Original Article

Adverse Drug Reaction Monitoring in a Tertiary Care Psychiatry Setting: A Comparative Study between Inpatients and Outpatients

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ABSTRACT

Background: Psychotropic medications are the mainstay of treatment in psychiatric disorders and are associated with ADRs which affect the compliance and treatment course. Previous studies have looked at the frequency, profile of ADRs and their management aspects. However, the systematic comparison between IP and OP was lacking even though there is a prescription pattern difference. Hence this study was aimed to compare the proportion, pattern, severity and resolution of ADRs once detected. **Methods:** This is a hospital based, prospective follow up study done in the psychiatry ward and outpatient setting for a period of 6 months. A total of 491 patients (200 IP, 291 OP) who received psychotropics were monitored in the study. UKU side effect rating scale was used to detect ADRs, WHO – UMC scale for causality, Modified Hartwig and Siegel Scale to assess severity of ADR and CDSCO suspected ADR form for reporting it. **Results:** Out of 491 patients who were recruited for the study, 83 patients developed ADRs (34 IP, 49 OP, $P = 0.963$). The mean number of ADRs per patient was found to be higher in IP (IP-2.17 ± 1.14, OP-1.65 ± 1.12, *P*-0.01). Severe ADRs were observed to be higher IP (IP-67.64%, OP-38.7%, *P*-0.014) which was statistically significant. There is no statistically significant difference in distribution of ADRs across all age groups (*P*-0.475). **Conclusion:** The study results emphasises the need for active pharmacovigilance so that ADRs are detected and managed at the earliest, hence reducing the morbidity and improving compliance. There is also need for systematic long term, multicentric study to further examine and correlatethe observations of our study.

Key words: *Adverse drug reaction, inpatients, outpatients, psychiatry*

INTRODUCTION

Psychotropic medications are the mainstay of treatment in moderate to severe psychiatric disorders and

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are especially important within acute inpatient setting.[1] Chronicity of the psychiatric illnesses necessitates long-term therapy with psychotropics. The response to a specific treatment regimen may vary among individual patients due to differences in individual pharmacokinetic (PK) and pharmacodynamic (PD) parameters.[2] A majority of the adverse drug reactions (ADRs) occur often due to considerable variabilities in the PD and PK parameters, drug interactions, increased reactive drug metabolites levels, and their impaired detoxification.[3]

Antipsychotics, antidepressants, and mood stabilizers, being the major classes of psychotropic agents, are accompanied with ADRs that can influence the compliance and course of treatment in patients. This invariably impacts the outcome as well. Identifying and preventing ADRs in all patients are crucial to ensure compliance and safe patient care.[4]

Various studies have addressed ADR monitoring of inpatients (IPs)[5,6] as well as outpatients (OPs)[7,8] in psychiatry setting. There are also studies which have looked at the frequency of ADRs and their management aspects.[9]

The studies done till date have looked at ADRs, their profile, and their management aspects;[9] however, they lack in the systematic comparison between IP and OP even though it is well known that there is a difference in prescribing pattern between these two settings. To the best of our knowledge, this study is a first of its kind that has emphasized upon the comparison of the correlates of ADRs between the IP department (IPD) and OP department (OPD), in the psychiatry setting at a tertiary care hospital. Comparison of ADRs between IP and OP is essential to know the proportion of different types of ADRs in these settings, their severity, and the outcomes of ADR management.

Objectives

The aim of the study was to compare the proportion, pattern, severity, and the resolution of detected ADRs between IPD and OPD, and also to compare the age- and gender-wise difference in occurrence of ADRs.

METHODOLOGY

This is a hospital-based, prospective follow-up study done in the psychiatry ward and outpatient setting at M.S. Ramaiah Hospital, Bengaluru, for 6 months. The study protocol was reviewed and approved by the Institutional Ethics Committee.

The patients who presented to the OPD and those admitted in the IPD, diagnosed with psychiatric illness by qualified psychiatrists using International Classification of Diseases-10 diagnostic guidelines and who received at least one psychotropic agent for the past 2 months were enrolled in the study. Patients who are on long-term treatment were excluded due to the possibility of recall bias. Informed consent was taken. Clinical pharmacists trained under the Psychiatry department screened the patients for ADR with the help of the psychiatrists in OPD.

