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Identification and management of adverse effects of antipsychotics in a tertiary care teaching hospital

Jisha Myalil Lucca[1], Ramesh Madhan[1], Gurumurthy Parthasarathi[1], Dushad Ram[2]

[1]Department of Pharmacy Practice, JSS University, Mysore, India

[2]Department of Psychiatry, JSS Hospital, Mysore, India

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Corresponding author:
Mrs. Jisha Myalil Lucca,
E-mail: jishajojo06@yahoo.co.in

ABSTRACT

Objective: Antipsychotics have revolutionized psychiatry by allowing significant numbers of patients in long-term hospital settings to be discharged and successfully maintained in the community. However, these medications are also associated with a range of adverse events ranging from mostly annoying to rarely dangerous. This study is carried out to identify the adverse drug reactions (ADRs) to antipsychotics and its management in psychiatric patients.
Methods: Prospective interventional study was conducted in the psychiatric unit of a tertiary care hospital. Patients of any age and either sex prescribed with at least one antipsychotic were included and monitored for ADRs.
Findings: Among the 517 patients receiving antipsychotics, a total of 289 ADRs were identified from 217 patients at an overall incidence rate of 41.97%. Sixty-seven different kinds of ADRs were observed in the study patients. Central and peripheral nervous system was the most commonly affected system organ class (n = 59) and weight gain (n = 30) was the most commonly observed ADR. Olanzapine was most commonly implicated in reported ADRs (n = 92) followed by risperidone (n = 59). Of the 289 ADRs, 80% required interventions including cessation of drug and/or specific/symptomatic/nonpharmacological treatment.
Conclusion: This post marketing surveillance study provides a representative data of the ADR profile of the antipsychotics likely to be encountered in psychiatric patients in an Indian tertiary care hospital.

Keywords: Adverse drug reaction; psychotropic medication; treatment

INTRODUCTION

Antipsychotic agents have revolutionized the treatment of many psychiatric disorders in last six decades.[1] More than 20 of these agents have been introduced in the market, and have substantially improved functioning and quality of life of patients with psychotic disorders.[1] However, these medications are also associated with adverse events ranging from mostly annoying to rarely dangerous and in some instances, result in serious morbidity and mortality.[2] adverse drug reactions (ADRs) were responsible for 0.3% of transfers from a psychiatric hospital to a medical facility and the cause of 10/1000 patient days in psychiatric hospitals.[3,4] According to various studies, most of the ADRs in the psychiatry department is reported with antidepressants and antipsychotics.[5-7] The second-generation antipsychotics, especially clozapine and olanzapine, generally tend to cause more problems relating to metabolic disorders but the older first-generation antipsychotics are more likely to be associated with movement disorders.[8] Identification of these side effects requires careful consideration of other psychiatric and medical disorders that may mimic antipsychotic-related side-effects.[9,10] Effective management of these unwanted effects of antipsychotics has the potential to improve patients compliance, quality of life and possibly the prognosis and ultimate outcome.[7,11] Knowledge of how the prevalence and severity of adverse effects vary for different antipsychotics allows clinicians to reduce the occurrence of these effects. Since the literature reviews

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have shown the lack of studies to identify ADRs and its managements in Indian psychiatric patients, we aim to study the pattern of ADRs to antipsychotics and their management in psychiatric patients.

METHODS

This prospective interventional study was conducted in mental health department of a tertiary care hospital in South India over a period of 2 years (March 2012-February 2014). Patients, who presented with psychiatric illness as diagnosed by International Statistical Classification of Diseases and Related Health Problems, 10th revision and were receiving at least one antipsychotic drug, were included in the study. Psychiatric patients receiving antipsychotics, but treated in other departments and patient who experienced adverse effects due to overdose were excluded from the study. The study protocol was reviewed and approved by Institutional Ethics Committee and the study was commenced after obtaining the approval.

The screening was carried out by a clinical pharmacist, trained in the psychiatric department for interviewing the patients with mental illness. All patients who met the study criteria were enrolled. All the outpatients and inpatients were intensively monitored for the occurrence of ADR and ADRs reported spontaneously also were taken into consideration. World Health Organization (WHO) definition of an ADR was adopted. This study was a nonquantitative report of ADRs, thus does not correlate the incidence or severity of ADRs to the medication dosage. All the identified and confirmed ADRs were brought into the notice of the consultant psychiatrist. Various interventions taken for the management of ADRs were followed and documented and if necessary appropriate suggestions/remedial actions were also provided. Drugs received and ADRs experienced by the study patients were recorded and coded using WHO Anatomical Therapeutic and Chemical classification and WHO-Adverse Reaction Terminologies respectively. The overall prevalence of ADRs was determined by taking the ratio of total number of patients who experienced ADRs to the total number of patients included in the study.

