Original Research Article

Comparative evaluation of efficacy and safety of aripiprazole versus amisulpiride as add on therapy to olanzapine in partial responders of schizophrenia

Saroj Kothari[1], Archana Rathore[2*], Vivek Dwivedi[3]

[1]Professor and Head, Department of Pharmacology, Gajra Raja Medical College Gwalior, MP, India
[2]MD Pharmacology, Gwalior, MP, India
[3]Assistant Professor, Department of Pharmacology, Veerchandra Singh Garhwali Government Medical College and Research Center, Srikot Shrinagar Pauri Garhwal, Uttrakhand, India

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Abstract

Objective: Many newer agents are proposed as adjunctive therapy to olanzapine for better treatment of schizophrenia. Therefore present study is planned to compare efficacy, tolerability & safety profile of olanzapine plus aripiperazole versus olanzapine plus amisulpiride combination in schizophrenic patients partially responded to olanzapine monotherapy. **Material and Methods:** This is a longitudinal, prospective, randomized comparative study conducted in department of pharmacology and out patients of psychiatry in J.A. group of hospitals, Gajra Raja Medical College, Gwalior, M.P.from February 2018 to March 2019 after seeking Institutional ethics committee approval. Total 112 diagnosed cases of schizophrenia who were partial responders to olanzapine monotherapy were chosen for the study. Patients were divided into two groups randomly. Group I(n=54)received olanzapine(20 mg) in combination with aripiprazole(10mg) and Group II (n=58)received olanzapine(20mg) with amisulpiride (100mg) orally for 8 weeks. Effectiveness was assessed by change in Positive and Negative Symptom Scale Score (PANSS) & Clinical Global Impression-Improvement (CGI-I) score at 4th and 8th week as compared to baseline values.Safety was assessed by recording adverse effects during treatment period. **Results:** 45 patients in each group completed the study. On 8th week , percentage change in mean PANSS score from baseline was 41.6%and 34% in group I and group II respectively and was significant ($P<0.05$)as compared to baseline values. On Inter group comparison difference was not statically significant ($P>0.05$).Olanzapine with aripiprazolecombination therapy showed 54% improvement in CGI-I scale and was significant ($P < 0.05$)as compared to 40% change with olanzapine and amisulpiride combination therapy. Aripiparazole add on therapy has shown less adverse effects to that of amisulpiride. **Conclusion**: Aripiprazoleas add on therapy to olanzapine has shown better efficacy safety and tolerability than that of amisulpiride.

Key Words: Aripiparazole, Amisulpiride , Schizophrenia,PANSS, CGI-I

Introduction

Schizophrenia is a chronic mental disorder associated with hallucination, delusion,and psychosisas positive symptoms and disruption of normal emotion and behavior as negative symptoms[1]. It is one of the important cause of morbidity in adolescents between the age of 15-39 years.Now a days mainstay of treatment of schizophrenia is by using atypical antipsychotics. Among all atypical antipsychotic drugs, olanzapine is most widely used drug in treatment of schizophrenia[2] With due course of time several adverse effects such as weight gain, sedation, anticholinergic effects are reported with the use of olanzapine.Schizophrenic patients need long term therapy and despite adverse effects physicians choose olanzapine because of its efficacy and tolerability[3]. About 40% of patients with psychotic symptoms do not respond to conventional antipsychotic monotherapyOn increasing the dose of olanzapine in partial responders, chances of adverse effect also increases, so in such patients, combined application of antipsychotic drugs is an established step in the treatment of schizophrenia[4].

Antipsychotic polypharmacy refers to the co-prescription of more than one antipsychotic drug for an individual patient. Reason for choosing polypharmacy by the clinicians, is the concern about a particular adverse effect risk with the antipsychotic monotherapy & to achieve greater therapeutic response, Selection of add on drug with low liability for that adverse effect to another antipsychotic are strategies that are used in clinical practice to treat schizophrenic patients who have partial or inadequate response to standard doses of a single atypical antipsychotic[5].

