

A RANDOMIZED SINGLE-BLIND COMPARATIVE STUDY OF THE EFFICACY AND SAFETY OF ARIPIPRAZOLE AS ADD-ON THERAPY TO SSRIS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Background: Depression is a major public health concern due to its high prevalence, associated disability, morbidity, and economic burden. AntiDepressant therapy (ADT) remains the primary treatment modality. Commonly used antidepressants—including selective serotonin reuptake inhibitors (SSRIs), Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs), Dopamine–Norepinephrine Reuptake Inhibitors (DNRIs), and Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs)—are largely based on the monoamine hypothesis. Aripiprazole, an atypical antipsychotic, has recently been approved as adjunctive therapy for Major Depressive Disorder (MDD). However, limited data are available regarding its efficacy and safety in the Indian population. This study aimed to compare the efficacy, safety, and tolerability of adjunctive Aripiprazole with SSRI monotherapy in patients with MDD. **Materials and Methods:** This was a randomized, single-blind, prospective interventional clinical study conducted over one year at the Department of Psychiatry, Tirunelveli Medical College Hospital. A total of 60 patients diagnosed with MDD were randomly assigned to two groups. One group received fluoxetine 20 mg/day with Aripiprazole 2 mg/day, while the other received fluoxetine 20 mg/day with placebo. Efficacy was assessed using the Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression scales (CGI-S and CGI-I). **Result:** Patients receiving adjunctive Aripiprazole demonstrated a significantly greater reduction in depressive symptoms compared to the placebo group. Significant improvements were observed in CGI-S and CGI-I scores, with higher remission rates in the Aripiprazole group (26.0% vs 15.7%, $p = 0.01$; 25.4% vs 15.2%, $p < 0.05$). Remission occurred earlier in the adjunctive Aripiprazole group, as early as weeks 1 and 2. Greater improvement on CGI-S scores was noted across mildly, moderately, and severely depressed patients. **Conclusion:** The combination of fluoxetine and Aripiprazole is more efficacious than fluoxetine with placebo in reducing HAM-D and CGI scores in patients with MDD. However, the Fluoxetine–Placebo combination was associated with fewer side effects compared to Fluoxetine–Aripiprazole therapy.

INTRODUCTION

Depression is a major public health problem associated with significant psychological, social, and economic burden. Major depressive disorder (MDD) is characterized by persistent low mood, loss of interest, cognitive impairment, and somatic symptoms that interfere with daily functioning.^[1] According to global estimates, depression is among

the leading causes of disability worldwide and is more common in women than men.^[2]

Although several antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are available, many patients fail to achieve adequate symptom control with monotherapy. Aripiprazole, an atypical antipsychotic with partial agonist activity at dopamine D2/D3 and serotonin 5-HT1A receptors, has recently been approved as adjunctive therapy for MDD.^[3] By modulating dopamine and serotonin

neurotransmission, Aripiprazole may enhance antidepressant response.^[4]

Limited Indian studies are available regarding the efficacy and safety of adjunctive aripiprazole therapy in depression. Hence, this study was conducted to compare the efficacy, safety, and tolerability of low-dose aripiprazole augmentation with SSRI monotherapy in patients with major depressive disorder.

Aim of the study

To evaluate the efficacy and safety of Aripiprazole adjunct to SSRI versus SSRI adjunct to placebo in Major Depressive Disorder patients.

MATERIALS AND METHODS

Study type: Interventional clinical study

Study design: Randomised, Single Blind, prospective clinical study

Study sample: Total number of 60 patients will be divided into 2 groups.

Study duration: 1 year

Study drug and dosage: Fluoxetine 20 mg with low dose Aripiprazole 2 mg/day versus Fluoxetine 20 mg/day with Placebo.

Study place: Department of Psychiatry, Tirunelveli Medical College Hospital, Tirunelveli.

Inclusion Criteria

- Patients with newly diagnosed depressive disorder as per ICD-10 criteria.
- Patients age between 18-50 years.
- Patients with recurrent depressive disorder who is not on any anti depressant drugs for the past 6 months.

