COMPARATIVE EFFICACY, SAFETY AND TOLERABILITY OF OLANZAPINE AND BLONANSERIN IN PATIENTS WITH SCHIZOPHRENIA: A PARALLEL GROUP STUDY

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Abstract. Background: The antipsychotic olanzapine is a first-line drug in the treatment of schizophrenia while blonanserin is indicated in resistant cases of schizophrenia when the first line antipsychotics have failed. There are very limited studies available world-wide as well as in India that compare blonanserin with other antipsychotics in the setting of schizophrenia. **Aims:** To study the efficacy, safety and tolerability of olanzapine and blonanserin in Schizophrenia. **Settings and Design:** The study was a prospective, observational, parallel group study done on schizophrenia patients aged between 18-50 years of both sexes at an outpatient Department of Psychiatry, in a tertiary medical college. The study was conducted from February 2015 to October 2016, with follow ups at weeks 4, 8 and 12. **Materials and Methods:** The efficacy parameters were measured by the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression (CGI) rating. The safety parameters included the vital signs, haematological profile, lipid profile, blood sugar monitoring. Adverse drug reactions and compliance to therapy was observed throughout the study period. Appropriate statistical tests were applied to detect any significant within and between group differences using Microsoft Excel 2007 and SPSS version 17. **Results:** There was significant decrease in the mean total score on the BPRS and CGI-S in the blonanserin arm at the 2nd and last follow up visit (p value < 0.001). Compliance was good in both groups ($\leq 20\%$ missed pills). Overall, 77 treatment-emergent adverse events were present from 56 patients. Twenty three subjects of the blonanserin arm and 33 subjects in the olanzapine arm at least experienced one adverse event ($p = 0.006$), metabolic adverse effects were more common with olanzapine, whereas insomnia, headache and somnolence were more often seen with blonanserin. **Conclusions:** In the present study, blonanserin provided significantly better outcomes than olanzapine with respect to BPRS, CGI-S scores.

Key words: blonanserin, efficacy, olanzapine, safety, schizophrenia, tolerability

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INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterised by positive symptoms, negative symptoms and cognitive impairment. Global prevalence of schizophrenia is 1% and the incidence remains 1.5 per 10000 population [1]. In India, the weighted prevalence of schizophrenia is 0.64% [2]. Schizophrenia patients suffer of higher morbidity and mortality [3]. Though pharmacotherapy is the mainstay of therapy, psychotherapy is also important. Antipsychotics like olanzapine used as 1st line agent for pharmacotherapy of schizophrenia, provide effective control for positive symptoms but the negative symptoms and cognitive impairment remain a challenge for social functioning, subjective well-being and long-term adherence to therapy. Second generation antipsychotic drugs should then be prescribed according to Canadian guidelines [4] which categorized recommendations into six areas.

The other challenges for therapy are non-adherence to therapy, social stigma, substance abuse, suicidal tendency and comorbidities. Atypical antipsychotics like blonanserin, having high affinity for D₂, D₃ and 5HT_{2A} receptors, are helpful in controlling negative symptoms and cognitive impairment as shown in animal studies as well as in humans [5, 6]. But these drugs are not free from adverse effects that limit effectiveness and compliance [7]. The atypical antipsychotic drugs have better safety profile [8]. Olanzapine is commonly used as a first-line drug in the treatment of acute symptoms and for maintenance therapy but its role in treating negative symptoms remains unclear [9]. Recent studies have shown that this drug is likely to induce weight gain and an increased risk for obesity-related diseases, as well as metabolic syndrome [10]. Olanzapine use was associated with hyperglycaemia [11]. Blonanserin is unlikely to cause metabolic side effects, is generally well tolerated and can cause less prolactin elevation [12]. It also improves cognitive function in patients with first-episode and chronic schizophrenia [13]. But there is a need of comparing blonanserin with other antipsychotics in schizophrenia in Indian patients. Global reports are also limited. Thus, the aim of this study was to compare efficacy, safety and tolerability of blonanserin for long term management compared with a standard atypical antipsychotic such as olanzapine.

MATERIALS AND METHODS

Study design and subjects

The study was a prospective, observational, controlled, parallel group, comparing blonanserin versus a standard atypical antipsychotic, Olanzapine.

Being an observational study, CTRI approval was not required. Ethics Committee approval was obtained prior to study from the appropriate Clinical Research Ethics Committee [BMC/PG/190/1(1), Dated 10/01/2015]. Patients presenting with history or symptoms of schizophrenia were screened and recruited as per subject selection criteria. Recruitment was subjected to satisfactory completion of the informed consent process. Laboratory parameters were assessed at baseline and at end of 4 weeks.

