Original Article

Comparative Study of Efficacy and Safety of Amisulpride and Aripiprazole in Patients of Schizophrenia in a Tertiary Care Centre of Eastern India

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ABSTRACT

Introduction: The key to evidence-based medicine is to identify similarities and differences between available drugs. There is difference among antipsychotic drugs with respect to frequency of common adverse effects clearly differ in propensity for causing common side-effects, such as extrapyramidal symptoms and weight gain, but meta-analyses also suggest a hierarchical structure for efficacy. Based on results of meta-analysis, amisulpride and amisulpride were found to be most effective drugs among first line antipsychotics.

Aims/ objective: To generate further evidence for decreasing controversies, we had planned this study to compare the efficacy and safety of amisulpride and aripiprazole in patients of schizophrenia.

Materials and Method: Change in mean PANSS total score; change in mean PANSS positive, negative, and general subscale score; change in mean CGI-S (Clinical Global Impression–Severity of Illness scale) and change in mean GAF (Global Assessment of Functioning) score from baseline to 1 year were compared between two groups. Patients were assessed for these outcome measures at baseline, 1 month, 3 months, 6 months, and 12 months. Categorical data were compared using fisher's exact test and continuous data were compared using unpaired t test. P-value less than 0.05 was taken as measure of statistically significant difference.

Results: Amisulpride was found superior to aripiprazole in pharmacotherapy of schizophrenia with regards to total PANSS score. There was significant improvement in positive and negative symptoms in both groups ($p<0.0001$). However, there was statistically significant better result in amisulpride groups with regard to PANSS positive subscale score ($p<0.0001$). The efficacy of amisulpride on improvement in negative symptoms was better than the improvement in positive symptoms.

Conclusion: Amisulpride was found more efficacious than aripiprazole regarding improvement in positive and negative symptoms and total PANSS score. Both amisulpride and aripiprazole had no significant effect on weight gain and extrapyramidal symptoms. Increase in dose of amisulpride had also no significant effect on frequency of adverse events.

Keywords: Amisulpride, Aripiprazole, Schizophrenia, Efficacy, Safety.

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INTRODUCTION

Schizophrenia is a complex and chronic psychological disorder which is characterised by range of symptoms that includes delusion, hallucination, altered speech or behaviour and defective cognition. The early onset of the disease, along with its chronic course, make it a disabling disorder for many patients and their families. Early onset and chronic course of this disease make it as a major limiting factor for lifestyle and productivity of the patient and his family[1]Disability in this disease is usually due to negative symptoms and symptoms related to cognition defect like altered attention, deficit memory, and lag in executive function. [2]

Further, there are chances of relapse due to positive symptoms such as suspicion, delusion, and hallucination[1,2] The inherent heterogeneity of schizophrenia has resulted in a lack of consensus regarding the disorder's diagnostic criteria, aetiology, and pathophysiology. The heterogeneity that is inherent in this disorder has led to limitation in consensus on diagnostic criteria of this disease and its aetiology and pathophysiology[1,3]

Identification of positive symptoms is most easy, and we can define them as psychotic behaviour that is not found in healthy people. [4] Such symptoms comprise of delusion, hallucination and altered motor behaviour at various level of severity.[5] Diagnosis of negative symptoms is difficult, and these symptoms lead to high morbidity by disturbing emotions and behaviour of patients. [4,5]It is essential to note thatnegative symptoms can have either primary relation to the diagnosis of schizophrenia or have secondary relation to concomitant diagnosis of psychotic disorder, drugs, or other environmental factors.[5,6]

As per guidelines of the American Psychiatric Association, atypical or second-generation antipsychotics (SGAs) are

the drugs of choice for first-line pharmacotherapy of schizophrenia.[6,7]Atypical antipsychotics are given priority over typical or first-generation antipsychotics (FGAs) because incidence of extrapyramidal adverse effects is low.[2] However, atypical antipsychotics are associated with metabolic adverse effects, such as obesity, dyslipidaemia, and insulin resistance. These side effects can also increase the risk of adverse cardiovascular outcomes in patients already burdened with schizophrenia.[8]

Psychotic symptoms are related to hyperactivity in dopaminergic systems of ventral striatum and its associated ganglia.[9]However, the neurobiological pathophysiology of defective cognition and negative symptoms are not fully clear. Some hypothesis points to their relationship with disturbances in cerebral networks and relationship with some extent to decreased dopaminergic activity in prefrontal cortex. [10]

Mechanism of action of typical and atypical antipsychotic drugs is antagonism of D2 receptors leading to inhibition of hyperactive dopamine turnover in the ventral and associated parts of striatum. Partial D2 agonists are put in the category of third-generation antipsychotics and are hypothesized to inhibit the hyperactive dopamine system in ventral striatum and stimulate dopamine-induced signalling in area of diminished dopamine activity such as prefrontal cortex. According to previous hypothesis, this can result in improvement in defective cognition and negative symptoms. [11]

