baseline	0.4±0.6	0.4±0.9	0.32
3rd month	0.2±0.5	0.6±1.1	0.13
6th month	0.4±0.6	0.3±0.7	0.56
9th month	0.2±0.4	0.3±0.7	0.70
12th month	0.1±0.5	0.3±0.5	0.69
Others			
Baseline	1.4±3.0	1.3±2.9	0.38
3rd month	2.1±3.4	2.1±3.7	0.86
6th month	2.3±3.4	1.4±2.2	0.22
9th month	2.0±3.1	1.6±3.2	0.47
12th month	1.6±2.8	2.1±3.0	0.80

SD – Standard deviation

Table 6: Comparison of body weight (baseline to 3rd, 6th, 9th, and 12th month), mean change in fasting blood sugar, total serum cholesterol, and serum prolactin (baseline to 12th month)

| | Mean±SD | | P |
	Olanzapine (*n*=36)	Risperidone (*n*=35)	
Body weight (kg)			
Baseline	54.1±10.3	52.9±10.9	0.64
3rd month	56.5±10.2	54.1±11.7	0.43
6th month	54.7±5.6	54.4±11.3	0.06
9th month	55.2±5.2	54.8±12.3	0.34
12th month	55.0±6.8	55.2±14.4	0.33
Fasting blood sugar (mg/mL)			
Baseline	100.7±69.1	93.4±26.7	0.59
Mean change at end point	108.9±61.7	91.7±20.7	0.48
Total serum cholesterol (mg/mL)			
Baseline	163.4±26.9	176.0±38.3	0.13
Mean change at end point	181.5±35.1	190.3±39.8	0.32
Serum prolactin (ng/mL)			
Baseline	18.7±31.9	11.7±11.2	0.36
Mean change at end point	20.8±27.1	44.4±31.9	0.03*

*Significant. SD – Standard deviation

higher improvement in the olanzapine group at 3rd, 6th, 9th and 12th, months of assessment. This suggests that olanzapine offers specific advantage with respect to negative symptoms compared to risperidone while efficacy is comparable in positive symptoms. The clinical superiority of olanzapine over risperidone in negative symptoms has been noted by Tran *et al*. in a 28-week prospective study.[10] An analysis of data from 12 randomized controlled trials studying the effects of atypical antipsychotics and haloperidol on various PANSS subscales using pharmacokinetic and pharmacodynamic modeling revealed that olanzapine is more efficacious than other drugs in treating negative symptoms.[27] In a meta-analysis studying the effect of various antipsychotics on negative symptoms, the effect size of olanzapine is larger than risperidone.[28]

The clinical advantage of olanzapine in negative symptoms and overall improvement persisted till the end of 1 year of the duration of the study. This suggests that starting a patient on schizophrenia with prominent negative symptoms on olanzapine in comparison to risperidone may offer an advantage that could persist beyond 1 year. Moreover, this benefit is visible within 3 months of initiating medications.

This is an important finding. As negative symptoms are closely associated with functional impairment, using olanzapine may be advantageous in shortening the socio-occupational dysfunction in comparison to risperidone. This finding may be particularly important in a low-middle income country such as India where even short duration of unemployment may have dire consequences for the family in the absence of the social security net. Because of the associated sedation, there is often reluctance from the clinicians to use olanzapine in situations where early improvement in functioning is highly desirable. Current findings suggest that there could be a clinical advantage with olanzapine which offsets the effects of sedation.

None of the participants experienced serious adverse events. Moreover, severity of extrapyramidal symptoms was significantly less over the course of the study in both groups. Both groups showed consistent weight gain after 3 months. The differences were not significant between the groups. Substantial health risks are associated with weight gain, a factor deserving careful consideration in long-term therapy.[29] In the present study, there were no significant differences in the changes in blood sugar levels between the olanzapine and risperidone groups. The rise in prolactin levels were significantly more in the risperidone group compared to olanzapine group (*P* = 0.03). This is consistent with previous studies.[30,31]

CONCLUSIONS

Both risperidone and olanzapine were generally well-tolerated and efficacious in the treatment of patients with schizophrenia. Olanzapine showed a significant advantage over risperidone in improving negative symptoms and overall clinical severity. This advantage is visible within 3 months of initiating treatment. The frequency and severity of extrapyramidal symptoms were considerably less and

comparable between the groups. Risperidone produced significant hyperprolactinemia.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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