Assessment of efficacy and tolerability of olanzapine, risperidone, amisulpride and quetiapine at 4weeks in newly diagnosed patients of schizophrenia at M.Y. Hospital, Indore

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Abstract

Objectives: Schizophrenia is a psychotic disorder characterized by hallucinations and delusions. Second generation antipsychotics are frequently used to treat the schizophrenia. As there are no clear-cut Indian guidelines for starting a particular drug for newly diagnosed cases of schizophrenia we decided to find out efficacy and tolerability of olanzapine, risperidone, quetiapine and amisulpride at 4 weeks after the initiation of treatment.

Materials and Method: Newly diagnosed cases of schizophrenia of either sex between age group 18 to 65 were recruited;30 cases in each group[N-120, n-30]. Patients were prescribed either of the study drugs in oral tablet form. Efficacy was assessed by comparing baseline [day 0] and week 4scores of PANSS, CGI and GAF score and tolerability was assessed by UKU PERT scale at 4 week.

Results: Olanzapine and risperidone statistically significantly reduced total PANSS score than amisulpride and quetiapine ($p<0.05$).Olanzapine, risperidone and quetiapine reduced PANSS positive sub score significantly than amisulpride ($p<0.05$).Quetiapine reduced the PANSS negative sub score significantly than amisulpride ($p<0.05$).Olanzapine and risperidone were slightly better than amisulpride and quetiapine in reducing CGI-S score and improving GAF score. All drugs were equally tolerable at the end of 4 weeks.

Keywords: Schizophrenia, PANSS, CGI, GAF.

Introduction

Schizophrenia is a psychotic disorder characterized by impairment in the perception or expression of reality, most commonly manifesting as auditory hallucinations, paranoid or bizarre delusions or disorganized speech and thinking in the context of significant social or occupational dysfunction.(1)

Second generation antipsychotics are frequently used worldwide to treat the schizophrenia.(2) In clinical practice, the choice of an atypical antipsychotic is mostly dependent on the potential side effect profile of the drug rather than on differential therapeutic characteristics.

They are preferred over first generation antipsychotics due to their better efficacy, less extra pyramidal side effects and better receptor profile.(3)

There are no clear cut Indian guidelines for choosing a particular second generation antipsychotic for starting the treatment of newly diagnosed cases of Schizophrenia. Olanzapine and risperidone are also most commonly prescribed atypical antipsychotics along with haloperidol in India.(4)

So we decided to compare the efficacy and tolerability of olanzapine, risperidone, quetiapine and amisulpride as these are most commonly used at our centre and freely available to patients.

Materials and Method

Study procedure: It was an observational, prospective, naturalistic, comparison of effectiveness and tolerability of olanzapine, quetiapine, risperidone, and amisulpride in newly diagnosed cases of schizophrenia.The study was conducted at psychiatry department MYH Hospital Indore.

All newly diagnosed cases of schizophrenia as per ICD 10 criteria of either sex between age group 18 to 65 by the consultant in-charge were evaluated and those fulfilling the selection criteria formed the sample for the study.(5)

Inclusion and exclusion criteria

Inclusion criteria

- Patients giving informed consent.
- Newly diagnosed cases of schizophrenia as per ICD-10 criteria.
- Age group 18 to 65.
- Patients needing oral anti-psychotic drug only.

Exclusion criteria

- Pregnancy and lactating women & patients with suicidal tendencies.
- Candidate for electroconvulsive therapy (ECT) & non co-operative patients.
- Patients receiving intravenous (i.v.) anti-psychotic drug.
- Patients of manic psychosis and acute psychosis& drug induced psychosis
- Cases where concomitant use of two drugs is inevitable.
- Patients who have received anti-psychotic drug in the last one month.

The Institutional Ethics committee approved the study based on above inclusion and exclusion criteria.

For the assessment of efficacy, the following four scales were used.

