Original Article

Analysis of Adverse Drug Reactions of Atypical Antipsychotic Drugs in Psychiatry OPD

Kiran G. Piparva, J. G. Buch[1], Kalpesh V. Chandrani[2]

ABSTRACT

Background: Novel atypical antipsychotics are superior to conventional antipsychotics as they significantly reduce both positive and negative symptoms of schizophrenia and have lower risk of extrapyramidal symptoms (EPS). However, these drugs have separate set of adverse drug reactions (ADRs). Therefore, this study was carried out to assess these ADRs, which can have impact on long-term compliance and achieving successful treatment. **Materials and Methods:** A prospective study of analysis of ADR of atypical antipsychotic drugs was carried out in the psychiatry outpatient department. Patients of psychotic disorder (any age, either sex), who were prescribed atypical antipsychotic drugs, were included. Those who were prescribed conventional antipsychotics or combinations of antipsychotics were excluded from the study. Apart from spontaneously reported ADRs, a questionnaire related to the likely ADR was used and patients' responses were recorded in the case record form. **Results:** Totally 93 ADRs were recorded from 84 prescriptions. Majority of the ADRs (82 out of 93) were seen with risperidone and olanzepine, as they were the commonly prescribed drugs. Weight gain, dizziness, sleep disturbance and appetite disturbance accounted for nearly 78% of the total events. With risperidone (at 4–6 mg/day) and olanzepine (at 10–15 mg/day), gastrointestinal and sleep disturbance were observed in the initial (within 7 days to 2–3 months after treatment) course of treatment, while EPS, fatigue, seizure, increased frequency of micturition and dizziness were observed after long-term (3–9 months) use. **Conclusion:** The present study adds to the existing information on the prevalence of adverse effects of atypical antipsychotic drugs. Role of active surveillance in post-marketing phase is also emphasized.

Key words: *Adverse drug reaction, atypical antipsychotics, extrapyramidal symptoms, Naranjo's criteria, pharmacovigilance, weight gain*

INTRODUCTION

Antipsychotics are the most widely used drugs in psychiatric practice. Conventional or "typical" antipsychotics were prescribed with associated limitations of poor efficacy against negative symptoms and unwanted extrapyramidal symptoms (EPS), particularly at higher doses.[1-3] Over the last few years, atypical antipsychotics have been increasingly used in the pharmacological treatment of schizophrenia and other related psychotic disorders. These agents improve quality of life, have better medication compliance, and also decrease suicidal tendencies and depression in these patients.[4-8] Atypical antipsychotics differ from conventional agents in that they have lower risk of EPS and significantly reduce both positive and negative symptoms of schizophrenia. Although the atypical antipsychotics have lower risk of extrapyramidal side effects, these agents present their own spectrum

Access this article online	
Website: www.ijpm.info	Quick Response Code
DOI: 10.4103/0253-7176.92067	

Departments of Pharmacology and [2]Psychiatry, P.D.U. Medical College, Rajkot, [1]Department of Pharmacology, GMERS Medical College, Sola-Ahmedabad, Gujarat, India

Address for correspondence: Dr. Kiran G. Piparva
Departments of Pharmacology, 12/15 Manhar Plot, "Panchjanya", Rajkot – 360 001, Gujarat, India. E-mail: kiranpiparva@yahoo.co.in

of adverse effects including hypotension, seizures, weight gain, increased risk of diabetes mellitus and hyperlipidemia. Therefore, there is growing concern among the healthcare personnel to assess the adverse drug reactions (ADRs) of atypical antipsychotics, which have an impact on long-term compliance and achieving successful treatment.[9-11] In India, pharmacovigilance activities are still in the nascent stage and data of ADRs particularly related to psychotropic drugs need to be strengthened.[12]

MATERIALS AND METHODS

A longitudinal prospective observational study of ADRs of atypical antipsychotic drugs was carried out in the Psychiatry Department of P.D.U. Medical College, Rajkot. Permission from the Institutional Ethics Committee was obtained. All newly diagnosed patients (or known cases who had not received any treatment in the last 1 month) of psychotic disorder of any age and either sex (excluding pregnant women) attending psychiatry outpatient department, who were prescribed atypical antipsychotic drugs, were included in the study. Prescriptions containing combinations of typical and atypical antipsychotics were excluded from the study. Consent was obtained from the patients or their guardians. Patients with other concurrent disease or treatments were allowed to involve in the study. ADRs noticed by the consultant, spontaneously reported by patients or their guardian were noted. In addition, a questionnaire was used asking the patients specific questions related to the likely ADRs and patients' responses were recorded in the case record form. Details of adverse event, suspected drug, concomitant medications, management of ADR as well as any laboratory investigation done were recorded in the format of National Pharmacovigilace program of India. Causality of adverse events was assessed by Naranjo's algorithm.[13] Severity of ADR was assessed by Hartwig's criteria. [14]