All IPs and OPs enrolled were observed intensively for the identification/detection of ADRs while the spontaneously reported ADRs were also noted. The data were collected from detailed clinical examination, medication history interview, medication charts, case sheets, and laboratory investigation reports. Udvalg for Kliniske Undersogelser (UKU) side effect rating scale[10] was employed to detect ADRs. Patient's demographic details, relevant medical history, diagnosis, treatment, laboratory investigation reports, ADR details including the nature of reaction, date of onset, severity, treatment offered, outcome, suspected drug including its dose, pharmaceutical dosage form, route of administration, and list of concomitant drugs were recorded in the suspected ADR form under the Pharmacovigilance Program of India directed by the Central Drugs Standard Control Organization.[11]

A total of 491 patients, who received the psychotropics, were monitored for the study of which 200 were from IPD and 291 from OPD. For the entire study period, OPs were systematically monitored on all of their follow-ups in OPD while IPs were intensely monitored during the hospital stay and subsequently on OPD basis postdischarge. The World Health Organization - Uppsala Monitoring Center[12] causality assessment criteria were employed. The ADRs with certain, probable, and possible causalities were considered for analysis. The severity of each ADR was assessed as mild, moderate, or severe using modified Hartwig and Siegel Severity Assessment Scale.[13] Suspected ADRs were reported to pharmacovigilance center at M.S. Ramaiah Medical College, who further uploaded it to the Indian Pharmacopoeia Commission (IPC), Ministry of Health and Family Welfare, Ghaziabad.

Statistical analysis

Mean and standard deviation were used to summarize the continuous variables in the data. The categorical variables were presented using frequencies and percentages. Chi-square test was employed to compare the differences in proportions for the categorical variables, whereas Student's *t*-test was used to compare the means for normally distributed data and Mann–Whitney U-test was used when the data were not normally distributed. $P < 0.05$ was considered as statistically significant. Data

were entered and analyzed using SPSS Software Version 18.0 (Chicago SPSS Inc. 2009).

RESULTS

Table 1 shows that a total of 491 patients were enrolled in the study of which 261 were males and 230 were females; 200 were admitted in IPD and 291 were treated on OPD basis. The difference in gender and mean age across the two arms (IPD and OPD) was not statistically significant.

Females were found to have more number of ADRs (21%) when compared to males (13%) and this difference was statistically significant ($P = 0.022$).

The detailed ADR pattern as per the UKU scale is given in Table 2. ADRs were considered as a whole, individual ADRs are not considered for analysis.

Out of 491 patients who were recruited for the study, 83 patients developed ADRs of which 34 were from IPD and 49 were from OPD. The difference in proportion of occurrence of ADRs between IP and OP was not statistically significant ($P = 0.963$) even though the percentage was higher in the OP.[14] However, the mean number of ADRs was found to be higher in IP (2.17 ± 1.14) than OP (1.65 ± 1.12, $P = 0.01$). More number of severe ADRs were observed in IP (67.64%) than compared to OP (38.7%). This difference in terms of severity of ADRs was also found to be statistically significant ($P = 0.014$).

The numbers of patients with ADRs were highest in 21–40 age groups [Table 3]. There is no statistically significant difference in distribution of ADRs across all the age groups.

DISCUSSION

To the best of our knowledge, this study is first of its kind study which has looked at the factors and profile of ADR between IP and OP. We observed a significant difference in severity of ADRs between the two groups, where IP has more severe ADRs than OP even though the numbers of ADRs were more in OP in comparison to IP. This difference may be because of the higher dose of medications, more severe disorders needing high dose as well as combination of treatments in IP along with faster dose escalation. The higher mean dose and faster escalation in IP setting were observed even in earlier studies, but the information about how it transformed to the ADRs and outcome was limited.[9,15] We also observed that combination treatments along with higher mean dose are usually used in treating the severely ill patients in IP setting since one of the criteria for admission

Table 1: Comparison of patients between inpatient department and outpatient department according to gender and age

	IPD (%)	OPD (%)	Total	*P*
Total patients				
Male	106 (53)	155 (53.3)	261	0.872[+]
Female	94 (47)	136 (46.7)	230	
Total	200	291	491	
Mean age	37.99±1.00	36.98±0.86		0.451[£]

[£]Student's *t*-test; [+]Chi-square. IPD – Inpatient department; OPD – Outpatient department

Table 2: Pattern and percentage of individual adverse drug reaction as per the Udvalg for Kliniske Undersogelser side effects rating scale

