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Original research article

A study of efficacy of new generation atypical antipsychotic (lurasidone) across positive & negative symptom-domains in fresh cases of schizophrenia

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Abstract

Background: Increasing antipsychotics have altered the course of schizophrenia. Few drugs have shown improvement in negative symptoms and cognitive deficits, compounded by intolerable side effects. Lurasidone is a relatively new entrant in the field of schizophrenia in the Indian context. This study evaluated the overall efficacy of lurasidone across the whole spectrum of symptoms of schizophrenia and compared the degrees of improvement in the positive and negative domains.

Methods: This is a longitudinal observational study. PANSS was administered at baseline, after 1 month, and after 3 months. A total of 57 patients, diagnosed using ICD-10 criteria, were recruited from the psychiatry OPD of MVJ Medical College and Research Hospital. 7 patients dropped out due to intolerability. The remaining was followed up. Statistical analysis of the data was done using the SPSS (Statistical Package for Social Sciences Software). Using appropriate statistical methods, dimensional comparisons were made using the central tendencies like means with S.D for lurasidone before and after treatment.

Results: In the positive scale of PANSS, the mean reduction of positive score at the end of 4 weeks was 6.13, at the end of 3 months the mean positive score was 10.900. Both scores were statistically significant. In the negative scale of PANSS, mean reduction of negative scores at the end of 4 weeks was 6.615, which were statistically significant; at the end of 3 months, the mean reduction on negative scores was 10.35 which were statistically significant.

Conclusions: The current study showed that Lurasidone has effect on both positive and negative symptoms of schizophrenia at week 4 & better efficacy at week 12. Overall results show better response to positive symptoms. However a longer follow up would help us study the influence of Lurasidone on the course of schizophrenia as well as response to individual domains and symptoms.

Keywords: Lurasidone, efficacy, Indian population, schizophrenia

Introduction

The management of schizophrenia has seen significant strides over the last decades, due to the increasing availability of a number of antipsychotics. Yet, the low efficacy in relation to the negative and cognitive symptoms of schizophrenia and the disturbing adverse reactions associated with current antipsychotics, reflect the need for better molecules targeting unexplored pathways.

Lurasidone is a relatively new entrant in the field of schizophrenia in the Indian context.

There are few systematic studies done in India, about the efficacy of lurasidone. Hence this study is an attempt to evaluate the efficacy of the new generation antipsychotic. Lurasidone, across various symptom domains of schizophrenia.Lurasidone is a newer atypical antipsychotic which is already FDA-approved

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for the treatment of schizophrenia[1].
Meyer JM, Loebel AD, Schweizer E *et al*. (2009)showed that lurasidone is highly protein-bound (99.8%), with affinity for albumin and alpha-1-glycoprotein[2].Citrome L, Gandelman K, Alderman JA, Glue P *et al*. (2009) showed in trials that food can affectthe absorption of lurasidone, akin what can be seen with ziprasidone, but possibly with a lowercaloric threshold than necessary with ziprasidone [3].According to Meyer JM, Loebel AD, Schweizer E *et al*. CYP3A4 is the primary metabolicpathway for lurasidone and; Chiu YY, Preskorn S, Sarubbi D, Cucchiaro J, Loebel A *et al*.(2010)presented that this has implications regarding the use of lurasidone in the presence of inducersand inhibitors of CYP3A4[4].Loebel A, CucchiaroJ,Silva R, Ogasa M, Severs J, Marder SR *et al*. (2010) showed that lurasidone was significantly superior toplacebo in improving all five PANSS factor scores. Week 6 change scores were significantlycompared with placebo among patients treated with 40,80, and 120 mg⁄days on the PANSpositive factor,negative factor,disorganized thought, hostilityand depression/anxiety[5].In a study by Cucchiaro J, Potkin SG, Ogasa M, Loebel A, *et al*. (2008) directly comparinglurasidone 120 mg/day with another antipsychotic, lurasidone's efficacy among stableoutpatients with schizophrenia was found to be similar to that of ziprasidone 160 mg⁄day[6].This is not a clinical trial and this medicine is not an experimental drug. It is already a fairly established medicine which is cleared for clinical usage across the world. The study involves only a clinical evaluation of this symptom response, without any invasive investigations or procedures. In that sense it's quite a safe study. A good number of schizophrenia patients would have been put on lurasidone anyway, in routine practice by the senior psychiatrists of this department. This study is only a systematic scoring of the improvements in various symptoms and recording those observations in a methodical way, without subjecting the patients to any untested or unapproved treatments or without compromising the patients' wellbeing in anyway.This study is also a small attempt, using only safe, noninvasive, clinical evaluation methods to add to the weight of evidence as to whetherlurasidone is effective enough in treating schizophrenia patients in Indian settings.

