Original Article

# Adverse drug reactions due to atypical antipsychotics in the absence of other centrally acting drugs among patients with mental illness

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## Abstract

**Background:** Atypical antipsychotics are known as the second-generation antipsychotics, which act through various receptors and are preferred over typical antipsychotics as they have a better safety profile. Adverse Drug Reactions (ADRs) of atypical antipsychotics have a negative impact on long-term compliance and in achieving specified treatment outcomes. The present study aimed to monitor and report the ADRs of atypical antipsychotics in a population that was free from typical antipsychotics, antidepressants, and antianxiety drugs. **Method:** It is a hospital-based prospective observational study conducted in inpatients and outpatients of the Dept. of Psychiatry. Naranjo's Causality Assessment Scale, WHO Probability Assessment Scale, and Hartwig's Severity Assessment Scale were used for ADR assessment and categorization. The data were analyzed using MS Office Excel 2016. **Results:** The study was carried out among 49 patients with a number of antipsychotics per prescription that were observed to be 1.2± 0.4. A total of 63 ADRs were reported in the study population among which olanzapine (44%) was found to be contributed to the maximum number of ADRs followed by risperidone (37%). Weight gain (13%) was the most common ADR found in the study population followed by sedation (10%) and constipation (8%). The reactions were assessed for preventability and predictability and it was noted that 67% and 76% were probably preventable and predictable. **Conclusion:** The study advocates for an important aspect of drug safety and improved monitoring among first-episode schizophrenia patients as most of the ADRs reported were predictable and preventable.

**Keywords:** Atypical antipsychotics, adverse drug reactions

## Introduction

Atypical antipsychotics, the second-generation antipsychotics act through a number of different receptors, including dopamine, serotonin, cholinergic, adrenergic, and histamine receptors [1]. Atypical antipsychotics are preferred over older (typical) antipsychotics as they have a better safety profile and less likely to produce extrapyramidal side effects (EPS) [2]. Even though the atypical antipsychotics have a lesser possibility of extrapyramidal side effects, these drugs exhibit their own spectrum of adverse events [3-7].

A meta-analysis report by Beijer and de Blaey [8] showed that the incidence of ADRs varied from 0.2% to 41.3% and imposed a significant burden on the health care system. ADR monitoring is a key process in recognizing high-risk category patients for the occurrence of ADR and to comprehend the nature and incidence of such reactions [9]. Safe and rational use of atypical antipsychotics can be promoted by providing awareness to health care providers regarding ADRs associated with atypical antipsychotics and how to manage it [10]. Pharmacovigilance activities in India are still in the initial

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**How to cite this article:** Subeesh, V., Maheswari, E., Singh, H., Beulah, E. Adverse drug reactions due to atypical antipsychotics in the absence of other centrally acting drugs among patients with mental illness. Arch Pharma Pract 2019;10(2):105-9.

stages and the data regarding ADRs need to be reinforced [11]. ADRs of atypical antipsychotics have a negative effect on long-term adherence and in achieving specified treatment outcomes. Hence, there is a rising disquiet among healthcare professionals to evaluate the ADRs of atypical antipsychotics and thus protect patients against unintended fatal consequences [12].

Most of the research addressed the ADRs of atypical antipsychotics in a population who were concomitantly taking other medications for anxiety, depression, or a combination of typical antipsychotics or benzodiazepines with atypical antipsychotics [11, 13-17]. Therefore, the criteria by which the aforementioned studies identified atypical antipsychotics as the primary suspect can be questionable.

In this research, we made an effort to monitor and report the atypical antipsychotics' associated ADRs in a population who were not treated with typical antipsychotics, antianxiety drugs, and antidepressants.

## Methodology:

This spontaneous ADR monitoring and reporting observational study was initiated after approval from the Institutional Human Ethics Committee (IHEC).