Inclusion criteria

All patients aged between 18 and 50 years of both sexes diagnosed with schizophrenia by the Structured Clinical Interview for DSM IV Axis-1 Disorders (SCID) and. The SCID has been used by most of the studies for diagnosis of schizophrenia. The SCID is an efficient, user-friendly and reliable clinical interview for making DSM diagnosis [14]. Patients with normal complete blood counts, blood sugar, lipid profile and normal ECG were included in the study.

Exclusion criteria

Pregnant and lactating women, immunosuppression due to drug or disease, severe psychosis and violent behaviour; patients who have already taken any other antipsychotic or antidepressant medication, presence of renal or hepatic impairment, substance abuse, participation in any other clinical trial within past 3 months, patients unable or not willing to give consent, diseases of vital organs, those receiving medications known to prolong QT-interval or capable of otherwise having drug-drug interaction with study medication.

Time schedule of visits and activities at each visit

Subjects were screened in the psychiatry outpatient department and the diagnosis was done by the Structured Clinical Interview for DSM IV Axis-1 Disorders (SCID) [14]. In addition, the selection criteria were checked and written informed consent was obtained from the patient. Laboratory examination included parameters such as haemoglobin (Hb), total leucocyte count (TLC), differential count (DLC), erythrocyte sedimentation rate (ESR), random blood sugar (RBS), blood lipid profile, plus blood pressure and ECG.

Concomitant medication was noted and non-permitted medications were withdrawn prior to the study. The baseline visit was scheduled five days after the screening visit to allow for any antipsychotic that had been taken to be washed out. The period of five days reflected the five half-lives of the commonly prescribed antipsychotic agents [15]. The dosage of Blonanserin

was 8-12 mg daily in two divided doses – with titration up to 24 mg [16]. The clinical pharmacokinetic profile of olanzapine supported once-daily oral administration, starting with a dose of 5-10 mg, with a target dose of 10 mg/day, and a maximum dose of 20 mg/day [17].

Patients were asked to report immediately any unwanted and unexpected reactions. They were followed up at weeks 4, 8 and 12 with possibility for interim follow up for assessing adverse events, if needed.

Measurements

The Brief Psychiatric Rating Scale (BPRS) [18] and the Clinical Global Impression (CGI) Severity [19] were measured at baseline, 4th week, 8th week and 12th week. The BPRS assesses several symptom domains due to the multidimensional nature of the scale. Psychometric investigations of various BPRS versions provide evidence for satisfactory to excellent inter-rater reproducibility [20].

CGI Severity and improvement scales offer a readily understood, practical measurement tool, thus can be easily administered by a clinician in a busy clinical practice setting to document the details, track responses to interventions and monitor and quantify patient progress [21].

Recorded adverse events included treatment-emergent events reported spontaneously by subjects at any time during the 12-week treatment. Causality analysis of adverse events was done by using the WHO-UMC Scale [22]. Compliance with therapy was assessed by the pill counting method.

Adherence to therapy was considered satisfactory if $\leq 20\%$ pills were missed [23].

Statistical considerations

The target sample was 33 in each group. This was calculated to detect a difference between groups of 6 in the Brief Psychiatric Rating Scale (BPRS) score with 80% power and 5% probability of Type 1 error, assuming a standard deviation of 10 for the same parameter. Considering a 20% drop-out rate, the number of patients required to be recruited in each group is 40 or 80 subjects overall.

Students independent t-tests were applied for age, and chi-square test for sex distribution, residence, literacy, occupation. Within-group analysis was done by Friedman ANOVA followed by post hoc analysis with Multiple Wilcoxon Signed Ranks test with a Bonferroni correction.

RESULTS

A total of 110 patients attending the out-patient Department of Psychiatry were screened for this study.

Among them 80 were finally randomised – 40 in each group. Of these, three patients were lost to follow-up, of which two from the blonanserin group and one from the Olanzapine group. 77 patients (39 in blonanserin group and 38 in Olanzapine group) fulfilled modified-intention-to-treat criteria [23] and their parameters were analyzed (Fig. 1). The demographic characteristics (Table 1) of both groups were comparable at baseline. The clinical characteristics of the subjects in both groups were comparable at baseline. (Mann-Whitney U-test).

Within group analysis showed that the mean total score of BPRS decreased significantly in both groups: with blonanserin from baseline (61.18 ± 4.29) to week 12 (27.10 ± 3.57 , $p < 0.001$), olanzapine from baseline (60.13 ± 4.23) to week 12 (31.61 ± 4.04 , $p < 0.001$) (fig. 2). The CGI-S score decreased from baseline (5.13 ± 0.61) at 12 weeks (1.72 ± 0.51) in Blonanserin group ($n = 39$) (p value < 0.001). In the Olanzapine Group ($n = 39$) the reduction was from 5.03 ± 0.59 at baseline to 2.16 ± 0.49 at 12 weeks ($p < 0.001$) (fig. 3).