Exclusion Criteria

- Patients having depression with psychotic symptoms.
- Patients with depressive episode in bipolar mood disorder.
- Patients with depression due to organic and medical etiology.
- Patients with comorbid conditions like neurological, metabolic (including type I diabetes), hepatic, renal, pulmonary, cardiovascular, gastrointestinal and/or urological disorder.
- Patients with a medical history of neuroleptic malignant syndrome and seizure disorder.

Efficacy Parameters

Primary End Point

- Mean change from baseline to Week 6 in HAM-D scale

Secondary End Point

- Mean change from baseline to Week 2 in HAM-D scale
- Mean change from Week 2 to Week 6 in HAM-D scale
- Mean change from baseline to Week 6 in CGI score

- Tolerability and safety profile of the drugs

Ethical Considerations: After obtaining institutional ethical committee approval the study was commenced. Written informed consent was obtained from all the patients included in this study, in their own vernacular language.

Schedule of Study Visit

a) Screening and recruitment: Patients who fulfilled the inclusion criteria were enrolled for the study. Demographic data of the patient will be noted. They were screened with baseline investigations like weight, BP, complete blood count, lipid profile, blood sugar, renal function test, liver function test. 60 patients were selected and randomly divided into two groups in 1: 1 ratio (by computer table) as group A and group B.

b) Treatment protocol:

Group A: Patients received getting Fluoxetine 20mg along with low dose Aripiprazole 2 mg/day after nightmeal, for 6 weeks.

Group B: Patients received getting Fluoxetine 20mg/day along with placebo after nightmeal, for 6 weeks.

Follow up: The efficacy of group A and group B was analyzed by applying Hamilton Depression Rating Scale (HAM-D) at the end of 2 and 6 weeks and its outcome analysed by Clinical Global Impression Score (CGI) at 6th week. The Hamilton, Rating Scale for Depression (HAM-D; Hamilton, 1960) is one of the longest, standing, most widely used measures, of depression severity in research and clinical practice. Adverse drug reactions were recorded and monitored by interviewing with patients, by physical examination and also by necessary lab investigations at the end of 6 weeks. Patients were insisted to maintain a diary to note any new occurrence of adverse drug reactions in between the follow up period. Suspected adverse drug reactions were documented in predesigned reporting form. Patient who developed severe intolerance or adverse effects and those who are not willing to continue the study were given freedom to withdraw from the study. Study results were analysed by standard statistical protocol using SPSS VERSION 21.0.

RESULTS

Based on the inclusion and exclusion criteria totally 74 patients were screened. Out of which 12 patients did not meet the eligibility criteria and 2 were not willing to participate in the study were excluded. 60 patients were enrolled for the study. They were randomly assigned in to 2 groups to receive fluoxetine + aripiprazole and fluoxetine + placebo through a computer generated random table. All the patients completed the study and the results were analysed.

Table 1: Comparison of age between groups

Age	GROUP		Total	p value
	Group A	Group B		
18-25	3	5	8	0.459*
26-35	12	8	20	
36-50	15	17	32	
Total	30	30	60	

*p value statistically insignificant

[Table 1] Shows comparison of age between Group A and B.

There were no significant difference in age between the 2 groups.
More patients belonged to the age group of 36-50.

Table 2: Comparison of sex between groups

Sex	GROUP		Total	p value
	Group A	Group B		
Male	9	13	22	0.284*
Female	21	17	38	
Total	30	30	60	

*p value statistically insignificant

[Table 2] Shows comparison of sex distribution between Group A and B.

There was a more female patient preponderance in both the groups.

There were no significant difference in sex distribution between the 2 groups.

Table 3: Comparison of occupation between groups

Occupation	GROUP		Total	p value
	Group A	Group B		
Skilled	4	4	8	0.624*
Semiskilled	4	7	11	
Unskilled	15	15	30	
Professional	4	1	5	
Student	3	3	6	
Total	30	30	60	

*p value statistically insignificant

[Table 3] Shows comparison of occupation status between Group A and B.

More patients were from unskilled occupation in both the groups.

There were no significant difference in occupation between the 2 groups.

