

**OBESITY IS AN UNAVOIDABLE ADVERSE DRUG REACTION TO ATYPICAL ANTIPSYCHOTICS**Hemlata Verma<sup>1</sup>, S. S. Rao<sup>2</sup>, V. K. Verma<sup>3</sup>**HOW TO CITE THIS ARTICLE:**

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**ABSTRACT:** Atypical antipsychotics are an important advance in the treatment of schizophrenia and other psychiatric illness, and have become widely used as first-line pharmacotherapy for psychosis. This study is a longitudinal prospective observational study of ADRs of Atypical Antipsychotic drugs in patients of psychiatric illness. Information of ADRs was data based and collected from OPD. The noted ADRs were assessed by using Naranjo's probability assessment scale, and WHO (UMC) causality assessment scale. Majority of patients in this study belonged to 21-30 years age group which was 24% of the total. According to the severity of ADRs, majority of cases were reported of having weight gain 38.46% followed by sedation 19.23%, dry mouth 13.46% and orthostatic hypotension 5.76%. 88.47% were reported as type A and 11.53% were reported as type B. Definite (certain) relationship was established in 30.40% patients while probable in 57.62% and 11.53% ADRs were categorized as possible. The ADRs can be prevented by collecting reliable information about their frequencies and possible risk factors.

**KEYWORDS:** Atypical antipsychotics, ADRs, Olanzapine, Risperidone, Obesity.

**INTRODUCTION-**Atypical antipsychotics are an important advance in the treatment of schizophrenia and other psychiatric illness, and have become widely used as first-line pharmacotherapy for psychosis. One of the main advantages of the atypical antipsychotics over standard antipsychotics is their broad spectrum of efficacy.<sup>(1)</sup> As with all drugs, efficacy must be accompanied by a tolerable side-effect profile to optimize clinical effectiveness. Extra pyramidal symptoms (EPS) are a major problem with conventional antipsychotics and often lead to poor compliance.<sup>(2)</sup> Atypical antipsychotics, however have been shown to cause less EPS than standard antipsychotics, although dose-related EPS do occur with some agents. Unlike conventional antipsychotics, different atypical antipsychotics often have clinically distinctive side-effects, So it is important to explore these side-effects alongside their potential for differing levels of compliance.<sup>(3)</sup>

In particular, weight gain, which is an important side-effect from the compliance perspective is emerging as a differentiator between atypical antipsychotics, and is most pronounced with olanzapine and clozapine.<sup>(4,5)</sup> It is generally believed that there are multiple mechanisms by which antipsychotic drugs induce weight gain but their precise nature remains unknown. Weight gain as a drug effect may be a multifactorial process, involving serotonergic, histaminergic, and/or adrenergic neurotransmission (Baptista, 1999). Treatment side-effects are among the most common causes of non-compliance<sup>(6)</sup> with extrapyramidal phenomena being the most widely studied,<sup>(7)</sup> although weight gain<sup>(8,9)</sup> and sexual disturbances are also important. Higher levels of medication compliance can therefore be expected with atypical antipsychotics, different atypical antipsychotics often have clinically distinctive side-effects. So it is important to explore these side-effects alongside their potential for differing levels of compliance.

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The consequences of excessive weight gain (Obesity) associated with antipsychotic drugs are likely to include poor compliance or even discontinuation of therapy by the patients. Poor adherence almost always leads to relapse and a worsened long- term outcome.<sup>(10)</sup>

**MATERIALS AND METHODS:** This study is a longitudinal prospective observational study of ADRs of Atypical Antipsychotics drugs in patients of psychiatric illness. The study was carried out in the department of Pharmacology Gandhi Medical College Bhopal. The cases included all the patients, visiting the Out Patients Department of Psychiatry, Hamidia Hospital, Bhopal (India) with suspected ADRs due to atypical antipsychotics. Information of ADRs was data based collected from OPD with the help of treating physician and other health care professionals in a specialized Performa. Selection of patients is based on the clinical diagnosis made by physician with the help of DSM-IV and ICD 10 criteria. The noted ADRs were assessed by using Naranjo's probability assessment scale,<sup>(10)</sup> new algorithm to identify the causality of ADR and WHO (UMC) causality assessment scale because it takes into account the clinical pharmacologic aspect.<sup>(11)</sup>

