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Study of adverse drug reactions of atypical antipsychotic drugs in the department of psychiatry in a tertiary care hospital of Assam

Abstract

Objective: To monitor the adverse drug reactions (ADRs) of atypical antipsychotic drugs in the outpatient department (OPD) of psychiatry in Silchar Medical College and Hospital (SMCH) of Assam, and also to find out the causality and severity of ADRs, related to the antipsychotic drugs. **Methodology:** It was a prospective observational study carried in OPD of psychiatry. Permission from the institutional ethical committee (SMCH) was obtained. Patients with any psychotic disorder above 18 years (excluding pregnant women) of either sex who were prescribed only one atypical antipsychotic were included. Prescription containing conventional antipsychotics was excluded. ADRs reported spontaneously by the patients and also responses obtained in a questionnaire related to the likely ADRs from the patients was recorded in the case record form. **Results:** Total 78 patients out of whom 48 males and 30 females were included in this study. Of these, 71 patients complained of different types of problems after taking the medicines. Incidence of ADRs was higher in male (46 patients [64.78%]) in comparison to female (25 patients [35.21%]). Total 31 different types of ADRs were detected with the use of these antipsychotics. Weight gain was the most common ADR observed in 38 patients (53.52%). Out of four atypical antipsychotic drugs which have been encountered during our study causing ADRs, olanzapine was commonest followed by risperidone and amisulpride. Causality assessment using Naranjo's scale revealed that 85 (51.20%) ADRs were found to be "probable" and 81 (48.79%) were found as "possible" ADRs. According to Hartwig's severity assessment scale majority of ADRs were assessed as mild (108 [65.06%]) and 58 (34.93%) ADRs were assessed as moderate. **Conclusion:** Study showed weight gain was the commonest ADR with atypical antipsychotic drugs. The commonest drug causing ADRs was olanzapine. Majority of ADRs were assessed as probable as per Naranjo's scale and mild according to Hartwig's severity assessment scale.

Keywords: Naranjo's Algorithm. Weight Gain. Olanzapine.

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Introduction

A noxious and unintended response that occurs at drug doses that is usually used in man for treatment, prophylaxis, or diagnosis of a disease or for alteration of physiological function is called an adverse drug reaction (ADR).[1] ADRs are common medication associated adverse events encountered in healthcare facilities all over the world.[2] Adverse events are any unpleasant medical occurrence associated with the use of a drug in humans whether or not considered drug related.[3] Other types of medication associated adverse events include therapeutic failures and adverse drug withdrawal events.[2] Unexpected adverse reactions are those that are not consistent with applicable product information or characteristics of drug.[3] A serious adverse event or reaction is any unpleasant medical occurrence at any dose resulting in the death of the patient or one that is life threatening, demands hospitalisation, or the prolongation of existing hospitalisation and which results in persistent or significant disabilities or incapacities.[4]

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects, or any other medication related problems is defined as pharmacovigilance. Pharmavigilantes are the professionals engaged in pharmacovigilance, which is an integral part of drug therapy and it is slowly gaining importance in our country as more numbers of ADR monitoring centres are developing under the Pharmacovigilance Programme of India (PvPI).[2,5] About five per cent hospitalisations all over the world are due to ADRs, which present sometimes with fatal symptoms leading to death.[6]

The second generation or "atypical" antipsychotic medications are the most widely used antipsychotic drugs in psychiatric practice because the first generation or conventional or "typical" antipsychotics are associated with

poor efficacy against negative symptoms and are associated with unwanted extrapyramidal signs and symptoms (EPS). Particularly at higher doses these typical antipsychotics commonly show bizarre body movements like Parkinsonism, rigidity, and tremors.[7-9] Currently available atypical antipsychotics are clozapine, olanzapine, risperidone, quetiapine, amisulpride, aripiprazole, zotepine, ziprasidone, asenapine, sertindole, paliperidone. These agents are used in various types of psychiatric manifestations including schizophrenia and they have shown to improve quality of life, have better medication compliance, decrease suicidal tendencies, and depression in these patients.[10-13] In cases of schizophrenia these agents have shown remarkably lower incidence of EPS and significantly reduce both positive and negative symptoms of schizophrenia. In spite of showing decreased incidence of EPS in schizophrenic patients, these atypical antipsychotic agents vary in their formulations, efficacy, tolerability, biochemistry, receptor binding site, and spectrum of ADRs like weight gain, tremor, insomnia, and gastrointestinal (GI) upset.[14-16]

Therefore, for achieving a successful treatment in patients with different psychiatric manifestations healthcare professionals have to detect and assess ADRs of atypical antipsychotic drugs and report, if any to PvPI which after analysing shall forward the data to Uppsala ADR monitoring in Sweden for signal generation. ADR reports from psychiatric units are very less.[17] To protect the population on antipsychotic medications from avoidable harm, assessment of ADRs in psychiatric department can play a vital role by detecting ADRs and alerting the physicians to the possibility and circumstances of such events.