RESULTS

A total of 100 patients were enrolled in the study, out of which 26 patients who did not return for at least one follow-up were excluded. Of the remaining 74 patients, 52 (70.27%) were males while 22 (29.72%) were females. In two cases, treatment was changed due to non-availability of the drug from hospital supply, while in eight patients, change in treatment was required due to appearance of ADR. These 10 patients were prescribed another antipsychotic drug, and hence ADRs had been analyzed out of 84 treatment schedules. Follow-up was possible for 1–3 months in 41 instances, while 43 cases were observed for 3–18 months. We encountered a total of 93 ADRs.

Risperidone (38) and olanzepine (34) were the most frequently prescribed atypical antipsychotic drugs, while aripiprazole, clozapine, quitiapine were less commonly used. Expectedly, majority of the adverse events (82 out of 93) were seen with risperidone and olanzepine [Table 1].

Eighteen different kinds of ADRs were noted [Table 2]. Out of total 93 adverse events, weight gain, dizziness, sleep disturbance and appetite disturbance accounted for nearly 78% of the events. There were no fatal adverse events; however, one instance of seizure was reported with olanzepine, necessitating hospitalization. Mild to moderate ADRs included constipation, nausea, vomiting, insomnia, mouth ulcer, somnolence, hypersalivation and EPS, and were treated by dose adjustment and/or relevant medications to treat the symptoms. Discontinuation of olanzepine was required due to weight gain (4 cases), perioral tremor (1 case) and seizure (1 case); while risperidone had to be discontinued (2 cases) due to sleep disturbance and EPS.

DISCUSSION

Atypical antipsychotics are now considered as first-line agents based on treatment efficacy, better tolerability and reduced risk of EPS. A knowledge, practice and attitude based study conducted in Norway found that ADRs can be prevented by collecting reliable information about their frequencies and possible risk factors.[15] Spontaneous reporting is the most common method used in pharmacovigilance and is the best one to generate signals on new or rare ADRs. Under reporting is a major drawback of this system due to lack of awareness both at the level of healthcare professionals and patients.

Present study for assessment of ADR of atypical antipsychotics was based on active surveillance through questionnaire in addition to the ADR spontaneously reported by patients or consultants. We found that spontaneous reporting by the patients was poor during initial visits and was restricted to those

Table 1: Number of times atypical antipsychotics were prescribed and adverse events associated with it

Atypical antipsychotics	No. of times the drugs have been prescribed *n*=84	No. of adverse events *n*=93	Incidence of ADE per 100 prescriptions
Risperidone*	38 (45.24)	34 (36.55)	87.47
Olanzepine*	34 (40.48)	44 (47.13)	129.41
Clozapine	06 (7.14)	10 (10.75)	166.67
Quitiapine	05 (5.95)	05 (5.37)	100.00
Aeripiprazole	01 (1.19)	–	0.00

*χ^2 – Statistically not significant (λ value – 1.29, $P>0.05$);
ADE – Adverse drug events; Figures in parenthesis are in percentage

Table 2: Causality of ADR by Naranjo's scale

Category of ADR*	Instances of event *n*=93 (%)	Adverse drug events	Offending drug(s)
Definite (01)	01 (1.07)	Seizure	Olanzepine
Probable (85)	14 (15.53)	Weight gain	Olanzepine (9), risperidone (5)
	10 (10.75)	Increased appetite	Olanzepine (6), risperidone (2), clozapine (2)
	09 (9.67)	Dizziness	Olanzepine (3), risperidone (3), clozapine (2), quitiapine (1)
	09 (9.67)	Decreased appetite	Risperidone (7), quitiapine(2)
	09 (9.67)	Insomnia	Olanzepine (5), risperidone (2), clozapine (1), quitiapine (1)
	08 (8.60)	Extrapyramidal reaction	Olanzepine (4), risperidone (4)
	08 (8.60)	Somnolence	Olanzepine (6), risperidone (2)
	04 (4.30)	Fatigue	Risperidone (3), clozapine (1)
	03 (3.22)	Increased frequency of micturition	Olanzepine (2), risperidone (1)
	03 (3.22)	Vomiting and diarrhea	Olanzepine (3)
	03 (3.22)	Headache	Clozapine (2), quitiapine (1)
	02 (2.15)	Hypersalivation	Risperidone (1), clozapine (1)
	01 (1.07)	Seizure	Risperidone
	01 (1.07)	Constipation	Clozapine
	01 (1.07)	Perioral tremor	Olanzepine
Possible (07)	02 (2.15)	Fatigue	Olanzepine (2)
	01 (1.07)	Palpitation	Olanzepine
	01 (1.07)	Constipation	Olanzepine
	01 (1.07)	Headache	Risperidone
	01 (1.07)	Mouth ulcer	Risperidone
	01 (1.07)	Leg muscle cramp	Risperidone
Total	93		

