Adverse Drug Reactions and their Impact on Quality of Life in Patients on Antipsychotic Therapy at a Tertiary Care Center in Delhi

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ABSTRACT

Context: Adverse drug reactions (ADR) due to antipsychotic therapy have significant impact on a psychiatric patient’s quality of life. Few studies have been conducted in India to monitor adverse drug reactions due to antipsychotics and none has been done to determine their impact on quality of life. Aims: The present study was conducted to monitor ADRs due to antipsychotics and ascertain the impact of ADRs on quality of life. Settings and Design: This prospective observational study was conducted in the psychiatry outpatients department in New Delhi for 1 year. Patients and Methods: A total of 224 patients enrolled were followed up for a period of 3 months. ADRs were monitored using the standard form of the Central Drugs Standard Control Organization and causality was determined using the Naranjo algorithm. The WHO Quality of Life BREF (WHOQOL-BREF) scale was used to study the effect of ADR on the quality of life. Statistical Analysis Used: The data were entered and analyzed using the statistical software SPSS 17.0. Unpaired t-test was used to compare the quality of life of patients who encountered ADRs and those who did not. P < 0.05 was considered statistically significant. Results: Of the total 224 patients, 38 adverse drug events occurred. Adverse drug events were mostly with risperidone (10), followed by olanzapine (8) owing to high usage. Majority of the events were classified as probable (34). The occurrence of adverse drug events decreased the scores on physical and psychological domain scores of WHO-QOL BREF at 3 months compared to baseline. Conclusions: The study provides information on the existing incidence of ADRs in the setup with an established pharmacovigilance center. The nature of ADRs correlates with the prevalence pattern of usage of atypical antipsychotics. Clinicians need to weigh benefit versus the impact on quality of life while prescribing antipsychotics.

Key words: Adverse drug reaction, antipsychotics, Naranjo scale, quality of life

INTRODUCTION

An adverse drug reaction (ADR), as per the WHO, is defined as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or for modification of a disease process.” This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

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How to cite this article: Chawla S, Kumar S. Adverse drug reactions and their impact on quality of life in patients on antipsychotic therapy at a tertiary care center in Delhi. Indian J Psychol Med 2017;39:293-8.
of physiological function."[1] These reactions pose a significant problem in view of increased morbidity and mortality, increasing costs of health care, and poor compliance.[1]

Few studies have been conducted worldwide as well as in India to observe the pattern of ADRs of psychotropic drugs and their causality assessment to a particular drug. A 6-month prospective observational study was conducted at an academic psychiatric hospital in New England.[2] This study reported atypical antipsychotics (37%) to be the most commonly implicated drugs for adverse drug events. The central nervous system (66.5%), cardiovascular and dermatologic reactions were among the common organ systems affected by adverse drug events.[2] ADR monitoring was conducted in psychiatry outpatient department of a tertiary hospital in Kolkata.[3] Of all the diagnoses, bipolar disorder (27%) followed by schizophrenia (24%) were most common. Thirty-three different ADRs were reported due to treatment. Antipsychotics (57.1%) were the most common class of psychotropic agents implicated in causing ADRs. Tremors (19.6%), weight gain (15.34%), and constipation (14.49%) were the most common ADRs in decreasing order of frequency.[3] Of all the antipsychotics, olanzapine (31.82%) followed by haloperidol (19.03%) were the most common drugs responsible for ADRs.[3]

A prospective study analyzing ADR to atypical antipsychotic agents was carried out in outpatients at a tertiary hospital in Gujarat.[4] ADRs were reported from a total of 84 prescriptions. Eighty-two of 93 ADRs were due to risperidone and olanzapine. Among the ADRs reported, weight gain, dizziness, and sleep and appetite disturbances were responsible for 78% of the adverse events.[4] Gastrointestinal and sleep disturbances were observed with risperidone at 4–6 mg/day dose and with olanzapine at 10–15 mg/day within 1 week to 3 months of initiating antipsychotic therapy. After a long term (3–9 months), extrapyramidal symptoms, fatigue, seizures, increased frequency of micturition, and dizziness were observed.[4]

Pharmacovigilance is still in its stages of infancy in India. Psychotropic drugs are being increasingly used in our country owing to the growing incidence and prevalence of psychiatric disorders. There are a large number of ADRs associated with the use of antipsychotic agents owing to their effect on multiple dopaminergic pathways as well. However, there is a lack of data on the exact incidence and magnitude of the problem in Indian setting.