Table 4: Comparison of marital status between

marital ST	GROUP		Total	p value
	Group A	Group B		
Married	14	20	34	0.217*
Unmarried	7	6	13	
Separated / widowed	9	4	13	
Total	30	30	60	

*p value statistically insignificant

[Table 4] Shows comparison of marital status between Group A and B.

Among marital status there were more patients who were married compared to separated and widowed.

There were no significant difference in marital status between the 2 groups.

Table 5: Comparison of duration of illness between groups

Dur of Illness	GROUP		Total	p value
	Group A	Group B		
< 1 month	7	6	13	0.699*
1-3 months	8	11	19	
4-6 months	8	9	17	
> 6 months	7	4	11	
Total	30	30	60	

*p value statistically insignificant

[Table 5] Shows comparison of duration of illness between Group A and B. However there were no significant difference between the 2 groups.

Out of 30 patients, 8 patients had duration of illness of 1-3 months in Group A and 11 patients had duration of 1-3 months in Group B. Similarly 8 patients in Group A had a duration of 4-6 months and 9 patients in Group B had similar duration.

Table 6: Comparison of family history with depression between groups

Family H/o	GROUP		Total	p value
	Group A	Group B		
Yes	2	5	7	0.228*
No	28	25	53	
Total	30	30	60	

*p value statistically insignificant

[Table 6] Shows comparison of family history between Group A and B. There were no significant difference between the 2 groups.

Among 30 patients only 2 patients had family history with depression in Group A and 5 patients had family history in Group B. There was no correlation of family history of depression between the groups.

Table 7: Comparison of H/O suicide attempt between groups

Suicide attempt	GROUP		Total	p value
	Group A	Group B		
Yes	8	7	15	0.766*
No	22	23	45	
Total	30	30	60	

*p value statistically insignificant

[Table 7] Shows comparison of H/O suicide attempt between Group A and B. There were no significant difference between the 2 groups.

Out of 30 patients only 8 patients in Group A and 7 patients in Group B had previous history of suicide attempt.

Table 8: Comparison of substance abuse between groups

Sub abuse	GROUP		Total	p value
	Group A	Group B		
ALCOHOL	2	5	7	0.307*
SMOKING	1	0	1	
NIL	27	25	52	
Total	30	30	60	

*p value statistically insignificant

[Table 8] Shows comparison of substance abuse between Group A and B. There were no significant difference between the 2 groups.

There were more patients without history of substance abuse followed by alcohol and then smoking in both the groups.

Table 9: Comparison of HAM-D score at 2 weeks in Group A

HAM-D- B	HAM-D- 2W			Total	p value
	Mild depression	Moderate depression	Severe depression		
Moderate depression	1	0	0	1	0.027*
Severe depression	7	1	0	8	
Very severe depression	5	13	3	21	
Total	13	14	3	30	

*p value statistically significant

[Table 9] shows the reduction in severity of depression assessed by HAM-D scale at 2 weeks in patients of Group A. This shows that among 21 patients who had very severe depression as baseline 3 patients changed to

severe depression, 13 patients changed to moderate depression and 5 patients changed to mild depression at the end of 2 weeks.

Table 10: Comparison of HAM-D scale at 6 weeks in Group A

HAM-D- B	HAM-D -6W			Total	p value
	Normal	Mild depression	Moderate depression		
Moderate depression	1	0	0	1	0.74*
Severe depression	8	0	0	8	
Very severe depression	17	2	2	21	
Total	26	2	2	30	

*p value statistically insignificant

[Table 10] shows no significant difference in HAM-D scale at 6 weeks in Group A. In group A, at the end of 6 weeks compared from baseline in HAM-D scale, among 21 very severe depression patients 2 patients

changed to moderate and mild and 17 patients changed to normal.

Among 8 severe depression patients all 8 changed to normal and among 1 moderate depression patient changed to normal at the end of 6 weeks.

