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A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF OLANZAPINE VERSUS RISPERIDONE AS AN ADJUNCT TO LITHIUM CARBONATE IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER AT A TERTIARY CARE HOSPITAL

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Keywords:

Bipolar affective disorder, Lithium, Olanzapine, Risperidone, Young Mania Rating scale, Hamilton Depression Rating Scale

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ABSTRACT: The objective of the research was to compare the efficacy and safety of Olanzapine versus Risperidone as an add-on to Lithium carbonate in patients with bipolar affective disorder. **Methods:** Prospective, randomized, comparative study conducted in psychiatric Department from Nov 2018 to May 2020. 80 BPAD patients who fulfilled eligibility criteria were randomized (1:1) into two groups of 40 each receiving Olanzapine with Lithium (Group A) or Risperidone with Lithium (Group B) for 12 weeks. Efficacy was measured by reduction in Young Mania Rating Scale (YMRS) score and Hamilton Depression Rating Scale (HAM-D) score at 6^{th} and 12^{th} week. Safety was assessed by monitoring treatment emergent adverse effect. Data analysed using repeated measure ANOVA, Mixed ANOVA, chi-square and descriptive statistics. **Results:** Olanzapine and Risperidone treated BPAD patients showed significant reduction in YMRS score from baseline to 12^{th} week ($p<0.001$) but there was no statistically significant interaction between time and groups ($p=0.71$). Significant reduction in HAM-D score from baseline to 12^{th} week was observed in both Olanzapine and Risperidone group ($p<0.001$) but no statistically significant interaction between time and groups was observed ($p=0.50$). > 50% reduction of YMRS score (responder rate) was observed in 97.5% and 95% of patients in Olanzapine group and Risperidone group respectively. Both the groups completed study with 100% medication adherence. **Conclusion:** Olanzapine and Risperidone acts as better adjunctive to Lithium in BPAD patients who do not responding to Lithium monotherapy.

INTRODUCTION: American Psychiatric Association defines Bipolar disorder as brain disorder that causes changes in person's mood, energy and ability to function. Bipolar Affective Disorder (BPAD) affected patients have intense emotional state which can be categorized as mania, hypomania or depression.

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It can present in different severity, varying from mild to serious, often associated with psychotic features. BPAD contributes to 48.8 million cases across the globe accounting for 0.4% of total Disability Adjusted Life Year (DALY) and its prevalence varies from 3-5% across the world, 0.3% in India [1].

First line drug used in treatment of BPAD is Lithium, at higher doses causes course tremors, ataxia, mental confusion and motor in-coordination and long-term use can cause weight gain, renal diabetes insipid us and thyroid dysfunction [2]. As Lithium has narrow therapeutic range serum monitoring is required to maintain its precise

plasma levels. Approximately 20-30% of patients don't or partially respond to Lithium monotherapy which necessitates the use of other drugs in adjunction [3]. Olanzapine and Risperidone are atypical antipsychotic acts blocking dopamine (D_2) and serotonin ($5HT_{2A}$) receptors which are responsible for manic and depressant effect [4]. Both these drugs have specific receptor affinity, better safety profile, minimal drug interactions and do not require plasma drug level monitoring. These beneficial pharmacological characteristics makes Olanzapine and Risperidone better adjunction to Lithium in treatment of BPAD. Due to paucity of Indian studies on use of atypical antipsychotics in combination with Lithium and head on comparison of Olanzapine and Risperidone as add-on to Lithium, this study was designed to compare the efficacy and safety of Olanzapine versus Risperidone as an add-on to Lithium carbonate in patients with Bipolar Affective Disorder.

MATERIALS AND METHODS: This was a randomised, open label, Comparative Study done during November 2018 to May 2020 on Out-patient/In-patient department of Psychiatry in Bangalore Medical College and Research Institute, Bengaluru. The study was commenced after getting approval from the Institutional Ethical committee [Ethical committee number: No.BMC/PG/124/2018-19 dated 03/11/2018]. Written informed consent was obtained in local vernacular language from every patient before enrolment.