Pattern of ADR	IPD, *n* (%)	OPD, *n* (%)	Total, *n* (%)
Psychic ADR			
Asthenia/increased fatigability	1 (1.4)	2 (2.5)	3 (1.9)
Sleepiness/sedation	7 (9.5)	12 (14.8)	19 (12.3)
Increased duration of sleep	3 (4.1)	0	3 (1.9)
Neurologic ADR			
Dystonia	2 (2.7)	1 (1.2)	3 (1.9)
Rigidity	9 (12.1)	6 (7.4)	15 (9.7)
Tremor	17 (23.0)	11 (13.6)	28 (18.0)
Hypokinesia	3 (4.1)	2 (2.5)	5 (3.2)
Hyperkinesia	3 (4.1)	4 (4.9)	7 (4.5)
Akathisia	2 (2.7)	1 (1.2)	3 (1.9)
Paresthesia	0	1 (1.2)	1 (0.6)
Autonomic ADR			
Accommodation disturbances	0	2 (2.5)	2 (1.3)
Increased salivation	4 (5.4)	2 (2.5)	6 (4.5)
Reduced salivation	2 (2.7)	1 (1.2)	3 (1.9)
Nausea/vomiting	1 (1.4)	5 (6.1)	6 (3.8)
Diarrhea	0	1 (1.2)	1 (0.6)
Constipation	3 (4.1)	1 (1.2)	4 (2.5)
Orthostatic dizziness	3 (4.1)	2 (2.5)	5 (3.2)
Others			
Pruritus	0	1 (1.2)	1 (0.6)
Photosensitivity	0	2 (2.5)	2 (1.3)
Weight gain	3 (4.1)	10 (12.3)	13 (8.4)
Amenorrhea	3 (5.4)	5 (6.1)	8 (5.8)
Galactorrhea	1 (1.4)	1 (1.2)	2 (1.3)
Diminished sexual desire	1 (1.4)	1 (1.2)	2 (1.3)
Erectile dysfunction	1 (1.4)	1 (1.2)	2 (0.6)
Headache	0	1 (1.2)	1 (0.6)
Miscellaneous (not mentioned in UKU scale)			
Bilateral pitting pedal edema	0	1 (1.2)	1 (0.6)
Facial edema	0	1 (1.2)	1 (0.6)
Nasal congestion	1 (1.4)	0	1 (0.6)
Delirium	2 (2.7)	2 (2.5)	4 (2.5)
Urinary retention	1 (1.4)	0	1 (0.6)
Dyspepsia	0	1 (1.2)	1 (0.6)
Loss of taste	1 (1.4)	0	1 (0.6)
Total ADRs	74 (47.7)	81 (52.2)	155

ADRs – Adverse drug reactions; IPD – Inpatient department; OPD – Outpatient department; UKU – Udvalg for Kliniske Undersogelser

included either the severity of the illness or treatment nonresponsiveness. This has transformed into more mean number of ADRs per patient in IP than OP, which we observed in our study. Psychotropic medications are found to produce more severe ADRs at higher doses.[14,15] A drug combination may sometimes cause synergistic toxicity, which is greater than the sum of the risks of toxicity of either agent used alone.[16] There is also evidence for more number of ADRs when drug combination is used due to additive effect, drug interactions, and synergistic effect of the drugs[3,19] (Alomer, 2014; Kingsbury *et al*., 2001). Even though most of the guidelines recommend drug adjustment after evaluating drug response and tolerability, we observed in our study that the IPs had significant faster escalations in the therapeutic dose than the outpatients.

The explanation by the clinicians is that the convenience of admission helps manage the ADRs at the earliest besides being able to reach the therapeutic dose faster by more flexible titration. This makes the observation of this study even more important as there is a significant change in the prescription pattern of psychotropic medication. More conservative approach was followed in treating the OPs who are not always available for continuous observation.

Our study found statistically significant difference in ADRs between males and females replicating the findings of earlier studies.[8,9] It is a well-studied aspect that there are variations in PD and PK profiles in males in comparison to females.[17] At the same dose, females would have more number or more severe ADRs in comparison to males. This limitation is usually managed using either low dose of the therapeutic level or slow escalation of medications. We also noticed that mean dose of almost all the psychotropics was less in females in comparison to males. This highlights the fact of keeping gender in mind when starting and titrating the dose of medications, which reduces the ADRs proportion significantly in females. All the patients in IP and OP were seen by consultant psychiatrist and the ADRs were managed as and when detected. We did not find any statistical difference in the management or resolution of ADRs. At the end of our study, 91.2% of inpatients and 81.64% of outpatients [Table 4] had complete or partial resolution of their ADRs and rest of the patients continued to have the same severity because of various clinical factors which are out of scope of this paper and discussed in subsequent papers. We observed that timely management of ADRs within few hours to days will bring the best outcome in managing the ADRs as noted in our study.

