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Original Article

Psychiatry/Mental Health Section

Recent Onset Cardiometabolic Effects amongst Patients Started on Psychotropics: A Cohort Study

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ABSTRACT

Introduction: Mortality rates in schizophrenia patients due to cardiovascular events are reported to be more than the general population. Dyslipidaemia, obesity, diabetes, and hypertension are some of the common illnesses these patients are vulnerable to develop. The drugs which are used to treat schizophrenia and other related disorders i.e. antipsychotics causes increase in weight, dyslipidaemia and insulin resistance in some patients. Some agent's i.e. Second Generation Antipsychotics (SGA) cause more of the above mentioned symptoms and than others agent's i.e. First Generation Antipsychotics (FGA). The novelty of the study includes the emergence of Metabolic syndrome (MetS) in drug naïve or drug free patients who were prescribed trifluoperazine and olanzapine and comparative study of them.

Aim: To assess the emergence of MetS in drug naïve patients of schizophrenia after the administration of trifluoperazine-FGA and olanzapine-SGA.

Materials and Methods: A cohort study was conducted from May 2019 to March 2021, in the Department of Psychiatry, Shyam Shah Medical College, and Rewa, Madhya Pradesh, India. Study was started after the clearance from institutional ethical committee. The study included 41 drug naïve indoor and outdoor patients, diagnosed as schizophrenia according to International Classification of Diseases 10 Diagnostic Criteria for Research (ICD 10 DCR). The patients were divided into two groups, one group was prescribed FGA trifluoperazine and other was prescribed SGA olanzapine. Twenty patients were prescribed olanzapine and 21 patient's trifluoperazine. Metabolic parameters were taken before onset of drug treatment therapy, after two and four months respectively. The patients were given medications for four months. The changes in metabolic parameters i.e., waist circumference, blood pressure, Fasting Blood Sugar (FBS), triglycerides, and Low HDL (High Density Lipoprotein) were compared using unpaired student's t-test and repeated measure Analysis of Variance (ANOVA) with p-value <0.05 considered as significant.

Results: It was found that out of total 41 patient, 4 patients (19.4%) and 12 patients (60%) patients prescribed trifluoperazine and olanzapine respectively developed Mets after four months of antipsychotic medication. Also, there was a significant change in various parameters of MetS in both groups as seen in repeated measure ANOVA.

Conclusion: SGA cause significantly more changes in the metabolic parameters and compared to the FGA, increasing the likelihood of developing MetS and associated disorders like cerebrovascular accidents and diabetes mellitus type-II.

Keywords: Cohort, Metabolic syndrome, Olanzapine, Schizophrenia, Trifluoperazine

INTRODUCTION

People experiencing extreme psychotic state, especially schizophrenia, have their average life span 20% less than general population. The causes of mortality are attributed to the cardiovascular and metabolic syndrome developed secondary to the use of antipsychotic medications. [1] The vast majority of mortality among these patients was not the suicide but premature death due to cardiovascular complications. Numerous psychotropic are orexigenic and can cause increase weight and dyslipidaemia, [2] possibly due to their action on 5HT2C receptors. There is progressing research testing these proposed components of activity inside each class FGA and SGA regarding the neurobiology of various mental disorders like acute psychosis, aggression, bipolar disorder and so on. It is unclear whether SGA offer advantages over older FGA [3]. Amisulpride, olanzapine, risperidone, and clozapine may be more effective but are associated with greater side-effects especially weight gain and MetS [4]. In patients with schizophrenia, the prevalence of MetS varies from 3.3% to 68.6%, and they often have a twofold (or greater) increased risk of getting MetS compared to the general population [5,6]. Additionally, it has been shown that first-degree relatives of Schizophrenia Drug-Naive (S-DN) patients have impaired glucose tolerance, raising the possibility of a hereditary link between diabetes and schizophrenia [5,7,8]. Compared to the general population, patients with schizophrenia usually lead unhealthy lifestyles, consume diets rich in fat and low in fibre, and engage in less regular exercise [6].