RESULTS

Of the 950 patients reviewed, 517 (54.42%) patients (220 outpatients and 297 inpatients) received at least one antipsychotic medication. A total of 289 ADRs were identified from 217 patients with an overall incidence rate of 41.97%. Average number of ADR per patient in our study was 1.6. The median age of patients with and without ADRs was 34.5 years (range: 13-90 years). Females were slightly more in ADR group (57.21% vs. 42. 25%). Number of medications prescribed was same in both groups (average: 4.6; range: 1-13). Majority of the patients were diagnosed to have had psychosis in both nonADR and ADR groups ([*n* = 89] 29.66%, vs [*n* = 58] 26.72%), respectively. Demographic characteristics of the study population are listed in Table 1.

Of the 298 suspected ADRs identified, nine ADRs could not be evaluated due to the nonavailability of the data. Of the 289 ADRs, 66.43% (*n* = 192) were detected by intensive monitoring, while 33.56% (*n* = 97) were spontaneously reported. Sixty seven different kinds of ADRs were observed in the study patients. Central nervous system (CNS) and peripheral nervous system (*n* = 59) was the most commonly affected system organ class. Weight gain (*n* = 30) was the most commonly observed ADR followed by extrapyramidal side-effects (EPS) (*n* = 20) and menstrual irregularity (*n* = 18). Metabolic disturbances, especially weight gain, were commonly

Table 1: Demographic details of the study patients

Variables	Number (percentage) of patients		
	Patients without ADR (*n*=300)	Patients with ADR (*n*=217)	Total (*n*=517)
Gender			
Male	211 (70.33)	98 (45.16)	309 (59.76)
Female	89 (29.66)	119 (54.85)	208 (40.23)
Age (years)			
≤18	20 (6.66)	11 (5.06)	31 (5.99)
19-29	88 (29.33)	81 (37.32)	169 (32.68)
30-39	87 (29.00)	57 (26.26)	144 (27.85
40-49	56 (18.66)	37 (17.05)	93 (17.98)
50-59	27 (9)	13 (5.99)	40 (7.73)
≥60	22 (7.3)	18 (8.29)	40 (7.73)
Category			
Inpatient	183 (61.00)	114 (52.53)	297 (57.44)
Outpatient	117 (39)	103 (47.46)	220 (42.55)
Number of medications			
≤2	88 (29.33)	65 (29.95)	153 (29.59)
3-4	82 (27.33)	75 (34.56)	157 (30.36)
≥5	130 (43.33)	77 (35.56)	207 (40.03)
Diagnosis			
Psychosis	89 (29.66)	58 (26.72)	147 (28.43)
Bipolar affective disorder	88 (29.33)	54 (24.88)	142 (27.46)
Depression	59 (19.6)	42 (19.35)	101 (19.53)
Schizophrenia	42 (14)	39 (17.97)	81 (15.66)
Others	22 (7.33)	24 (11.05)	46 (8.89)
Comorbidity			
Yes	80 (26.6)	55 (25.34)	135 (26.11)
No	220 (73.3)	162 (74.65)	332 (73.88)

ADR=Adverse drug reaction

associated with the use of olanzapine. There were no fatal adverse events; however, one instance of bradycardia and electrocardiogram (ECG) changes was reported with quetiapine, necessitating intensive care. System organ class affected by ADRs is presented in Table 2. Olanzapine was most commonly implicated in reported ADRs (n = 92) followed by risperidone (n = 59). The antipsychotics most commonly implicated in ADRs are shown in Table 3. Of the 289 ADRs, 80% required interventions, including drug dose reduction (n = 43) and/or specific (n = 27), or symptomatic (n = 43) treatment. In 66 cases, nonpharmacological interventions were used and in 49 cases, the suspected drug was withheld.