**Aims and objectives**

- To monitor the ADRs with the use of antipsychotic drugs
- To determine the impact of ADRs on the quality of life of patients.

**PATIENTS AND METHODS**

**Study settings**

The study was conducted in the Department of Pharmacology, Maulana Azad Medical College, and Department of Psychiatry, Govind Ballabh Pant (G. B. Pant) Hospital, New Delhi. G. B. Pant Hospital is a 600-bedded super specialty hospital which provides health services to patients from New Delhi and neighboring regions. The outpatients department (OPD) of psychiatry provides services from 9.00 AM to 1.00 PM from Monday to Saturday.

**Study design**

This was a hospital-based prospective and observational study.

**Study population**

The study population were outpatients visiting the Psychiatry Department of G. B. Pant Hospital.

**Study duration**

The study was conducted for 1 year (January 2014–January 2015). The patients enrolled were followed up for a period of 3 months (90 days).

**Inclusion criteria**

All patients who were 18 years and above, of either sex, who had been newly diagnosed and prescribed one or more antipsychotic drugs were included in the study. The study included only outpatients visiting the hospital.

**Exclusion criteria**

Patients excluded from the study were as follows:

- Inpatients
- Patients on substance abuse.

**Informed consent**

Patients and/or their attendants were made to understand the purpose, their rights, and the procedure of the study with the help of patient information sheet, and written informed consent was prepared in Hindi and English. Left thumb impression fingerprint was taken in the presence of an appropriate witness for illiterate patients.

**Data collection**

A total of 224 patients were enrolled after obtaining written informed consent and as per the inclusion
criteria. Prescriptions of patients visiting OPD of G. B. Pant Hospital, New Delhi, were collected on the 1st day of visit, and ADR monitoring was done using the standard form of the Central Drugs Standard Control Organization.[5] The causality assessment of adverse events was performed by Naranjo algorithm.[6] A baseline quality of life assessment of these patients was performed using WHO Quality of Life BREF (WHO-QOL BREF) scale.[7]

The patients were followed up for 3 months or 90 days both telephonically as well as during subsequent visits to the OPD. In the OPD, patients were followed up every 2 weeks for medication refills as well. These approaches were undertaken to decrease the bias arising due to loss to follow-up. At 3 months, the second quality of life assessment was done.

The Naranjo algorithm, Naranjo scale, or Naranjo nomogram is a questionnaire designed for determining the likelihood of whether an ADR is actually due to the drug rather than the result of other factors. Probability is assigned through a score termed definite, probable, possible, or doubtful. Values obtained from this algorithm are sometimes used in peer reviews to verify the validity of author’s conclusions regarding ADRs. It is also called the Naranjo scale or Naranjo score. Score can range from 0 (doubtful ADR) to ≥9 (definite ADR), detailed scoring is described as follows:[6]

- ≥9 = definite ADR
- 5–8 = probable ADR
- 1–4 = possible ADR
- 0 = doubtful ADR.

The effect of ADRs on the quality of life was also determined using the WHO-QOL BREF scale. The WHO-QOL BREF scale is a validated, cross culturally available, and wide field-tested instrument used to assess the quality of life. It consists of 26 items which broadly cover four broad domains, i.e., physical health, psychological health, social relationships, and environment. The analysis was done as per the instructions given in the WHO manual for scoring. Raw scores on the four domains were calculated by adding the values of single items and transformed on a scale ranging from 0 to 100, where 100 is the highest and 0 is the lowest QOL.[7] It took about 30 min to complete the questionnaire.

Statistical analysis
The data were entered and analyzed using the statistical software SPSS version 17.0 (Chicago: SPSS Inc.). The demographic data were presented as mean ± standard deviation. The WHO-QOL BREF was computed with a SPSS syntax file. The comparison between patients who encountered an ADR and those who did not in the subgroup analysis was done using unpaired t-test. For all statistical analyses, $P < 0.05$ was considered statistically significant at a confidence interval of 95%.

RESULTS

Majority of the patients belonged to the age group of 31–40 years (31.4%), followed by the age group of 18–30 years (28.6%) and 41–50 years (27.5%). Other age groups of 51–60 years (7.3%), 61–70 years (3.1%), and >70 years (2.1%) constituted minority of the patients.

Males constituted 52.7% ($n = 118$) while females were 47.3% ($n = 106$) of the total participants.

In terms of marital status, 59% of the patients were married while 32% of the patients were single/unmarried. A small fraction of patients were either widowed (7%) or divorced (2%).

