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Comparative Evaluation of Efficacy and Safety of Lurasidone & Olanzapine in Patients of Schizophrenia: A Randomized, Parallel Group Clinical Study

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Abstract

Background: Since very few studies were available in Indian population about efficacy, safety of lurasidone versus olanzapine, so these were compared in this trial.
Objective: To compare the efficacy and safety of lurasidone with olanzapine in the treatment of schizophrenia and study the adverse effects of lurasidone.
Materials and Methods: Sixty-four schizophrenic patients were recruited into one of the assigned groups for random allocation to olanzapine or lurasidone (n=32 in each group) in open- label, 12 week clinical trial and their guardians informed consent was taken. PANSS (positive and negative syndrome scale) was used as the primary outcome measure and Clinical Global Impression Severity Score (CGI-S) was employed as secondary scale.
Results: Within-group analysis both of olanzapine and lurasidone were significantly effective for improvement of PANSS total score and CGI-S ($P < 0.0001$). But in between-group analysis there is statistically significant reduction in PANSS total score ($P < 0.001$) and CGI-S score ($P < 0.0001$) in lurasidone group than olanzapine.
Conclusion: Lurasidone is superior to olanzapine in efficacy and safety in patients of schizophrenia. Lipid profile and blood sugar monitoring should be done in patients on long-term olanzapine therapy.
Keywords: Antipsychotics, Positive and negative syndrome scale, Psychotic disorders, lurasidone, olanzapine, schizophrenia.

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1. Introduction

Lurasidone is a second-generation antipsychotic agent that received regulatory approval in the USA in 2010 and 2016 in India.[1,2] The antipsychotic action of lurasidone is mediated mainly through antagonistic activity at $5HT_7$ (antagonism), α_2c, $5HT_{1A}$ (partial agonism), $5HT_{2A}$, and D_2 receptors.[3,4] Olanzapine is a well-established atypical antipsychotic, with a high affinity for $5HT_2$, H_1, with α_1 , D_1 and D_2 receptors and is effective without producing disabling extrapyramidal adverse effects associated with older typical antipsychotic drugs.[5,6] However, is associated with significant increases in body weight, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and fasting insulin.[7] At high doses it also produces anticholinergic effects.[8] 20% patients of schizophrenia keep on switching amongst drugs in hope for optimal relief. [9]

There are no studies available in Indian population about efficacy, safety of lurasidone. Hence the study was planned with an aim to evaluate and compare the efficacy and safety of Lurasidone with Olanzapine.

2. Materials and methods

A prospective, randomized, active-controlled, parallel-group, comparative, open-label, phase IV study was carried out at psychiatry outpatient department (OPD) of a tertiary care teaching hospital in central India. Eligible subjects were of either sex aged between 18-65 years who attended psychiatry outdoor clinic for a first time with clinical diagnosis of schizophrenia (as per Diagnostic and Statistical Manual of Mental Disorder, edition V) [and] fulfilled the criterion of PANSS (positive and negative syndrome scale) score ≥ 80. Exclusion criteria were: (i) Pregnant, nursing women and children; (ii) Patients requiring other psychotropic medications, central nervous system active drugs; (iii) Patients with neurologic disorders (dementia, seizures, stroke), obesity, serious or unstable organic disorders (neoplasia, cardiovascular, pulmonary, uncontrolled type 1 or 2 diabetes); (iv) Patients with any other psychiatric disorders; (v) Patients with history of abnormal renal/hepatic functions. The study was approved by the Institutional Ethics Committee in tertiary care hospital and was carried out in accordance with Good Clinical Practice guidelines and the ethical principles as mentioned in the Declaration of Helsinki. Also study was registered in Clinical Trial Registry of India (CTRI/2018/01/011393)

Eligible patients were randomized using random number with allocation ratio of 1:1 to receive either Tab Lurasidone 40 mg daily in the evening with meals or Tab Olanzapine 20 mg daily in evening after meals, as per requirement of patient, decided by psychiatrist for a period of 12 weeks after obtaining their guardians written informed consent. The follow-up period was 12 weeks and total duration of study was 18 months. All expenses were born by principal investigator. Primary efficacy parameter was change in score on positive and negative syndrome scale (PANSS) from baseline to week 12. Patients were called as responders if there is decrease of ≥ 20% PANSS total score from baseline And Secondary efficacy parameters was change in score on Clinical Global Impression Severity Score (CGI-S) from baseline to week 12.