Table 11: Comparison of HAM-D scale at 2 weeks in Group B

HAM-D- B	HAM-D- 2W			Total	p value
	Mild depression	Moderate depression	Severe depression		
Moderate depression	3	0	0	3	<0.0001*
Severe depression	0	9	0	9	
Very severe depression	0	7	11	18	
Total	3	16	11	30	

*p value statistically significant

[Table 11] shows significant reduction in HAM-D scale at 2 weeks in Group B.

very severe depressive patients 11 changed to severe and 7 changed to moderate depression.

In group B at the end of 2 weeks comparison of HAM-D scale from baseline, showed that among 18

Table 12: Comparison of HAM-D scale at 6 weeks in Group B

HAM-D- B	HAM-D -6W			Total	p value
	Normal	Mild depression	Moderate depression		
Moderate depression	3	0	0	3	0.023*
Severe depression	7	2	0	9	
Very severe depression	5	4	9	18	
Total	15	6	9	30	

*p value statistically significant

[Table 12] shows significant reduction in HAM-D scale at 6 weeks in Group B.

Comparison of HAM-D scale from baseline at the end of 6 weeks in group B patients showed that, among 18 very severe depression patient 9 changed to moderate, 4 changed to mild and 5 changed as normal patient.

[Figure 1] shows reduction of HAM-D scale in both groups from baseline to week 2 and 6.

There was more reduction of HAM-D scale in Group A from baseline to 2 and 6 weeks than Group B.

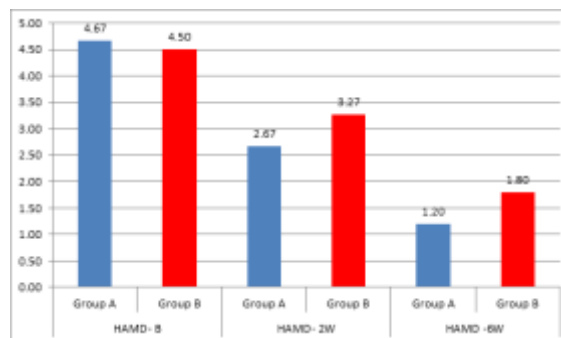


Figure 1: Kruskal-Wallis H test (HAM-D Scale comparison between group A and group B).

Table 13: Comparison of CGI Score at 6 weeks in Group A

CGI - B	CGI 6W				Total	p value
	Very much improved	Much improved	Minimally improved	No change		
Moderately ill	1	10	2	0	13	0.026*
Markedly ill	2	3	2	2	9	
Severely ill	1	1	1	5	8	
Total	4	14	5	7	30	

*p value statistically significant

[Table 13] shows significant reduction in CGI score at 6 weeks compared from baseline in group A.

There was significant decrease in CGI score among 13 moderately ill patients, where 2 were minimally

improved, 10 were much improved and 1 were very much improved among Group A patients at the end of 6 weeks.

Table 14: Comparison of CGI score at 6 weeks in Group B

CGI – B	CGI 6W					Total	p value
	Very much improved	Much improved	Minimally improved	No change	Minimally worse		
Mildly ill	1	0	0	0	0	1	0.025*
Moderately ill	2	2	6	1	0	11	
Markedly ill	0	3	4	3	0	10	
Severely ill	1	1	1	3	1	7	
Among the most extremely ill pts	0	0	0	0	1	1	
Total	4	6	11	7	2	30	

*p value statistically significant

[Table 14] shows significant reduction in CGI score compared from baseline to the end of 6 weeks in group B.

Among 11 moderately ill patients 6 minimally improved, 2 much improved and 2 very much improved. In 10 markedly ill patients 4 minimally improved and 3 much improved at the end of 6 weeks in Group B.

[Figure 2] shows significant reduction in CGI score at 6 weeks compared from baseline CGI score in both groups.

This shows that there was more significant reduction of CGI score baseline to CGI score at 6 weeks in group A compared to group B.