MetS (also called as syndrome X) is a grouping of at any three of five of the accompanying ailments: waist circumference raised blood pressure, raised fasting plasma glucose, high serum triglycerides, and low HDL (High Density Lipoprotein) levels. [9] It has been determined that each element of the MetS represents a separate risk factor for cardiovascular disease. National Cholesterol Education Program (NCEP) Adult Treatment Panel-III (ATP-III)-defined criteria for MetS [9] is the presence of atleast three of five criteria: fasting triglyceride >150 mg/dL, fasting high-density lipoprotein <40 mg/dL for men or <50 mg/dL for women, waist circumference >40 inches for men or >35 inches for women and blood pressure >130/85 mmHg. MetS is becoming more prevalent globally, however it depends on sex, age, race and ethnicity of the community being investigated [6]. It is also affected by various lifestyle factors like, substance use (predominantly alcohol and tobacco), exercise; medical illness like hepatobiliary diseases, polycystic ovary disease, etc [10]. The most significant components are hereditary qualities, maturing, diet (especially sugar-improved drink utilisation), stationary conduct or low physical movement, upset chronobiology/sleep, mood disorders temperament issue, psychotropic drug utilise and over the top liquor use [11-13]. The pathophysiology of

MetS consists of insulin resistance, dyslipidaemia, neurohormonal activation, and inflammation hypothesis [14-17].

Furthermore, there were several studies in the past where MetS is studied in patients on SGA, there is dearth of studies on comparison between FGA and SGA [18,19]. Consequently, this study was designed to assess emergence of MetS in the drug naïve patients of schizophrenia after the administration of FGA and SGA and comparing metabolic parameters, socio-demographic and clinical, variables in both the groups.

MATERIALS AND METHODS

A cohort study was conducted from May 2019 to March 2021, in the Department of Psychiatry, Shyam Shah Medical College, Rewa, Madhya Pradesh, India. Study was started after the clearance from Institutional Ethical Committee (IEC) 9471/SS/PG/MC/2019 dated 22/5/2019.

Inclusion criteria: Patients giving informed written consent, aged 15-60 years, of either sex and patients who were drug naïve or drug free for atleast six months were included in the study.

Exclusion criteria: Patients who did not give written consent, having serious co-morbid medical illness, requiring emergency psychiatric care, having premorbid obesity, dyslipidaemia, hypertension, diabetes or metabolic syndrome were excluded from the study.

Sample size calculation: Samples were selected using purposive sampling. Around 60 samples were selected considering 10-20% dropouts based on the experience in Vindhya region. At the end of the study around 19 patients were lost in follow-up. The final sample came out to be 41. All the patients attending the outpatient and inpatient wings of Psychiatry department with the diagnosis of schizophrenia were selected. Diagnosis was made using the ICD-10 DCR (International classification of diseases 10 Diagnostic Criteria for Research) [20]. The patients were called for follow-up at two- months and four months.

Study Procedure

Patients were explained the principle of the study, subsequent to which, written informed consent from the patient's legally accepted representative was taken. Thorough history and examination- general and systemic-for any co-morbid medical and neurological illness of each patient was carried out in the beginning. Biochemical examination including lipid profile (fasting blood triglycerides, fasting high-density lipoprotein in mg/dL) and FBS (in mg/dL) were taken at baseline, two months, and four months. Baseline measurements of weight in kilograms, blood pressure in millimetres of mercury (mmHg), and waist circumference in inches were also taken, which were followed-up at two months and four months. Electronic weighing scale was used to measure the body weight. Blood pressure was measured using digital sphygmomanometer with patient made comfortable either in sitting position or lying down position with the position of the instrument at the level of the heart. Three readings were taken at a difference of 10 minutes each and the mean of three readings was taken as final. Waist circumference was measured at the level of the highest point on bilateral iliac crest at the point of gentle exhalation using non stretchable tape. The study group (n=41) was further divided into two subgroups, subgroup A (21 patients) were given Trifluoperazine and subgroup B (20 patients) were given Olanzapine for a period of four months. It was clinician's choice as per study design and availability of medicines in hospital supply system, however, patients and caregivers were made aware of the associated effects and side-effects. The treatment decision was jointly agreed between caregivers, patients and doctor. Each party was involved in treatment decision and aware of it.