Methodology

Source of data

Patients diagnosed with schizophrenia using ICD 10 criteria on lurasidone treatment attended the psychiatry OPD at MVJMC & RH, which is a tertiary care referral hospital.

Sample size: 50 cases of schizophrenia patients will be assigned.

Age group: Patients of age 18-60 years will be selected for the study to keep the groups more homogenous and to avoid the spurious effect of age-related cognitive decline.

Methods of collection of data (including sampling procedure if any)

1) Sampling procedure

- The cases will be recruited and the data will be collected over a period of 1 year and 10 months (NOV 2016-SEP 2018). Selection will be made in a serial consecutive way that consent to participate in the study.
- Permission was obtained from our college Ethical Committee.

2) Inclusion criteria

1. Newly diagnosed case of schizophrenia.
2. Age groups between 18-60 years are included for homogeneity.
3. Written Informed consent.

3) Exclusion criteria

1. Other psychiatric disorders will be excluded.
2. Patients with schizophrenia already receiving treatment.
3. Patients who would not show an adequate response when put on lurasidone, even after a sufficient amount of time (6 weeks) and adequate dose (60- 120mg) will be switched on other antipsychotics in the best interest of patients. They will be considered as dropouts from the study.
4. Patients suffering from severe and debilitating comorbid medical and surgical illness.

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Results

57 patients fulfilling the inclusion criteria were approached for the current study, 50 were able to complete the study the rest7 subjects dropped out due to intolerability of lurasidone.
Out of 57 of study population, 35 were males (61.4%), 22 were females (38.6%).

Table 1: Distribution of the study participants according to age group

AgeGroup	Male N= 35 (%)	Female N= 22 (%)	Total N= 57 (%)
20-29 Years	24 (68.6%)	17 (77.3%)	41 (71.9%)
30-39 Years	9 (25.7%)	5 (22.7%)	14 (24.6%)
40-49 Years	2 (5.7%)	0	2 (3.5%)

The participants were 20 to 49 years of age. Majority of age group were 20 to 29 years (71.93%), where as 30 to 39 years was 24.56% and 40 to 49 years was 3.51%.

Table 2: Educational status of the study participants

Education	Male N= 35 (%)	Female N= 22 (%)	Total N= 57 (%)
Primary (0-7)	3 (8.6%)	3 (13.6%)	6 (10.5%)
Secondary (8-10)	19 (54.3%)	6 (27.3%)	25 (43.9%)
Intermediate/ PUC	10 (28.6%)	12 (54.5%)	22 (38.6%)
Graduate	3 (8.6%)	1 (4.5%)	4 (7.0%)

Total 6 (10.53%) were educated till primary school (0 to 7); 25 (43.86%) were educated up to secondary school (8 to 10); 22 (38.6%) were educated till PUC or intermediate; 4 (7.02%) were graduates.

Table 3: Distribution of the study participants according to their occupation

Occupation	Male N= 35 (%)	Female N= 22 (%)	Total N= 57 (%)
Unemployed/ Housewife	0	10 (45.5%)	10 (17.5%)
Unskilled worker	4 (11.4%)	3 (13.6%)	7 (12.3%)
Semiskilled worker	12 (34.3%)	3 (13.6%)	15 (26.3%)
Skilled worker	12 (34.3%)	4 (18.2%)	16 (28.1%)
Clerical, Shopowner	5 (14.3%)	1 (4.5%)	6 (10.5%)
Semi professional	2 (5.7%)	1 (4.5%)	3 (5.3%)

Table 3 shows the distribution of the study participants according to their occupation, which includes unemployed/housewife, unskilled workers, semiskilled workers, skilled workers, clerical/shop owners, and semi-professional.
Majority of 16 (28.1%) were skilled workers; 15 (26.3%) were semiskilled workers; 10 (17.5%) were unemployed/housewife; 7(12.3%) were unskilled workers; 6 (10.5%) were clerical/shop owners and 3(5.3%) were semiprofessional.