Amisulpride has relative selective antagonistic action on D2 receptor antagonist but is not classified as third generation antipsychotic due to selective action on limbic system.[12]Its effect is also hypothesized to be on negative symptoms because it has some affinity for presynaptic D1 receptors in striatum, and this effect has been proven in meta-analysis especially at doses less than 300 mg.[13]Some improvement in cognition by amisulpride and other second-generation antipsychotics has also been reported in few research but this can also be associated with.[14,15]

Aripiprazole was the first partial agonist of D2 receptor approved for pharmacotherapy of schizophrenia. In research, which has compared the efficacy of aripiprazole with first-generation antipsychotics, aripiprazole was found to be effective in treating negative symptoms.[16]

The key to evidence-based medicine is to identify similarities and differences between available drugs. Large group-level effect sizes have been demonstrated with use of many antipsychotic drugs for short term pharmacotherapy of schizophrenia.[17] Treatment guidelines consider tolerability and adverse-effect profiles as cornerstone for choosing antipsychotic drug for pharmacotherapy.[18]There is difference among antipsychotic drugs with respect to frequency of common adverse effects clearly differ in propensity for causing common side-effects, such as extrapyramidal symptoms and weight gain, but meta-analyses also suggest a hierarchical structure for efficacy.[17] Based on results of meta-analysis, amisulpride and amisulpride were found to be most effective drugs among first line antipsychotics. [17]

In this background and to generate further evidence for decreasing controversies, we had planned this study to compare the efficacy and safety of amisulpride and aripiprazole in patients of schizophrenia.

MATERIALS AND METHODS

This was an open label, randomised controlled trial with 1:1 allocation ratio. The study was conducted in outpatient department of psychiatry in tertiary care hospital of Bihar between June 2021 to June 2022. The study was conducted after getting approval from institutional ethics committee and taking written informed consent from study participants after explaining them full procedure in patient information sheet.

Inclusion Criteria

Patients of age more than 18 years. Patients diagnosed within the schizophrenia-spectrum as per ICD-11 diagnostic criteria F20–29. [21]Patients having symptoms of psychosis with a score of 4 or more on at least one of the following Positive and Negative Syndrome Scale (PANSS) parameters: P1 (delusions), P3 (hallucinations),P5 (grandiosity), P6 (suspiciousness or persecution) orG9 (unusual thought content).[22] Diagnosis was done using structured clinical interview by trained clinicians.

Exclusion Criteria

Hypersensitivity to atypical antipsychotics. Pregnant or breastfeeding women. Patients unable to understand local language. Use of medication that can cause torsade de pointes. Use of levodopa. Risk of angle closure glaucoma. Pheochromocytoma. Smoking, alcohol or drug misuse.

Primary End Point

Change in mean PANSS total score from baseline to 52 weeks.

Secondary End Points

Change in mean PANSS positive, negative, and general subscale score from baseline to 1 year. Change in mean CGI-S (Clinical Global Impression–Severity of Illness scale) from baseline to 1 year.[23] Change in mean GAF (Global Assessment of Functioning) score from baseline to 1 year.[24] Frequency of adverse drug reactions (ADRs).

With anticipated decrease of 30 ± 3 in PANSS score after 52 weeks in amisulpride group and 28 in aripiprazole group, the minimum sample size with 80% power and alpha value of 0.05 was found to be 70. So, 100 patients were enrolled in study to deal with expected 20% attrition rate.

Randomisation was done using web generated random numbers and patients were equally allocated to each group to receive either amisulpride or aripiprazole. Dosing was as per decision of clinician in department of psychiatry depending upon the condition of patient. Dose of

amisulpride ranged from 50-1200 mg per day orally and dose of aripiprazole ranged from 5-30 mg per day orally.

Patients were assessed for primary and secondary outcomes measures at baseline, 1 month, 3 months, 6 months, and 12 months.

Statistical Analysis

Data collected was presented in tabular form and interpreted using Microsoft Excel 365 software. Categorical data were compared using fisher's exact test. Continuous data were compared using unpaired t test for inter-group comparison and repeated measure ANOVA for within group comparison. P-value less than 0.05 was taken as measure of statistically significant difference.

RESULTS

A total of 100 patients were enrolled in the study and randomised in two groups with 50 patients in each group. 8 patients in amisulpride group and 5 patients in aripiprazole group were lost to follow-up. So, analysis was done on 42 patients in amisulpride group and 45 patients in aripiprazole group.