About 31% of the patients included in the study were illiterate, and the same proportion had education level up to primary school (31%). Only 26% of the patients went to secondary school while 10% had had a graduation and only a meager 2% were professional.

Of the 224 patients included in the study, 53% were employed while 47% were unemployed.

The patients in the study were almost equally distributed among those living in a nuclear family (49.7%) and those living in a joint family (50.3%).

Incidence of adverse drug reaction
Of the total 224 patients, ADRs were observed in 28 patients. These 28 patients had a total of 38 ADRs. Therefore, incidence rate per 100 patients was calculated to be 16.96 (38/224 × 100 = 16.96).

The highest number of adverse effects was noted with risperidone (10) followed by olanzapine (8) and aripiprazole (3) as shown in Table 1. The incidence of ADR per 100 prescriptions was maximum in case of fluphenazine as one ADR was reported from its single prescription.

Table 2 shows the causality assessment of the 38 ADRs reported in the study. The causality assessment was done using the Naranjo algorithm. Majority of them ($n = 34$) were classified as probable ADRs. Some of the most common “probable” ADRs reported were sexual dysfunction, decreased libido, weight gain, and menstrual irregularities. Among the total ADRs, five of them were assessed as “possible” ADRs, of which myalgia was the most common.
Effect of adverse drug events on domain scores of WHO Quality of Life BREF

The effect of presence of ADRs on various domain scores, i.e., physical, psychological, social, and environmental of WHO-QOL BREF was determined using unpaired t-test with a confidence interval of 95%, and \( P < 0.05 \) was considered statistically significant.

The occurrence of an adverse drug event decreased the mean change on physical domain scores at 3 months versus at baseline \( (P = 0.01) \) compared to those patients with no ADR [Figure 1]. A decrease in mean change on psychological domain scores \( (P = 0.02) \) was also observed from baseline to 3 months compared to those patients with no ADR [Figure 2]. However, the occurrence of an ADR was not found to have statistically significant effect on social and environmental domains of QOL scale [Figures 3 and 4].

### Table 1: Number of adverse drug events and associated antipsychotics

| Antipsychotic Drug | Number of times prescribed \( (n=293) \) | Number of adverse events \( (n=38) \) | Incidence of adverse drug event per 100 prescriptions |
|---------------------|------------------------------------------|-----------------------------------|-----------------------------------------------------|
| Risperidone         | 131                                      | 10                                | 7.63                                                 |
| Olanzapine          | 102                                      | 8                                 | 7.84                                                 |
| Aripiprazole        | 21                                       | 3                                 | 14.28                                                |
| Clozapine           | 15                                       | 5                                 | 33.33                                                |
| Quetiapine          | 8                                        | 2                                 | 25.00                                                |
| Trifluoperazine     | 8                                        | 4                                 | 50.00                                                |
| Haloperidol         | 7                                        | 4                                 | 57.14                                                |
| Amisulpride         | 4                                        | 1                                 | 25.00                                                |
| Fluphenazine        | 1                                        | 1                                 | 100.00                                               |

**DISCUSSION**

In a study conducted in New England, atypical antipsychotics (37%) were found to be the most commonly implicated drugs for causing ADRs among all psychotropic agents studied.[2] Another study reported that atypical antipsychotics were responsible for 57.1% of ADRs reported at a tertiary hospital in Kolkata.[3] Tremors (19.6%), weight gain (15.34%), and constipation (14.49%) were the most common adverse reactions.[3] Olanzapine (31.82%) followed by haloperidol (19.03%) were the most common drugs responsible for ADRs.[3] Similarly, an OPD of a Gujarat-based hospital reported 93 ADRs from just 84 prescriptions.[4] Maximum ADRs were due to risperidone and olanzapine.[4] Common ADRs reported were weight gain, dizziness, and sleep and appetite disturbances.[4] A study conducted in Assam reported 33 patients (9.19%) of 359 outpatients to be having ADR due to antipsychotics.[8] Likewise, in the present study, ADRs were reported in 28 patients. There were a total of 38 adverse drug events in 28 patients with an incidence rate of 16.96/100 patients. Risperidone (10) accounted for maximum ADRs followed by olanzapine (8). Majority of the ADRs were classified as “probable” as per Naranjo's scale. Common ADRs reported were decreased libido, weight gain, menstrual irregularity, and appetite disturbance. Therefore, different centers have variable incidence rates of ADR. A high incidence of ADR could be related to polypharmacy or prescription of more than one antipsychotic. The incidence of polypharmacy and prescription of more than one antipsychotic was found to be low in our study compared to other centers. A low incidence rate in studies could be attributed to underreporting of ADRs, practice