Higher numbers of patients were in the age group 21–40. There was no statistical difference in ADRs in this group even though this group contributed to the maximum number of ADRs [Table 3].

Table 3: Distribution of adverse drug reactions between inpatient department and outpatient department according to the age group

Age	ADR		
	IPD (%)	OPD (%)	Total
1-20	6 (17)	7 (14.3)	13
21-40	14 (41.2)	27 (55.1)	41
41-60	9 (26.5)	12 (24.5)	21
61-80	5 (14.7)	3 (6.1)	8
Total (*n*)	34	49	83
P	0.475		

ADR – Adverse drug reaction; IPD – Inpatient department; OPD – Outpatient department

Table 4: Comparisons of various adverse drug reaction parameters between inpatient department and outpatient department

Parameters	IPD, *n* (%)	OPD, *n* (%)	*P**
Number of patients having at least one ADR	34 (17)	49 (16.8)	0.963^{+}
Mean age of patients with ADR	38.20±2.75	35.18±2.20	0.390$^{£}$
Mean of ADRs/patient	2.17±1.14	1.65±1.12	0.01*,$^{\#}$
ADR severity			
Mild	11 (32.35)	30 (61.23)	0.014*
Moderate to severe	23 (67.64)	19 (38.77)	
ADR treated			
Yes	29 (85.3)	35 (71.4)	0.187^{+}
No	5 (14.7)	14 (28.6)	
ADR resolution			
Complete	19 (55.9)	19 (38.79)	0.273^{+}
Partial	12 (35.3)	21 (42.85)	
None	3 (8.8)	9 (18.36)	

*$P<0.05$; $^{£}$Student's *t*-test; $^{\#}$Mann–Whitney test; $^{+}$Chi-square. ADRs – Adverse drug reactions; IPD – Inpatient department; OPD – Outpatient department

Treating multiple ADRs becomes complex as it involves different treatment strategies. The study emphasise the need for observation for ADRs so that it can be monitored and intervened early to prevent development of subsequent ADRs. More than 50% of our patients had more than one ADRs.

Active monitoring by psychiatrists or physicians requires additional time and effort. In this study, we also studied the mean time spent by clinicians with patients. Psychiatrists spent 105 min/week for inpatient and 20–45 min/week for outpatient. Even though it is not practical to give the same amount of time for both IP and OP setting, physician monitoring along with the intensive 24/7 monitoring by the nursing staff in IP, and awareness in patients and family members about the initial signs of ADRs can ensure better pharmacovigilance activity.

Strengths of our study

- ADR profile between IP and OP
- Follow-up of both groups including management and resolution
- Adequate number of patients
- Relevant, valid, and robust scales were used
- ADRs were clinically evaluated, diagnosed by qualified psychiatrists
- Suspected ADRs were reported to pharmacovigilance center at M.S. Ramaiah Medical College, further uploaded to IPC, Ministry of Health and Family Welfare, Ghaziabad.

Limitations of present study

The study was conducted only for a short period (6 months) at a single center.

Although routine hematological and clinical chemistry (e.g., blood sugar, lipid profile) reports were available, we could not generally order tests such as electrocardiogram screening of patients for QT prolongation or blood sampling to determine serum levels for practical reasons of affordability, convenience, and funding.

There was no access to therapeutic drug monitoring apart from lithium.[18]

CONCLUSION

There is a steady growth in people seeking help for psychiatric disorders, and this study highlights the need for active pharmacovigilance in both inpatient and outpatient setup for early recognition and effective management of ADRs. Pharmacovigilance is lacking in most of the clinical setting and a dedicated team will complement the clinicians' effort in better overall outcome of the patients. There is also a need for systematic long-term, multicentric studies to further investigate the observation of our study to improve the psychiatric management and reduce the morbidity. This also helps understand the PD and PK profiles of various psychotropics in different treatment settings.

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Conflicts of interest

There are no conflicts of interest.

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