2.1 Follow-up visits

PANSS and CGI-S score was evaluated at weeks 0, 2, 8 and 12 weeks. The safety assessment was done by the clinician at every visit which included the adverse effects reported by the subjects. Laboratory investigations such as random blood sugar (RBS), Serum glutamic pyruvic transaminase (SGPT), Serum glutamic oxaloacetic transaminase (SGOT), Low density lipoprotein (LDL), Total cholesterol, Triglycerides as well as weight measurement were done at baseline and at 12 weeks.

2.2 Sample Size calculations

Sample size was estimated based on Change in PANSS score from baseline = 8 & SD = 10.7 from previous studies, with level of significance $\alpha = 0.05$ %, power = 80%. The sample size was calculated as 29 patients in each group. Considering dropout rate of 10%, sample size of 32 patients in each group was calculated. Sample size was assessed by using Power and Sample size calculation software version 3.0.4.

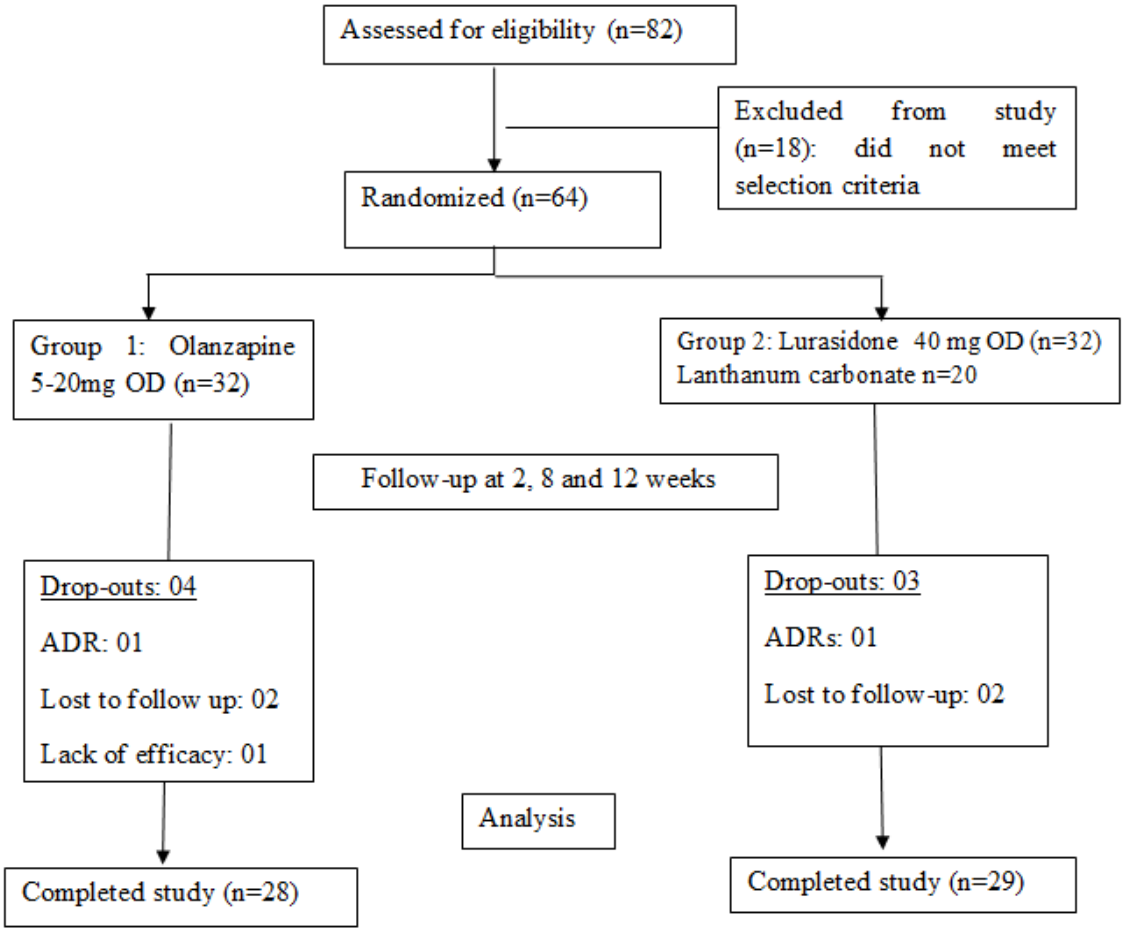
2.3 Statistical analysis

For comparisons between groups of continuous variables, independent sample t-test (unpaired t-test) and for within group, the paired t-test was used. All primary and secondary efficacy parameters were analysed by Friedmann test followed by Dunn's post-hoc test for within group comparison at different follow-up visits while Mann-Whitney U test was used for comparison between groups. Categorical data was analysed by Fisher's exact test. Value of $P \leq 0.05$ was considered statistically significant. Graph pad prism version 5.01 was used for analysis.