### Study Criteria:

### Inclusion Criteria:

1. Patients, who developed ADRs by atypical antipsychotics, which was used for the management of schizophrenia, psychosis or bipolar disorder
2. Patients who have given informed consent for study participation

### Exclusion criteria:

1. Patients with other psychiatric illness
2. Pre-treated with atypical antipsychotics for other indications
3. Use of atypical antipsychotics for off-label indications

**Sources of Data:** The data were collected from medication charts, case sheets, patient's previous medical records and prescriptions, laboratory reports, and by conducting a medication history interview. Predesigned data collection form was used for data collection.

**Study Procedure:** It is a prospective observational hospital-based study conducted in inpatients and outpatients of the Dept. of Psychiatry. Patients satisfied the study criteria of either sex were included in the study. Patients' case notes, lab reports, medication charts, previous records, and all other relevant documents were reviewed, and details were recorded in a predesigned data collection form to analyze the drug utilization pattern. The case notes were screened for ADRs; those observed by healthcare professionals and self-reported by patients were also considered. ADR details including nature of the reaction, date of onset, suspected drug, treatment drugs, severity, dose of the drug, route of administration, pharmaceutical form, list of concomitant drugs, and all other relevant details were recorded in the data collection form. In a situation of ambiguity, a psychiatrist was available for consultation.

**Causality Assessment:** The causality association between suspected ADR and drug therapy was established using Naranjo's Causality Assessment Scale and classified into definite, probable, and possible. The extent of association between the suspected drug and ADR was analyzed using the WHO Probability Assessment Scale and was categorized into certain, probable, and possible.

**Severity Assessment:** Severity assessment done using Hartwig's Severity Assessment Scale. The severity of each ADR was broadly classified into mild, moderate, and severe.

**Predictability Assessment:** Based on incidence rate and patient tolerability, ADR can be classified as predictable and not predictable. System Organ Classification: The ADRs were classified following WHO-System organ classification.

**Statistical Analysis:** All the information, which was collected from the patients' case notes were uploaded in MS Office Excel 2016 for easy accessibility, storage, retrieval, and analysis of the collected data.

## Results

It was found that 51% of the study population was female and the maximum number of patients were in the age group of 30-40 years. The mean age of the study population was observed to be 37.75±13.54 with a minimum age of 15years and a maximum age of 80 years. The study population was analyzed for atypical antipsychotic use and categorized according to their medical condition for which they have used atypical antipsychotics. It was observed that 18 (36%) patients were using atypical antipsychotics for the treatment of schizophrenia. The various atypical antipsychotics used in the subjects are tabulated in Table 1.

The study population was analyzed for the use of atypical antipsychotics and it was found that risperidone (27%) and olanzapine (27%) were utilized the most followed by quetiapine (23%).

The number of antipsychotics per prescription was assessed and it was observed that the mean number of atypical antipsychotics per prescription was 1.2±0.4. The details are depicted in Table 2.

A total of 63 ADRs were reported in the study population. Olanzapine (44%) was observed to contribute the maximum number of ADRs followed by risperidone (37%). The

primary suspects of ADR are depicted in Table 3. Mean of 1.28±0.51 ADRs were found per prescription. Weight gain (13%) was the most commonly occurring ADR found in the study population followed by sedation (10%) and constipation (8%). The ADRs identified in the study population is illustrated in Figure 1.

The organ system which is found to be most commonly affected by the atypical antipsychotics was neurological (41%) followed by endocrine (21%) as depicted in Table 4.

Causality assessment using the WHO causality assessment scale indicated that 76% of the ADRs were 'probable' and 14% was 'possible'. The 'certain' was observed in only six ADRs as only a few were re-challenged.