Aripiprazole is one of the newer antipsychotic drug has a mechanism of action different from other atypical antipsychotics, so creates interest in this field.Aripriparazole causes weight loss in patients who have increase of body weight when treated with olanzapine[6,7]. Amisulpride is another new safe and efficient atypical antipsychotic drugexhibits a unique pharmacological profile & has a high affinity and selectivity for dopamine D2 and D3 receptor subtype. The substance ameliorates negative symptoms and exerts only small increase in body weight[8].

No scientific studies are available to best of our searchin literature to know which adjunctive therapy to olanzapinehas the better outcome between aripriparazoleandamisulpiride. Therefore present study is planned to compare efficacy, safety and tolerability of addition of aripriparazole versus amisulpiride to olanzapine in patients of schizophrenia.

Material and methods

Study design

This is a prospective, randomized, open-labeled, comparative study conducted in the department of Pharmacology and Psychiatry at J.A. Group of Hospital, G.R. Medical College, Gwalior (M.P) from March 2018 to February 2019 after taking approval from Institutional Ethics Committee. The study included participant or family members willing to give written informed consent, those patients diagnosed with schizophrenia according to DSM-V diagnostic criteria and showed <20% improvement in PANSS score after treatment with 20 mg oral olanzapine as monotherapy for 6 weeks. Patients excluded from study include age below 18 yrs and above 60 yrs, any other psychiatric

*Correspondence
Dr. Archana Rathore
MD Pharmacology, Gwalior, MP, India
E-mail: archiholdoff@gmail.com

condition, history of seizures, diabetes mellitus, hypertension, hepatic & renal disease, and pregnant/nursing females.Informed written consent was taken from all patients before enrolling them in the study.

Procedure of study

Total 112 patients were enrolled and were randomly distributed in Group I and Group II '

Group I:Aripiprazole 10 mg once a day was administered as add on therapy for 8 weeks to all patients in Group I (n=54) who were already receiving tablet olanzapine 20 mg

Group II: Amisulpiride 100 mg once a day was administered as add on therapy for 8 weeks to all patients in Group II (n=58) who were already receiving tablet olanzapine 20 mg

Assessments of all the patients were done for improvement in symptoms and presence of adverse effect after 4th& 8th week of therapy.

Efficacy assessment

1. Positive and negative syndrome scale (PANSS) is used to check improvement in positive and negative symptoms.Decrease of ≥20% in the PANSS defined as a positive response of the treatment[9]. Efficacy was assessed by recording PANSS scores at 4th& 8th weeks after treatmentand was compared from baseline values.
2. CGI-I(Clinical Global Impression-Improvement) scale- This is a 7 point scalethat measures overall improvement in symptoms of illness[10]. CGI scores at 4th& 8th weeks of therapy were recordedand compared from baseline values.

Safety assessment

During the study, various adverse drug reactions were reported by patients like somnolence, asthenia, headache, dry mouth, agitation, weight gain, insomnia, menstrual irregularities and extra pyramidal side effects or any other were recorded. Adverse effects observed in two groups were compared to judge safety between the two groups[10].

Tolerability assessment

Tolerability of drug combination was assessed & compared in terms of dropout rate due to adverse events & frequency of adverse effects at 4th and 8th week.

Statistical analysis

All the data analysis was performed by using SPSS version 20 software. Quantitative variables were expressed as the mean and standard deviation. Comparison between the groups was done by Student's t-test and within the groups by ANOVA test. P<0.05 was considered as significant.