There is a definite lack of Indian studies on pharmacovigilance activities in mental health sector. Hence, the present study was conducted to evaluate the surveillance of ADRs of atypical antipsychotic drugs in the department of psychiatry in a tertiary care hospital of Assam.

Objectives

1) To monitor ADRs of atypical antipsychotic drugs in the outpatient department (OPD) of psychiatry in Silchar Medical College and Hospital (SMCH) of Assam.
2) To find out the causality and severity of ADRs related to the antipsychotic drugs.

Methodology

This is a prospective observational study in the OPD of psychiatry in SMCH for a period of six months from June 2015 to November 2015. Permission from the institutional ethical committee (SMCH) was taken. Newly diagnosed patients and patients who had not taken any antipsychotic medication for last one month and patients above 18 years with any psychotic disorder irrespective of sex (pregnant women were excluded) who were prescribed single atypical antipsychotic drug were included. Consent for the study was taken from the patients or their relatives. Prescriptions containing conventional or typical antipsychotics and combination of antipsychotics were excluded. Patients were examined when they came for first scheduled revisit or after one month whichever was earlier. Contact numbers were obtained for future communication from every patient. ADRs noticed by psychiatrist or reported spontaneously by the patients were recorded. Responses obtained in a questionnaire related to the probable ADRs from the patients were also noted in a record form. Adverse reactions' details, suspected drug, concomitant medications (if any), management of ADR as well as any associated laboratory investigation were noted in the format of PvPI. Naranjo's algorithm was used to assess the causality of ADRs.[18] Severity of ADR was assessed by Hartwig's criteria.[19]

Results

Total 78 patients enrolled in our study. Out of which, seven patients who did not show any signs and symptoms of ADRs even after three months of monitoring period were excluded from the study. Of the remaining 71 patients, 46 (64.78%) were male and 25 (35.21%) were female, and prescribed atypical antipsychotic medications were olanzapine, risperidone, amisulpride, and quetiapine. Two patients with violent behaviour were hospitalised. It was later found out and confirmed that they had those problems due to the nonadherence with the treatment schedule prescribed by the psychiatrists and not because of any medication related event. Same treatment was restarted for both the violent patients and discharged after four days with improvement. Every effort was done to follow up the patients in monthly schedule. Follow up was done maximum up to four months and was successfully completed to each and every patient. Thirty one different kinds of ADRs were noted and a total of 166 ADRs were encountered. Olanzapine (76.05% [54 patients]) and risperidone (11.26% [eight patients]) were the most repeatedly prescribed atypical antipsychotic drugs. Amisulpride (9.85% [seven patients]) and quetiapine (2.81% [two patients]) were less commonly used. Olanzapine and risperidone comprised a total of 148 (89.14%) ADRs compared to 18 (10.83%) ADRs combining with amisulpride and quetiapine (Table 1).

Out of all of ADRs, weight gain, GI upset, insomnia, sedation, aggressive behaviour, and anxiety accounted for nearly 64% of the events (Table 2).

Mild to moderate ADRs included headache, tremor, concentration difficulty, fatigue, anaemia, dizziness, constipation, restlessness, EPS, asthenia, and were treated by changing the dose and/or relevant medications to treat the symptoms. Discontinuation of medication was required for olanzapine due to weight gain in three patients, and for risperidone due to EPS in two patients. Causality assessment

Table 1: Number of ADRs according to the prescribed atypical antipsychotic drug

Atypical antipsychotic drug	Number of times prescribed (N=71)	Number of ADRs (N=166)	Incidence of ADRs (%)
Olanzapine	54	120	72.28
Risperidone	8	28	16.86
Amisulpride	7	11	6.62
Quetiapine	2	7	4.21