DISCUSSION

This is the largest prospective study of management of ADRs to antipsychotics in Indian psychiatric patients. Several studies are published on ADRs of antipsychotics from India.[12-15] Compared with our study, these studies evaluated ADRs in either inpatient or outpatient settings or only to first or second generation antipsychotics and for a short duration of period. None of the studies assessed the strategies for the management of ADRs. The prevalence of ADRs to antipsychotics in our study (42.4%) was much higher when compared to various Indian studies conducted by Sengupta *et al*.[5] (17.27%), Lahon *et al*.[14] (28.82%) and Shah *et al*.[15] (32.8%.) and also a western study conducted by Thomas *et al*. (20.2%).[16] In this study, approximately 80% of the ADRs required interventions for the management. In general, the management of ADRs begins with understanding of potential for ADRs, not only of psychiatric drugs, but also for co-prescribing psychiatric and nonpsychiatric drugs. Management of this side-effect predominantly depends on severity, type of ADRs and body system they affect rather than by specific antipsychotic medication.

It is well-reported that ADRs are slightly more common in females,[17] and the present study showed no discrepancy with this regard. The mean age (36.5 years) of patients presented with ADRs falls within the range observed in Sengupta *et al*. study.[5] Approximately, one-third of the patients were at the age of 19-29 years. One of the reasons could be that onset of the most of the psychiatric disorders such as schizophrenia and psychosis were typically begun at early adult hood. There is no difference between age group and development of ADRs. The study didn't observe any diversity in severity and type of ADRs in different age groups. One of the reasons

Table 2: Organ systems affected due to adverse drug reactions

SOC (WHO-ART SOC code)	Number (percentage) of ADRs (n=289)	Suspected ADRs (number of affected patients)
Central and peripheral nervous system (0410)	59 (20.41)	Giddiness (8), tremors (16), headache (2), dizziness (3), numbness (2), extra-pyramidal side effects (20), slurred speech (5), tingling sensation (3)
Gastrointestinal system disorders (0600)	52 (17.99)	Dry mouth (14), constipation (14), abdominal pain (1), indigestion (2), vomiting (2), abdominal distension (1), epigastric pain (1), gastritis (3), excessive salivation (8), drooling (5), mouth ulcer (1)
Psychiatric disorders (0500)	40 (13.84)	Decreased sleep (3), increased sleep (6), sedation (4), drowsiness (5), decreased libido (3), anxiety (1), dyskinesia (1), disturbance in appetite (13), sexual dysfunction (4)
Metabolic and nutritional disorders (0800)	37 (12.8)	Weight gain (30), weight loss (3), metabolic syndrome (1), increased thirst (3)
Reproductive system disorder (1420)	25 (8.6)	Menstrual irregularity (18), galactorrhea (7)
Cardiovascular disorders (1010)	23 (7.9)	Orthostasis (13), increased blood pressure (5), decreased blood pressure (4), electrocardiogram changes (1)
Application site disorders (1820)	11 (3.8)	Thrombophlebitis (11)
Urinary system disorders (1300)	8 (2.7)	Increased micturation (4), incontinence (3), facial puffiness (1)
Skin and appendages disorders (0100)	7 (2.4)	Pimples (4), diaphoresis (3)
Body as a whole general disorders (1810)	8 (2.7)	Fatigability (5), fever (2), stooped posture (1)
Heart rate and rhythm disorders (1030)	5 (1.7)	Palpitation (1), bradycardia (1), tachycardia (3)
Special sense and other disorders (0433)	4 (1.3)	Taste disturbance (4)
Platelet bleeding and clotting disorders (1230)	3 (1.03)	Thrombocytopenia (3)
Red blood cell disorders (1210)	2 (1.03)	Anemia (2)
Vascular disorders (1040)	2 (0.6)	Peripheral edema (2)
Musculoskeletal disorders (0200)	2 (0.6)	Myalgia (2)
Respiratory system disorders (1100)	1 (0.34)	Epistasis (1)

WHO-ART=World Health Organization-Adverse Reaction Terminologies, SOC=System organ class, ADRs=Adverse drug reactions

Table 3: Drugs commonly implicated in adverse drug reactions with their frequency of use

Antipsychotic medication	Frequency of use	Total number (percentage) of ADRs (*n*=289)
Olanzapine	211	92 (31.83)
Risperidone	241	59 (20.41)
Quetiapine	176	56 (19.37)
Amisulpride	112	36 (12.45)
Haloperidol	168	19 (6.5)
Clozapine	20	15 (5.1)
Flupentixol	8	7 (2.4)
Iloperidone	5	2 (0.6)
Paliperidone	2	1 (0.3)
Aripiprazole	7	1 (0.3)
Asenapine	2	1 (0.3)

ADRs=Adverse drug reactions

could be that psychiatrists possibly consider the special requirements of elderly and pediatric patients and monitor them more intensively, prescribe lower dosages or avoid high-risk drugs and dangerous combinations thus reduces the risks of ADRs in these patients.