Results

Out of 112 patients, 90 patients completed study consisting of 45 patients in each group. The mean age of schizophrenic patient in this study was 30 years. Male: Female ratio was 1.5:1.Other characteristics in the two groups were near about similar.(Table1)

Table 1: Baseline characteristics of randomized patients under study

Characteristics	Group I	Group II	Total
Number	45	45	90
Male	26	28	54
Female	19	17	35
Age (mean) in years	29.72	30.29	30
Married/unmarried/ divorcee/ widow	19/22/3/1	27/28/0/0	46/50/3/1
Rural/Urban	23/18	16/26	39/44

Efficacy assessment

Effect on PANSS score: The mean changes in PANSS score from baseline were statistically significant(P<0.001) at 4th and 8th week in both groups. Percentage change in mean PANSS score from baseline was 27% and 41.6% in Group I and was 19 and 34% respectively in Group II on 4 week and 8 weeks of treatment respectively. Though clinical improvement was more in group I on 4th as well as on 8thweek, but was not significant statistically (P=0.142)and (P=0.1035)as compared to Group II on 4th week and on 8th week respectively.(Table 3)

Table 2: Positive and negative syndrome scale (PANSS) score

	Week 0	Week 4	Week 8	Intra group comparison	Inter group comparison
Group I	125 ± 1.17	91.37 ± 1.22	73.24 ± 1.26	P<0.001	P>0.05
Group II	117 ± 1.9	95.35 ± 1.23	77.62 ± 1.38	P<0.001	P>0.05

Group I =Olanzapine + Aripiprazole, Group II =Olanzapine + Amisulpiride, Values are expressed as Mean ± SD, Intragroup comparison shows highly significant values (P<0.001) at all-time points when compared to baseline value of respective group. Values were not significant (P>0.05) in intergroup comparison.

CGI-I score: There was significant reduction in CGI-I score at 4th& 8th week in both the groups (P<0.001). (Table3). The total change in CGI score from baseline in group olanzapine plus aripiprazole was 54% and in group olanzapine plus amisulpiride 40% after 8weeks. On comparing the two groups the mean change in CGI score is statistically significant in Group I (P<.001) as compared to Group II. This analysis indicates that patient on aripriprazole combination therapy showed much improvement and with amisulpiride combination therapy showed minimal improvement.

Table 3: Clinical global impression-improvment (CGI-I) score

	Week 0	Week 4	Week 8	Intra group comparison	Inter group comparison
Group I	5.82 ± 0.101	4.2 ± 0.105	2.62 ± 0.177	P<0.001	P<0.01
Group II	5.46 ± 0.15	4.04 ± 0.09	3.26 ± 0.18	P<0.001	P<0.01

Group I = Olanzapine + Aripiprazole, Group II =Olanzapine + Amisulpiride, Values are expressed as Mean ± SD, Intragroup comparison shows highly significant values (P<0.001) at all-time points when compared to baseline value of respective group. Values were significant (P<0.01) in intergroup comparison.

Tolerability assessment

In Group I (olanzapine plus aripiprazole), total 54 patients were enrolled, out of which 45 patients completed study. Thus 9 patients were dropped from Group I and dropout rate was 16.66%.Out of 9 drop outs only 4 patients left the study on account of adverse effects and remaining 5 left the study voluntarily.In Group II (olanzapine plus amisulpiride), a total of 58 patients were enrolled, out of which,

45 patients completed the study. Thus 13 patients were dropped out and the dropout rate was 22.41 % (13 patients). Out of 13 drop outs 9 patients left the treatment due to adverse effectsand remaining 4 left the study voluntarily. (Graph1).Dropout rate due to adverse events was more in Group II than Group I

