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STUDY OF ADVERSE DRUG REACTIONS TO ATYPICAL ANTIPSYCHOTIC DRUGS IN PSYCHIATRIC ILLNESS

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ABSTRACT

Atypical antipsychotics are commonly used drugs for mental disorders, so early detection of ADRs in patients treated with antipsychotics becomes necessary. 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. We recorded 104 ADRs due to atypical antipsychotics. 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.

KEY WORDS- Atypical antipsychotics, ADRs, Olanzapine, Risperidone, Obesity

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INTRODUCTION

There is a steep rise in patient population with schizophrenia and allied diseases. This may be due to stress and strain in day to day life. Antipsychotics are commonly used drugs for mental disorders, so early detection of ADRs in patients treated with antipsychotics becomes necessary to minimize morbidity and economic burden to the patients as well as to the country. These drugs are used for months, years or lifelong so monitoring of ADRs is very important. Atypical antipsychotic drugs are also prescribed which have a unique pharmaco-vigilance profile and a different spectrum of ADRs as compared to the conventional antipsychotics (1). The novel or second generation antipsychotic medications-clonazapine, olanzapine, risperidone, ziprasidone, quetiapine and aripiprazole have been gaining wide usage throughout the United States since 1980, and also worldwide. These medications generally are perceived as effective antipsychotic agents with more favorable extra pyramidal side effect profiles compared with conventional antipsychotic medications (2, 3, 4, 5). Despite their efficacy and the lack of extra pyramidal side effects, these medications have their own unique side effects profiles. The most important side effects that are emerging are weight gain and metabolic disturbances. Cardiovascular effects and hyper-prolactinemia are troublesome issues for some of the members of this class of agents. Weight gain and sexual dysfunction can lead to non adherence to treatment and ultimately contribute to relapse. Cardiovascular and metabolic disturbances can lead to long term health consequences, such as diabetes and coronary artery disease (6, 7, 8, 9).

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 proforma. 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 (10), new algorithm to identify the causality of ADR and WHO (UMC) causality assessment scale because it takes into account the clinical pharmacologic aspect (11). The use of WHO-UMC system for standardized case causality assessment (accessed from http://www.WHO-UMC.org/graphics/4409pdf) included routine haemograms, 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 (12). 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. A P value of <0.05 was considered significant unless specified otherwise.

RESULTS

During the study 2540 patients were treated with atypical antipsychotics, out of these 87.61% treated with olanzapin e, 11.02% treated with risperidone and 2.37% treated with clozapine (Table no 1). We recorded 104 ADRs due to atypical antipsychotics - 3.55% with olanzapine, 6.42% with risperidone and 13.33% due to clozapine (Table no 1). Majority of patients in this study belonged to 21-30 years age group which was 24% of the total (Table no.2). 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%. ADR in form of oculogyric crises and hyperprolactinemia was reported in 2 patients of each group (Table no.3). 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 Hyperprolactemia due to Risperidone and 2 patients of oculogyric crises caused by Olanzapine (Table no.4) 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 salivation due to Clozapine, 4 patients of Hyperprolactemia due to Risperidone and 2 patients of oculogyric crises caused by Olanzapine.(Table no.3) 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(Table no.5). 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 (Table no.6) 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(Table no.)

Table No 1
No.of patients treated with Atypical antipsychotics and ADRs

Name of drugs	No. of patients	ADRs
Olanzapine	2200(87.61%)	78(3.55%)
Risperidone	280(11.02%)	18(6.42%)
Clozapine	60(2.37%)	08(13.33%)
	2540	104

Table no. 2
Severity of ADRs in different age group

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%

Chi sq = 7.06 p value=0.720 (Not Significant)

Table no.3
Number of ADRs for individual Atypical Antipsychotic

Side effects	Clozapine	Risperidone	Olanzapine	Total	Percentage
CNS-					
EPS					
Dystonia			2^{+}	02	1.92%
Headace			2^{+}	02	1.92%
Sedation	2^{+}	$2^{+},2^{++}$	$4^{+},8^{++},2^{+++}$	20	19.26%
CVS					
Orth.hypotension	2^{+}	$2^{+},2^{++}$		06	5.76%
QTc prolongation					
Metabolic Disorder					
Weight gain	2^{+++}	4^{+}	$8^{+},20^{++},6^{+++}$	40	38.46%
Diabeties mellitus			6^{++}	06	5.76%
Dislipedemia			6^{++}	06	5.76%
Anticholinergic					
Dryness of mouth		2^{+}	$6^{+},4^{++},2^{+++}$	02	1.92%
Excessive salivation	2^{+++}				
Others					
Oculogyrus criss			2^{++}	02	1.92%
Agranulocytosis					
Hyperprolectemia		4^{++}		04	3.48%
Total	8	18	78	104	

