Original Research Article

Drug emergent metabolic syndrome among patients taking olanzapine: A prospective interventional study

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Abstract

Introduction: Olanzapine is one of the most commonly used atypical antipsychotic and is associated with significant deterioration of the metabolic profile among the patients taking it. **Aim:** To assess the emergence of drug induced metabolic syndrome among patients taking olanzapine. **Materials and method:** Eighty cases with diagnosis of Schizophrenia, schizoaffective disorders, bipolar affective disorder, persistent delusional disorder, unspecified nonorganic psychosis and no history of treatment with atypical antipsychotics in last 6 months were recruited from outpatient/ inpatient department of Institute of Mental Health, Amritsar, by purposive sampling after baseline screening and applying inclusion and exclusion criteria. It was a Prospective Interventional study. Patients were assessed for their metabolic profile at baseline, 2- and 4-months. **Result:** Statistically significant difference was found in all the metabolic parameters, including body weight, blood pressure, BMI, fasting blood glucose, fasting triglycerides and fasting HDL, after 4 months of initiating olanzapine as compared to baseline. One-fifth of the patients had attained the criteria of metabolic syndrome at the end of four months, and this ratio showed minimal variation with gender. **Conclusion:** Metabolic impairments have become a persisting menace with currently preferred patterns of lifestyles and drug management. Psychiatrists must be vigilant enough towards the potential metabolic side effects of antipsychotic medications so that appropriate precautions can be implemented in a timely manner. The general treatment provided to patients with severe mental illness should be at par with care provided to other patients.

Key words: Olanzapine, Metabolic Syndrome, Weight gain, Atypical-antipsychotics.

Introduction

Atypical antipsychotics have demonstrated an improved therapeutic profile compared to that of typical ones. However, they are not devoid of significant adverse effects, which are usuallyanticipated in patients treated with atypical antipsychotics, causing alot of concern. Accordingly, the focus of the clinicians worldwide has nowshifted away from extrapyramidal side-effectsto weight gain, blood glucose imbalance and other metabolic effects associated with them[1].

Olanzapine is one of the most commonly used atypical antipsychotic and is associated with adverse effects like obesity, drowsiness, postural hypotension, diabetes, dyslipidemia, etc. The most common of the lot being somnolence and weight gain[2]. Extrapyramidal side effects are infrequent with olanzapine, althoughtremors and muscle rigidity may be encountered in some[3].

A serious concern among the patients started on olanzapine is the development of obesity characterized by increased waist circumference, hypertension, hypertriglyceridemia and impaired glucose tolerance, which together along with the low levels of serum HDL, lay the basis of metabolic syndrome, also known as syndrome X[4]. The metabolic syndrome is an intermediate step toward the final endpoint of type II diabetes and cardiovascular disease in the general population[5,6]. Etiology of metabolic syndrome is thought to be multifactorial. Important risk factors for development of metabolic syndrome being abdominal obesity and insulin resistance[7,8]. It has been elucidated that metabolic syndrome and other risk factors associated with cardiovascular disorder are highly prevalent in people with severe mental illnesses like schizophrenia[9]. People with severe mental illnesses are more often found to be obese, to be smoking and to be suffering with hyperglycemia/ diabetes, hypertension and dyslipidemia. Partly, these risk factors are also associated withan unhealthy and sedentary behavior. Patients are at heightened risk for premature mortality due to these comorbidities and overall poorer quality and limited access to physical health care. The negative impact of atypical antipsychotic agents on many of the modifiable risk factors of cardiovascular disorders has been repeatedlysubstantiated over the years now[10].

