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Case Report

Adverse Drug Reactions Affiliated with Atypical Antipsychotics in Patients with Schizophrenia

Shweta Oommen[1], Elango P[2,*], Alwar MC[1], Susan Solomon[3]
[1]Department of Pharmacology, Pondicherry Institute of Medical Sciences, INDIA.
[2]Department of Pharmacology, Sri Ramachandra Medical College,Chennai, INDIA.
[3]Department of Psychiatry, Pondicherry Institute of Medical Sciences, INDIA.

ABSTRACT

An Adverse drug reaction cannot be avoided especially with drugs like antipsychotics which are the mainstay for the treatment of schizophrenia, a chronic disease, as well for the treatment of psychosis. Hence monitoring of adverse drug reactions is the key factor in ensuring patient compliance and safety. This study was a prospective, descriptive, follow up study. The reported ADRs were assessed for causality using both WHO causality assessment scale and Naranjo's algorithm. The severity of the reported reactions was assessed using Modified Hartwig and Siegel scale. The predictability and preventability of the reported ADRs was assessed using developed criteria for determining predictability of an ADR and Modified Schumock and Thornton scale respectively. A total of one hundred and forty three adverse drug reactions were observed from One hundred and two patients that were recruited. ADR's were noted and the majority of these adverse reactions was seen with Olanzapine and Risperidone. These include weight gain, sedation, tremors, drug induced parkinsonism and disturbances in menstrual cycle. Mild ADR's using Hartwig scale were fatigue, dry mouth, insomnia, weight gain and GI disturbances. Moderate ADR's were tardive dyskinesia, pill rolling movements, drug induced parkinsonism and hyper salivation. Severe reactions included disturbances in lipid profile, delirium, menstrual disturbances and hypertension Of the ADR's, 92% were predictable and 7.4% unpredictable. 67.8% ADR's were not preventable, 29.6% ADR's were definitely preventable and 3.70% probably preventable. WHO causality assessment revealed 55.5% ADR's to be certain, 29.6% to be probable and 14.8% to be possible. Need of the hour is active surveillance of adverse drug reaction with an efficient pharmacovigilance centre in every established hospital.

Key words: Adverse drug reaction, World Health Organization, Pharmacovigillance, Atypical antipsychotics, Schizophrenia.

Correspondence

Dr. Elango P,

Professor, Department of Pharmacology, Sri Ramachandra Medical College, Chennai-600001, Tamil Nadu, INDIA.

Phone no: +91-9444644886

Email: shweta.oommen@gmail.com

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INTRODUCTION

Antipsychotics are the mainstay of treatment for patients with schizophrenia and other psychotic illnesses. The typical antipsychotics or First Generation Antipsychotics (FGA's)such as chlorpromazine and haloperidol were introduced in early 1950'-s but the major drawback of these drugs were side effects such as Extra Pyramidal Symptoms (EPS) and tardive dyskinesia[1] This led to the introduction of newer antipsychotics which were labelled as atypical antipsychotics or Second Generation antipsychotics. (SGA's) The advantage of these newer generation antipsychotics was lack of side effects such as EPS and tardive dyskinesia. However, SGA's have their own limitations such as development of metabolic syndrome with altered lipid and glucose metabolism and weight gain.[2]

World Health Organization (WHO), defines Adverse Drug Reactions (ADR) as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosi, or for modification of physiological function".[3] ADR's pose many problems such as an increase in morbidity and mortality, poor compliance and increase in the cost burden.[4]

Adverse drug reactions of atypical antipsychotics were analyzed in 2014 and Lucca *et al.* found that risperidone and olanzapine produced majority of the adverse drug reactions.[5] According to Marder SR, monitoring treatments and managing adherence in schizophrenia is important and it can be done with appropriate interventions and support.[6]

Pharmacovigilance in India is still inchoate. There is increased use of psychotropic drugs due to the rising need and therefore adverse drug effects are also on the rise which can even be fatal. Although atypical antipsychotics are known to produce fewer side effects long term treatment causes their own range of adverse effects such as increased risk of diabetes and hyperlipidemia, weight gain, hypertension and seizure. Hence there is a need for constant monitoring of these ADR's so that the user population can be protected from various harms caused by these drugs.[7] However, there is lack of data on the exact rate and enormity of problems in South Indian setting and hence this study was carried out with the objective of identifying the adverse drug reactions affiliated with atypical antipsychotics in a tertiary care center.