Sample size of total 80 patients (40 patients in Group A and 40 patients in Group B) were included. Patients of either sex & aged between 18 to 60 years, willing to give written informed consent and diagnosed as bipolar affective disorder according to ICD 10 (F31.1). Patients on Lithium (monotherapy) for at least 4 weeks with baseline score of Young manic rating scale ≥ 16 were included. Patients on mood stabilizers other than Lithium, with history of Epilepsy, Parkinson's disease and other serious illness, organic mental disorder, psychiatric co-morbidities other than anxiety, substance abuse, suicidal tendencies, allergic to study drug were excluded.

Randomisation and Treatment Protocol: After enrolment subjects were randomised into two groups (group A and group B) with the help of the computer-generated random table.

Group A: Tablet Lithium 300 mg thrice daily was given along with tablet Olanzapine 5 mg twice daily initially and dose was titrated up to 10 mg twice daily depending on the clinical response and tolerability. (n=40).

Group B: Tablet Lithium 300 mg thrice daily was given along tablet Risperidone 1mg twice daily initially and dose was titrated up to 3 mg twice daily depending on the clinical response and tolerability (n=40).

Screening and Recruitment: During enrolment, following details like demographic data, psychiatric history, family history and general physical examination, mental state examination were recorded after enrolment. Details of drug prescription by the treating psychiatrist was recorded in the study proforma and related investigations like Random blood glucose, serum triglyceride level were documented Anthropometric parameters like weight, waist to hip ratio were measured and Body mass index (BMI) was Baseline score of YMRS and HAM-D were noted.

Follow up: At 6th & 12^{th} week follow up, patient's medication adherence, any inter current illness, withdrawal of medication and the reason for the same were recorded, Efficacy of drugs was assessed using Young Manic Rating Scale (YMRS), Hamilton Depression Rating Scale (HAM-D 17). In case of acute exacerbation of mania injection Lorazepam 2 mg was given as rescue medication.

