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Original research article

The emergence of metabolic syndrome due to second-generation antipsychotics as compared with conventional (typical) antipsychotics

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Abstract

Persons with schizophrenia are reported to be more likely to die from cardiovascular illness than those in the general population, and are at a greater risk of developing obesity, diabetes type 2, hypertension and dyslipidemias. Trials have been done with innumerable options including a number of pharmacological agents starting from those of ancient days through typical antipsychotics to atypical ones in later times. But problems came hand-in-glove with each of these options. As extrapyramidal side effects of typical antipsychotics compelled clinicians to move towards the atypical ones, these newer, so-called novel agents have brought with them a gamut of adversities, the various metabolic side effects.

The study includes 120 patients, both indoor and outdoor, suffering from schizophrenia, diagnosed using the ICD-10 criteria. The patients were grouped into three categories, i.e. control group and two study groups, control group having 30 patients and study groups with 45 patients each.

Thirty patients were given conventional antipsychotics and 90 were given second-generation antipsychotics, including risperidone and olanzapine.

At the end of 18 months it was observed that a significant number of subjects developed metabolic syndrome in both the atypical drugs, Olanzapine and Risperidone (p-value <0.0001). Comparatively the incidence was more in Olanzapine (26%) than Risperidone (22%), with higher increases especially in weight, fasting blood sugars and lipid profile changes in the subjects treated with Olanzapine. The same random sample showed little changes in the parameters when treated with conventional antipsychotic Haloperidol. Thus, even though there was a lesser incidence of extra- pyramidal symptoms with atypical antipsychotics, it should be borne in mind that the incidence of metabolic syndrome adds to the cardiovascular risk of patients with Schizophrenia and the need to tailor a drug based on patient profile is always the better option.

Keywords: Metabolic syndrome, Second-generation antipsychotics, conventional antipsychotics

Introduction

Antipsychotic medications, the mainstay for the treatment of psychoses, are also widely used in many other psychiatric conditions. For people who respond well, antipsychotics can mean the difference between leading an engaged, fulfilling community life and being severely disabled [1]. The first generation antipsychotics are effective in treating positive symptoms of psychosis, such as hallucinations and delusions. However, first generation antipsychotics do not adequately alleviate many other common and important aspects of psychosis, such as negative symptoms. In addition, all first generation antipsychotics can produce significant extrapyramidal side effects at clinically effective doses, which include dystonic reactions, drug-induced Parkinsonism, akathisia, and tardive dyskinesia. These side effects can make treatment intolerable for some people leading to subjective distress, diminished function, stigma, and non-adherence [2].

The effort to find more effective medications with fewer and less severe side effects led to the development of second-generation antipsychotics, often referred to as the "atypical antipsychotics".

Since the introduction of second-generation antipsychotics, these agents have been widely prescribed for the management of patients with schizophrenia. The increasing use of second generation antipsychotics is in part due to the evidence suggesting its beneficial effects on positive symptoms, negative symptoms and cognition in schizophrenia, combined with a lower propensity for extrapyramidal symptoms or tardive dyskinesia compared to first generation antipsychotics. The improved tolerability of the atypical agents compared to the typical agents and the emerging data suggesting improved psychiatric outcomes, has led the clinicians to begin prescribing these agents widely. But now, a few decades after the first atypical antipsychotic came in scenario, researchers and clinicians have gradually come to realize that while extrapyramidal symptoms and tardive dyskinesia occur less commonly with atypical agents, these

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medications may present a different set of adverse effects than typical agents. Of particular concern are the metabolic side effects of glucose intolerance, new-onset type 2 diabetes mellitus, weight gain and hypertriglyceridemia [3, 4].

Methodology

Inclusion Criteria

1. Adult males/females of age between 18 and 60 years, who are cases of schizophrenia diagnosed as per the ICD-10 criteria.
2. Only physically active patients will be included (patients are considered to be physically active if they regularly engaged in an aerobic type of activity at least twice per week for 20 min; these activities included walking, jogging, swimming or garden/yard work).

Exclusion Criteria

1. Patients who had received prior antipsychotic medication in the last 6 months.
2. Patients having any of the five features of metabolic syndrome, patients having any type of cardiovascular disorder, whether under treatment or not, and known patients of diabetes (even if having fasting blood sugar controlled below 110 mg/dl by any diabetic medication) will be excluded.
3. Patients with history of co-morbid substance abuse, pregnant patients, patients having family history of diabetes and patients having co- morbid chronic medical illness will also be excluded.