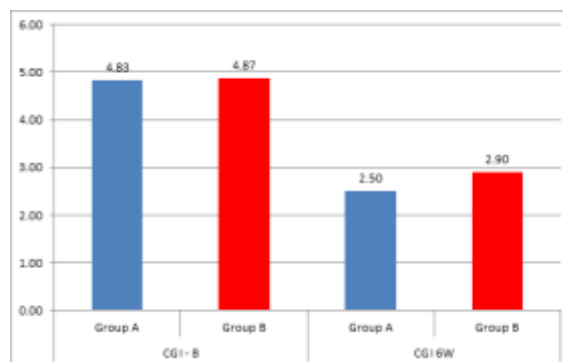


Figure 2: Kruskal-Wallis H test (CGI score comparison between group A and group B).

Table 15: Comparison of weight between Group A and B

GROUP		Mean	Std. Deviation	p value
Weight- B	Group A	55.80	12.16	0.945*
	Group B	55.60	9.93	
Weight-6W	Group A	56.13	12.24	0.954*
	Group B	55.97	10.12	

*p value statistically insignificant.

This shows that there was no significant difference in body weight in both the groups at baseline and week 6.

Both groups had a mean value of around 55 both in baseline and at the end of 6 weeks.

Table 16: Comparison of blood pressure between Group A and B

GROUP		Mean	Std. Deviation	p value
SBP- B	Group A	110.33	8.09	0.334*
	Group B	113.00	12.64	
SBP- 6W	Group A	109.33	5.83	0.06*
	Group B	112.33	6.26	
DBP- B	Group A	72.33	7.28	0.032*
	Group B	76.67	8.02	
DBP- 6W	Group A	74.33	5.68	0.628*
	Group B	73.67	4.90	

*p value statistically insignificant

[Table 16] shows that there was no significant difference in SBP and DBP in both the groups compared from baseline to the end of 6 weeks.

Table 17: Comparison of Random blood sugar between Group A and B

GROUP		Mean	Std. Deviation	p value
RBS- B	Group A	96.20	23.12	0.098*
	Group B	106.73	25.30	
RBS -6W	Group A	92.30	14.34	0.051*
	Group B	102.17	22.95	

*p value statistically insignificant.

[Table 17] shows that there was no significant difference in blood sugars in both the groups compared from baseline to week 6.

In Group A mean value changed from baseline 96.2 to 92.3 at 6 weeks, whereas in Group B mean value changed from baseline 106.73 to 102.17 at 6 weeks.

Table 18: Comparison of lipid parameters between Group A and B

GROUP		Mean	Std. Deviation	p value
Tot chl-B	Group A	127.73	43.11	0.064*
	Group B	147.07	35.95	
Tot chl-6W	Group A	118.43	31.97	0.02*
	Group B	138.60	33.14	
TGL -B	Group A	108.47	39.07	0.244*
	Group B	119.67	34.46	
TGL -6W	Group A	98.73	27.84	0.052*
	Group B	113.33	29.19	
LDL-B	Group A	71.53	31.43	0.017*
	Group B	88.97	22.75	
LDL-6W	Group A	68.50	30.23	0.012*
	Group B	86.10	21.87	
VLDL-B	Group A	47.63	31.37	0.384*
	Group B	54.13	25.74	
VLDL-6W	Group A	46.43	28.78	0.272*
	Group B	54.10	24.63	
HDL-B	Group A	73.67	14.46	0.27*
	Group B	70.00	10.74	
HDL-6W	Group A	75.63	11.22	0.115*
	Group B	71.50	8.63	

*p value statistically significant ($p < 0.05$) only in LDL value.

Other lipid parameters showed statistically insignificant values.

This shows that there is significant decrease in LDL value in both the groups compared from baseline to 6 weeks.

Other lipid parameters shows no significant change in both the groups at baseline and week 6.

Table 19: Comparison of SGOT & SGPT between Group A and B

GROUP		Mean	Std. Deviation	p value
SGOT-B	Group A	32.07	18.43	0.12*
	Group B	25.63	12.56	
SGOT-6W	Group A	32.63	16.80	0.047*
	Group B	24.97	12.15	
SGPT - B	Group A	21.37	13.89	1.000*
	Group B	21.37	6.63	
SGPT - 6W	Group A	22.77	14.40	0.837*
	Group B	22.17	6.67	

*p value statistically insignificant.