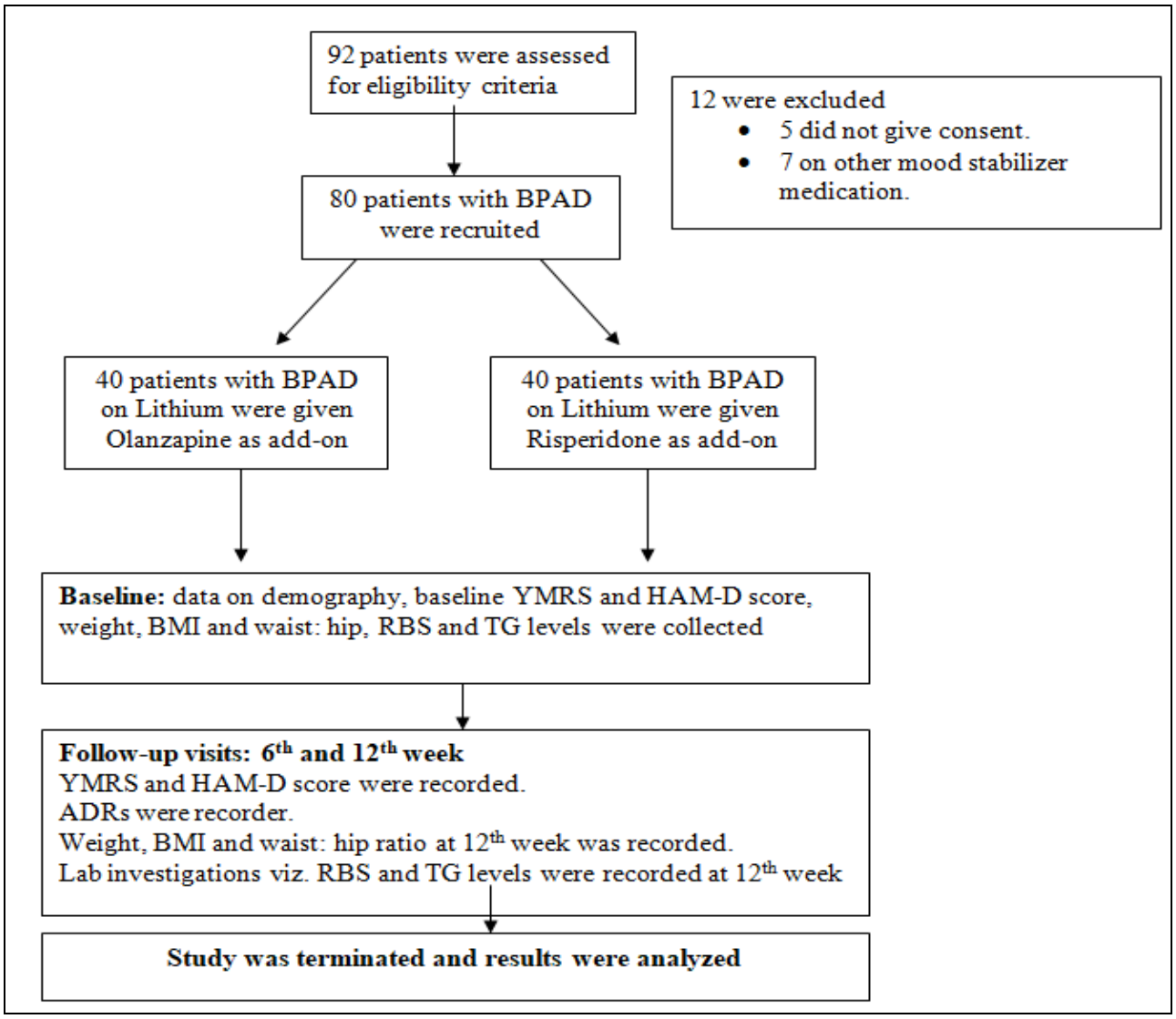
Efficacy Parameters: Response rate- defined as decrease in YMRS and HAM-D score of ≥50% from the baseline and change in YMRS and HAM-D score at 6^{th} and 12^{th} week.

Safety Assessments: Adverse drug reactions were recorded using CDSCO-ADR form and graded according to severity.

Statistical Analysis: The descriptive data was analysed using mean (SD), frequency, percentage. Quantitative parameters was compared between and within groups using Mixed-ANOVA and Repeated measure Analysis of variance (RM-

ANOVA). Qualitative parameters were compared between and within groups using Chi-square test or Mann-Whitney test. p-value of <0.05 was considered statistically significant.

Patient Disposition: Consort Diagram:



RESULTS: The mean age in Group A and Group B were 34.2 (6.15) and 33.75 (7.7) years respectively and there was no significant difference between the groups (p = 0.77). Totally 43 (54%) males and 37 (46%) females were enrolled in the study, among them 23 males and 17 females were present in Group A and 20 males and 20 females were present in Group B. There was no statistically significant difference between two groups (p =0.50). Baseline characteristics were similar in both the groups **Table 1.**

TABLE 1: DEMOGRAPHIC CHARACTERISTICS IN GROUP A AND GROUP B

Variable		Group A (n = 40)	Group B (n = 40)	p value
Age in years (mean ± SD)		34.2±6.15	33.82±7.8	0.77*
Gender n(%)	Male	23 (57.5%)	20 (50%)	0.50#
	Female	17 (42.5%)	20 (50%)	
	BPAD with depression	2 (5%)	1 (2.5%)	
Family History of mood disorder n(%)	Yes	3 (7.5%)	4 (10%)	0.99$
	No	37 (92.5%)	36 (90%)	

Group A = Lithium+ Olanzapine, Group B = Lithium+ Risperidone, n = Number of patients in each group, p<0.05 considered as statistically significant. *(unpaired t test), # (Chi square test), $(Fischer exact test), BPAD – Bipolar Affective Disorder.