The risk of causation as well as worsening of pre-existing diabetes has been found to be higherwith olanzapine thanmost of the other commonly prescribed second- generation antipsychotic drug. It is one of the most likely antipsychotic drugs to induce weight gain, obesity and associated metabolic side effects[1,11,12]. While itcan be implied that in long-term, metabolic dysregulation predisposes to cardiovascular disease and ultimately premature death[13], but even in a shorter run, weight gain secondary to drug treatment reduces treatment compliance, thereby increasing the risk of relapse of psychosis[14]. Most of the studies regarding the emergence of metabolic syndrome among patients takingolanzapineare of western origin, therefore there is a need to study such emergence in Indian population as they are said to be more prone to develop metabolic syndrome. In this context, the current study was planned to assess the emergence of drug induced metabolic syndrome among patients taking olanzapine.

Materials and method

In order to achieve the abovementioned aim, two objectives were set. Firstly, to assess the emergence of metabolic syndrome after 4

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months in thestudy population as compared to baseline.Secondarily, the mean change in each parameter which includes body weight, body mass index, abdominal obesity as waist circumference, blood pressure, fasting blood glucose, serum triglycerides, HDL cholesterol in the study population at 2-, 4- months was also assessed. The study included out-patient and in-patient units of a tertiary care center in North India, i.e., Institute of Mental Health, Amritsar.

Inclusion criteria

- Patients diagnosed as schizophrenia, schizoaffective disorder, bipolar disorder,persistent delusional disorder, unspecified nonorganic psychotic disorder aged18–65 years using ICD-10 criteria[15].
- No prior treatment with atypical antipsychotic in past 6 months.
- Willing to give a valid consent for participation in study.

Exclusion criteria

- Patients having any of the five features of metabolic syndrome.
- Patients having cardiovascular disorder, whether under treatment or not.
- Patients of diabetes (even if having fasting blood glucose controlled below 110mg/dl by any diabetic medication) will be excluded.
- Patients with endocrinal disorder or having co-morbid chronic medical illnesspreventing use of olanzapine like liver failure.

Eighty cases were recruited into study by purposive sampling after baseline screening, applying inclusion and exclusioncriteria. It was a Prospective Interventional study. Appropriate ethical and scientific clearance was obtained prior to conduction of the study.

Tools and Instruments

1. The Tenth Revision of the International Classification of Diseases and RelatedHealth Problems (ICD-10 DCR) classification of mental and behaviouraldisorders[15].
2. Adult Treatment Panel (ATP III) diagnostic guidelines for metabolic syndrome[16].

According to the NCEP ATP III definition, metabolic syndrome is present ifthree or more of the following five criteria are met: waist circumference over102 cm (men) or 88 cm (women), blood pressure over 130/85 mmHg, fastingtriglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL)cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fastingblood glucose over 100 mg/dl.The NCEP ATP III definition is one of the most widely used criteria ofmetabolic syndrome. It incorporates the key features of hyperglycemia/insulinresistance, visceral obesity, atherogenic dyslipidemia and hypertension. It usesmeasurements and laboratory results that are readily available to physicians, facilitatingits clinical and epidemiological application.

Methodology

Patients with diagnosis of Schizophrenia, schizoaffective disorders, bipolaraffective disorder, persistent delusional disorder, unspecified nonorganic psychosis andno history of treatment with atypical antipsychotics in last 6 months were recruited fromoutpatient or inpatient department of Institute of Mental Health, Amritsar. Thediagnosis of all the patients was confirmed by consultant psychiatrist at Institute ofMental Health, Amritsar.

Most of the already published studies in this regard had samplesize of around 50 patients[17,18,19,20], considering that the lower sample size a methodologicalweakness; we recruited 91 patients initially after baseline screening, applying inclusionand exclusion criteria. 11 patients dropped out due to various causes (nonresponse, poor tolerability etc.). Ultimately, 80 cases entered the study. After takingconsent they were assessed in detail using semi structured pro-forma, baselinemetabolic parameters as per ATP- III criteria and mean metabolic parameters of each group at baseline, 2 and 4 months.