1. The Positive and Negative Syndrome Scale (PANSS).[6]
2. The Clinical Global Impression – Severity scale (CGI-S)[7]
3. The Clinical Global Impression – Improvement scale (CGI-I)[7]
4. Global Assessment of Functioning scale (GAF).[8]

For the assessment of tolerability UKU-SERS scale was used.[9]

The **Positive and Negative Syndrome Scale** (**PANSS**) is a medical scale used for measuring symptom severity of patients with schizophrenia by treating physician. Though there is no clear cut off score for diagnosis of schizophrenia, score in the range of severity mild to extreme is considered highly associated with schizophrenia.

It consists of

1. Positive scale (7 Items, minimum score = 7, maximum score = 49)
2. Negative scale (7 Items, minimum score =7, maximum score = 49)
3. General Psychopathology scale (16 Items, minimum score = 16, maximum score = 112).

The Clinical Global Impression rating scales are commonly used measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders. The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. The Clinical Global Impression – Improvement scale (CGI-I) is also a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention.

The Global Assessment of Functioning (GAF) is a numeric scale (1 through 100) used by mental health clinicians and physicians to rate subjectively the social, occupational, and psychological functioning of adults, e.g., how well or adaptively one is meeting various problems-in-living. The score is often given as a range.

After obtaining written consent patients were grouped into 4 groups [N-120, n-30]. Baseline score of each scale for efficacy was taken on day 0 and each patient was prescribed either of the study drugs in standard doses oral tablet form. Doses of the drugs were olanzapine [10 to 20 mg/day], risperidone[2 to 4mg/day], amisulpride[400 to 800 mg/day], quetiapine [200 to 300 mg /day] as per the physicians choice.[10] Each patient was followed up to 4 weeks and after 4 weeks again efficacy score was noted and tolerability was assessed using UKU SERS scale and side effects were noted as mild, moderate and severe as per scale.

Results

The study included the newly diagnosed cases of schizophrenia. Total 160 patients were enrolled out of which 40 dropped out. Out of the remaining 120 patients, 80 were males and 40 females. Mean age group of patients was around 50 to 60 years.

The results were assessed in two criteria, efficacy and tolerability. Efficacy was assessed by three scales PANSS scale, GAF scale and CGI scale. Tolerability was assessed by UKU SERS scale. All values are expressed as MEAN±SEM, df: 3,116.

One way ANOVA test was employed followed by post hoc tukey's test for all comparisons below.

$p<0.05$ was considered as statistically significant.

a= $p<0.05$ as compared to amisulpride.

c=$p<0.05$ as compared to olanzapine.

b=$p<0.05$ as compared to quetiapine.

d=$p<0.05$ as compared to risperidone

Table 1: Total PANSS score of olanzapine, risperidone, amisulpride and quetiapine at baseline & week 4

Sr No	Drug Group	Day 0	Week 4
1	Amisulpride	175.07±.953	136.30±.906
2	Olanzapine	175.73±.955	130.77±.725[a,b]
3	Quetiapine	176.47±.873	134.07±.782
4	Risperidone	175.93±.977	130.20±.849[a,b]
	F	0.379	12.317
	P	>0.05	<0.05

Inference: Olanzapine and risperidone were significantly better in reducing total PANSS score at the end of week 4 than amisulpride and quetiapine.

Table 2: PANSS positive & PANSS negative sub-score of the olanzapine, risperidone, amisulpride and quetiapine at baseline & week 4

Sr No	Drug Group	Day 0		Week 4	
		PANSS positive subscore	PANSS negative subscore	PANSS positive subscore	PANSS negative subscore
1	Amisulpride	42.70±.272	45.07±.401	38.07±.291	34.33±.293
2	Olanzapine	42.97±.330	45.27±.235	31.30±.413[a]	33.43±.202
3	Quetiapine	42.33±.305	44.30±.487	31.23±.397[a]	32.50±.317[a]
4	Risperidone	43.37±.200	44.57±.502	31.47±.479[a]	33.43±.207

	F	2.404	1.122	70.621	8.300
	P	>0.05	>0.05	<0.05	<0.05

Inference: At week4 **olanzapine, risperidone and quetiapine** were significantly better than amisulpride in reducing PANSS positive sub score. Also At week 4 **quetiapine** was significantly better than amisulpride in reducing PANSS negative sub score.