METHODOLOGY

The study was conducted in the Department of Psychiatry, Pondicherry Institute of Medical Sciences, Pondicherry. The study was a prospective observational study and the study population consisted of outpatients visiting the Psychiatry OPD. One hundred and two patients were recruited from October 2016 to February 2017 and were followed up for one year. Patients of either sex between 20-50 years of age, diagnosed with schizophrenia according to DSM-5 criteria and being treated with any of the atypical antipsychotic drugs such as Olanzapine, Risperidone, Amisulpride, Quetiapine, Aripiprazole and Clozapine were included in

the study. Written informed consent emphasizing the need for one year follow up was obtained from the patient as well as the care giver. Patients who were treated with antipsychotics for other psychiatric illness were excluded from the study.

During this study period a total of one hundred and forty-three adverse drug reactions was observed. The adverse effects were reported based on the onset and severity of the ADR experienced, the impact of ADR on the treatment, work capacity of the patient, details of the suspected medication and whether any drug was discontinued because of the ADR. Information on any past or current occurrence of adverse effects due to antipsychotic drugs that were administered to the patients was collected from patients themselves by direct interview. Particulars regarding ADRs such as offending drug, laboratory investigations and treatments of ADRs done were recorded according to National Pharmacovigilance Program of India.

The reported ADRs were assessed for causality using both WHO causality assessment scale[8] and Naranjo's algorithm.[9] The severity of the reported reactions was assessed using Modified Hartwig and Siegel scale.[10] The predictability and preventability of the reported ADRs was assessed using developed criteria for determining predictability of an ADR and Modified Schumock and Thornton scale respectively.[11]

The WHO causality assessment scale determines the causal relationship of a suspected drug to the ADR in question and causality is categorized into "certain", "probable", "possible", "unlikely", "conditional/unclassified" and "unassessable/unclassifiable". Naranjo's algorithm has 10 objective questions with three options for answers – yes, no, do not know. Scores are given accordingly and the causality of the drug can be classified as "definite", "probable", "possible" and "unlikely". The Modified Hartwig and Siegel scale classifies severity of ADR as "mild", "moderate" or "severe" with various levels, depending on a number of factors like requirement for change in treatment, duration of hospital stay and the disability produced by the ADR. The developed criteria for determining predictability of an ADR categorizes ADR as "predictable" or "not predictable" based on the incidence rate of reported adverse drug reaction and history of allergy or previous reaction to drug. The Modified Schumock and Thornton scale determines the preventability of an ADR and classifies them as "definitely preventable", "probably preventable" and "not preventable".

RESULTS

Out of 102 patients 68 (66.6%) were male and 34 (33.3%) were female. Follow up was possible for 12 months and the authors recorded 143 ADR's with atypical antipsychotics. It was found that Olanzapine and Risperidone were the antipsychotics that were prescribed more often than Aripiprazole, Amisulpride, Quetiapine and Clozapine, which is shown in Table 1.

Twenty-eight different ADR's were noted and the majority was seen with Olanzapine and Risperidone. These include weight gain, sedation, tremors, drug induced parkinsonism and disturbances in menstrual cycle, described in Table 2. These accounted for 70.62% of the total adverse events that were recorded. Mild ADR's using Hartwig scale were fatigue, dry mouth, insomnia, weight gain and GI disturbances. Moderate ADR's were tardive dyskinesia, pill rolling movements, drug induced parkinsonism and hyper salivation. Severe reactions included disturbances in lipid profile, delirium, menstrual disturbances and hypertension as depicted in Figure 1.

Reduction in doses were required for Olanzapine and Risperidone due to akathisia and extra pyramidal symptoms. Aripiprazole induced akathisia was observed in one patient which led to change in medication to Quetiapine. Addition of Amisulpride to Clozapine and reduction in

Table 1: Drugs responsible for the adverse drug reactions and the total percentage.

Drugs responsible for adverse drug reactions (*n*=143)	Number (Percentage of all adverse drug reactions)
Olanzapine	61(42.6)
Risperidone	40(27.9)
Amisulpride	28(19.5)
Aripiprazole	3(2.09)
Quetiapine	5(3.49)
Clozapine	6(4.19)

Suspected drugs causing adverse drug reactions and the total percentage (*n*=143)

Table 2: Causality Assessment using Naranjo's Algorithm.