Procedure

All new persons attending out- patient department with the diagnosis of first episode drug naive schizophrenia as per ICD-10 diagnostic criteria. Metabolic parameters like BMI, Waist/Hip ratio, Lipid Profile, Fasting blood sugars, and Blood Pressure will be taken before onset of drug treatment and after 18 months.

The study will include 120 patients, both indoor and outdoor, suffering from schizophrenia, diagnosed using the ICD-10 criteria. The patients will be grouped into three categories, i.e. control group and two study groups, control group having 30 patients and study groups with 45 patients each.

Thirty patients will be given conventional antipsychotics and 90 will be given second-generation antipsychotics, including risperidone and olanzapine.

Results

Table 1: Comparison between baseline and After 18 months for the parameter Triglyceride's among the groups Haloperidol, Olanzapine and Risperidone.

Groups	Minimum	Maximum	Mean	SD	P-value
Hal –BL	122	187	144.9	13.9	
Hal- A18M	137	211	153.6	18.1	<0.0001
OL – BL	129	181	153.5	12.69	
OL- A18M	136	247	178.7	29.3	<0.0001
Res – BL	129	187	149.5	15.05	
Res- A18M	136	234	173.2	25.4	<0.0001

Table 2: Comparison between baseline and After 18 months for the parameter High-density Lipoprotein (HDL) among the groups Haloperidol, Olanzapine and Risperidone.

Groups	Minimum	Maximum	Mean	SD	P-value
Hal –BL	45	61	51.4	4.18	
Hal- A18M	33	56	44.8	5.62	<0.0001
OL – BL	40	66	51.9	5.3	
OL- A18M	34	61	45.9	7	<0.0001
Res – BL	42	60	51.5	4.73	
Res- A18M	34	56	45.9	5.27	<0.0001

Table 3: Comparison between baseline and After 18 months for the parameter Fasting blood sugars among the groups Haloperidol, Olanzapine and Risperidone.

Groups	Minimum	Maximum	Mean	Sd	P-value
Hal –BL	67	123	89.6	13.02	
Hal- A18M	71	167	96.5	21.78	0.001
OL – BL	70	121	95.9	14.11	
OL- A18M	77	203	117.6	28.62	<0.0001
Res – BL	74	123	98.2	12.09	
Res- A18M	74	171	112.2	24.63	<0.0001

Table 4: Comparison between baseline and After 18 months for the parameter Systolic blood pressure among the

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groups Haloperidol, Olanzapine and Risperidone.

Groups	Minimum	Maximum	Mean	SD	P-value
Hal –BL	90	130	116	10.03	
Hal- A18M	90	150	119.2	12.67	<0.0001
OL – BL	90	135	115.6	10.43	
OL- A18M	90	170	129	17.58	<0.0001
Res – BL	100	135	115.6	9.37	
Res- A18M	100	155	126.1	15.55	<0.0001

Table 5: Comparison between baseline and After 18 months for the parameter Diastolic blood pressure among the groups Haloperidol, Olanzapine and Risperidone.

Groups	Minimum	Maximum	Mean	SD	P-value
Hal –BL	60	90	78.9	7.51	
Hal- a18m	70	100	80.7	7.4	<0.0001
OL – BL	60	95	78.1	8.04	
OL- a18m	60	110	85.3	10	<0.0001
Res – BL	70	90	78.9	6.57	
Res- a18m	70	100	83.6	7.68	<0.0001

Table 6: Comparison among the groups Haloperidol, Olanzapine and Risperidone to the incidence of Metabolic Syndrome.

Group	Yes	No	P value
Haloperidol	2 (6.7%)	28 (93.3%)	<0.0001
Olanzapine	11 (26.2%)	31(73.8%)	<0.0001
Risperidone	9 (22%)	32 (78%)	<0.0001

Discussion

In one study, the prevalence of metabolic syndrome in patients hospitalized with bipolar disorder (56%) was dramatically higher than the prevalence observed in community samples (25%).The magnitude of comorbid metabolic disorders correlated positively with the severity of the mood disorder.

The role of antipsychotic medications in the development of diabetes and other pre-diabetic states remains controversial. As per some authors, attributable risk is low and traditional risk factors most probably account for much of the diabetes seen in schizophrenia populations. But in the recent literature, Type 2 diabetes mellitus has received significant attention; in part related to the association with atypical antipsychotic therapy, and concern over long-term health burden in patients with schizophrenia, especially the marked increase in cardiovascular disease risk [5].