Table 1: Comparison of Baseline Demographic and Clinical Characteristics between Two Groups

Parameters	Amisulpride (n = 42)	Aripiprazole (n=45)	P-Value
Age in years (mean ± SD)	31.7 ± 10.8	32.8 ± 12.6	0.6641 (Unpaired t test)
Gender			
Male	27	29	1.0000 (Fisher's Exact Test)
Female	15	16	
Lifestyle			
Living alone	20	19	0.6695 (Fisher's Exact Test)
Living with family	22	26	
Employment			
Employed	13	11	0.6320 (Fisher's Exact Test)
Un-employed	29	34	
Duration of illness in years (mean ± SD)	5.6 ± 2.1	6.3 ± 2.9	0.2035
Diagnosis			
Schizophrenia F20	27	25	
Schizotypal F21	0	1	
Delusional disorder F22	5	6	0.3759 (Fisher's Exact Test)
Acute and transient F23	7	4	
Schizoaffective F25	3	4	
Other nonorganic F28	0	2	
Unspecified nonorganic F29	0	3	
Body Mass Index (BMI) in kg/m^2	25.9 ± 4.7	26.7 ± 5.2	0.4547

There was no significant difference between two groups with respect to age, sex, lifestyle, diagnosis, duration of illness and body mass index (p>0.05).

Table 2: Comparison of PANSS positive subscale score between two groups

Parameters	Amisulpride (n = 42)	Aripiprazole (n=45)	P-Value (Unpaired t test)
Baseline	22.5 ± 0.8	22.2 ± 0.6	0.1050
1 Month	13.1 ± 0.7	16.4 ± 0.9	<0.0001
3 Months	12.2 ± 0.9	14.7 ± 0.8	<0.0001
6 Months	11.1 ± 1.0	12.8 ± 0.9	<0.0001
12 Months	10.3 ± 1.1	11.9 ± 1.2	<0.0001
P Value (ANOVA)	<0.0001	<0.0001	

Table 3: Comparison of PANSS negative subscale score between two groups

Parameters	Amisulpride (n = 42)	Aripiprazole (n=45)	P-Value (Unpaired t test)
Baseline	18.5 ± 1.0	18.1 ± 0.9	0.0529
1 Month	15.3 ± 1.1	16.5 ± 1.1	<0.0001
3 Months	14.9 ± 1.1	16.1 ± 1.1	<0.0001
6 Months	14.1 ± 1.2	16.3 ± 1.2	<0.0001
12 Months	12.7 ± 1.2	15.2 ± 1.5	<0.0001
P Value (ANOVA)	<0.0001	<0.0001	

Both groups were having similar baseline PANSS positive and negative subscale score (p>0.05). There was significant improvement in positive and negative symptoms in both groups (p<0.0001). However, there was statistically significant better result in amisulpride groups with regard to PANSS positive subscale score (p<0.0001). The efficacy of amisulpride on improvement in negative symptoms was better than the improvement in positive symptoms.

Table 4: Comparison of PANSS general subscale score between two groups

Parameters	Amisulpride (n = 42)	Aripiprazole (n=45)	P-Value (Unpaired t test)
Baseline	41.2 ± 1.4	40.9 ± 1.3	0.3030
1 Month	32.3 ± 1.5	32.4 ± 1.6	0.7648
3 Months	29.1 ± 1.6	29.5 ± 1.7	0.2624
6 Months	27.9 ± 1.8	27.2 ± 1.8	0.0734
12 Months	25.7 ± 1.8	27.8 ± 2.2	<0.0001
P Value (ANOVA)	<0.0001	<0.0001	

Amisulpride and aripiprazole has similar efficacy regarding improvement in PANSS general subscale score till 6 months of therapy (p>0.05).

Table 5: Comparison of total PANSS scores between two groups

Parameters	Amisulpride (n = 42)	Aripiprazole (n=45)	P-Value (Unpaired t test)
Baseline	82.2 ± 2.6	81.2 ± 2.5	0.0709
1 Month	60.7 ± 2.8	65.3± 2.9	<0.0001
3 Months	56.2 ± 3.0	60.6± 3.0	<0.0001
6 Months	53.1 ± 3.2	56.3± 3.2	<0.0001
12 Months	48.7 ± 3.2	54.9 ± 4.0	<0.0001
P Value (ANOVA)	<0.0001	<0.0001	

Amisulpride was found superior to aripiprazole in pharmacotherapy of schizophrenia with regards to total PANSS score.