*Causality assessment as per Naranjo's scale; ADR – Adverse drug reaction

ADRs that were troublesome. It was observed that spontaneous reporting rate increased after exposure to the questionnaire. A Bulgarian study reported that the ADR frequency of individual psychotropic drugs studied was less than 1%,[16] whereas we recorded 93 ADRs in 84 prescriptions. This suggests that active surveillance is very important in reporting of ADR.

Ordinarily, in spontaneous reporting, adverse effects, status of the patient, disease and the drug(s) are recorded at that particular time only. In this study, we have tried to relate the ADR not only with the dose but also with the duration of treatment with that particular drug. Certain ADRs require comparison with previous status in the same patient (e.g., weight gain is a common adverse effect associated with atypical antipsychotics).

Weight gain

Weight gain is considered clinically significant if it exceeds 7% of the initial weight after 10 weeks.[1,2,17] We observed weight gain with olanzepine as well as risperidone, which accounted for 15.53% of total ADRs. Difference of occurrence of weight gain by risperidone and olanzepine was statically insignificant. Meyer reported that weight gain in older patients (>60 years) treated with atypical antipsychotics is lower than that seen in younger adults.[9] In our study, mean age for weight gain (14 cases) was 38 years. Magnitude of weight gain and its time course varies among atypical antipsychotics. Four out of nine events of weight gain with olanzepine were observed on long-term (6–9 months) use, while in five cases it occurred on short-term use. These findings are similar to those of a previous study where clozapine and olanzepine are reported to be associated with the weight gain on short- as well as and long-term use.[9] Weight gain can be a disincentive to comply with treatment and complicates co-morbid medical conditions such as obesity and heart diseases.

Sleep disturbance(s)

US product labeling information suggests that somnolence is a common ADR with atypical antipsychotics. Incidence of somnolence varies from 5 to 39% among various atypical antipsychotics (from risperidone to aeripiprazole). Olanzepine causes both somnolence as well insomnia.[2,18] Incidence of insomnia was 9.60% and that of somnolence was 8.60% in our study. Somnolence was more frequent in patients with olanzepine than with risperidone.

Anticholinergic side effects

Anticholinergic side effects like dizziness, constipation, palpitation and hypersalivation (paradoxical response with clozapine) accounted for 15.03% of the total ADRs. Incidence of these side effects was least with risperidone (3 in 38 cases), more with olanzepine (8 in 34 cases), while it was maximum with clozapine (4 in 6 cases). Clozapine and olanzepine show higher affinity for the muscarinic receptors.[19,20]

Risperidone

With risperidone, gastrointestinal sleep disturbance were obversed in the initial (within 7 days to 2–3 months after treatment) course of treatment, while EPS, fatigue, seizure and dizziness were observed after long-term (3–9 months) use. All ADRs with risperidon were observed at therapeutic dose (4 mg/day) except EPS, seizure and hypersalivation that occurred at the dose of 6 mg/day. EPS were managed by dose reduction and adding central anticholinergic. Clinical trial data suggest the risk of EPS with risperidone is dose related (>10 mg/day), and at this dose, it causes an incidence of EPS comparable to haloperidol.[21] Risperidone alone was used on 25 occasions and ADR occurred in 11 cases, whereas if risperidone was combined with central anticholinergic, incidence of cholinergic ADR was 4 out of 13. Although it appears from this that co-administration of central anticholinergic results in less frequent ADR our sample size was small to come to any definite conclusion and a controlled study is required.

Olanzepine

Among the different ADRs observed with olanzepine, gastrointestinal and sleep disturbances were more frequently observed in the initial course of treatment (within 7 days to 2–3 months after treatment), while EPS, seizure and increased frequency of micturition were observed on long-term (6 months to 1 year) use of olanzepine. Generally, olanzepine should be initiated with 5 mg/day and the dose is gradually increased up to maximum of 20 mg/day.[22] All the ADRs reported here were found with the dose range of 10–15 mg/day except a single case of perioral tremor, which occurred at a dose of 20 mg/day. Olanzepine and clozapine use has also been linked to disturbances in glucose regulation and triglyceride level.[23]

One case of seizure was observed with olanzepine, requiring hospitalization for 1 week and change in antipsychotic medication.