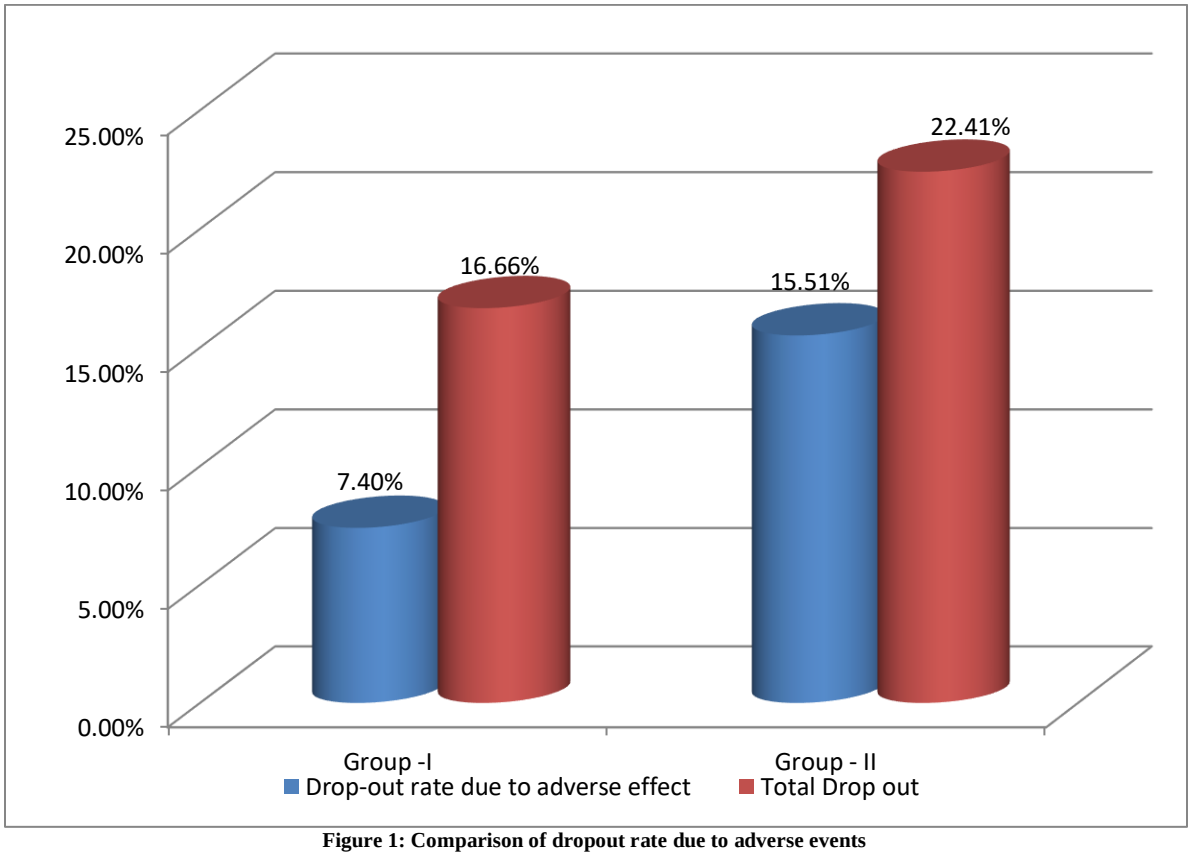

Figure 1: Comparison of dropout rate due to adverse events

Safety assessment

Frequency of adverse effects is defined as % of patients who had at least one treatment emergent adverse drug reaction in aparticular group. The frequency of adverse effects at 8th week in Group I was32%. The most common side effect noticed was somnolence in 22% patients. Then next was asthenia seen in 15.5%, agitation in13%, headache, weight gain& menstrual change in 6.66% and less common side effects were, dry mouth, constipation, insomnia in 4.44% patients. No extra pyramidal side effects were noticed in Group I(Table 4)

Table 4: Adverse drug reactions

Adverse drug reactions	Number of patients Group I	Number of patients Group II
Somnolence	10	12
Asthenia	7	5
Headache	3	4
Dry mouth	2	4
Constipation	2	1
Agitation	6	-
Weight Gain	3	7
Insomnia	2	-
Extra pyramidal side effects	-	1
Menstrual changes	3	5

Group I =Olanzapine + Aripiprazole, Group II =Olanzapine + Amisulpiride

In Group II (olanzapine plus amisulpiride), the frequency of adverse effects at 8th week was 35%.The most common adverse effect noticed was somnolence which was seen in 26.6% patients. Next common adverse effect was weight gain 15.5% followed by asthenia & menstrual changes in 11% patients.Less common were headache & dry mouth in 8.8% extra pyramidal side effect and constipation in 2.22% patients. Those patients who have completed the study did not dropped out because of adverse drug reactions.