As per the Naranjo scale, 76% of the reactions were 'probable', 14% of 'possible', and 10% of 'certain' with a score range of 5 to 8, 1 to 4, and above 9 respectively. The severity of the reported reactions was assessed using a modified Hartwig and Siegel scale and accordingly, 46% of the reactions were categorized as moderate, 30% as mild, and 24% were severe. The preventability assessment revealed 67% of the ADRs to be 'probably preventable', 30% of the ADRs to be 'definitely preventable' and 3% to be 'not preventable'. The reactions were assessed for their predictability and it was observed that a majority of the ADRs (76%) were predictable.

## Discussion

Atypical antipsychotics, the second-generation antipsychotics act through a number of different receptors, including dopamine, serotonin, cholinergic, adrenergic, and histamine receptors [1]. Even though the atypical antipsychotics have a lesser chance of extrapyramidal side effects, these drugs exhibit their own spectrum of adverse events. However, ADRs associated with atypical antipsychotics without co-administration of any centrally acting drugs are seldom studied. In this chapter, we discussed the ADRs of atypical antipsychotics among psychiatric patients.

We enrolled patients who developed ADRs by atypical antipsychotics, which was used for the management of schizophrenia, psychosis, or bipolar disorder. Patients with other psychiatric illnesses and atypical antipsychotics used for other indications were excluded from the study. A total of 5324 patients were prescribed with atypical antipsychotics, however, 49 satisfied the study criteria and accounted for 63 ADRs.

The Adverse Drug Reactions (ADRs) in the department of psychiatry were almost equally distributed between both genders, females (n=25, 51%) and males (n=24, 49%). However, Alomar MJ et al., stated that females are more prone to ADR [18], which may be because of lower body weight and organ size, different gastric motility, more body fat, and lower glomerular filtration rate in women. In our study, we identified that the maximum numbers of patients were in the age group of 30-40 years and the mean age of study population was 37.75 ± 13.54, which was similar to the study carried out by Sridhar SB et al. [10].

In the present study, risperidone (27.12%) and olanzapine (27.12%) were the most frequently prescribed antipsychotics followed by quetiapine (23.73%), and aripiprazole (16.95%), and amisulpride (1.69%) was the least prescribed.

A study conducted in 2008 reported that quetiapine was utilized the most followed by risperidone, aripiprazole, and olanzapine respectively [19]. A drastic increase in the olanzapine use may be attributed to its increased effectiveness in terms of the general mental state i.e. greater increase in Positive and Negative Syndrome Scale (PANSS) score [20]. The atypical antipsychotics utilization for schizophrenia from 1995-96 was 51%, which gradually decreased to 24% in 2008 [19]. However, in our study schizophrenia (36.73%) was the mental disorder for which atypical drugs were given the most, followed by psychosis (30.61%) and bipolar affective disorder (16.33%), respectively.

Olanzapine was found to contribute to the maximum number of ADRs with the common ADR as weight gain in our study (Table 1). The CATIE study reported that 30% of the olanzapine group showed an increase in 7% of their baseline body weight [21]. Weight gain associated with olanzapine has been observed to be suggestively more than with other antipsychotics.

The underlying mechanism includes insulin resistance and appetite stimulation [22]. Interventions for antipsychotic-related weight gain include switching patients to antipsychotics less likely to cause dietary restriction, weight gain, exercise, and behavior modification programs. If there is an increase in 5% of baseline body weight post drug initiation, a change in antipsychotic must be considered as recommended by the American Diabetes Association.

## Conclusion

Olanzapine and risperidone were reported the most for adverse drug reactions. The majority of the ADRs were found to be preventable and predictable, which demands a pivotal aspect of drug safety and improved monitoring among patients with first-episode schizophrenia. It is imperative to understand the appropriate therapy and reduce the drug burden to improve patient care.

### Conflicts of interest

Declarations of interest: None

### Conference Details

Adverse Drug Reaction Monitoring of Atypical Antipsychotics: Exploration and Establishment of Risk Factors. Subeesh V, Singh H, Maheswari E, Pudi C. ISPOR

Asia Pacific 2018, 8-11 September 2018, Tokyo, Japan. Awarded with top 10% rosette.