Table 3: CGI-S & CGI-I and GAF scale score of the olanzapine, risperidone, amisulpride and quetiapine at baseline & week 4

Sr No	Drug Group	Day 0		Week 4		Week 4
		CGI-S	GAF	CGI-S	CGI-I	GAF
1	Amisulpride	6.47±093	25.70±.410	4.37±.131	3.67±.161	56.27±.355
2	Olanzapine	6.50±093	25.57±.423	4.23±.104	3.20±.088	55.93±.328
3	Quetiapine	6.53±093	25.87±.433	4.57±.149	3.53±.164	56.50±.358
4	Risperidone	6.60±091	25.63±.388	4.33±.121	3.27±.106	55.87±.361
	F	.381	.097	1.206	2.689	0.712
	P	>0.05	>0.05	>0.05	>0.05	>0.05

Inference: There was reduction in CGI-S & CGI-I score in all groups at week 4 follow up though it was not statistically significant. Also there was improvement in GAF score in all groups at week 4 follow up though it was not statistically significant.

Table 4: PANSS general psychopathology subscore of olanzapine, risperidone, amisulpride and quetiapine at baseline and week 4

Sr No	Drug Group	Day 0	Week 4
1	Amisulpride	87.30±.993	63.90±1.031[b]
2	Olanzapine	87.50±.957	66.03±.804
3	Quetiapine	89.87±.968	70.27±.880
4	Risperidone	88.00±1.086	65.47±.994[b]
	F	1.364	8.526
	P	>0.05	<0.05

Inference: Amisulpride and **risperidone** were significantly better than quetiapine in reducing PANSS general psychopathology subscore at week 4.

Table 5: Observed side effects using UKU Side Effect Rating Scale [UKU-SERS] Scale Grade 1 –Mild; Grade 2- Moderate; Grade 3- Severe.

Drug Group →	Olanzapine [n-30]		Risperidone [n-30]		Amisulpride [n-30]		Quetiapine [n-30]	
Side effects ↓	Grade	No of patients	Grade	No of patients	Grade	No of patients	Grade	No of patients
Psychic side effects								
Concentration difficulty								
Sedation	1	03	1	5			3	20
Increased duration of sleep	1	03	1	5			3	20
Neurological Side Effects								
Dystonia			1	3	1	4		
Rigidity			1	2			1	3
Hypokinesia/Akinesia	1	4	1	4			1	4
Hyperkinesia	1	4			1	3	1	3
Tremor	1	3	1	3	1	4	1	2
Akathisia					1	4	1	3
Autonomic Side Effects								
Orthostatic dizziness							2	10

Palpitations/Tachycardia								
Other Side Effects								
Weight gain	2	15						

Inference: Moderate weight gain was observed with olanzapine while **Severe sedation and moderate hypotension** was observed with quetiapine. **Mild EPS** were observed with all drugs.

Discussion

Efficacy: Baseline total mean PANSS score at day 0 of all four groups was 175.55 with mean range from 160 to 187 which represents moderate to severe symptoms of schizophrenia. The sample thus represents a heterogeneous group of patients suffering from moderate to severe schizophrenia.

At the end of follow up at week 4, all study groups showed gradual remission of the symptoms and reduction of total PANSS score which shows there potent antipsychotic activity which is due to their D2 antagonism[11] [Table 1].

At the end of week 4, it was found that olanzapine and risperidone each reduced the total PANSS score statistically significantly than both amisulpride and quetiapine groups. This shows an early onset of antipsychotic activity of the Olanzapine and risperidone.

Mean baseline positive sub score of all 4 groups on day 0 was 42.84 which represents moderate severe to severe positive symptoms. At week 4 olanzapine, risperidone and quetiapine significantly reduced positive symptoms than amisulpride [$p<0.05$] [Table 2].