The incidence of ADRs in the outpatient (46.81%) is higher than inpatients (38.38%). Majority of the ADRs in the inpatient settings were severe and required treatment, while in outpatients setting majority of the ADRs were mild and self-limiting. CNS and application site disorders were the most commonly affected system organ class in inpatients; whereas in outpatients, it was gastrointestinal system disorders and metabolic and nutritional disorders.

The most common organ system affected by ADRs was the CNS and peripheral nervous system (20.41%). This finding is immensely correlated with the most of the Indian studies.[12-15] This result perhaps may due to the pharmacological actions of the drugs implicated in ADRs. EPS accounted for almost 50% of the CNS and peripheral nervous system ADRs. In all these cases the suspected drug was withheld and specific treatments such as anticholinergic, benzodiazepines, and beta-blockers were given. The second most commonly reported ADR in CNS was tremors. For most of our patients, tremors were self-limiting, but patients with distressing and troublesome tremors were managed by dose reduction and adding central anticholinergic drug.

The most common metabolic adverse effects observed in our study include weight gain, weight loss, and metabolic syndrome, as mentioned in Table 2. This finding is immensely correlated with the other published studies.[5,12] Weight gain was most commonly observed with olanzapine[15] and quetiapine,[8] which accounted for 10.53% of total ADRs. Approximately 90% of the patients with weight gain were enrolled into weight management program (nonpharmacological intervention). If it exceeds 7% of the initial weight after 10 weeks, then switching to another antipsychotic was considered. Anticholinergic side-effects such as dry mouth, constipation, urinary retention, and tachycardia accounted for 15.03% of the total ADRs and were managed by symptomatic treatments.

Menstrual irregularities, amenorrhea and galactorrhea were the most commonly reported ADRs associated with reproductive system (n = 25). Among the second-generation antipsychotics, risperidone and amisulpride were reported to cause a marked and sustained increase in serum prolactin levels in other studies[18,19] and a similar trend were observed in our study also. The time to onset of galactorrhea was ranged from 4 to 75 days after commencement of amisulpride. This finding is immensely correlated with the finding of the other study.[19] Except one case, serum prolactin level could not be estimated as patients were not willing for the test. All cases, menstrual irregularities and amenorrhea were managed by withdrawal of the suspected drug. Patients with galactorrhea were managed by switching to prolactin sparing agents like aripiprazole but, in two cases, galactorrhea was treated with pharmacological interventions like cabergoline and bromocriptine.

Risperidone, olanzapine, quetiapine, haloperidol and amisulpride were the most frequently prescribed atypical antipsychotic drugs, while clozapine, aripiprazole, and asenapine were less commonly used. Expectedly, majority of the adverse events were seen with risperidone and olanzapine. Thrombophlebitis was most commonly associated with the patients who were on haloperidol, thrombocytopenia with clozapine and anemia with risperidone. The study observed 13 cases of orthostasis and was subsided within the first few days to weeks of the therapy.

As a limitation, Due to the limited human resource and unavailability of electronic medical records we could not review all patients visited the study site. Routine hematological, clinical chemistry or ECG screening of the patients or taking blood samples for sugar, lipid and prolactin measurement was not possible routinely. Furthermore, the prevalence and severity of adverse effects can also be explained by other diseases and co-medications, while we did not consider this correlation in our study.

This study thus adds to the existing information on prevalence of adverse effects to atypical antipsychotic drugs. Although antipsychotics clearly reduce the morbidity and mortality of psychiatric illness, they

may also be associated with adverse side-effects, which often cause distress to the patient and may lead to noncompliance. Thus, the recognition of these side-effects and their management can lead to strategies, which ensure optimal care for the patient.

AUTHORS' CONTRIBUTION

All authors contributed the idea of research, design of study, data analysis and manuscript preparation.

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