During each follow ups body weight, blood pressure, BMI were recorded. Fasting bloodglucose, fasting triglycerides and fasting HDL were recorded on baseline, 2 month and 4months. All this data was recorded on study pro-forma and later assessed.Mean change in metabolic parameters at baseline, 2, 4 months and drugemergent metabolic syndrome in the studypopulation were assessed. Chi-square testwas used to compare discreet variables, and unpaired t-test was used for comparingcontinuous variables during statistical analysis.

Observations and result

As a part of the study 80 patients who finally entered the study were assessed. The diagnosis was made on the basis of ICD 10 criteria.[15]Body weight, blood pressure, BMI, fasting blood glucose, fasting triglycerides and fasting HDL were recorded on baseline, 2-months and 4- months. Patients weredirected to come after at least 12 hours of fasting beforeinvestigation. After 4 months patientswere assessed forthe development of metabolic syndrome. All the data were recorded on study pro-forma. Following observations were seen on datacompilation:

Majority of the patients belonged to the 21-30 years age group and the proportion of elderly patients (>60 years) was minimal. Most of the patients were male and belonged to rural background. Two-thirds of the patients were literate, mostly educated up to secondary level and almost a similar proportion of patients were married. Around three-fourth of the study population were working as farmers and labourers. (Table 1)

Patients were assessed for their metabolic profile at baseline, 2- and 4- months. Statistically significant difference was found in all the parameters after 4 months of initiating olanzapine as compared to baseline. (Table 2)

Further, it was found that one-fifth of the patients had attained the criteria of metabolic syndrome at the end of four months, and this ratio showed minimal variation with gender. (Table 3)

Table 1: Socio-demographic profile of the study population (n=80).

Characteristics		Frequency	Percentage
Age (years)	10-20	12	15.00%
	21-30	26	32.50%
	31-40	13	16.25%
	41-50	15	18.75%
	51-60	11	13.75%
	>60	03	03.75%
Gender	Male	52	65.00%
	Female	28	35.00%
Residence	Urban	34	42.50%
	Rural	46	57.50%
Education	Illiterate	24	30.00%
	Up to Primary	09	11.25%
	Up to Secondary	33	41.25%
	Graduate	14	17.50%

Employment	Unemployed/ Not working	18	22.50%
	Farmer	13	16.25%
	Labourer	45	56.25%
	Government/ Private Job	04	05.00%
Marital status	Married	50	62.50%
	Unmarried/ Divorced	30	37.50%

Table 2: Metabolic profile at baseline, 2- and 4- months

Weight (kg)	Height (metre)	BMI	Waist Circumference (cm)	Blood Pressure		Fasting Blood Sugar (mg/dL)	S. TG level (mg/dL)	S. HDL level (mg/dL)
				Systolic	Diastolic			
Baseline								
64.98 ±8.05	1.67±0.91	23.35±2.10	78.32 ±5.72	118.55±6.30	77.47±4.39	85.35±9.56	97.38±15.08	52.76±6.18
After 2 months								
68.67 ±8.47	-	24.77±2.61	80.15 ±7.50	122.12±6.70	80.50±4.82	96.58±10.70	117.31±16.80	45.84±5.70
After 4 months								
70.93±8.93	-	25.43±2.46	80.99 ±6.39	124.20±6.38	82.45±5.73	101.76±12.56	127.98±20.86	42.37±5.73
Statistical significance of the change in the metabolic parameters after 4 months as compared to the baseline (p <0.05: significant)								
Significant	-	Significant	Significant	Significant	Significant	Significant	Significant	Significant

Table 3: Drug Emergent metabolic syndrome in study population

Study population	With metabolic syndrome	Without metabolic syndrome	Percentage of patients with metabolic syndrome
Male (n=52)	10	42	19.23%
Female (n=28)	06	22	21.42%
Total (n=80)	16	64	20.00%

Discussion

The current study showed that most of the patients were young adults, with age less than 40 years, which happens to coincide with the pattern of age distribution in psychotic patients. The study by Jain et al showed same type of age distribution, with median age of the population being 39.3 years approximately[21]. Various studies in foreign population, dealing with atypical antipsychotic induced metabolic syndromes also show such patterns of age distribution[18,22,23]. This pattern might be due to earlier onset of psychotic symptoms, and apparently greater concern regarding metabolic syndromes in young adults, as these might have a very disastrous implication on their future wellbeing.