Non-prospective studies suggest that atypical antipsychotic medications can cause diabetes mellitus and other metabolic effects in some patients. However, retrospective studies cannot quantify this risk or determine whether it varies between drugs and how it compares with recognised risk factors such as race, increasing age and obesity. These important clinical questions can only be answered by well-designed prospective studies that take into account potential confounders. Clozapine and olanzapine causes more derangements, risperidone and quitiapine to the moderate extent. Ziprazidone, Aripiprazole have doubtful liabilities [6].

The current study is one of few studies done in first episode drug naive persons to eliminate the disease effect and very few studies were done in these populations.

At the end of 18 months in metabolic derangements, there are no differences among gender, educational status, marital status, religion, and occupation.

Of the 2 persons who developed metabolic syndrome, in the Haloperidol group, it was more due to the illness and sedentary lifestyle pattern than that can be attributed to the drug's effects. There was no strict adherence to physical activity and dietary regimens in these two patients.

The p value for this group, as depicted shows a significant p-value (<0.0001) for the Null hypothesis, ie., there is significance for not progressing to metabolic syndrome for the drug Haloperidol. Studies to compare between typical and atypical drugs showing no metabolic derangements with typical antipsychotics were conducted by Sernyak and Newcomer *et al*. But the studies had potential bias in using healthy controls, as schizophrenic patients proved to have propensity for glucose dysregulation, in earlier studies [7, 8].

Incidence was comparatively higher with the drug Olanzapine (26%) compared to that of Risperidone (22%). The incidence was statistically significant with a p-value <0.0001. Comparison for the incidence in relation to gender was non-significant in all the three drug groups Haloperidol (p-value 1.000), Olanzapine (p-value 0.298) and Risperidone (p- value 0.128), implying that there was no gender bias in collecting the sample.

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The incidence of metabolic syndrome in comparison to the socio- economic statuses revealed that the lower socio- economic group had no to minimal incidence of metabolic syndrome in the Haloperidol group with a significant p-value 0.034, supportive of the NULL hypothesis. Noteworthy is that two subjects out of the 30 in control group treated with Haloperidol, have developed metabolic syndrome at the end of 18 months, while the majority of patients did not. These two subjects were observed and closely followed up throughout the duration of study and the incidence of metabolic syndrome was more due to the disease, Schizophrenia itself than to consider it the effects of the drug as these patients were not strictly adhering to the advised physical activity and dietary restrictions. Similar findings were previously documented about the inherent risk of Schizophrenics to develop cardio-vascular complications and metabolic risks during the course of their illness [9, 10].

Psychiatric disorders can be a risk factor for, as well as a complication of, diabetes. Diabetes is highly prevalent among the schizophrenia population. The prevalence of this disorder in patients with schizophrenia is approximately 10–15%, or twice that of the general population. The reasons for it are likely to be multi factorial. It has been found that first-episode, drug-naive patients with schizophrenia have impaired fasting glucose tolerance, more insulin resistance and higher levels of plasma glucose, insulin, and cortisol than healthy comparison subjects. A stress model of schizophrenia can explain the tendency of people with this disorder to develop disturbance in glucose homoeostasis. Numerous studies report over activation of the HPA (Hypothalamo-Pituitary- Adrenal) axis with attenuated feedback inhibition and increased cortisol output. Such a biological vulnerability would render individuals even more susceptible to the negative effects of poor dietary pattern and lack of exercise which lead to weight gain and dyslipidaemia [11, 12].

The same when assessed for the incidence of metabolic syndrome in the subjects treated with the atypical drugs Olanzapine and Risperidone (pie charts 6 to 9), it was observed that there was significant rise in the middle in upper echelons compared to the lower. The p-values for Olanzapine were 1.26 and for haloperidol 0.0007 for the same in this study.

Conclusion

- Significant difference between the two study groups Olanzapine (26%) and Risperidone (22%) show, among the second generations, risperidone may be considered as a safer alternative when it comes to changes in metabolic profile.
- Haloperidol has little to no risk for metabolic risk factors when compared to the atypical drugs in the study.
- Atypical antipsychotic drugs both risperidone and olanzapine cause significant rise in plasma glucose, triglycerides, HDL cholesterol.

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