Table 4: Distribution of the study participants according to their socio-economic status

Socio-Economic Status	Male N= 35 (%)	Female N= 22 (%)	Total N= 57 (%)
Class 2	4 (11.4%)	2 (9.1%)	6 (10.5%)
Class 3	9 (25.7%)	5 (22.7%)	14 (24.6%)
Class 4	16 (45.7%)	7 (31.8%)	23 (40.4%)
Class 5	6 (17.1%)	8 (36.4%)	14 (24.6%)

The sample was categorized in to various socio-economic groups based on the Modified B.G. Prasad's classification.Table 4 depicts the distribution of the study participants according to their socio-economic status by Modified B.G. Prasad's classification.
Out of which 6 (10.5%) were of Class 2; 14 (24.6%) were of Class 3, a majority of about 20(40.4%) belonged to Class 4 andClass 5 consisted of 14 (24.6%), there was no patient from class 1Socio-

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economic status.

Table 5: Distribution of the study participants according to their area of residence

Area of Residence	Male N= 35 (%)	Female N= 22 (%)	Total N= 57 (%)
Rural	24 (68.6%)	14 (63.6%)	38 (66.7%)
Urban	11 (31.4%)	8 (36.4%)	19 (33.3%)

Table 5 shows the distribution of study participants according to their area of residence. Rural study participants consisted of 24 males and 14 females, a total of about 38 (66.7%). Urban study participants consisted of 11 males and 8 females, a total of about 19 (33.3%).

Table 6: Distribution of the study participants according to their marital status

Marital Status	Male N= 35 (%)	Female N= 22 (%)	Total N= 57 (%)
Single (Unmarried/Divorced/Widowed)	9 (25.7%)	10 (45.5%)	19 (33.3%)
Married	26 (74.3%)	12 (54.5%)	38 (66.7%)

Table 6 showsdistribution of the study participants according to their marital status. Of which 9 males and 10 females are Single (unmarried, divorced, widowed), which is about 19 (33.3%) of the total study population. 26 males and 12 females were married, which is about 38 (66.7%) of the total study population.

Table 7: Distribution of the study participants according to the type of family

Family Type	Male N= 35 (%)	Female N= 22 (%)	Total N= 57 (%)
Joint	11 (31.4%)	6 (27.3%)	17 (29.8%)
Nuclear	24 (68.6%)	16 (72.7%)	40 (70.2%)

Table 7 depicts the distribution of study participants according to the type of family.Our study consists of 17 (29.8%) participants belonging to the joint family and nearly 70% of the study participants belong to the nuclear family.

Table 8: Association between positive scales at different visits

SL. No.	Positive scale at different visits	Mean	N	Std. Deviation	Std. Error Mean	t Value*	df	p Value
1	1st Visit	26.519	52	.9391	.1302	43.503	51	.0001
	2nd Visit	17.000	52	1.0479	.1453			
2	1st Visit	26.560	50	.9293	.1314	74.858	49	.0001
	3rd Visit	10.900	50	1.1473	.1623			
3	2nd Visit	16.900	50	.9313	.1317	35.496	49	.0001
	3rd Visit	10.900	50	1.1473	.1623			

*Paired `t' test was used to test the association between different quantitative variables. At 95% CI, a probability value (p value) of ≤ 0.05 was considered as statistically significant.

The above table (Table 8) shows the association between positive scales at different visits.
In this present study, at the first visit, that is, before giving Lurasidone at baseline, there were 57 participants.There were a significant improvement in the positive scale from the first visit to the second visit i.e., there was improvement in positive scale after giving the lurasidone. The mean score at the first visit was 26.519, the mean score at the end of 2nd visit was 17.000, and the mean at the end of 3rd visit was 10.900.