Probable	Suspected Drug	Number of events
Weight Gain	Olanzapine, Risperidone, Aripiprazole, Clozapine	10,12,7,1
Tardive Dyskinesia	Olanzapine, Risperidone	7,5
Dry Mouth	Olanzapine, Quetiapine	4,1
Increase in Lipids	Olanzapine	7
Tremors	Olanzapine, Risperidone, Quetiapine	9,8,1
Sedation	Olanzapine, Risperidone, Aripiprazole	3,5,1
Pin rolling movements	Olanzapine	2
Restless leg syndrome	Olanzapine, Risperidone	5,2
Akathisia	Olanzapine, Aripirazole	3,7
Constipation	Olanzapine, Cloazpine	2,1
Drug Induced Parkinsonism	Risperidone	6
Galactorrhea	Risperidone	1
Hypersalivation	Clozapine	6
Agranulocytosis	Clozapine	1
Myoclonic Jerks	Clozapine	1
Delerium	Clozapine	1
Perioral movements	Quetiapine	1
Menstrual Disturbances	Risperidone	7
Possible		
Itching	Olanzapine	1
Hypertension	Olanzapine	1
Bradykinesia	Olanzapine	1
Increase in serum prolactin	Risperidone	2
Joint pain	Aripirazole	4
Insomnia	Aripirazole	3
Impairment in hearing	Amisulpride, Quetiapine	1,1
Bleopharospasm	Amisulpride	1
Edema	Amisulpride	1

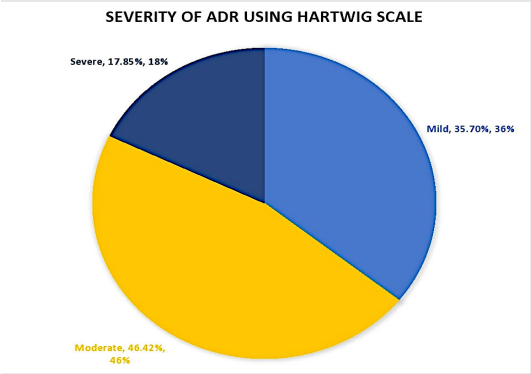

Figure 1: Severity of Adverse drug reactions.

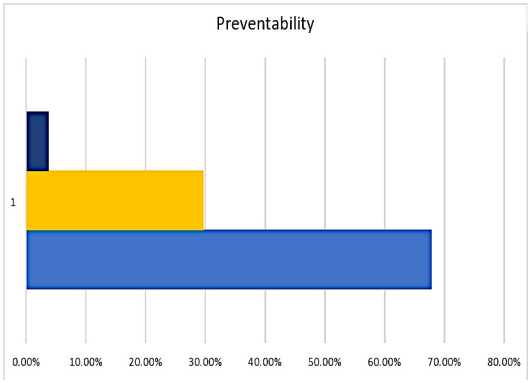

Figure 2: Predictability of Adverse drug reactions.

the dose of Clozapine was needed in one patient due to tachycardia. Of the ADR's, 92% were predictable and 7.4% unpredictable as shown in Figure 2 and 67.8% ADR's were not preventable, 29.6% ADR's were definitely preventable and 3.70% probably preventable as depicted in Figure 3. WHO causality assessment revealed 55.5% ADR's to be certain, 29.6% to be probable and 14.8% to be possible as shown in Table 3.

DISCUSSION

The development of atypical antipsychotics has led to the betterment of the user population in terms of reduction in extra pyramidal symptoms and tardive dyskinesia. However, newer adverse drug reactions are stumbled upon when drugs are used in larger and different populations than studied during the different phases of clinical trials. It is at this juncture, the importance and role of pharmacovigilance comes into play. Systematic reporting of ADR's plays a crucial role in determining a drug's side effect profile. This can be made feasible only by an aggressive drug safety program.[12]

In pharmacovigilance, the most common method used in generating signals of new ADR's is known as spontaneous reporting. This technique is most efficient but the lack of awareness at the level of healthcare professionals and patients leads to underreporting.[13] Active surveillance is another method used in pharmacovigilance which can be achieved by reviewing patient records or interviewing the patients at the time of visit in OPD. In our study, the investigators interviewed the patients during their visit and accessed their medical records in addition to the spontaneous reporting done by doctors and patients. Once these patients were exposed to these questionnaires for ADR' s during follow up visit the rate of spontaneous reporting increased drastically which was also similar

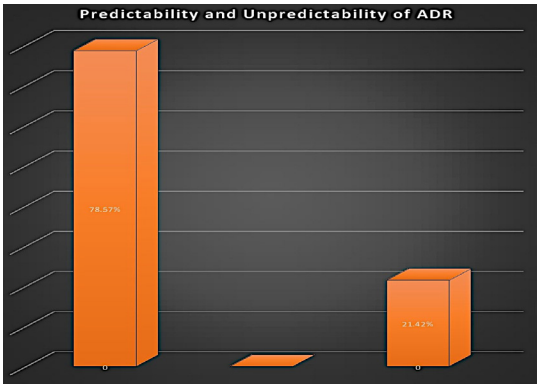

Figure 3: Preventability of Adverse drug reactions.