ADR: Adverse drug reaction

Table 2: Spectrum of suspected ADRs noted among 71 patients

Type of ADRs	Number (%) of all ADRs
Weight gain	38 (53.52)
Gastrointestinal (GI) upset	22 (30.98)
Insomnia	19 (26.76)
Sedation	11 (15.49)
Aggressive behaviour	8 (11.26)
Anxiety	8 (11.26)
Tremor	7 (9.85)
Headache	6 (8.45)
Restlessness	5 (7.04)
Anorexia	5 (7.04)
Fatigue	3 (4.22)
Concentration difficulty	3 (4.22)
Extrapyramidal signs and symptoms (EPS)	3 (4.22)
Asthenia	3 (4.22)
Increased appetite	3 (4.22)
Anaemia	2 (2.81)
Somnolence	2 (2.81)
Burning sensation on palm	2 (2.81)
Constipation	2 (2.81)
Dizziness	2 (2.81)
Dry mouth	2 (2.81)
Oedema	1 (1.40)
Abdominal pain	1 (1.40)
Sexual dysfunction	1 (1.40)
Amenorrhoea	1 (1.40)
Myalgia	1 (1.40)
Leg muscle cramp	1 (1.40)
Burning sensation on sole	1 (1.40)
Confusion	1 (1.40)
Hypersalivation	1 (1.40)
Blurred vision	1 (1.40)

ADR: Adverse drug reaction

using Naranjo's scale revealed that 85 (51.20%) events were found to be "probable" and 81 (48.79%) were found to be "possible" ADRs (Table 3). As per Hertwig's adverse drug severity scale 108 events were assessed as mild followed by 58 events that were assessed as moderate.

Discussion

Atypical antipsychotics are considered as the first-line agents for the treatment of specific psychotic disorders. Psychiatrists have been preferring these drugs because of their better treatment efficacy, better tolerability, and reduced risk of EPS. In spite of efficacy, tolerability, and reduced risk of EPS there are several types of ADRs which can occur because of these antipsychotic agents. So, the prevention of ADRs can be done by collecting reliable information about their frequencies and possibilities of their risk factors.[20] The major drawback of pharmacovigilance system is under reporting. It is due to the lack of awareness at both the level of healthcare professionals and patients. The most common method used in pharmacovigilance is the spontaneous reporting and it is the best method to generate signals on new and sometimes rare ADRs of established drugs.

Present study was undertaken for assessment of ADRs of atypical antipsychotic drugs and it was based on active surveillance through questionnaire in addition to the ADRs spontaneously reported by patients or detected by consultants. In the study we found that during initial visits of the patients, the spontaneous reporting of ADR was very less. They were restricted to those ADRs that were very troublesome and uncomfortable to them. It may also be due to the initial or early relief of psychotic signs and symptoms encountered by the patients. We also observed that after giving an exposure to specific questionnaire related to probable ADRs the spontaneous reporting rate increased. We recorded total 166 ADRs in 71 prescriptions and we can say that active surveillance is very effective in reporting of ADRs.

In this study, we tried to make a relationship between the ADR with the dose and duration of treatment with the particular drug. Few ADRs required comparison with previous status and the present status in the same patient. With olanzapine we encountered different kinds of ADRs where GI upset, sleep disturbances (insomnia), sedation, and aggressive behaviour were more frequently observed in the initial course of treatment (within two to three months after treatment), while weight gain, EPS, tremor, headache, anxiety were observed on long term (more than three months) use of olanzapine.

Olanzapine is initially started with 5 mg/day and the dose is gradually increased up to maximum of 20 mg/day. All the ADRs encountered were at the dose range of 10–15 mg/day. Weight gain accounted with olanzapine, risperidone, as well as with amisulpride was about 23% of total ADRs. Weight gain is considered clinically significant if it exceeds seven per cent of the initial weight after ten weeks.[7,8,21] In this study, the mean age for the weight gain was 36 years. We observed that 14 out of 31 weight gainers with olanzapine occurred within a short term (three to four months) and 17 cases on long term (more than four months) use. With risperidone, four out of six weight gains were seen in short duration and two on long duration. The weight gain with amisulpride were seen only on long term use.

With risperidone, sedation, anxiety, GI upset, and tremor were observed in the initial (two to three months) course of treatment, while weight gain, EPS, anorexia, fatigue, leg muscle cramp were observed after long-term (more than four months) use. Risperidone was given at a dose of 2-6 mg per day and all ADRs with risperidone were observed at the same dose. Most common ADR we encountered with risperidone was weight gain (75%) followed by sedation (62.5%). Weight gain with risperidone was alarmingly high among all of the antipsychotic drugs. EPS were seen in two out of eight patients with risperidone which was about 25% and were managed by reducing the dose and by adding a central anticholinergic drug.