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Table 9: Association between negative scales at different visits

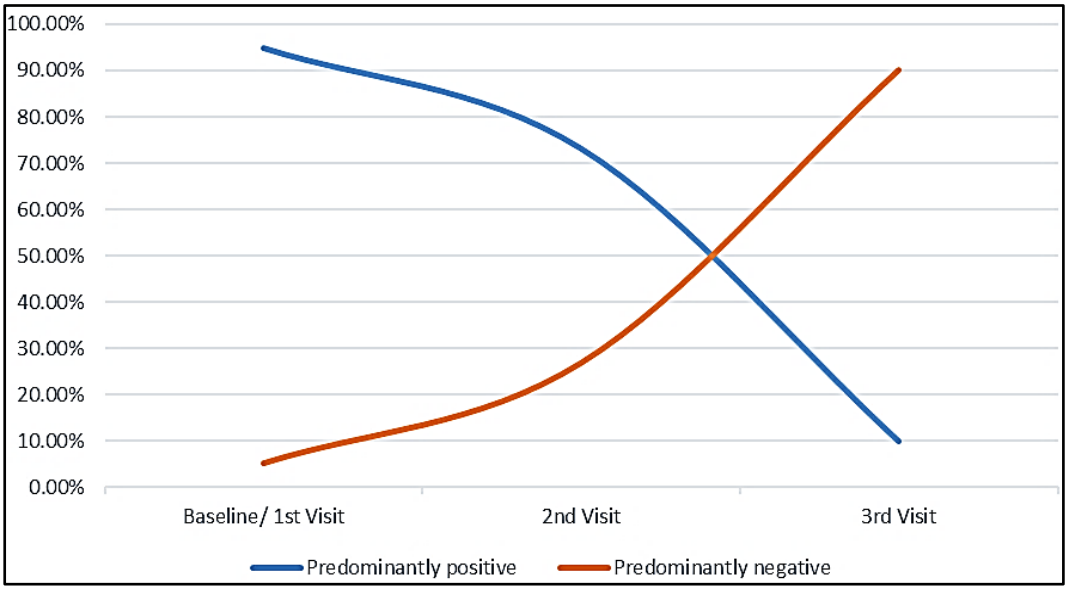
Sl. No	Negative scale at different visits	Mean	N	Std. Deviation	Std. Error Mean	tValue	df	p Value
1	1st Visit	23.250	52	2.4565	.3407	19.095	51	.0001
	2nd Visit	16.635	52	1.0484	.1454			
2	1st Visit	23.220	50	2.4932	.3526	28.787	49	.0001
	3rd Visit	12.900	50	.8144	.1152			
3	2nd Visit	16.560	50	.9930	.1404	20.888	49	.0001
	3rd Visit	12.900	50	.8144	.1152			

The above table (Table 9) depicts association between the negative scales at different visits.
There is a significant improvement in the negative syndrome scale after administration of the Lurasidone. The mean negative syndrome scale score at the end of 1st visit was 23.250, whereas after treatment with Lurasidone for one month, i.e. At the second visit it was 16.635 and at the 3rd visit it was 12.900.

Table 10: Association between positive and negative scales at different visits

Sl. No	Scales at different visits	Mean	N	Std. Deviation	Std. Error Mean	tValue	df	p Value
1	Positive scale on 1st visit	26.509	57	.9087	.1204	9.039	56	.000
	Negative scale on 1st visit	23.351	57	2.3867	.3161			
2	Positive scale on 2nd visit	17.000	52	1.0479	.1453	1.827	51	.074
	Negative scale on 2nd visit	16.635	52	1.0484	.1454			
3	Positive scale on 3rd visit	10.900	50	1.1473	.1623	-9.707	49	.000
	Negative scale on 3rd visit	12.900	50	.8144	.1152			

At baseline, the positive scale was higher compared to the negative scale in the study participants. After administration of lurasidone, both scales had similar improvement, i.e., lurasidone had equal effect on both the positive as well as negative scale. Mean positive scale score at the end of 1st visit was 26.509 and mean negative syndrome scale score at the end of 1st visit was 23.351,where as mean positive scale score on 2nd visit was 17.000 and mean negative syndrome scale score on 2nd visit 16.635 and Mean positive scale score at the end of 3st visit was 10.900 , mean negative syndrome scale score at the end of 3st visit was 12.900.
The mean scores of both positive and negative symptom scales have decreased over 3 visits as shown in Graph 1. It shows that there is an improvement in both positive and negative symptom scales with the administration of lurasidone.