Clozapine

Adverse events seen with clozapine were gastrointestinal disturbance, hypersalivation, dizziness and fatigue. Since the frequency of use of clozapine was very less, further analysis was not possible.

Study limitations

Indoor patients and those receiving more than one psychotropic drug were excluded from the study. Routine hematological, clinical chemistry or ECG screening of patients or blood sample for sugar, lipid and prolactin estimation was not possible routinely.

CONCLUSION

The present study thus adds to the existing information on prevalence of adverse effects to atypical antipsychotic drugs. Role and of active surveillance in post-marketing phase is emphasized.

REFERENCES

1. Serretti A, De RD, Lorenzi C, Beradi D. New antipsychotics and schizophrenia: A review on efficacy and side effects. Curr Med Chem 2004;11:343-58.
2. Liblin H, Eberhard J, Levander S. Current therapy issues and unmet clinical needs in the treatment of schizophrenia: A review of the new generation antipsychotics. Int Clin Psyhcopharamcol 2005;20:183-98.
3. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: A critical overview. CMAJ 2005;172:1703-11.
4. Keck PE, McElroy SL. Clinical pharmacodynamics and pharmacokinetics of antimanic and mood stabilizing medication. J Clin Psychiatry 2002;63(supp 4):3-11.
5. Shriqui CL. Medicaments antipsychotiques, troubles de la personnalite, conduites d' agitation, conduites suicidaries et addictions. In: Olie JP, Dalery J, Azorin JM (editors.) Antipsychotic drugs: Evoluton ou revolution? Paris Acanhus Publishing, 2001. p.467-87.
6. Bayle FJ, Llorca PM. Actions symptomatiques des antipsyhcotiques atypiques: Anxiete, impulsivite, agitation, aggressivite, obsession-compulsion. In: Olie JP, Dalery J, Azorin JM (editors.)Antipschotic Drugs: Evoluton or revolution? Paris Acanhe, Publishing: 2001. p. 489-54.
7. Zanarini MC, Frankenburg FR. Olanzepine treatment of female borderline personality disorder patients: A double blind, placebo-controlled pilot study. J Clin Psychiatry 2001;62:849-54.
8. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, *et al*. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158:131-4.
9. Meyer JM. Effects of atypical antipsychotics on weight and serum level lipid levels. J Clin Psychiatry 2001;62 (suppl 27):27-34.
10. Haupt DW, Newcomer JW. Hyperglycemia an antipsychotic medications. J Clin Psychiatry 2001;62(suppl 27):15-26.
11. Sussman N. Review of atypical antipsychotic and weight gain. J Clin Psychiatry 2001;62(suppl 23):5-12.
12. Sengupta G, Bhowmick S, Hazra A, Datta A, Rahaman M. Adverse drug reaction monitoring in psychiatry out-patient department of an Indian teaching hospital. Indian J Pharmacol 2011:43:36-9.
13. Naranjo C, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
14. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
15. Castberg I, Reimers A, Sandvik P, Amo TO, Spiqset O. Adverse drug reactions of antidepressant and antipsychotics. Experience, knowledge and attitudes among Norwegian psychiatrists. Nord J Psychiatry 2006;60:227-33.
16. Dimitorva Z, Doma A, Petkova V, Getov I, Verkkunen E. Psychotropic drugs in Bulgaria-frequency and risk of adverse drug reactions. Boll Chim Farm 2002;141:75-9.
17. Csernansky JG, Schuchart EK. Relapse and rehospitalization rates in patients with schizophrenia: Effects of second

generation antipsychotics. CNS Drugs 2002;16:473-84.
18. Stanniland C, Taylor D. Tolerability of atypical antipsychotics. Drug Saf 2000;22:195-214.
19. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for Schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry 2005;10:79-104.
20. Alphs LD, Anand R. Clozapine: The commitment to patient safety. J Clin Psychiatry 1999;60(suppl 12):39-42.
21. Owens DG. Extrapyramidal side effects and tolerability of risperidone: A review. J Clin Psychiatry 1994;55 (suppl 2):29-35.
22. Leo RJ, Regno PD. Atypical antipsyhcotic use in the treatment o psychosis in primary care: Primary care companion. J Clin Psychiatry 2000;61:194-204.
23. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004;65:267-72.

How to cite this article: Piparva KG, Buch JG, Chandrani KV. Analysis of adverse drug reactions of atypical antipsychotic drugs in psychiatry OPD. Indian J Psychol Med 2011;33:153-7.

Source of Support: Nil, **Conflict of Interest:** None.