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Original Article

Psychiatry/Mental Health Section

Effect of Olanzapine on Metabolic Syndrome- A One Year Follow-up Study

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ABSTRACT

Introduction: Patients with schizophrenia have increased risk of cardiovascular mortality and this is partly attributed to antipsychotics. Olanzapine, one of first line antipsychotic for the management of schizophrenia is associated with Metabolic syndrome (MetS). There is paucity of follow-up studies on course of metabolic parameters with Olanzapine.

Aim: To understand the effect of Olanzapine on weight, Fasting blood glucose, Triglycerides (TG), High Density Lipoprotein (HDL), and Waist Circumference (WC) in patients with schizophrenia.

Materials and Methods: This was a prospective observational study where metabolic parameters of patients with schizophrenia were assessed prior to initiation of olanzapine and after one year. Physical health [Blood Pressure (BP), WC, Weight] and laboratory indices (fasting blood sugar, HDL and TG) were evaluated and compared. The association between qualitative variables were assessed using chi-square test and differences in metabolic parameters before and after olanzapine was assessed using paired t-test.

Results: The prevalence of MetS before initiation of olanzapine was 15.4% which increased to 56.9% in one year as per Adult Treatment Protocol of the National Cholesterol Education Program (NCEP ATP III) criteria. There was statistically significant difference in weight, fasting blood glucose, TG, HDL and WC at the end of one year when compared to baseline (p-value <0.05).

Conclusion: Olanzapine has high propensity to derange metabolic parameters in patients with schizophrenia. Close monitoring and lifestyle modification is advised to prevent adverse metabolic effects of olanzapine.

Keywords: Cardiometabolic risk factors, Psychosis, Schizophrenia, Second generation antipsychotic

INTRODUCTION

Schizophrenia is a severe mental disorder with lifelong course. It is characterised by an array of symptoms like delusions, hallucinations, disorganised behaviour and decreased motivation to do activities of daily living leading to socio-occupational dysfunction [1]. Several studies have shown that life span of persons with schizophrenia is 10 to 20 years less than general population [2-4]. Hypertension, chronic obstructive pulmonary disease, and diabetes are common medical co-morbidities in such population, all of which increase the risk of cardiovascular disease and associated mortality [5]. One of the widely accepted explanations for increased cardiovascular risk in these individuals is MetS. MetS is an array of conditions like abdominal obesity, deranged lipid profile, hyperglycaemia and hypertension. There are many definitions of MetS available in the literature and NCEP ATP III is commonly used [6].

Antipsychotics are the first line of drugs for the management of schizophrenia. Antipsychotics are classified basically into first and second generation antipsychotics based on their mechanism of action. Many studies have shown similar efficacy of both the drug classes with varying side effect profiles [7,8]. Second generation antipsychotic drugs are more frequently used in clinical practice in view of their better tolerability, secondary to less propensity to cause extrapyramidal symptoms [9]. Multiple studies across nations have shown the association of second generation antipsychotics and MetS [10,11]. Olanzapine, a second generation antipsychotic agent, commonly used in clinical practice is associated with MetS [12].

Majority of them were cross-sectional studies done either on drug naïve population or on treated population [13,14]. The prevalence of MetS is lower in untreated or drug naïve individuals when compared to treated individuals with schizophrenia [15]. The number of follow-up studies regarding course of MetS in schizophrenia is limited [16,17]. There is need for follow-up studies to get better understanding on the course of metabolic parameters. The objectives of the study were to estimate the baseline prevalence of metabolic derangements in patients before starting them on olanzapine and prevalence of metabolic derangements after a year of treatment.

MATERIALS AND METHODS

This was a prospective observational study conducted from September 2018 to December 2019, and included Schizophrenia patients initiated on Olanzapine at the Department of Psychiatry in a tertiary care teaching hospital of Southern India. The protocol was approved by the institutional ethics committee (CSP/MED/18/SEP/46/140). All consecutive adult patients in the age group of 18-60 years who were initiated on Olanzapine medication for Schizophrenia during the recruitment period of September 2018-December 2018 were included in the study after obtaining written informed consent and were followed-up after one year. A total of 84 patients were started on olanzapine during the recruitment period, out of which 12 lost follow-up and seven patients had change of antipsychotic medication. Patients with severe mental retardation, Organic brain syndromes and major physical illness (other than those included in the criteria of MetS) were excluded. Physical health (BP, WC, and weight) and laboratory indices (fasting blood sugar, HDL, TG) were assessed at the time of initiation of Olanzapine and at one year follow-up. Body weight was measured using a portable weighing scale with a ±100g error. WC was measured using a tape at a plane between the umbilical scar and the inferior rib border. BP was measured manually using sphygmomanometer. Fasting blood glucose, HDL and TG were measured using venous blood sample early morning (7am) after eight hours of fasting by a blood technician and analysed in NABL accredited laboratory.