### Table 2: Adverse drug events and implicated drugs

| Category          | Number of events \( n=38 \) (%) | Adverse drug event | Implicated drug |
|-------------------|---------------------------------|--------------------|-----------------|
| Definite (Certain)| 0                               | Nil                | Nil             |
| Probable          | 4                               | Weight gain        | Olanzapine (3), Risperidone (1) |
|                   | 1                               | Decreased sleep    | Risperidone (1) |
|                   | 2                               | Extrapyramidal reaction | Haloperidol (1), Fluphenazine (1) |
|                   | 1                               | Increased sleep    | Olanzapine (1)  |
|                   | 2                               | Hypersalivation    | Trifluoperazine (1), Haloperidol (1) |
|                   | 1                               | Fatigue            | Amisulpride (1), Risperidone (1) |
|                   | 1                               | Tremors            | Trifluoperazine (1) |
|                   | 1                               | Slurred speech     | Haloperidol (1)  |
|                   | 2                               | Dry mouth          | Haloperidol (1), Risperidone (1) |
|                   | 1                               | Agranulocytosis    | Clozapine (1)    |
|                   | 3                               | Disturbance in appetite | Clozapine (2), Quetiapine (1) |
|                   | 3                               | Sexual dysfunction | Risperidone (2), Aripiprazole (1) |
|                   | 5                               | Decreased libido    | Olanzapine (2), Risperidone (1), Quetiapine (1), Trifluoperazine (1) |
|                   | 3                               | Menstrual irregularity | Risperidone (2), Clozapine (1) |
|                   | 2                               | Galactorrhoea      | Trifluoperazine (1), Aripiprazole (1) |
| Possible          | 1                               | Headache           | Clozapine (1)    |
|                   | 2                               | Myalgia            | Olanzapine (1), Risperidone (1) |
|                   | 1                               | Dizziness          | Aripiprazole (1) |
|                   | 1                               | Orthostasis        | Olanzapine (1)   |
of rational prescribing, high usage of newer atypical agents which carry a favorable safety profile compared to older typical agents, or a better follow-up, wherein pre-emptive palliative measures to prevent ADR were undertaken. In the present setup, the study hospital is one of the centers for conducting pharmacovigilance activities, wherein adverse drug event reports are collected and workshops are organized for clinicians and nurses to create awareness regarding the program. Furthermore, the patients in the study were followed up regularly and even contacted telephonically over the study period to ensure adherence to treatment and to report any ADR at the earliest.

In the present study, the effect of ADRs on the various aspects of health using quality of life scale was determined. The occurrence of an adverse drug event decreased the mean change on physical domain scores at 3 months versus at baseline in patients who developed an ADR versus those who did not (*P = 0.01). A decrease in the mean change on psychological domain scores (*P = 0.02) was also noticed in patients encountering ADR compared to those who did not. However, the occurrence of an ADR was not found to have statistically significant effect on social and environmental domains of QOL scale. A study to determine the association of quality of life with adverse effect of antipsychotics in patients with bipolar disorder and schizophrenia in remission was conducted in Taiwan. The authors of the study developed a Questionnaire on Adverse Effects of Medication for Bipolar Disorder and Schizophrenia to assess the perception and determine the severity of adverse effects. They correlated the results from this questionnaire with the WHO-QOL BREF score to find negative association of adverse effects on the physical and environmental domains. In the present study, neither this questionnaire nor a severity scale was used to determine the effect of ADR on the various domains of WHO-QOL. Compared to the study conducted in Taiwan, we found that the occurrence of an adverse drug event negatively affected the physical and psychological domain scores but not the environmental domain scores at 3 months versus at baseline. Although the study in Taiwan was conducted among patients of schizophrenia and bipolar disorders in remission, our study included all patients on antipsychotics, a comparison cannot be wholly justified. We could not find any other studies comparing the association of ADRs with the quality of life. With this study, we have tried to determine which domain of QOL scale is maximally affected by an ADR without using any questionnaire.
CONCLUSION

Owing largely to the use of atypical antipsychotics, the nature of adverse drug reactions were confined to reproductive, gastrointestinal, and neurological systems. The presence of an adverse drug reaction compromised the physical and psychological aspect of quality of life of patients during the study period. The authors of the study recommend caution in prescribing antipsychotic drugs which are known to have higher incidence of adverse effects. The impact of an ADR on the quality of life and the total cost incurred whether due to use of an expensive antipsychotic or indirectly due to ADR needs to be considered.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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