Evaluation of Efficacy Parameter: Mean YMRS score was 23.6 and 24.5 at baseline, reduced to 7.05 and 7.55 at 12th week in group A and group B respectively. There was significant reduction in YMRS scores from baseline to 12th week in both the groups (p<0.001). The main effect of group (F=1.979, p=0.13) and interaction between group & time (F=0.251, p=0.712) were not significant **Table 2, Fig. 1.**

TABLE 2: COMPARISON OF MEAN YMRS SCORE BETWEEN TIME & GROUPS AND WITH IN GROUP A AND GROUP B FROM BASELINE TO 12TH WEEK IN EACH GROUP

Groups	Baseline Mean (SD)	6th week Mean (SD)	12th week Mean (SD)	p value* (With in groups)
Group A n= 40	23.6 (3.1)	12.18 (1.92)	7.05 (2.07)	<0.001
Group B n= 40	24.5 (3.2)	12.53 (2.8)	7.55 (3.16)	<0.001
p value (Between groups)		p value 0.71(NS)		

Group A = Lithium+ Olanzapine, Group B = Lithium+ Risperidone, n = Number of patients in each group, *RM-ANOVA with Bonferroni multiple comparison test, p<0.05 considered as statistically significant, YMRS – Young Mania Rating Scale.

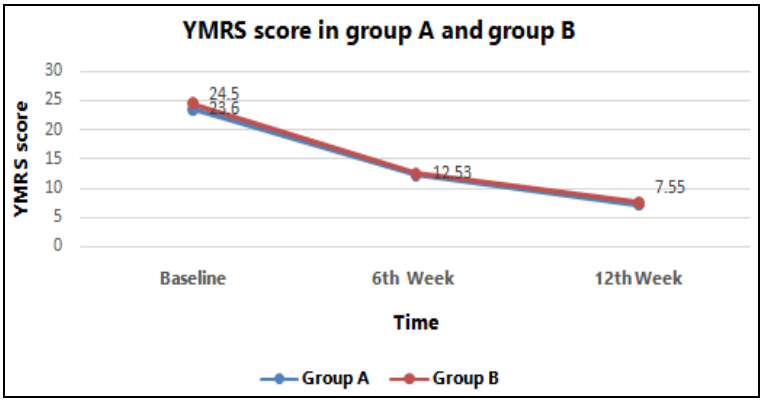


FIG. 1: COMPARISON OF ESTIMATED MARGINAL MEANS OF YMRS SCORE BETWEEN THE GROUPS IN RELATION TO TIME. Group A – Lithium+ Olanzapine, Group B – Lithium+ Risperidone

Responder rate is defined as >_ 50% improvement in YMRS score from baseline. Responder rate was 60% and 65% at 6th week, increased to 97.5% and 95% at 12th week in group A and group B respectively. There was no significant difference in responder rate between the groups at 6th (p=0.65) and 12th week (1.0) **Table 3.**

TABLE 3: RESPONDER RATE BETWEEN GROUP A AND GROUP B ACROSS DIFFERENT VISITS

Visits	Group A n (%)	Group B n (%)	p value
6 week	24 (60%)	26 (65%)	0.64 (NS) #
12 week	39 (97.5%)	38 (95%)	1.0 $

Group A = Lithium+ Olanzapine, Group B = Lithium+ Risperidone, n = Number of patients in each group, # chi square test, $= Fischer Exact test, p<0.05 considered as statistically significant, NS = Not significant.

Mean HAM-D score was 6.78 and 7.02 at baseline, reduced to 4.00 and 3.90 at 12th week in group A and group B respectively. There was significant reduction in HAM-D scores from baseline to 12th week in both the groups (p<0.001).