[Table 19] shows no significant difference in SGOT and SGPT in both the groups at baseline and week 6.

Table 20: Adverse drug reactions between group A & B

ADR	Group A	Group B
Nil	1	8
Akathisia	2	0
constipation	4	3
Dyspepsia	2	1
Fatigue	6	4
Headache	10	8
Insomnia	7	2
Nausea	10	3
Sweating	1	1
Vomiting	1	0
Dizziness	2	1
Drowsiness	1	0
Decreased appetite	4	4
Weight gain	1	1
Dry mouth	0	1

Among adverse drug reactions reported between groups headache and nausea was the most commonly reported adverse event in both the groups, followed by decreased appetite, fatigue and constipation. Akathisia was the adverse event which was reported only in group A but not reported in group B. In group

A only 1 patient had no ADR whereas in group B 8 patients had no ADR.

This implies that adverse drug reactions were more common in patients of group A compared to group B.

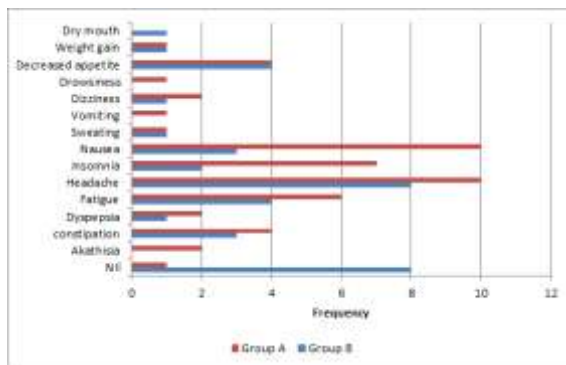


Figure 3: Adverse drug reactions among groups

DISCUSSION

A total of 60 patients were enrolled: 30 in Group A (Fluoxetine + Aripiprazole) and 30 in Group B (Fluoxetine + Placebo). Most patients were aged 36–50 years, similar to findings by M. Mohebbi et al.^[5,6] Females showed higher prevalence of depression than males, consistent with meta-analyses suggesting greater risk and severity among women.^[7,8] Unskilled workers showed higher prevalence of depression. About 70% of patients were married, similar to Andrew et al.^[9] Family history of depression was present in 7 patients, comparable with Zalar et al.^[10] HAM-D and CGI scores were used to assess efficacy. Both groups showed significant reduction in HAM-D and CGI scores from baseline at weeks 2 and 6 ($p < 0.05$). Between-group comparison also showed significant improvement with Aripiprazole augmentation. The findings support Aripiprazole augmentation with SSRIs in depression. Previous studies also reported significantly higher remission rates with adjunctive Aripiprazole than placebo.^[8-15] Stewart et al. and Marcus et al. demonstrated greater improvement in depressive symptoms with adjunctive Aripiprazole.^[16-18] Metabolic parameters, blood sugar, liver enzymes, and most lipid values showed no significant differences between baseline and week 6, similar to Robert et al. and Stewart et al.^[17,16] LDL alone showed significant reduction. Weight gain findings differed from Eric et al., who reported greater weight increase with Aripiprazole.^[8] Around 80% of patients experienced adverse reactions. Headache, nausea, insomnia, fatigue, constipation, and decreased appetite were common in Group A, while headache, fatigue, nausea, and constipation predominated in Group B. These findings were similar to Stewart et al.^[16] Akathisia occurred only in two patients receiving Aripiprazole, supporting reports by Eric et al. and Nelson et al. that akathisia is a known but usually mild side effect.^[6,8,15,18]

No patients reported suicidal ideation during the study. Consistent with Robert et al., Nelson et al., Berman et al., Simon et al., and Worthington et al., adjunctive Aripiprazole produced significantly better remission rates than placebo in patients with major depressive disorder.^[6,9,10,11,17]

CONCLUSION

To conclude, based on the results, combination of fluoxetine and Aripiprazole is more efficacious than combination of Fluoxetine and placebo in reducing HAM-D scale and CGI score, but combination of Fluoxetine and placebo produces less side effects than combination of Fluoxetine and Aripiprazole.

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