The use of WHO-UMC system for standardized case causality assessment (accessed from <http://www.WHO-UMC.org/graphics/4409pdf>) included routine hemogram, Peripheral blood smear, Liver function test, Lipid profile, Blood sugar FBS, PPBS, ECG and measurement of weight in every visit. ADRs are also divided in to type A (Predictable) and type B (Unpredictable) by Rawlins and Thompson classification scheme.<sup>(12)</sup> All patients above 12 years of age attending OPD with ADRs to atypical antipsychotics were recruited in this study. Pregnant women, patients of known cases of diabetes mellitus and patients with known neurological disorders and hematological disorders were excluded.

**STATISTICAL ANALYSIS:** Analysis was done by using Microsoft Excel and SPSS 10. 0.1 for windows. Univariate analysis was carried out using Chi Square test and Z test for proportions. Multivariate analysis was performed to assess the independent risk of variables found significantly on univariate analysis by performing a stepwise logistic regression analysis. P value of <0.05 was considered significant unless specified otherwise.

**RESULT:** During the study 87.61% patients were treated with olanzapine, 11.02% treated with risperidone and 2.37% treated with clozapine. We recorded 104 ADRs due to atypical antipsychotics - 3.55% with olanzapine, 6.42% with risperidone and 13.33% due to clozapine. Majority of patients in this study belonged to 21-30 years age group which was 24% of the total. According to the majority of ADRs, majority of cases were reported of having weight gain 38.46% followed by sedation 19.23%, dry mouth 13.46% and orthostatic hypotension 5.76%. ADR in form of oculogyric crises and hyperprolactinemia was reported in 2 patients of each group. According to severity of ADRs involvement of different system- Majority of ADRs seen were of weight gain (metabolic syndrome) 38.46%, followed by 19.23% sedation (CNS), 13.36% of dry mouth (Anticholinergic) and 5.76% of orthostatic hypotension (CVS).

During our study we also recorded 2 patients of having excessive salivation due to Clozapine, 4 patients of Hyperprolactinemia due to Risperidone and 2 patients of oculogyric crises caused by Olanzapine. According to the severity of ADRs by individual drugs 13.46% had severe ADRs. Out of these 9.61% patients had severe ADRs due to Olanzapine and 3.84% by Clozapine. 53.84% patients were reported to have moderate ADRs. Out of these 11. 53.84% had moderate ADRs due to Olanzapine and 7.69% due to Risperidone. During this study we also reported 2 patients of excessive

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salivation due to Clozapine, 4 patients of Hyperprolactinemia due to Risperidone and 2 patients of oculogyric crises caused by Olanzapine. Onset of ADRs after starting atypical antipsychotics was maximum in 0-1 weeks 42.30% and in 6-12 weeks 42.30% followed by 11.5% in 3-6 weeks and 3.84% in 1-2 weeks. The type of ADRs were classified by Rawlins and Thompson classification as Type A and Type B. Accordingly, 88.47% were reported as type A and 11.53% were reported as type B.

The causal link between ADRs and suspected atypical antipsychotic drugs was analysed by WHO scale, according to which definite (certain) relationship was established in 30.40% patients while probable in 57.62% and 11.53% ADRs were categorized as possible.

Age group	Mild	Moderate	Severe	Total	Percentage
12-20	6	6	0	12	11.52 %
21-30	8	20	6	34	32.69 %
31-40	8	16	6	30	28.85 %
41-50	8	4	0	12	11.52 %
51-60	4	8	2	14	13.46 %
>60	0	2	0	2	1.92 %
	34(32.69%)	56(53.84%)	14(13.46%)	104	100%

Table no. 1: Severity of ADRs in different age group

Chi sq =7.06 p value=0.720 (not significant).