There was significant difference in within subject factor (time) with p<0.001 but no significant interaction was observed between time and groups (F=0.5, p= 0.54) **Table 4, Fig. 2.**

TABLE 4: COMPARISON OF MEAN HAM-D SCORE BETWEEN TIME & GROUPS AND WITHIN GROUP A AND GROUP B FROM BASELINE TO 12TH WEEK

Mean (SD)	Baseline	6th week	12th week	P value* (with in groups)
Group A n= 40	6.78 (1.8)	5.30 (1.15)	4.00 (1.2)	<0.001
Group B n= 40	7.02 (1.4)	5.32 (0.9)	3.90 (1.17)	<0.001
P value (Between groups & time)		0.54 (NS)		

Group A = Lithium+ Olanzapine, Group B = Lithium+ Risperidone, n = Number of patients in each group, * RM-ANOVA with Bonferroni multiple comparison test, p<0.05 considered as statistically significant, HAM-D – Hamilton Depression Rating Scale.

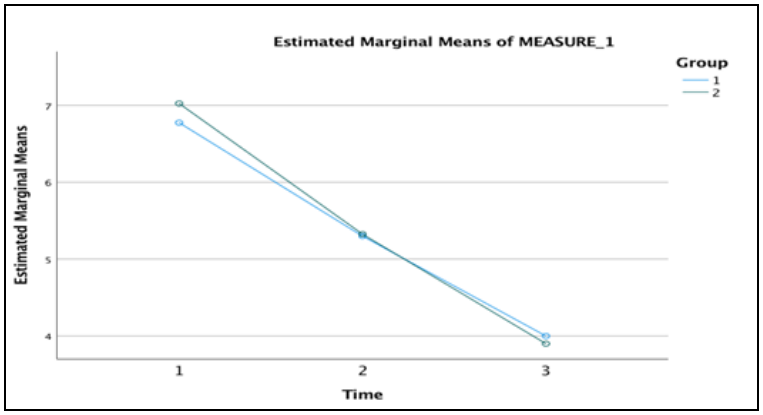


FIG. 2: COMPARISON OF ESTIMATED MARGINAL MEANS OF HAM-D SCORE BETWEEN THE GROUPS IN RELATION TO TIME. Group A – Lithium+ Olanzapine, Group B – Lithium+ Risperidone.

Responder rate is defined as >_ 50% improvement in HAM-D score from baseline. Responder rate was 7.5% and 10% at 6th week, increased to 40% and 50% at 12th week in group A and group B respectively. There was no significant difference in responder rate between the groups at 6th (p=1.0) and 12th week (0.36) **Table 5.**

TABLE 5: RESPONDER RATE BETWEEN GROUP A AND GROUP B ACROSS DIFFERENT TIME PERIOD

Visits	Group A n (%)	Group B n (%)	P value
6 week	3 (7.5%)	4 (10%)	1.0$
12 week	16 (40%)	20 (50%)	0.36*

Group A = Lithium+ Olanzapine, Group B = Lithium+ Risperidone, n = Number of patients in each group, $= Fischer Exact test, * Chi-square test, p<0.05 considered as statistically significant.

Evaluation of Safety Parameters: 22(55%) patients in group A 16 (40%) patients in group B reported adverse drug reaction (ADR). The most commonly reported ADRs were drowsiness 10 (12.5%) and headache 9 (11.2%). Extrapyramidal symptoms were exclusive to group B and tardive dyskinesia was most common (3 out of 4) in it. During the study period, we only encountered mild to moderate ADRs associated with both groups which did not require hospitalization or discontinuation of medication. Causality was assessed using WHO causality assessment scale. All ADRs were possible in causality as none of the patients required discontinuation of drug. Severity of ADR was assessed by Hartwig-Siegal scale. Among all ADRs 18.45% were moderate in nature and most of them (81.5%) were mild in nature.