3. Results

57 (28 in Olanzapine group and 27 in Lurasidone group) patients completed the study according to the protocol in regular follow-up with 7 dropouts. (Fig 1) Data was analysed in accordance with per protocol analysis. Demographic characteristics of patients at baseline in both groups were comparable. Also, baseline scores of PANSS and CGI-S were comparable in both groups ($p = 0.91$ and 0.26, respectively)

Figure 1: Flow chart of the study participants



Within-group analysis showed that decrease in PANSS scores from baseline to following visits in both treatment groups were statistically significant ($P < 0.0001$). At the end of 12 week, there is statistically significant reduction of the mean PANSS scores in lurasidone group compared to olanzapine group ($P < 0.001$) [Table 1].

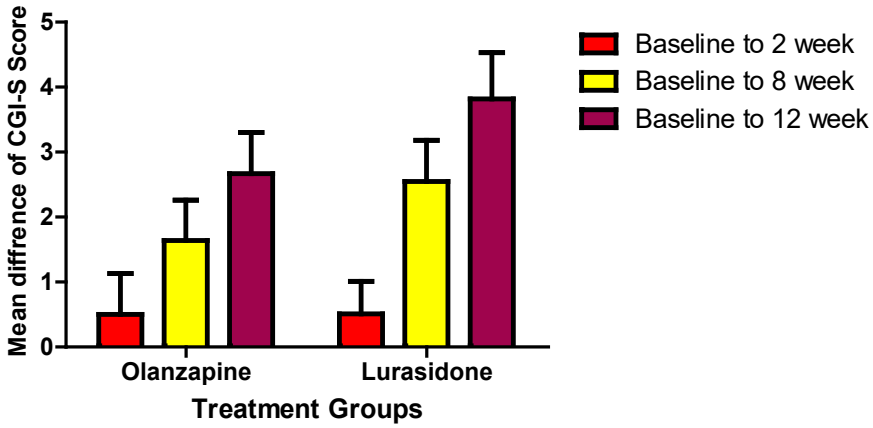
Table 1: Comparison of mean difference of PANSS scores between both treatments groups in patients of schizophrenia at 2, 8 and 12 weeks of treatment

Visits	PANSS Score	
	Olanzapine (n=28)	**Lurasidone (n=29)**
Baseline to 2 weeks	1.28 (0.71)	1.20 (0.77)
Baseline to 8 weeks	29.78 (6.14)	36.24 (8.24)*
Baseline to 12 weeks	46.5 (8.02)	53.79 (11.50)*

Values are expressed as mean (SD).
Mann-Whitney test is applied; *- P <0.001 compared to olanzapine group. PANSS: Positive and negative syndrome scale.