ADRs	Mild	Moderate	Severe	Total	Percentage
CNS					
EPS					
Dystonia	2			2	1.92%
Headace	2			2	1.92%
Sedation	8	10	2	20	19.23%
CVS					
Ort. Hypotension	4	2		6	5.76%
QTc prolongation					
Metabolic disorders					
Weight gain	12	20	8	40	38.46%
Diabeties		6		6	5.76%
Dyslipidemia		6		6	5.76%
Anticholinergic					
Dryness of mouth	8	4	2	14	13.46%
Excessive salivation			2	2	1.92%
Others					
Oculogyruscrises		2		2	1.92%
Agranulocytosis					
Hyperprolactinemia		4		4	3.84%

Table no. 2: Majority of ADR Involvement of Different system according to severity

Chi sq=22.3641 p=0.1496.

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ADRs	Clozapine	Risperidone	Olanzapine	Total	Percentage
CNS					
EPS					
Dystonia	2			2	1.92%
Headache	2			2	1.92%
Sedation	8	10	2	20	19.23%
CVS					
Ort. Hypotension	4	2		6	5.76%
QTc prolongation					
Metabolic disorders					
Weight gain	12	20	8	40	38.46%
Diabeties		6		6	5.76%
Dyslipidemia		6		6	5.76%
Anticholinergic					
Dryness of mouth	8	4	2	14	13.46%
Excessive salivation			2	2	1.92%
Others					
Oculogyruscrises		2		2	1.92%
Agranulocytosis					
Hyperprolactinemia		4		4	3.84%

**Table No. 3: Number of ADRs for individual Atypical Antipsychotics**

ADRs	0-1 wks	1-2 wks	2-3 wks	3-6 wks	6-12 wks	Total
CNS						
EPS						2(1.92%)
Dystonia	2					2(1.92%)
Headache	2					20(19.26)
Sedation	20					
CVS						
Ort. Hypotension	6					6(5.76%)
QTc prolongation						
Metabolic disorders						
Weight gain	12			8	32	40(38.46%)
Diabeties				2	4	6(5.76%)
Dyslipidemia				2	4	6(5.76%)
Anticholinergic						

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Dryness of mouth	10	4				14(13.46%)
Others						
Excessive salivation						
Agranulocytosis						
Hyperprolactinemia						
Excessive salivation	2					2(1.92%)
Oculogyrus crisis	2					2(1.92%)
Hyperprolactemia					4	4(3.84%)
<b>Total</b>	<b>44(42.30%)</b>	<b>4(3.84%)</b>	<b>0(0%)</b>	<b>12(11.53%)</b>	<b>44(42.30%)</b>	<b>104</b>

Table No. 4: Onset of ADRs

Chi sq=68.39 p Value <0.0001.

Antipsychotics	No. of ADRs	Type A	Type B	Z Value	P Value
Clozapine	8	6	2	2.3094	0.0209
Olanzapine	78	72	6	19.3363	<0.0001
Risperidone	18	14	4	0.0556	<0.0001
<b>Total</b>	<b>104</b>	<b>92(88.47%)</b>	<b>12(11.53%)</b>		

Table No. 5: Types of ADRs (Rawlins and Thompson classification)

Atypical Antipsychotic	No. of ADRs	Certain	Probable	Possible
Clozapine	8	4	2	2
Risperidone	18	8	6	4
Olanzapine	78	20	52	6
<b>Total</b>	<b>104</b>	<b>32(30.75%)</b>	<b>60(57.6%)</b>	<b>12(11.53%)</b>

Table No. 6: Causality assessment (WHO -UMC scale) of ADRs

Chi Sq = 2.31 p Value = 0.889.