Approximately a thirdof the study population consisted offemales, mostly residing in rural areas, with most of the population having less than or upto secondary level education. Similar demographic profile is frequently described in the literature dealing with the psychotic population in this country[24].

The present study showed that there was an increase in body weight as well as the BMI at 2- and 4- months after initiation of olanzapine as compared to the baseline. The increase was found to be statistically significant upon analysis. Similar were the findings in the study by Wirshing et al and other studies, which state that olanzapine is one of the most likely anti-psychotics to cause weight gain based on various measures[1,11,12,25]. Although waist circumference is actually an indirect indicator of obesity, weight gain and insulin resistance, a trend similar to body weight and BMI was found with waist circumference at the end of 2- and 4- months in the study population as compared to the baseline.

This study shows a gradual but steady increase in both systolic and diastolicblood pressure among the patients which was statistically significant.These findings are in synchrony with the other studies assessing the bloodpressure parameters in different populationsolanzapine[26,27]. The increase in blood pressure might be due to the metabolic derangements likehyperlipidemia, and hyperglycemia. These derangements might be responsible foratherosclerosis, leading to loss of vascular elasticity, which further may result inincreased blood pressure[28].

This study showed significant increase in the meanfastingplasma glucose (FBG) in study population at 4 months. While most of the studies have found an increase in the FBG, few of them have them have not found it to be statistically significant[29,30].

The fasting lipid profile among the patients showed a gradual, but steadyderangement in lipid profile. Thisderangement is marked by the gradual reduction in fasting HDL concentration, as wellas gradual increase in serum fasting TGA level. These findings are in line with other studies assessing metabolic profile of olanzapinein various populations[29,31]. It shows that the local action of olanzapine on gastrointestinal hormonesmight play little role in the metabolic derangements[32].

A significant number of patients developed clinicallyidentifiable metabolic syndrome as per ATP III criteria within four months of startingof therapy with olanzapine. It was found thataround 19% of males, as well as 21% of female patients developed clinically detectablemetabolic syndrome within 4 months of treatment initiation. 22.5% of Patients onOlanzapine standard were fulfilling criteria of metabolic syndrome, finding are inunison with study by Gautam et al[33].

The incidence of metabolic syndrome varieswidely in various studies across the world, depending upon the patient population, theirfood habit, lifestyle, diagnosis, as well as antipsychotic used by them[34,35]. The study bySadichchha et al (2006) showed around 31% incidence of development of metabolicsyndrome in females with first episode schizophrenia[36]. As the metabolic syndrome progress gradually, the patient is exposed tosignificant morbidity, and mortality, which is again aggravated by various co-administereddrugs, and sedentary lifestyle in psychotic patients under treatment[37].

Thisleads to relentless search and research to protect the patients from these serious sideeffects of the atypical antipsychotics.Various strategies for prevention and treatment have been tried including diet, exercise, psychotherapy, adjunctive medication[38]. Approaches include medical nutrition therapy[39], pharmacological approaches using adjunctive medications, for example, metformin[40] and amantadine[41], other than novel approaches likedelivering the drugby bypassing gastric mucosa.

Conclusion

Cardiovascular disease in patients with severe mental illness has become a persisting menace with currently preferred patterns of lifestyles and drug management.Psychiatrists must be aware of the potential metabolic side effects of antipsychotic medications, evaluating the risk/benefit ratio while selecting an antipsychotic treatment and must be vigilant enough so that appropriate precautions

can be implemented in a timely manner. The general treatment provided to patients with severe mental illness should be at par with care provided to other patients.[42]

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