Graph 2: Trend of positive and negative symptom scale composite score over 3 visits

Composite scores were calculated by subtracting the negative symptom score from the positive symptom

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score. It ranges from -42 to +42. It shows the predominance of one syndrome in relation to the other.
The predominantly positive score gradually decreased over the 3 visits, whereas the predominantly negative scores gradually increased over the 3 visits as shown in Graph 2.

Discussion

This study attempted to evaluate the overall efficacy of lurasidone across a spectrum of symptoms of schizophrenia. It also tried to evaluate which symptom domain – positive or negative - Lurasidone had a higher impact in terms of resolution.
A semi structured proforma based on BG Prasad's socio-economic classification was used to record the socio-demographic data. Prasad's socioeconomic classification is widely used in Indian medical literature. It was proposed for the first time by Prasad on per capita income per month and then revised by him based on cost of living.[2] Our study population consisted mostly of subjects from rural backgrounds, educated up to secondary high school and were unemployed at the time of study. 66.7% of the participants were from rural areas,43.86% were educated up to secondary school. As such, the population had lesser demanding jobs cognitivelyand may have a higher load of negative symptoms, either primary or secondary, but could have been reported far less than the case. A distinction between primary and secondary negative symptoms cannot be made using the PANSS scale and this is one of the limitations of the study. The reduction in positive and negative scores corroborated with those of other studies, but there may have been a slightly higher response considering the unique socio-economic background of the population. This response could not be brought out by our study protocol.
The current study showed that Lurasidone has an effect on both positive and negative symptoms of schizophrenia at week 4 & better efficacy at week 12.The mean positive score at baseline was 26.519. The early improvement rate in study group was estimated based on the mean reduction of positive score onPANSS from baseline to 1 month. In positive scale of PANSS, mean reduction of positive score at the end of 4 week was 6.13 which was statistically significant. At the end of 3 months the mean positive score was 10.900, there was a mean reduction of 10 on positive score on PANSS which was statistically significant.The mean negative score at baseline was 23.250. The early improvement rate in group was estimated based on the mean reduction of negative score on PANSS from baseline to 1 month. In negative scale of PANSS, mean reduction of negative score at the end of 4 week was 6.615 which were statistically significant; at the end of 3 months the mean reduction on negative score was 10.35 which were statistically significant.
Our results were similar to previous studies done by M Nakamura et al. (2009), ALoebel*et al*. (2010)who concluded that treatment with lurasidone was associated with statistically significant and greater improvement than placebo on the primary efficacy measure.[14,11] PANSS total score showed a similar pattern of statistically significant early and sustained improvement with lurasidone. Compared to other studies, our results indicate a significant reduction in positive domain scores at the end of 1st month and a significant reduction in negative domain at the end of 3rd month, while other studies have reported a statistically significant response at 6 weeks and 12 weeks, but our study did not have an intermediate assessment point between the end of 1st month and the end of 3rd month. Overall reduction in PANSS score was similar to other studies mentioned above, but a higher response to positive than negative symptoms was noted. However, a longer follow-up would help us study the influence of lurasidone on the course of schizophrenia as well as the response to individual domains and symptoms.

Conclusion

This study attempted to evaluate the overall efficacy of lurasidone across a spectrum of symptoms of schizophrenia. It also tried to evaluate which symptom domain, positive or negative lurasidone had a higher impact in terms of resolution. The current study showed that lurasidone affects both positive and negative symptoms of schizophrenia at week 4 & better efficacy at week 12. Overall reduction in PANSS score was similar to other studies done in the past, but a higher response to positive than negative symptoms was noted. However, a longer follow-up would help us study the influence of lurasidone on the course of schizophrenia as well as the response to individual domains and symptoms.

Funding

No funding sources.

Conflict of Interest

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None declined.

Ethical Approval
The study was approved by the ethical committee.

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