At the end of two and four months patients receiving antipsychotic treatment were subjected to the NCEP Adult Treatment Panel-III (ATP-III)-defined criteria for MetS [9] to find out the incidence of MetS in these patients. As per NCEP ATP-III, MetS is defined as the presence of atleast three of five criteria: fasting triglyceride >150 mg/dL, fasting high-density lipoprotein <40 mg/dL for men or <50 mg/dL for women, waist circumference >40 inches for men or >35 inches for women and blood pressure >130/85 mmHg. Socio-demographic variables which were included are age, gender, marital status, education, profession, religion and per capita income.

STATISTICAL ANALYSIS

Statistical analysis was done using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) statistics for windows version 21.0 (IBM corp. Armonk, NY). Data were presented in mean, standard deviation, percentages, and p-values. Continuous variables were compared using unpaired student's t-test and repeated measure ANOVA to compare changes over time [21,22]. All the statistical test was two-sided, and level for statistical significance was p-value 0.05.

RESULTS

As per the study criteria, 41 patients diagnosed with schizophrenia according to ICD-10 DCR and meeting the inclusion criteria were selected. Out of 60 patients selected at baseline, 19 patients, were drop out (poor affordability, travel difficulties, improvement in symptoms, poor drug compliance, lack of communication facilities, migration for work, lack of caregivers) and the study comprised of 41 patients who were drug naïve or drug free for past six months, resulting in group A having 21 patients and group B having 20 patients respectively.

[Table/Fig-1] showed that among those prescribed trifluoperazine (seven out of twenty-one) and olanzapine (seven out of twenty) maximum patients belonged to age group of 21-25 years and

Variables	Trifluoperazine (N=21) n (%)	Olanzapine (N=20) n (%)	Total (N=41) n (%)
Age (years)			
16-20	4 (19)	7 (35)	11 (26.8)
21-25	7 (33)	1 (5)	8 (19.5)
26-30	4 (19)	0	4 (9.8)
31-35	4 (19)	2 (10)	6 (14.6)
36-40	0	2 (10)	2 (9)
41-45	1 (5)	1 (5)	2 (9)
>45	1 (5)	7 (35)	8 (19.5)
Gender			
Male	16 (76.2)	11 (55)	27 (65.85)
Female	5 (23.8)	9 (45)	14 (34.15)
Marital status			
Single	8 (38.1)	10 (50)	18 (43.9)
Married	13 (61.9)	9 (45)	22 (53.7)
Separated	0	1 (5)	1 (2.4)
Education			
Illiterate	0	5 (25)	5 (12.2)
Primary	7 (33.3)	5 (25)	12 (29.3)
Middle	9 (42.9)	4 (20)	13 (31.7)
High school	5 (23.8)	4 (20)	9 (22)
Inter/Diploma	0	1 (5)	1 (2.4)
Professional	0	1 (5)	1 (2.4)
Religion			
Hindu	21 (100)	18 (90)	39 (95.1)
Others	0	2 (10)	2 (4.9)
Occupation			
Unemployed	12 (57.1)	12 (60)	24 (58.6)
Unskilled	6 (28.6)	4 (20)	10 (24.4)
Skilled	3 (14.3)	3 (15)	6 (14.6)
Professional	0	1 (5)	1 (2.4)

[Table/Fig-1]: Distribution of study subjects according to various socio-demographic profile (N=41).

16-20 years respectively. In both the groups males 27 out of 41 (65.85%) were more in numbers as compared to the females 14 out of 41 (34.15). In group prescribed trifluoperazine most of them were married 13 out of 21 (61.9%) whereas it was seen that the number between single 10 out of 20 (50%) and married nine out of twenty (45%) in those prescribed olanzapine were almost equal. Group prescribed trifluoperazine showed maximum patients from middle school nine out of 21 (42.9%) while equal number five out of 20 (25%) of illiterate and primary education was found in olanzapine prescribed group. Majority of the patients in both the groups were Hindu 39 out of 41 (95.1%) and unemployed 24 out of 41 (58.53%).