STATISTICAL ANALYSIS

Data was analysed using SPSS software version 20. Descriptive analyses (frequencies, means and standard deviations) were used to describe socio-demographic and clinical variables. Association

between categorical variables was analysed using Chi-square test. A paired t-test was employed to compare means of continuous variables before and one year after Olanzapine in patients with schizophrenia. Mc Nemar test was used to assess differences in dichotomous categorical variables before and after olanzapine initiation. Multivariate logistic regression was used to assess predictors of MetS after one year of olanzapine. The significance level was set at p<0.05.

RESULTS

A total of 84 patients were recruited and 65 patients were available at one year follow-up for final analysis. The mean age of the patients at baseline was 34±9.47 years. About 44 (67.7%) of them were married. The mean age of onset of illness was in early 20's and had less than one year of illness duration at the time of starting Olanzapine. The mean dose of olanzapine at one year follow-up was 18.46 mg with 6.99 mg of standard deviation [Table/Fig-1].

Demographic variable	N (%)	p-value
Gender		
Male	42 (64.6%)	0.07
Female	23 (35.4%)	
Marital status		
Married	44 (67.7%)	0.37
Single/separated	21 (32.3%)	
Habitat		
Urban	38 (58.5%)	0.92
Rural	27 (41.5%)	
Literacy		
Literate	51 (78.5%)	0.48
Illiterate	14 (21.5%)	
Age of the patient		
18-30 years	26 (40%)	0.18
31-45 years	30 (46.2%)	
46-60 years	9 (13.8%)	
Age of onset of illness		
Less than/equal to 25 years	29 (44.6%)	0.29
More than 25 years	36 (55.4%)	
Duration of illness at the time of Olanzapine initiation		
Less than one year	48 (73.8%)	0.62
1-5 years	14 (21.5%)	
More than 5 years	3 (4.6%)	

[Table/Fig-1]: Socio-demographic and clinical variables and its association with metabolic syndrome at baseline.
Chi-square test for categorical variables was used to obtain p-values comparing patients with and without metabolic syndrome at baseline

There was significant increase in weight, waist circumference, fasting blood glucose, triglycerides and decrease in HDL [Table/Fig-2].

Metabolic variable	At baseline mean (SD)	At the end of one year mean (SD)	p-value
Weight (in kg)	49 (6.08)	57 (3.60)	0.04*
Waist circumference (in cm)	85.57 (7.99)	88.36 (8.28)	<0.001**
Fasting blood glucose (mg/dL)	105.75 (52.29)	122.15 (40.63)	0.02*
Triglycerides (mg/dL)	122.55 (73.21)	158.05 (66.67)	<0.001**
HDL (mg/dL)	38.48 (9.13)	33.05 (6.12)	<0.001**

[Table/Fig-2]: Comparison of metabolic parameters at baseline and after one year.
*denotes p-value less than 0.05; **denotes p-value less than 0.001; Paired t-test for continuous variables was used to compare means at baseline and at the end one year after olanzapine initiation

The number of patients with MetS increased from 15.4 % to 56.9% at one year follow-up [Table/Fig-3].

Logistic regression analysis with MetS at one year as response variable demonstrated that male gender and higher age at onset of illness had significantly higher odds of satisfying NCEP ATP III criteria of MetS. Among component criteria, male gender has higher odds of having elevated FBS and TG. Higher age at illness onset has more odds of having elevated TG, low HDL, and elevated BP [Table/Fig-4].

Metabolic parameter	At baseline N%	At one year follow-up N%	p-value
FBS >110 mg/dL	12 (18.5%)	30 (46.2%)	<0.001**
TG >150 mg/dL	13 (20%)	28 (43.1%)	<0.001**
HDL <40 mg/dL in men or <50 mg/dL in women	44 (67.7%)	61 (93.8%)	<0.001**
Blood pressure >130/85 mm of Hg	5 (7.7%)	18 (27.7%)	0.01*
Waist circumference >102 cm in men or >88 cm in women	14 (21.5%)	17 (26.2%)	0.25
Metabolic syndrome (more than or equal to three criteria present)	10 (15.4%)	37 (56.9%)	<0.001**

[Table/Fig-3]: Prevalence of metabolic derangements at baseline and at one year follow-up.
*denotes p-value less than 0.05; **denotes p-value less than 0.001; Mc Nemar test for related categorical variables was done to compare prevalence of metabolic syndrome and their component criteria before and after initiation of olanzapine