Table 3: WHO Probability analysis of adverse drug reactions.

Adverse Drug Reaction	WHO Probability analysis
Weight Gain	Certain
Tardive Dyskinesia	Certain
Dry Mouth	Probable
Increase in Lipids	Certain
Tremors	Certain
Sedation	Probable
Pin rolling movements	Certain
Restless leg syndrome	Certain
Akathisia	Certain
Constipation	Possible
Drug Induced Parkinsonism	Certain
Galactorrhea	Probable
Hypersalivation	Certain
Agranulocytosis	Certain
Myoclonic Jerks	Certain
Delirium	Certain
Perioral movements	Certain
Menstrual Disturbances	Probable
Itching	Possible
Hypertension	Possible
Bradykinesia	Possible
Increase in serum prolactin	Probable
Joint pain	Certain
Insomnia	Certain
Impairment in hearing	Certain
Bleopharospasm	Certain
Edema	Certain

to the findings in the study conducted in 2011 by Kiran *et al.*[13] This emphasizes that active surveillance be included in reporting ADR's.

In the present study, we found out that Olanzapine and Risperidone had the maximum number of adverse effects. This is in accordance with the study conducted by Lucca *et al.* in 2014 where adverse drug reactions of atypical antipsychotics were analyzed and results indicated that Risperidone and Olanzapine produced majority of the adverse drug reactions.[5]

Olanzapine is a second generation (atypical) antipsychotic agent and a thienobenzodiazepine derivative which has demonstrated effectiveness against the positive and negative symptoms of schizophrenia.[14] Olanzapine is started at a dose of 5mg/day and is gradually increased to a maximum dose of 20mg/day.[15] The ADR's observed with Olanzapine were weight gain, tremors, tardive dyskinesia and GI disturbances at the dose of 10-15mg/day. Tardive dyskinesia is a defacing adverse effect of Olanzapine. The patient reports of involuntary movements of lips, tongue, jaws and other parts of the body which adds on to the burden of the disease.[16] In our study, seven cases of tardive dyskinesia have been recorded with Olanzapine. One case of akathisia was observed at a dose of 20mg/day which led to the reduction in dose of Olanzapine to 15mg/day. Two cases showed disturbances in lipid profile caused by Olanzapine and this is found to be in correlation with the study conducted in 2004 by the American Diabetes Association.[17] Two cases of pill rolling movements were observed with Olanzapine at a dose of 15mg/day. A Cochrane database systemic review conducted in 2010 revealed Olanzapine to be related to slightly more extra pyramidal symptoms compared to other atypical antipsychotics.[18]

A rare case of hypersensitivity reaction was observed with Olanzapine at a dose of 10mg/day within 5 days of initiating treatment. Antihistamines were given as intervention and the reactions subsided within 7 days and Olanzapine 10mg/day was continued.

This atypical antipsychotic has a profile similar to Clozapine in respect to negative symptoms. In the present study, Risperidone was prescribed 31 times and 40 ADR's was recorded. Six cases of drug induced parkinsonism were observed at a dose of 4mg/day. An anticholinergic prescribed as intervention reduced the symptoms to a great extent.[13] Probably a prescription that involves an anticholinergic like Trihexyphenidyl might bring down the number of EPS among patients taking Risperidone.[19] Increase in serum prolactin and disturbances in menstrual cycle is a major drawback of this drug and this was observed in our study in seven patients. A Cochrane database study conducted in 2011 proved Risperidone to be a culprit in increased serum prolactin compared to other comparators.[20] Prolactin plays an important role in the reproductive cycle of both men and women. In men, abnormality in prolactin level leads to erectile dysfunction, decreased libido and gynaecomastia. Increased prolactin level in women may increase the chances of osteoporosis, breast cancer and cardiovascular complications.[21]