**DISCUSSION:** Weight gain is associated with many conventional and some atypical antipsychotics (Allison et al., 1999a) and its degree is dependent on the drug and the individual patient. Weight gain occurs shortly after starting treatment but may plateau or even decrease after 1 year. Weight gain is linked to a decreased metabolic rate, increased calorie intake, and decreased physical activity (Weinsier et al., 1998; Baptista, 1999), although it is not yet known by which precise mechanisms it is induced by atypical antipsychotics.

During our study we recorded 104 ADRs due to atypical antipsychotics, the maximum number of ADRs reported was weight gain 38.46% followed by 19.23% of sedation, 13.46% of dryness of mouth. There were 5.76% patients who developed Diabetes, 5.76% hyperlipidaemia and

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3.84% irregular menstruation. The result of this study showed that the mean age of patients was below 30 years, however a recent Indian study has reported that the commonest age group among these patients was 33 years. Age is an important risk factor for ADRs, and incidence of ADRs increases steadily with age. This is due to pharmacodynamic and pharmacokinetic changes which, together with impairment of homeostatic mechanisms and the effect of coexisting disease, contribute to a significant increase in the incidence of ADRs. Another reason for the increased incidence of ADRs in elderly is increased consumption of medicines.<sup>(13)</sup> The male preponderance identified in this study was similar to studies conducted by Padmini et al.<sup>(14)</sup> In our study the number of male patients were 52% and female 48%. Significant weight gain may be seen with these drugs (particularly clozapine and olanzapine), and may compound any preexisting risk of diabetes, but hyperglycemia and diabetes have been reported in the absence of weight gain.

The mechanism of this adverse effect is unknown, but may be via either increased insulin resistance or decreased insulin secretion due to direct pancreatic  $\beta$ -cell inhibition via the serotonin 5-HT<sub>1A</sub> receptor. Lipid abnormalities (Increased LDL and triglycerides and decreased HDL) have also been reported in association with the use of these drugs.<sup>(15)</sup> The weight gain refer to an increase of over 7% of body weight and BMI of over 25 is considered obesity. FDA mandated data greater than or equal to 7% of their initial body weight gain during short term clinical trial of Olanzapine was 29% and 18% with Risperidone which is comparable to our study.<sup>(16)</sup> Sernayek and Colleagues found that the prevalence of diabetes was higher among the patients treated with atypical antipsychotics than conventional. We also reported 5.76% cases of diabetes due to Olanzapine.<sup>(17)</sup> Ossar and Colleague reported significant hyperlipidemia among the patients of Olanzapine. During our study we reported 5.76% patients of dyslipidemia. 42.30% ADRs reported in 6-12 weeks duration after starting atypical antipsychotics were weight gain, diabetes, dyslipidemia and hyperprolactenemia. Occer and colleagues in a 12 weeks study found significant increase in body weight, serum triglycerides and blood sugar in patients treated with atypical antipsychotics, which is comparable to our study.<sup>(18)</sup>

The high incidence of Type A reaction in comparison with type B reaction (88.47% v/s 11.53%) indicate that majority of ADRs were avoidable. Causality assessment of ADRs (WHO Scale) were reported probable in 57.6%, possible 11.53% and 30.75% as certain. A Bulgarian study reported that the ADR frequency of individual psychotropic drugs studied was less than 1%.<sup>(19)</sup> In our study we recorded a 3% prevalence of ADRs due to Atypical antipsychotics.

**CONCLUSION:** The consequences of excessive weight gain (obesity) associated with atypical antipsychotic drugs are likely to include poor compliance or even discontinuation of therapy by the patients. Poor adherence almost always leads to relapse and a worsened long term outcome (Bernstein, 1987; Fenton et al, 1997). The ADRs can be prevented by collecting reliable information about their frequencies and possible risk factors. Till date the actual extent of the problem of ADRs attributable to different drugs including antipsychotics is not documented mainly because of their under reporting.

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