## Criteria for inclusion in the authors'/ contributors' list

All authors have read and approved the final manuscript. All the authors contributed equally.

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**Table 1:** Atypical antipsychotics used in the study population

| Drug | No. of Patients | % |
|---|---|---|
| **Amisulpride** | 1 | 1.695 |
| **Aripiprazole** | 10 | 16.95 |
| **Risperidone** | 16 | 27.12 |
| **Quetiapine** | 14 | 23.73 |
| **Olanzapine** | 16 | 27.12 |
| **Ziprasidone** | 2 | 3.39 |

**Table 2:** Number of antipsychotics per prescription

| Number of antipsychotics per prescription | No of patients | % |
|---|---|---|
| Monotherapy | 39 | 80 |
| Dual therapy | 10 | 20 |

**Table 3:** Primary suspects of ADRs in the study Population

| Sl. No | Primary suspect | No. of Patients | % |
|---|---|---|---|
| 1 | Aripiprazole | 14 | 28.57 |
| 2 | Risperidone | 18 | 36.73 |
| 3 | Olanzapine | 22 | 44.89 |
| 4 | Quetiapine | 8 | 16.32 |
| 5 | Ziprasidone | 1 | 2.04 |

**Table 4:** Organ System Affected by ADR

| Sl. No | Organ System Affected by ADR | No. Patients | % |
|---|---|---|---|
| 1 | Cardiovascular | 3 | 4.762 |
| 2 | Dermatologic | 2 | 3.175 |
| 3 | Ophthalmologic | 1 | 1.587 |
| 4 | Endocrine | 13 | 20.63 |
| 5 | Gastro-Intestinal | 10 | 15.87 |
| 6 | Neurological | 26 | 41.27 |
| 7 | Psychiatric | 5 | 7.937 |
| 8 | Reproductive | 1 | 1.587 |
| 9 | Respiratory | 1 | 1.587 |
| 10 | Other | 1 | 1.587 |

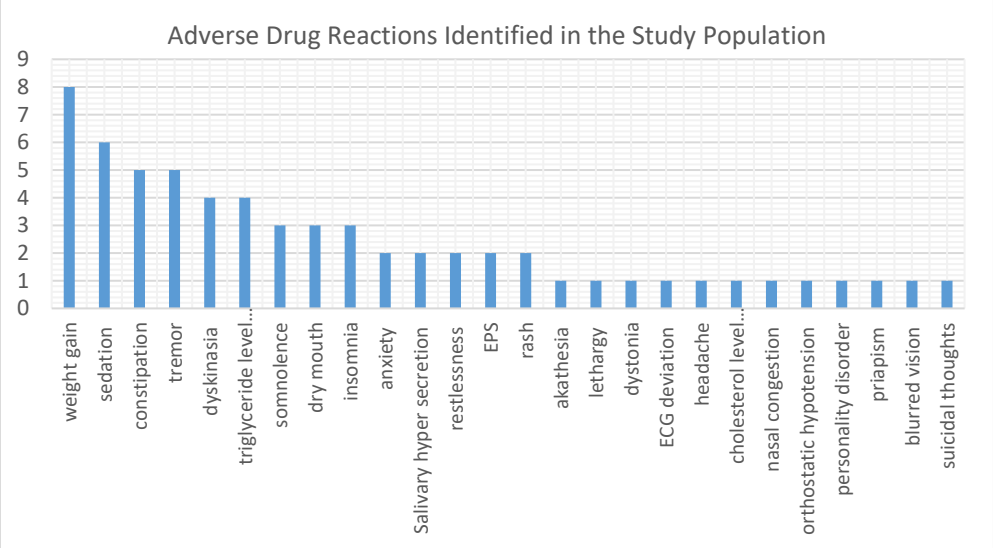


**Figure 1:** Adverse Drug Reactions Identified in the Study Population