DISCUSSION: Around 1/3rd of the patients do not respond adequately to Lithium monotherapy which necessitates adjunct therapy. US-FDA has approved Olanzapine, Risperidone, Quetiapine, Aripiprazole for the adjunctive therapy of BPAD and even NICE guidelines recommends use of antipsychotics. Hence this study was conducted to compare efficacy of Olanzapine versus Risperidone as an adjunct to Lithium in patients with BPAD. Our study mean age was similar to the study conducted by Chi -un pae *et al*, [5], in which mean age was 29 years. A study by Kroon JS [6] showed bimodal age distribution with first peak in early adolescence (15-24 years) and second peak between 30-40 years of age but in our study majority of patients were between 30-40 years of age, may be due to delay in diagnoses, because ours is a tertiary care centre and only the later age group patients were approaching the hospital. Our study was similar to study done by Suominen K *et al*, [7] on gender difference in bipolar disorder, showed more number of male patients because men are more likely to have early onset of maniac symptoms compared to females [8]. Family studies indicated 7 fold higher risk in first degree relatives of bipolar patients [9].

In our study family history of mood disorder was observed in 8.7% of the patients. 91.3% of the patients did not have family history suggesting non hereditary factors *viz*. high stress, traumatic event, damaged relationship, drug abuse are other major attributing factors for BPAD. Most of the patients in this study had mania (96.25%) at the time of diagnosis. Study by Saddock BJ reported that in bipolar disorder, mania was the first presenting

symptom [10]. Bipolar depression may be under diagnosed most of the times due to its symptoms resembling major depressive disorder, which could be one of the reasons for less bipolar depressive patients in the study. In our study, Olanzapine group showed significant reduction (p<0.001) in mean YMRS score from baseline to 12th week (-16.55), this study result was similar to study conducted by Tohen *et al.*, a 6 week double blind RCT showed significant reduction (p<0.003) in mean YMRS score at the end of 6th week (-13.11) when compared to Lithium monotherapy (-9.10) [11]. In another 4 week double blind placebo controlled RCT showed statistically significant (P< .001) improvement in YMRS score (-14,8 vs -8.1) [12]. Even Cochrane review done by Rendell M *et al.,* which included 2 trial with 246 participants concluded that weighted mean difference (WMD) for Olanzapine (-5.94) was significantly higher (P<0.001) compared to placebo (-4.01) in reducing YMRS score [13]. All these finding suggests synergistic effect Lithium and Olanzapine which acts by blocking 5-HT_{2A} receptor.

A 3 week double blind placebo controlled RCT by Gary SS *et al.,* on 156 bipolar patients on efficacy of Risperidone as add-on to mood stabilizer showed significant improvement (p= 0.009) in YMRS score at the end of 3rd week (-16.6 vs -13.4) [14] which was similar to our study in which Risperidone group showed significant reduction (p<0.001) in mean YMRS score from baseline to 12th week (-16.95). These findings suggest anti-manic effect of Risperidone which could be due to 5-HT_{2A} antagonistic activity. In our study, there was no statistically significant interaction between treatment groups and time (F= 0.251, p= 0.71). These results were similar to an observational study conducted by McIntyre *et al* [15].

In our study, 60% of patients in Olanzapine group showed >50% reduction in YMRS score (responder rate) at 6th week which was increased to 97.5% at 12th weeks. Poor adherence to treatment regimen could be the reason for less responder rate in 1st follow up visit which was improved after psychoeducation. A study conducted by Tohen M *et al*, on Olanzapine monotherapy showed responder rate of 72% at 6th week and 96% at 12th week [11]. In another double blind placebo controlled RCT by Jacobs TG *et al.,* on efficacy of Olanzapine in acute mania with 115 patients showed higher responder rate (65% vs 43%) [12]. These results showed that Olanzapine have better clinical response and can be used as even monotherapy. Pharmacokinetic properties like lipophilicity, long $t_{1/2}$ (24hrs) could be responsible for its longer duration of action with higher responder rate. In a study conducted by Yatham LN *et al.,* Risperidone combined with mood stabilizer showed 59% responder rate at the end of 3 weeks [16]. Another placebo controlled study by Haas M *et al.,* on 169 young patients regarding efficacy of Risperidone showed greater response rate (57.1% vs 26.3%) [17]. Risperidone is metabolized to 9-OH Risperidone, an active metabolite which could prolong the duration of action and increase the clinical responder rate. In another study by Vieta E *et al.,* on role of Risperidone in treatment of bipolar disorder on 430 patients also showed significant improvement (p<0.001) in HAM-D score at endpoint (8.8 to 2.6) [18].