Co-variates	Models with the following indicator as response variable					
	MetS	FBS	TG	HDL	BP	WC
Age (years)						
OR	0.98	1.07	0.96	0.85	0.90	0.98
CI	(0.90-1.07)	(0.99-1.15)	(0.88-1.04)	(0.68-1.07)	(0.81-1.00)	(0.90-1.07)
Gender						
OR	7.47*	4.39*	5.41*	0.42	0.04*	0.04*
CI	(1.65-33.90)	(1.20-16.03)	(1.40-20.88)	(0.03-7.03)	(0.00-0.20)	(0.08-0.20)
Marial status						
OR	0.28	1.63	0.67	0.74	0.43	0.43
CI	(0.06-1.38)	(0.41-6.40)	(0.17-2.62)	(0.23-2.34)	(0.08-2.46)	(0.07-2.46)
Literacy						
OR	0.55	0.48	0.28	0.75	0.77	0.77
CI	(0.12-2.34)	(0.12-1.98)	(0.06-1.30)	(0.12-2.81)	(0.13-4.71)	(0.13-4.71)
Habitat						
OR	1.70	2.65	1.06	0.12	0.79	0.79
CI	(0.46-6.27)	(0.76-9.30)	(0.30-3.80)	(0.00-4.90)	(0.15-4.08)	(0.15-4.08)
Age of illness onset						
OR	1.22*	1.05	1.15*	1.05*	1.13*	0.99
CI	(1.07-1.40)	(0.97-1.14)	(1.02-1.30)	(0.82-1.34)	(1.00-1.28)	(0.90-1.10)
Illness duration (months)						
OR	0.99	1.00	0.98	0.91	0.99	1.00
CI	(0.96-1.02)	(0.97-1.03)	(0.95-1.02)	(0.82-1.00)	(0.96-1.03)	(0.97-1.04)

[Table/Fig-4]: Multivariate regression analysis with the presence of metabolic syndrome and their component criteria regressed on demographic/clinical criteria.
*denotes p-value <0.05;The displayed values were odds ratios, their 95% confidence intervals (in parantheses); MetS-Metabolic syndrome as per NCEP ATP III criteria; FBS-Fasting blood glucose TG-Triglycerides; HDL-High density lipoprotein; BP-Blood pressure; WC-waist circumference

DISCUSSION

The main finding of this study was that the prevalence of MetS increased among schizophrenia patients in a follow-up period of one year.

This study has found no association between MetS at baseline and socio-demographic and clinical characteristics. There is lack of any significant difference in age, gender, habitat, literacy, age of onset of illness and duration of illness in patients with and without MetS similar to other studies [18-21].

The prevalence of MetS was 15.4% before initiation of Olanzapine which was much higher than prevalence of 3.8% observed in a study on drug naïve individuals by Padmavathi R et al., [15]. This could be explained by the previous antipsychotic treatment taken by the patient. The prevalence of MetS at one year after initiation of Olanzapine was 56.9%, which is 40% more than the baseline prevalence. This increase is higher than another Indian follow-up study done on schizophrenic patients on different antipsychotics which showed an increase of 11.66 % in four months, and also concluded that olanzapine has maximum potential to cause MetS [22]. This increase can be compared to phase 1 trial of CATIE where the metabolic prevalence increased from 34.8% to 43.9% in patients on olanzapine after three months [23]. However, this prevalence at one year after olanzapine was higher when compared to other cross-sectional studies done on prevalence of MetS by Centorrino F et al., (29.5%), Park MJ et al., (29%), and Aekplakorn W et al., (23.2%) [18,24,25].

There is some literature showing dose dependent effect of olanzapine on weight gain, present study population was too homogenous to make this conclusion possible [26]. When components of MetS were analysed separately there was statistically significant increase in the prevalence of hyperglycemia, hypertriglyceridemia, hypertension and abdominal obesity. This was similar to studies done by Srisurapanot M et al., and Yoca G et al., [27,28]. There was a mean increase of eight kilograms after an year of olanzapine. A similar follow-up study of olanzapine by Salviato Balbão M et al., documented a weight gain of 11 kilograms at the end of one year [17]. There was also increase in WC at the end of one year similar to a study done by Kainanen J et al., [29]. There was increase in TG and decrease in HDL at one year. A study done by Roohafza H et al., which compared lipid profile of patients on conventional antipsychotics in comparsion to atypical antipsychotics concluded that there was no statistically significant difference of HDL in both the groups [30]. A study by Duncan EJ et al., had shown that patients who had Olanzapine have lower HDL and higher TG [31] which was similar to the results of current study. There was also increase in number of individuals with elevated BP at the end of one year which was consistent with the literature [32,33].

Limitation(s)

The limitations of this study are that only two cross-sectional evaluations were performed instead of assessment with regular intervals. We could assess only 65 patients, which is a smaller sample and limits generalisability of present study findings. This study has not evaluated the impact of diet and physical activity on development of MetS, which could be a potential confounder.

CONCLUSION(S)

MetS was found to be increased among schizophrenic patients on olanzapine through time. Olanzapine has high potential to worsen all the metabolic parameters with time and should be monitored thoroughly.

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