Inter-group analysis (Independent-Sample t test) revealed that the BPRS score and CGI-S score were declining over the treatment period in both groups. This decline was statistically significant ($p < .001$) when compared between visits of the both treatment arms in second and end follow up visit [Tables 2 and 3]. The end-of-study compliance (per protocol) assessment indicated excellent adherence to treatment for all patients in both treatment groups ($\leq 20\%$ missed dose).

Not a single participant encountered a serious adverse event and there were no hospitalizations. During the 12-week study period a total of 68 subjects were suspected of having at least one adverse drug reaction (ADR). On causality assessment, 12 of these 68 cases (17.65%) were considered with WHO-UMC causality status “unlikely”. From the remaining 56 subjects, 77 ADRs (93.5%) belonged to the “probable” category, whereas 5 (6.49%) were of “possible” type according to the WHO-UMC scale. No case could be labelled “certain”, as re-challenge was not attempted by the attending psychiatrist, once a drug was withdrawn. Overall, out of 77 treatment-emergent adverse events from 56 patients: 23 subjects in the Blonanserin arm and 33 subjects in the Olanzapine arm reported at least one event. (Table 2) ($p = 0.006$ by chi-square test).

Table 1. Demographic profile of the study population (N = 77)

Category	Blonanserine group (n = 39)	Olanzapine group (n = 38)
Age (Years)	18 to 50	18 to 50
Mean $\pm$ SD	31.51 $\pm$ 5.86	32.66 $\pm$ 7.14
Gender		
Male	56.4%	47.4%
Female	43.6%	52.6%

Table 2. Changes in the BPRS score over 12 weeks

BPRS	Blonanserine group (n = 39) Mean $\pm$ SD	Olanzapine group (n = 38) Mean $\pm$ SD	p value (between groups)
Baseline	61.18 $\pm$ 4.29	60.13 $\pm$ 4.23	0.284
1st follow-up	54.00 $\pm$ 3.33	54.53 $\pm$ 3.65	0.511
2nd follow-up	38.10 $\pm$ 3.06	44.11 $\pm$ 4.11	< 0.001
End of study	27.10 $\pm$ 3.57	31.61 $\pm$ 4.04	< 0.001

Table 3. Changes in the CGI-S score over 12 weeks

CGI-S	Blonanserine group (n = 39) Mean $\pm$ SD	Olanzapine group (n = 38) Mean $\pm$ SD	p value (between groups)
Baseline	5.13 $\pm$ 0.61	5.03 $\pm$ 0.59	0.452
1st follow-up	4.41 $\pm$ 0.50	4.42 $\pm$ 0.50	0.924
2nd follow up	2.87 $\pm$ 0.41	3.45 $\pm$ 0.50	< 0.001
End of study	1.72 $\pm$ 0.51	2.16 $\pm$ 0.49	< 0.001

Table 4. Individual reported adverse drug reactions

Adverse event	Blonanserine group (n = 39)	Olanzapine group (n = 38)	p value (between groups)
Insomnia	8	4	0.227
Somnolence	7	4	0.352
Nausea	2	7	0.087
Tremor	2	4	0.431
Anxiety	5	5	1.000
Headache	4	0	0.115
Vomiting	1	6	0.056
Constipation	0	2	0.240
Weight gain	3	10	0.675
Increased salivation	0	1	0.494
Akathisia	0	2	0.240

(Chi-square test for insomnia and somnolence and Fisher's exact test for the rest)

Fig. 1. Study subjects recruitment flow chart

Fig. 2. The BPRS score at different visits in two treatment arms

Fig. 3. The CGI-S score at different visits in two treatment arms

DISCUSSION

Schizophrenia is a functionally and socially debilitating chronic psychiatric illness that necessitates long term therapy at a high cost. Second generation antipsychot-

ics are the best options when efficacy, safety and tolerability profiles are concerned [24] and this study is trying to find a new option. We found no study that compared the two drugs olanzapine and blonaserin in the treatment of schizophrenia globally and in our country.

Patients having severe psychosis or severe disease condition were excluded from our study as those subjects would be very difficult to handle. The study subjects were assessed in four visits which helped thorough assessment of the patients regarding efficacy, safety and adverse drug reactions. There were no significant difference in the duration of illness of both groups (blonanserin – 21.15 ± 5.48 months, olanzapine – 22.37 ± 5.29 months, p value 0.270). The majority of subjects in our study belonged to younger age groups because of the wide prevalence of the disease in younger age [1] and so other co-morbidities associated with advanced age were avoided. Our study showed that most of the patients were in their thirties with a nearly equal gender distribution. The WHO statistics also found a greater incidence of schizophrenia in the third decade of life, though males were shown to be suffering more often from the disease [1]. This difference can be due to a small sample size in our population. Other demographic profiles were comparable in both treatment arms.