A surprisingly uncommon side effect of Aripiprazole is weight gain. Aripiprazole was introduced as a weight neutral drug. However, two cases of Aripiprazole induced weight gain was reported in the year 2005.[22] In our study also, it was observed that Aripiprazole caused weight gain in seven patients at a dose of 10mg/day. Akathisia at a dose of 10mg/day was observed in two patients. This led to noncompliance in one patient and hence the medication had to be changed to Quetiapine. A study conducted in 2015 revealed that risk of akathisia was higher for Aripiprazole, Asenapine and Lurasidone.[23] Chronic insomnia is a problem in Schizophrenics and two cases of insomnia was reported at a dose of 5mg/day. The addition of benzodiazepine resolved this problem. Eleven cases of sedation were reported in patients taking Aripiprazole 10mg/day. There are very few studies reporting sedation as ADR caused by Aripiprazole. Interestingly, a literature review conducted in 2009 by Greenway *et al.* states sedation as an adverse effect.[24]

Amisulpride has less ADRs compared to other atypical antipsychotics in this study. One case of dystonia of eye lids was reported with a dose of 600mg/day. Reduction in the dose with addition of an anticholinergic drug relieved the patient from the symptoms. Infact, varied kinds of dystonia caused by low dose Amisulpride have been reported by Sevincok *et al.* in 2008.[25]

A Cochrane database systemic review conducted in 2010 reports Quetiapine to have less side effects in terms of EPS and movement disorders compared to Olanzapine and Risperidone.[26] In the present study also, only two cases of tremors were recorded at a dose range of 100-200 mg.

This antipsychotic drug is related to tricyclic compounds such as imipramine and was developed in 1960s. It is used only in schizophrenia cases resistant to other antipsychotic drugs. However, this drug has a dangerous side effect profile. Decrease in absolute neutrophil count is one such effect which was observed in one patient in our study. The patient had failed trials of many antipsychotics and was responding very well to Clozapine. After 2 months of treatment with Clozapine at a dose of 250mg/day there was a decrease in the absolute neutrophil count to 2800. Further decrease could lead to agranulocytosis. However, patient was closely monitored, complete blood count was checked at regular intervals and dose was reduced to 200mg/day. The patient slowly improved over time. Similar case was observed in 1993 by Alvir *et al.* Emphasis has been made on close monitoring of complete blood count even after six months of the therapy.[27]

Tachycardia was observed in one patient on clozapine 500mg/day. Dose was gradually reduced to 250mg/day and Amisulpride at a dose of 250mg/day was added which controlled the symptoms. According to the study Jagadesh *et al.* most adverse drug effects of Clozapine are dose related and can be controlled with titration in dose, one such example being tachycardia.[28]

Myoclonic jerk was seen in a patient after 8 months of treatment with Clozapine at a dose of 600mg/day. Sodium valproate at a dose of 1g/day was started to prevent seizures. A similar case was reported by Osborne *et al.* in 2015 where the patient complained of myoclonic jerks which was followed by tonic clonic seizure. Sodium valproate at a dose of 1g/day prevented a seizure.[29]

Clozapine is a drug with intricate pharmacology. It is an antagonist at D_1, D_2, D_3 and D_4 receptors. It also blocks M_1, M_2, M_3, M_5, Alpha $_1$ and Alpha $_2$ adrenergic receptors, H_1 histamine receptors and 5-HT_2 serotonin receptors. It has agonistic activity at M_4 receptor.[30] Berlan *et al.* in 1992 proposed a theory for hypersalivation. The article stated that agonistic activity of Clozapine at M_4 receptor and α_2 antagonistic activity could be the reason for hypersalivation.[31] In the present study, six cases of hypersalivation were reported with Clozapine at a dose range of 200-600mg/day. The treatment intervention was the addition of muscarinic antagonist and relief in symptoms were observed.

LIMITATIONS OF THE STUDY

A major limitation of this study is the small sample size and that few patients had a change in medication due to adverse drug reactions towards the end of study period. Hence, these patients could not be followed up for 12 months to record any new adverse effects with the new treatment, if any.

CONCLUSION

This study contributes to and adds to established information on the prevalence of adverse drug reactions. Need of the hour is active surveillance of adverse drug reaction with an efficient pharmacovigilance Centre in every established hospital.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

FGA: First generation antipsychotics; **SGA:** Second Generation Antipsychotics; **EPS:** Extra pyramidal symptoms; **WHO**: World Health Organization; **ADR:** Adverse Drug Reaction.

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