Discussion

Aripiprazole and amisulpiride are newer antipsychotic drugs and are being used as add on therapy to olanzapine[12]. No scientific study is available in literature so as to know which combination is better on safety efficacy and tolerability parameters. Olanzapine is effective as monotherapy in 40 percent cases of schizophrenia at 20 mg dose. Efficacy increases with increase of dose but it also leads to increased

adverse effects like metabolic side effect:weight gain, hypoglycemia and other long term complications[4].

Many patientsshow partial response to a prescribed antipsychotic with a clinical status that lies between full responder and treatment resistance. The management of these patients is a major challenge and constitutes a serious public health concern with the associated social and economic burden[13]. Combination of drugs that can overcome these adverse effects and increases efficacy when added to small dose of olanzapine is the current need.

In present study olanzapinetreated partial responders of schizophrenia were administered either aripriprazole or amisulpiride as add on therapy.Baseline characteristicsof the two groups were similar in terms of age, male female ratio.Most common age group involved was 21-30 years.55% of the patients were married. Our results are consistent withprevious studies[14] Resultof present study revealed that botharipiprazole and amisulpiridecombination therapy showed significant decrease in symptoms and severity of illness of schizophrenia.Combination with aripiparazole showed better efficacyin PANSS score as compared to aripiprazolebut was statistically non significant. Our results are in accordance with a report by *Licanin&Senad* where partial response to olanzapine, was augmented when aripiprazole was added at the dose of 15 mg daily. PANSS score dropped to 56% after 6weeks with olanzapine-aripiprazolecombination[15]. Improvementin partial responders of present study might be due to additional partial agonistic activity at D2 receptor and antagonistic activity at the serotonin receptors as well as at postsynaptic D2 receptors with aripiprazole[16] Literature also revealed that olanzapine when used alone found to have better efficacy than aripiprazole alone treatment.This might be because of olanzapine acts at various receptors such as 5HT2A, D4 D2, α1, M1, H1 receptor[17]. Amisulpiride combination group in this study showed significant change in PANSS scoreat 8th weekwhich is similar to a previous randomized trial showed beneficial effects with both drug combination on several neuropsychological domains and decrease in PANSS score[18]. This might be on account of high affinity and selectivity for dopamine D2 and D3 receptor subtype by amisulpiride, the second generation atypical antipsychotic agent[8].

Testing on another efficacy parameter CGI-Iscorearipiprazole-olanzapine combination therapy showed significantly better improvement thanamisulpiride-olanzapine combination. This shows that patient'ssatisfaction was more with olanzapine plus aripiprazole combination might be due to unique mechanism of action of aripiprazole[19].

Both the drug combinations were well tolerated in patients who have completed the present study. Dropout rate was high in Group II due to adverse effects.The frequency of adverse reactionswas higher in GroupII suggesting aripiprazole to be safer than amisulpiride. The most common side effects in both the groups were somnolence. This is in accordance with several previous studies on atypical antipsychotic agentsdepicting greater incidence of somnolence with olanzapine when used alone.Weight gain were the next common adverse reactions in both groups but the incidence was lesser in aripriprazole Earliar study suggest that weight gain was observed more frequently in the olanzapine alone treated group (22.20%) as compared to aripiprazole (7.70%). Addition of aripiprazole in present study might have resulted in better control of glucose and triglycerides level responsible for this protection as reported earliar[20] Menstrual irregularities and extra pyramidal effect were seen with Group II can be explained by the fact that amisulpiride blocks presynaptic D2 receptors and increases prolactin level thereby has lesser protection against somnolence and weight gain and menstrual irregularities when added to olanzapine.Thus addition of aripiprazole to olanzapine is better in increasing safety of patients.

Conclusion

It is evident from the study that aripiparazole or amisulpiride combinations with olanzapine showed significant clinical improvement in patients of schizophrenia partially improved with olanzapine alone.However aripriprazole found better as add on therapy with olanzapine as compared to amisulpiride in terms of efficacy and safety. The limitation of this study includes conduction of study using small number of patients for short duration. Further long term studies with large number of patients at multiple centers are warranted to confirm the results.

Acknowledgement

Nil

Conflict of interest

Nil

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