Table 6: Comparison GAF and CGI-S scores between two groups

Parameters	Amisulpride (n = 42)	Aripiprazole (n=45)	P-Value (Unpaired t test)
GAF Score			
Baseline	37.7 ± 1.9	38.5 ± 2.0	0.0595
1 Year	60.8 ± 3.1	57.9 ± 3.2	<0.0001
CGI-S score			
Baseline	4.9 ± 0.8	4.6 ± 0.9	0.277
1 Year	2.7 ± 0.4	3.2 ± 0.5	<0.0001

No suspected and unexpected adverse drug reactions were reported from patients of either group. Mean body mass index (BMI) increased from 25.9 from baseline to 28.3 in amisulpride group whereas it increased from 26.7 to 28.5 in aripiprazole group.

DISCUSSION

In our study, both drugs show significant improvement with respect to PANSS score, GAF score and CGI-S score. Amisulpride was found to be superior to aripiprazole regarding reduction in PANSS total score in 1 year. This superiority of amisulpride effectiveness was also seen during PANSS positive, negative, and general subscale scores. However, no significant difference in GAF and CGI-S score was found between two groups.

Compared to other studies, there was greater reduction in PANSS score in our study. [25] However, our results are nearer to naturalistic and pragmatic study findings that has more capability to be perceived on everyday clinical practice thus contributing more to evidence-based medicine. A reduction of 60% of symptoms from baseline to 1 year was reported in research done on effectiveness of antipsychotic drugs.[26]

In this study, we found no statistically significant difference in improvement of symptoms and adverse drug reactions between the group in which patients were given starting dose of 200 mg amisulpride and the group starting dose of 400 mg was given. We found no statistically significant differences between the groups with different starting dose with respect of increase in BMI and symptomatic improvement as measured by changes from baseline PANSS total score, PANSS negative subscale score, CGI-S, and GAF scores. However, the sample size of subgroup with different sample size was small and there is requirement of statistically more powerful study with larger sample size with better assessment. In a 6-week open label randomized study which compared effectiveness between 400 mg and 800 mg dose group of amisulpride in acute exacerbation of schizophrenia, no statistically significant differences were reported in the overall frequency of adverse events.[27]

In our study, no increase in incidence and severity of extrapyramidal symptoms was found after initiation of amisulpride pharmacotherapy and there was also no significant increase in BMI of the patients. In an earlier study done to evaluate outcome of adding amisulpride to oral or parenteral risperidone, there was reduction in frequency and severity of extrapyramidal symptoms at end of study after addition of amisulpride.[33] Another study regarding addition of amisulpride to olanzapine also reported significant reduction in the number of patients having moderate EPS from baseline to 12 weeks after addition of amisulpride. [28] However, in a randomised controlled trial done to compare addition of amisulpride and placebo to clozapine, it was found that there was higher reporting of adverse effects such as weight gain, dyslipidaemia, sexual dysfunction and deterioration of subjective experiences with respect to the Antipsychotic Non-Neurological Side Effects Scale assessments designed for systematic and comprehensive assessment of compete range of adverse effects in the group with amisulpride augmentation. [29]

Previously, the recommendation of guidelines was to avoid multiple antipsychotics for schizophrenia and monotherapy with atypical antipsychotics was advised if possible.[30] However, in a recent study that was done to assess relation between rehospitalization in patients of schizophrenia with monotherapy or combination therapy with antipsychotics reported that there was least risk of rehospitalization with combination therapy of aripiprazole and clozapine. Based on findings of the study, it was suggested that the treatment guidelines need modification.[31] The current guidelines released by the American Psychiatric Association guideline recommends that addition of second atypical antipsychotics may be considered by the clinician but augmentation with another antipsychotic can be considered but also states that the trial with clozapine monotherapy should be considered first because evidence for the effectiveness of clozapine on treatment resistant schizophrenia is well established. [32]An open label observational study on addition of amisulpride to risperidone who were not well controlled with monotherapy reported that there was significant improvement in CGI-S, Brief Psychiatric Rating Scale, and Side Effect Rating Scale scores.[33] In similar study on patients who were partially controlled with olanzapine monotherapy reported that addition amisulpride for three months increased the response rate to 75.51%. [28]

Our study had certain limitations. Blinding was note done to eliminate bias associated with patients and investigator. The small sample size also reduced the capability of our study for better generalisability of results. In addition, the chances of effect of previous antipsychotics on the improvement of symptoms after administration of amisulpride and aripiprazole was also not completely eliminated by our study design.

CONCLUSION

Amisulpride was found more efficacious than aripiprazole regarding improvement in positive and negative symptoms and total PANSS score. Both amisulpride and aripiprazole had no significant effect on weight gain and extrapyramidal symptoms. Increase in dose of amisulpride had also no significant effect on frequency of adverse events. There is need of study with large sample size with larger subgroup size to compare efficacy and safety of different dose and add on therapy with second generation antipsychotics to strengthen evidence-based pharmacotherapy of schizophrenia.

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