Above findings suggest anti-depressant effect of Risperidone which shares 5-HT_{2A} antagonistic action with other antidepressants like fluoxetine, trazadone, mirtazapine. There was no statistically significant interaction between treatment groups and time (F=0.50, p=0.54) which could be due to lesser sample size and shorter duration of study. Study with large sample size and long study period would give better picture on significance of interaction between study groups and time. Another comparative study by Perlis RH *et al.,* on 329 patients on efficacy of Olanzapine (dose 5-20mg/dl) versus Risperidone (dose 1-6mg/day) showed significantly better efficacy with Olanzapine (p= 0.04), which was not seen in our study, could be due to the smaller sample size of our study [19].

Both Olanzapine and Risperidone acts on 5-HT_2 receptor which could be responsible for their similar effect. Olanzapine group showed > 50% reduction in HAM-D score (responder rate) in 7.5% of patients at end of 6 weeks, which was increased to 40% at 12th weeks in our study. A study by Tran PV *et al.,* on efficacy of Olanzapine versus Haloperidol in schizoaffective disorder showed significant response rate (> 40 reduction in BPRS score) in Olanzapine group compared to Haloperidol group (51.1% vs 29.6%) [20]. In our

study, Risperidone group showed responder rate of 40% patients at the end of 6 weeks, which then raised to 50% at 12th week. A study by Tran PV *et al.,* showed 70% response rate for Risperidone in person with psychotic depression [21]. It has been noted that low dose Risperidone (1mg) increases the clinical response rate when added to Selective Serotonin Reuptake Inhibitor (SSRI) in SSRI non responders.

In this study, 22 (55%) patients in Olanzapine group and 16 (40%) patients in Risperidone group reported ADRs. The most common reported ADRs were drowsiness (12.5%) and headache (11.2%). we encountered only mild to moderate adverse drug reactions (ADRs). Change in laboratory parameters *viz*. random blood sugar (RBS), triglyceride (TG) from baseline to 12th week showed no significant difference between the groups (0.69 and 0.88 respectively) but there was significant increase ($p < 0.001$) in weight, Body Mass Index (BMI), and Waist to hip ratio in Olanzapine group.

Generally increase in weight considered to go in hand with changes in serum lipids levels, but in our study despite of significant change in weight, BMI and waist to hip ratio in Olanzapine group, there were only minimal changes in blood parameters. We tried to assess the efficacy and safety of Olanzapine versus Risperidone as an add on Lithium among Indian patients on which the data was scarce. This study was conducted at a tertiary centre, randomized study and at academic institution which was the Strengths of our study.

Limitations of our Study: The study was conducted for only 12 weeks after which the patients were not followed up long term. We assessed only 80 patients with BPAD and paediatric age group was excluded from the study. Further there is a need for a multicentre study involving large number of patients for a longer duration to evaluate efficacy of Olanzapine and Risperidone and their adverse effects.

CONCLUSION: Olanzapine and Risperidone were effective in significantly reducing maniac and depressive symptoms as add-on to Lithium among patients with BPAD. More of the ADRs were mild in nature. Olanzapine can act as better substitute in BPAD patients who do not tolerate Risperidone and vice versa.

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CONFLICTS OF INTERESTS: Declare none

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