Mean baseline negative sub score of all 4 groups on day 0 was 45.05 which represents moderate severe to severe negative symptoms. All drug groups reduced the negative sub score gradually at 4 week follow up. At week 4, quetiapine significantly reduced negative symptoms than amisulpride while, olanzapine and risperidone were slightly better than amisulpride though not statistically significant.[Table 2]

All drug groups reduced the general psychopathology sub score gradually at the end of 4 week followup. Overall assessment of General psychopathology subscore was that amisulpride and risperidone were statistically significant than quetiapine while olanzapine was slightly better than quetiapine.[Table 4].

Possible explanation of all these findings lies in the receptor profile and the affinity of binding of the drugs to these receptors.

Olanzapine has receptor profile of H1>5HT2A>5HT2B>D2>D4>α1[12] while receptor profile of risperidone is 5HT2A>D2>D4>α1.[13]

Quetiapine has receptor profile as H1> α1> 5HT2B> 5HT2A> 5HT7> 5HT2C> D2[14] and amisulpride has D3>D2>5HT2B>5HT7.[15]

As per the above mentioned receptor profile, olanzapine and risperidone have better D2 affinity than quetiapine and amisulpride so they reduced total PANSS score more than the other two drugs.

The theoretical biological basis for the mesolimbic dopamine hyperactivity particularly at D2 receptor is thought to be associated with the positive symptoms of schizophrenia.[16] Olanzapine, risperidone and quetiapine were better than amisulpride at 4 weeks in reducing positive symptoms. This shows that these drugs have early onset due to better affinity towards D2 than amisulpride. At week 4, quetiapine significantly reduced negative symptoms than amisulpride. Possible explanation for this lies in receptor profile of quetiapine. Quetiapine has 5HT2B, 5HT2A and 5HT7 antagonist action which is responsible for its antidepressant effect too.[17] So it appeared to be more efficacious in reducing negative symptoms earlier than amisulpride at week 4 while olanzapine and risperidone were slightly better than amisulpride which shows their consistent effectiveness across all symptoms.

General psychopathology subscore represents cognition and general assessment of mental well being. Amisulpride and risperidone were significantly better than quetiapine in reducing General psychopathology subscore which is evident from their receptor profile. Also olanzapine was better than quetiapine but not statistically significant. Olanzapine and quetiapine being H1 antagonist may have less reduced general psychopathology score than the rest two drugs.

Clinical Global impression Scale is composed of two parts CGI-S and CGI –I. Overall all drugs showed improvement by reducing CGI-S score which shows they are almost equally efficacious. Severity of symptoms reduced from severely ill to borderline ill gradually from baseline to 4 weeks. In both the scales, olanzapine and risperidone were slightly better than amisulpride and quetiapine. [Table 3]

GAF scale considers psychological, social, and occupational functioning of mental health-illness. At day 0, the patients had score of average 21 to 30 which represents that behaviour was considerably influenced by delusions or hallucinations or serious impairment in communication or judgment.

All drug groups improved the GAF score up to mean score of 55 gradually across 4 week follow-up. It highlights improvement of symptoms of schizophrenia successively in 4 weeks from severe to moderate grade.

Tolerability [Table 5]

Tolerability was assessed using UKU SERS scale. Observed side effects and the number of patients were noted in each group. The outcomes for tolerability were generally the same across groups with minimum side effects.

Olanzapine was consistently associated with moderate weight gain, perhaps because of its antihistaminic and 5HT2C antagonist properties.[18]

Quetiapine showed severe sedation due to its prominent H1 antagonist properties probably contributing to its ability to enhance sleep.[19] Quetiapine also showed moderate orthostatic dizziness perhaps due to its α1 antagonist action. Also all drug groups showed mild EPS and were equally tolerable.

Thus in overall assessment, we found olanzapine and risperidone better in efficacy and tolerability than amisulpride and quetiapine. Both of these drugs reduced the severity of symptoms consistently more than amisulpride and quetiapine as explained above.

Conclusion

The study was a naturalistic approach to understand the better antipsyhotic among the four study drugs with given criteria's. Olanzapine and risperidone were far better than quetiapine and amisulpride in terms of all study parameters.

Thus olanzapine and risperidone are better drugs to start with newly diagnosed cases of schizophrenia however further studies and follow ups are needed for long term results of better safety profile and efficacy.

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