Within-group analysis showed that change in CGI-S score at every follow-up compared to baseline was statistically significant in both the treatment groups (P <0.0001). When compared between the two treatment groups, decrease in the mean CGI-S score was statistically significant in lurasidone group compared to olanzapine group at succeeding follow-up visits and at the end of 12th week ($P < 0.0001$) [Figure 2]

Figure No. 2: Comparison of mean difference in CGI-S score between lurasidone and olanzapine groups in patients of schizophrenia



Values are expressed as mean (SD);
Mann Whitney test is applied; *- P < 0.0001 compared to olanzapine. CGI-S: Clinical Global Impression Severity Score

Safety data analysis revealed that 6 out of 29 patients (20.68%) in the lurasidone group and 9 out of 28 patients (32.14%) in the olanzapine group reported at least one adverse event. The adverse events reported were sedation, nausea, insomnia, headache, dry mouth and dizziness. Weight gain was statistically significantly greater in olanzapine group compared to baseline ($P < 0.001$). Statistically significant increase in Random blood sugar, Total Cholesterol, LDL and Triglycerides was observed in olanzapine groups but not in lurasidone group compared to baseline at the end of 12th week. Other parameters such as liver enzyme (SGPT, SGOT) were in normal range in both the treatment groups at 12th week. [Table 2]

Table 2: Effect of study drugs on laboratory parameters after 12 weeks of treatment in patients of schizophrenia

Laboratory Parameters		Study drugs	
		Olanzapine (n=28)	Lurasidone (n=29)
RBS (mg/dl)	Baseline	99.21 (10.72)	96.37 (9.23)
	12 weeks	104.14 (10.98)	96.48 (8.83)
	p value	<0.0001	0.75
Total Cholesterol (mg/dl)	Baseline	139.21 (7.35)	143.31 (9.64)
	12 weeks	143.82 (7.46)	142.96 (9.53)
	p value	<0.0001	0.31
LDL (mg/dl)	Baseline	70.75 (8.24)	70.44 (7.81)
	12 weeks	75.53 (7.86)	70.93 (7.85)
	p value	<0.0001	0.69
Triglycerides (mg/dl)	Baseline	115.35 (9.48)	113.27 (9.24)
	12 weeks	121.71 (16.14)	113.27 (9.24)
	p value	<0.001	0.73

Values are expressed as mean (SD),
Paired t test. When 12 week reading compared to baseline. RBS - Random blood sugar; LDL - Low density lipoprotein.

4. Discussion

Both study drugs showed significant decrease in PANSS score and CGI-S score at the end of eight weeks as well as at 12 weeks, in comparison to baseline. Similar results have been reported by Ogasa *et al* and Correll *et al*.[10,11] In our study significant reduction in scores compared to baseline was evident at eight weeks in both groups. In some studies significant reduction in PANSS scores following lurasidone treatment was reported as early as one to three weeks with 40 and 120 mg/day [12] and some at 6 weeks. [10,13]

In our study, better efficacy of lurasidone is probably attributed to its additional mechanisms compared to other available second-generation antipsychotics. They are –

1) High binding affinity for serotonin 5-HT$_7$ receptors (antagonistic effects)

2) Moderate affinity for noradrenaline α_2c receptors (antagonistic effects)

In addition, it also shows high affinity and antagonist effects at dopamine D_2 and serotonin 5-HT_{2A} receptors. The precise contribution of these receptor binding affinities (1 and 2 above) towards the clinical outcomes observed with lurasidone in individuals with schizophrenia is unknown. The receptor binding profiles have predicted this potential effects.[14] Although further research will explore the facts.

Most of the studies evaluating the efficacy of lurasidone have used a dose of 40, 80 and 120 mg/day. All the three doses have reported statistically significant beneficial effects when compared with placebo.[10,12] But dose escalation of lurasidone did not show additional improvement in efficacy. On the contrary it showed increase in adverse effects.[14] Hence, we used 40 mg dose of lurasidone in our study.

In our study, olanzapine was associated with weight gain while lurasidone was not. Probable mechanism of weight gain could be blockade of histamine-1(H_1) and serotonin ($5HT_{2C}$) receptors by olanzapine.[15] But lurasidone has no significant affinity for histamine H_1 and serotonin $5HT_{2C}$ receptors.[16]

Limitation: This was an open label study

5. Conclusion

- Lurasidone is more efficacious antipsychotic drug compared to olanzapine when used for 12 weeks.
- It has a better safety profile compared to olanzapine with respect to weight gain, rise in LDL, total cholesterol, triglycerides as well as random blood sugar.

Further clinical studies are needed to support the results of our study.

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Conflicts of interest: There are no conflicts of interest.

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