Table 3: Causality assessment of ADRs using Naranjo's algorithm categorised as probable (n=85) or possible (n=81) offending agents

ADRs	Total number of ADRs (n=166) (%)	Offending drug (s) with	
		Probable events	Possible events
Weight gain	38 (22.89)	38 (O [31], R [6], A [1])	0
Gastrointestinal (GI) upset	22 (13.25)	0	22 (O [17], R [2], A [3])
Insomnia	19 (11.44)	4 (O [3], A [1])	15 (O [12], R [1], A [2])
Sedation	11 (6.62)	11 (O [6], R [5])	0
Aggressive behaviour	8 (4.81)	8 (O [8])	0
Anxiety	8 (4.81)	0	8 (O [4], R [2], A [2])
Tremor	7 (4.21)	3 (O [3])	4 (O [2], R [2])
Headache	6 (3.61)	1 (Q [1])	5 (O [4], R [1])
Restlessness	5 (3.01)	2 (R [1], A [1])	3 (O [2], R [1])
Anorexia	5 (3.01)	0	5 (O [4], R [1])
Fatigue	3 (1.80)	2 (O [2])	1 (R [1])
Concentration difficulty	3 (1.80)	2 (O [1], R [1])	1 (O [1])
Extrapyramidal signs and symptoms (EPS)	3 (1.80)	1 (O [1])	2 (R [2])
Asthenia	3 (1.80)	2 (O [2])	1 (O [1])
Increased appetite	3 (1.80)	0	3 (O [2], R [1])
Anaemia	2 (1.20)	0	2 (O [2])
Somnolence	2 (1.20)	2 (O [1], Q [1])	0
Burning sensation on palm	2 (1.20)	0	2 (O [2])
Constipation	2 (1.20)	0	2 (O [2])
Dizziness	2 (1.20)	2 (O [1], Q [1])	0
Dry mouth	2 (1.20)	0	2 (O [1], Q [1])
Oedema	1 (0.60)	0	1 (O [1])
Abdominal pain	1 (0.60)	1 (O [1])	0
Sexual dysfunction	1 (0.60)	0	1 (O [1])
Amenorrhoea	1 (0.60)	1 (O [1])	0
Myalgia	1 (0.60)	1 (O [1])	0
Leg muscle cramp	1 (0.60)	0	1 (R [1])
Burning sensation on sole	1 (0.60)	1 (Q [1])	0
Confusion	1 (0.60)	1 (Q [1])	0
Hypersalivation	1 (0.60)	1 (A [1])	0
Blurred vision	1 (0.60)	1 (Q [1])	0

ADR: Adverse drug reaction, O: Olanzapine, R: Risperidone, Q: Quetiapine, A: Amisulpride

We have seen that uses of amisulpride were very common in patients with schizophrenia in psychiatric practice. It may be due to better tolerability and decreased incidence of intolerable side effects in psychiatric patients. It is used 200-400 mg per day depending on the severity of the psychiatric illness. We recorded seven patients with amisulpride and noticed non-serious adverse events like GI upset, insomnia, and anxiety commonly. Hypersalivation which is an anticholinergic side effect seen in a patient who was on amisulpride only. All ADRs with amisulpride were seen after two to three months suggesting that initial period with this drug is relatively safe.

We encountered only two patients with quetiapine during our monitoring period in OPD and both the patients tolerated the drug very well. ADRs noted were headache, somnolence, dry mouth, burning sensation on sole, dizziness, confusion, and blurred vision. It was prescribed as 50 mg per day dose. These ADRs had not affected the day to day life of the patients and were seen after the third month of starting treatment.

Whatever patients we have encountered with psychotic illness in OPD, maximum patients were from low socioeconomic status. Only a few were from well to do families who can give better treatment and care to the patients, to motivate continuous adherence with the antipsychotic drugs, and to follow up the patient regularly with proper investigation suggested by the psychiatrist. Low level of education is also a major factor which plays an important role in the outcome of these patients. Improper hygiene, lower nutritional status, and social discriminating factor along with poor communication may add to the increase amount of ADRs seen with these patients.

Limitations

We did not include indoor patients and patients who were receiving more than one antipsychotic medications. As our study had outpatient based design, so the routine examination of blood, urine, electrolyte level, liver function test, kidney function test, or echocardiography (ECG) screening of patients or blood sugar level, lipid and prolactin estimation were difficult to obtain. A recent study from this part of the globe has shown elevated prolactin in olanzapine users.[22]

Conclusion

The antipsychotic medications used from early times have been associated with many ADRs. Atypical antipsychotics are used in different types of psychotic disorders including schizophrenia, bipolar disorder, and non-specific psychosis. With discovery of these atypical antipsychotics, ADRs have been reduced to a great extent. This study shows that olanzapine is associated with maximum number of ADRs followed by risperidone. These documented ADR reports and the results may be helpful for the future researchers regarding the ADRs of these second generation antipsychotic drugs. With this exercise awareness on pharmacovigilance is inculcated on the healthcare professionals and the patients are also sensitised.

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