[Table/Fig-2] showed that 16 (39.02%) patients developed MetS. Further it was found that 4 (19%) and 12 (60%) prescribed trifluoperazine and olanzapine developed MetS at the end of four months respectively.

Duration		Trifluoperazine (N=21) n (n %)	Olanzapine (N=20) n (n%)	Total n (n%)
At Baseline	No	20 (95.2)	17 (85)	37 (90.24)
	Yes	1 (4.8)	3 (15)	4 (9.7)
At 2 months	No	17 (81)	12 (60)	29 (70.73)
	Yes	4 (19)	8 (40)	12 (29.26)
At 4 months	No	17 (81)	8 (40)	25 (60.9)
	Yes	4 (19)	12 (60)	16 (39.02)
Total	Yes	4 (19.4%)	12 (60%)	16 (39.02%)

[Table/Fig-2]: Distribution of study subjects according to occurrence of MetS with respect to antipsychotics (N=41).
(No statistical test is applied here. Data is presented in percentages)

[Table/Fig-3] shows that there was a significant difference between trifluoperazine and olanzapine for all parameters of MetS, with the exception of TG and fasting blood glucose (at baseline and 2 months).

Drugs (N=41)	Duration	Trifluoperazine (N=21)	Olanzapine (N=20)	Unpaired student t-test	
				t-value	p-value
Waist Circumference (inch)(Mean±STD)	0 months	35.61±3.45	31.05±4.65	3.58	**0.0009**
	2 months	34.27±3.63	31.61±5.68	25.24	**0.0001**
	4 months	34.18±4.10	33.28±6.30	19.36	**0.0001**
Triglyceride (TG) (mg/dL) (Mean±STD)	0 months	115.09±54.19	139.3±77.45	1.16	0.251
	2 months	113.95±57.98	146.85±76.64	1.55	0.128
	4 months	116.72±54.14	153.47±66.32	1.94	0.058
Low HDL (mg/dL) (Mean±STD)	0 months	31.52±14.79	52.05±22.80	3.43	**0.0014**
	2 months	39.86±20.52	56.38±25.88	2.27	**0.02**
	4 months	40.04±24.14	64.19±28.70	2.29	**0.0058**
Systolic BP(mm Hg) (Mean±STD)	0 months	118.38±9.10	127.4±10.40	2.95	**0.0052**
	2 months	122±9.92	130.5±10.71	2.63	**0.011**
	4 months	123.52±10.55	132.3±12.21	2.46	**0.018**
Diastolic BP (mm Hg) (Mean±STD)	0 months	77.80±4.24	81.5±4.43	2.73	**0.009**
	2 months	79.83±5.86	83.8±5.40	2.25	**0.03**
	4 months	79.71±6.31	85.9±6.20	3.16	**0.003**
Fasting blood glucose (mg/dL) (Mean±STD)	0 months	95.33±8.75	95.85±12.62	0.15	0.87
	2 months	102.53±14.08	105.9±18.08	0.66	0.50
	4 months	101.19±16.41	112.9±19.09	2.10	**0.0414**

[Table/Fig-3]: Distribution of study subjects at baseline, 2 and 4 months according to each criteria of Mets with respect to drug administered (n=41).
Unpaired student t-test. p-value <0.05 (bold) is statistically significant

[Table/Fig-4] shows result for repeated measure ANOVA using Greenhouse-Geisser correction for both groups. It determined that mean HDL, mean SBP and waist circumference differed statistically significantly between time points for Trifluoperazine group, whereas, mean HDL, fasting blood glucose, mean SBP (systolic blood pressure), mean DBP (diastolic blood pressure) and waist circumference differed statistically significantly between time points for Olanzapine group.