The vital signs recorded at baseline were analogous in both the treatment arms. The laboratory parameters were within normal limits in both groups.

Regarding efficacy, the BPRS scale (a short version of PANSS) [25] and the CGI-S showed significant improvement from 2nd follow-up visits to end of study visit in the blonanserin group compared to the olanzapine group. Woo YS (2019) showed significant reduction in BPRS that support our study findings [26]. Another study of Woo YS (2016) showed significant reduction in CGI-S with blonanserin [27].

Blonanserin induced improvement in the negative symptoms and cognitive impairment with less adverse effects in various short and long term studies [28]. It has been shown that cognition improvement more than 0.5 SD improves quality of life [29]. In the present study, blonanserin induced a significantly better outcome as assessed by the BPRS and CGI-S scores. We found no study compared blonanserin with olanzapine in therapy of schizophrenia, but other studies with other antipsychotics showing superior efficacy of blonanserin compared with haloperidol [30], risperidone [31], aripiprazole [32], amisulpride [33].

When safety parameters were considered (vital signs such as the pulse rate, systolic and diastolic blood pressure), they were comparable at baseline and at treatment end in both medication groups. In the current study, an increase in haemoglobin in both the treatment groups was registered, however between groups comparisons did not reveal any relation. The mean values of other haematological parameters did not vary at baseline and end of study visits in either

of the two treatment arms. No other studies corroborated with this observations [6].

In respect to lipid profile tests there were significant increases of post treatment mean values of total cholesterol, triglycerides, LDL-cholesterol, VLDL-cholesterol and a significant decrease of post treatment mean values of HDL-cholesterol in both treatment arms. In between groups comparisons all the biochemical parameters were comparable except for serum total cholesterol, which was increased more at study end by olanzapine than by Blonanserin. This highlighted the need for checking their lipid profile every 3 months when administering these medications. Studies done by Huh L, Lee BJ (2019) [34] and Lally J, McCabe JH (2015) [8] support our findings. The random blood glucose levels at baseline and study-end were comparable – both within and in-between the two treatment arms. However, many studies showed a strong association of olanzapine with the incidence of type 2 diabetes mellitus [34].

The treatment-emergent side effects are depicted in table 4. The patients in both groups complained of many adverse events from which 93.5% were ADRs belonging to the “probable” category, whereas 6.5% fell in the “possible” category, according to the WHO-UMC causality assessment scale [35]. The incidence of adverse events was significantly higher in the olanzapine arm in which weight gain, GI disturbances were more common. On the other hand, insomnia, somnolence, headache were more frequently reported by Blonanserin treated patients. The incidence of anxiety was equal in both treatment arms. The RCT done by Gründer, Gerhard & Heinze in 2016 revealed similar findings also [24].

Blonanserin, an atypical antipsychotic with dopamine D3, D2, 5HT2A receptor antagonism has proved to be effective in the management with least metabolic, extrapyramidal and hyperprolactinaemic side effects. Blonanserin does not produce sedation due to its low affinity for the 5HT2C, adrenergic α_1 , histamine H1 and muscarinic M1 receptors [36]. Switching to blonanserin can reverse medication – induced hyperprolactinemia found in female patients making it is a suitable antipsychotic [12].

Study subjects showed good compliance to therapy as there were $\leq 20\%$ missed doses in both groups. The lack of troublesome adverse events helped in this regard. Also, most of them (both patients and family members) were well educated to understand the nature of the disease and the medication effect. In addition, good communication could be established before signing the consent form. This may be also due to small sample size. Such compliance in

the patients favours the adherence to therapy with either of the medications [23].

The limitations of our study include the small sample size was calculated on the basis of a relatively large effect size with respect to BPRS score. A larger sample may have shown a clear statistical difference between groups in other measures such as CGI-S and CGI-I rating. Antipsychotic drugs may increase serum prolactin [23] but we could not measure prolactin levels because of logistic constraints due to lack of infrastructure and man power. There was no scope for assessing comparative effectiveness of long-term therapy or the detection of delayed adverse events. There is poor generalizability of our results due to the strict exclusion criteria [38].

CONCLUSION

The short-term efficacy of both drugs (Olanzapine and Blonanserin) was comparable on the short term, but on long term (12 weeks) Blonanserin induced better outcomes in comparison to olanzapine. In respect to safety, Blonanserin is a promising candidate in the treatment of adult patients with schizophrenia which has low propensity to cause weight gain and metabolic abnormalities. Adherence to therapy was also good in both treatment groups. Keeping in mind the effect of blonanserin on negative symptoms and cognitive function with preferable ADR profile, large-scale long-term trials, comparing blonanserin with olanzapine and with other second generation antipsychotics, have to be carried out to establish its efficacy, safety, and tolerability of schizophrenia treatment options.

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