+=non or non -34(32.69%) ++=moderate-56(53.84%) +++=severe14(13.46%)

Table no.4
Severity of ADR Involvement of Different system according to severity

ADRs	Mild	Moderate	Severe	Total	Percentage
Central nervous system					
EPS					
Dystonia	2			2	(1.92%)
Headace	2			2	(1.92%)
Sedation	8	10	2	20	(19.23%)
CVS					
Orth.Hypotension	4	2		6	(5.76%)
QTc prolongation					
Metabolic disorders					
Weight gain	12	20	8	40	(38.46%)
Diabeties mellitus		6		6	(5.76%)
Dyslipedemia		6		6	(5.76%)
Anticholinergic					
Dryness of mouth	8	4	2	14	(13.46%)
Excessive salivation			2	2	(1.92%)
Others					
Oculogyrus crises		2		2	(1.92%)
Agranulocytosis					
Hyperprolectemia		4		4	(3.84%)

+=non or non -36(32.69%) ++=moderate-56(53.84%) +++=severe14(13.46%)
Chi sq = 22.3641 p value = 0.1496

Table no.5
Onset of ADRs

ADRs	0-1wks	1-2wks	2-3wks	3-6wks	6-12wks	Totals%
Central nervous system						
EPS						
Dystonia	2					2(1.92%)
Headache	2					2(1.92%)
Sedation	20					20(19.26%)
Cardiovascular						
Orth.hypotension	6					6(5.76%)
QTc Prolongation						
Metabolic Disorders						
Weight gain				8	32	40(38.46%)
Diabetes Mellitus				2	4	6(5.76%)
Dislipedemia				2	4	6(5.76%)
Anticholinergic						
Dryness of mouth	10	4				14(13.46%)
Excessive salivation	2					2(1.92%)
Others						
Oculogyrus crises	2					2(1.92%)
Neuroleptic Malignant Syndrome						
Hyperprolactemia					4	4(3.84%)
Total	44(42.30%)	4(3.84%)	0(0%)	12(11.53%)	44(42.30%)	104

Chi Sq =68.39 p Value <0.0001

Table no.6
Types of ADRs(Rawlins and Thompson classification)

Antipsychotics	No. of ADRs	Type A	Type B	Z Value	P Value
Clozapine	8	06	2	2.3094	0.0209
Olanzapine	78	72	6	**19.3363**	**<0.0001**
Risperidone	18	14	4	**4.0556**	**<0.0001**
Total	104	92(88.47%)	12(11.53%)		

Table no.7
Causality assessment (WHO –UMC scale) of ADRs

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

Chi Sq = 2.31 p Value = 0.889

DISCUSSION

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% hyperlipedaemia and 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.(13) The male preponderance identified in this study was similar to studies conducted by Padmini et al.(14).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 pre-existing risk of diabetes, but hyperglycaemia 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 β-cell inhibition via the serotonin 5-HT_{1A} receptor. Lipid abnormalities (increased LDL and triglycerides and decreased HDL) have also been reported in association with the use of these drugs.(15) Maximum number of ADRs were attributed to clozapine 13% followed by Risperidone 6.42% and Olanzapine 3.55%. Only 4 patients of irregular menstruation and hyperprolactenimia were observed with Risperidone treatment(16).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(17). Sernayek and Colleagues (18) 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.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(19).Crawfrod and coworkers in a 6 weeks study found that women seemed more susceptible and had mild to moderate hyperprolactinemia by 6 week end point which is again comparable to our study(20). The number of drug in a prescription is an important factor as drug combinations increase the risk of ADRs due to drugs interaction. In our study, mean number of drugs in prescription were found to be two on an average. This study revealed that most commonly prescribed drugs combination was Olanzapine and trihexiphenidyl followed by olanzapine and haloperidol, risperidone and trihexiphenidyl and clozapine and trihexiphenidyl. Padmini et al in a retrospective study found that a majority of cases were prescribed polydrug therapy (21).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% (22).In our study we recorded a 3% prevalence of ADRs due to Atypical antipsychotics.

CONCLUSION

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. Atypical antipsychotics are most widely used drugs in psychiatric patients; atypical antipsychotics have their own ADRs profile, therefore further studies of ADRs caused by atypical antipsychotics is needed for early detection, prevention and management of ADRs and reduced morbidity.

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