Patients (n=41)	Trifluoperazine (n=21)		Olanzapine (n=20)	
	F-value	p-value	F-value	p-value
Triglyceride (TG) (mg/dL)	6.69	0.051	2.91	0.08
Low HDL (mg/dL)	12.41	**0.01**	1.35	**0.026**
Fasting blood glucose (mg/dL)	7.47	0.09	92.31	<0.001
Systolic BP (mm Hg)	3.77	**0.041**	27.71	<0.001
Diastolic BP (mm Hg)	4.4	0.36	12.00	<0.001
Waist Circumference (inch)	25.08	<0.001	9.37	**0.005**

[Table/Fig-4]: Comparison of parameters of metabolic syndrome in both groups at 0,2 and 4 months.
*Repeated measure ANOVA

DISCUSSION

Literature regarding the comparative study of metabolic side-effects between FGA and SGA is limited. There is also a paucity of literature with respect to MetS in patients who are drug naïve. Major findings in present study (i) comparative demographic profile of both study groups, (ii) 19.4% patients of trifluoperazine and 60% of patients of olanzapine group had metabolic syndrome at the end of four months, (iii) both groups differed significantly in all parameters of MetS at all time points except for mean TG and mean blood glucose (at baseline and two months), (iv) there was a significant change over time in various parameters of MetS in both groups due to antipsychotics treatment.

Since schizophrenia is a disease of late adolescence and early adulthood, maximum patients reported belongs to age group 16-20 years followed by age group 21-25 years and >45 years. Owing to early age of onset primarily during school years, hamper their education hence there job. Low male to female ratio might be due to underreporting of female patients. Majority of population in Rewa, Madhya Pradesh is Hindu therefore maximum reported patients were Hindu. The socio-demographic profile of this study was similar to previous study conducted by Grover S et al., [23] and Grover S et al., [24], Padmavati R et al., [25] and Lee NY et at., [26]. Response of various drugs administered was in accordance with the previous study conducted by Riordan HJ et al., [27], Jeon SW and Kim YK [28]. Metabolic effects were in accordance with the study conducted by Lakka HM et al., [29], Mitchel AJ et al., [30]. There was strong association found between both the drugs and low HDL level. In the patients who were on olanzapine, no significant association was found between any socio-demographic variables for change in the abdominal circumference, triglyceride level, systolic blood pressure, HDL levels. In trifluoperazine (N=21) there was a strong association found to change in the SBP and no association found in DBP, the low potency agents have the highest, and the high-potency agents have the lowest, potential to cause cardiovascular and metabolic dysfunction.

Though there are many studies that highlight emergence of MetS in patients on antipsychotics, present study was a novel study highlighting the association of individual drugs with MetS, especially in Indian population. However, further studies can be planned assessing other lifestyle factors and prevalence of MetS in different schizophrenia subtypes.

Limitation(s)

There were many limitations in the study. There was a lack of longitudinal follow-up (till four month) as the Coronavirus Disease-2019 (COVID-19) pandemic had affected follow-up of patients. The study sample was small and he baseline assessment was not matched. Confounding factors may be present as the study did not evaluate lifestyle, calorie intake, level of physical activities. Futher studies with a larger samples and evaluation of the confounding factors can be conducted in the future. Technical issues like the problem with the machines, lack of supply of medicines, difficult

access of the patients can be worked upon to achieve better results.

CONCLUSION(S)

From the previous studies, it was found that the SGA causes more MetS than the FGA, which is corroborated in this study also. Also, the efficacy of olanzapine is well-established, however, it carries an inevitable and disabling side-effect of MetS which is also evident in present study. Despite this, both antipsychotics had significant changes in various parameters of MetS (except triglyceride) at the end of four months, indicating the need for continuous monitoring of MetS.

Author's contribution: Dr. PM designed the study, helped in concepts, literature search, data acquisition, data analysis and manuscript preparation and editing with assistance from Dr. SKA and Dr. Nimisha Mishra directed the implementation of study design, literature search, data acquisition and manuscript preparation. Dr. PM will act as the guarantor of the manuscript.

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