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Original Research Article

Adverse drug reaction profile at psychiatry outpatient department of a tertiary care centre

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ABSTRACT

Background: Monitoring adverse drug reactions (ADRs) helps in alerting physicians and developing strategies to prevent and minimize the risk of developing ADRs. Data regarding pattern of ADRs due to psychotropic medications is scanty. Hence, the study was planned to assess ADRs among psychiatry outpatients of a tertiary care hospital in Maharashtra.
Methods: A prospective, observational study was conducted in psychiatry outpatient department of a tertiary care centre for 3 months. Cases were enrolled by active and passive surveillance after obtaining informed consent. Demographic details, adverse event details, history of medications were recorded. Pattern of ADRs was studied according to demographic parameters, drug class, organ system affected, causality (WHO - Uppsala Monitoring Centre Scale) and severity (modified Hartwig and Siegel Scale).
Results: Out of total 1200 patients screened, 77 qualified the inclusion and exclusion criteria and 92 ADRs were reported; overall incidence rate of 6.41%. Maximum ADRs were reported in the age group of 31- 40 years. 63.63% subjects received more than 2 psychotropic drugs. Among 24 types of ADRs observed, tremor (13.04%) was the commonest, closely followed by somnolence. Antipsychotics (45.65%) were most frequently incriminated and central nervous system (46.73%) the most often affected. Trifluoperazine (11.96%) was the commonest drug, followed by olanzapine and haloperidol (10.53% each). Causality analysis yielded 66 ADRs as "probable" and on severity analysis 80.43% were mild.
Conclusions: The study provides an insight into pattern of ADRs in psychiatry outpatients. It is prudent to communicate this to treating physicians as well as counsel patients (and caregivers). Initiatives and concerted efforts involving all stakeholders in healthcare can go a long way in decreasing drug-related morbidity and health costs.

Keywords: Drug-related side effects and adverse reactions, Psychotropic agents, Psychiatry outpatients, Pharmacovigilance

INTRODUCTION

Mental health problems are one of the main causes of the overall disease burden worldwide.[1] According to the National Mental Health Survey 2015-16 (India), excluding tobacco use disorders, mental morbidity of individuals above the age of 18 years was 10.6%.[2] Recent figures indicate that there is increasing reliance on psychotropic medications for the treatment of mental health problems.[3] Various reasons that can be cited for increasing use of psychotropic drugs are increased incidence of mental ill-health, improvement in mental health literacy among general population, reduction in stigma associated with mental illness, increase in drug treatment options, better availability and accessibility to drugs and/or more vigorous marketing of such medications.[4] The association of psychotropic medications with adverse drug reactions (ADRs) is not uncommon and can occur even at the normal

doses used in the management of acute and maintenance phases of psychiatric disorders. ADRs associated with psychotropic drugs can lead to noncompliance, and at times even discontinuation of therapy.[5] Antipsychotic polypharmacy is being practiced with increasing frequency. Polypharmacy is known to increase the risk of developing ADRs.

Pharmacovigilance in psychiatry units can play a vital role in detecting ADRs and alerting physicians to the possibility and circumstances of such events, thereby protecting the user population from avoidable harm.[6] India rates below 1% in terms of ADR reporting against the world's rate of 5%.[7] ADRs are known to be an important cause of morbidity and may, at times, contribute to mortality. Studying the pattern of ADRs helps to identify risk factors for developing ADRs and to determine their incidence. ADR monitoring helps to develop appropriate interventional strategies to manage, prevent and minimize the risk of developing ADRs and thereby increasing the quality of life and reducing the cost of care.[8]

Data regarding ADRs due to psychotropic medication and their patterns in patients with psychiatric disorders is scanty. This study was therefore planned to monitor and assess the ADRs at the psychiatry outpatient department (OPD) of a tertiary care hospital.

METHODS

A prospective observational study was conducted in the Psychiatry OPD of a tertiary care teaching hospital in Solapur, Maharashtra over a period of 3 months from October 2016 to December 2016 after obtaining approval from the Institutional Ethics Committee. Patients / Caregivers of the patients visiting the Psychiatry OPD were screened for ADR(s) on three days of a week by interviewing them - active surveillance and those patients / caregivers who spontaneously reported their ADRs at the Psychiatry OPD were also included in the study - passive surveillance. Patients were enrolled for the study after obtaining informed consent. Patients diagnosed with a psychiatric disorder and prescribed psychotropic drugs by psychiatrist were included in the study. Patients with history of substance abuse (alcohol / tobacco), those suffering from serious disease (like organ failure, severe heart disease, advanced stages of cancer) or assessed to be at risk of suicide, not accompanied by caregiver / guardian, those with ADR due to a drug not prescribed at the psychiatry OPD, causality category of ADR lower than 'possible' (OR information insufficient for causality assessment) were excluded from the study.

Patient demographic details, adverse event details, history of medication(s) suspected of having caused the ADR(s) and details of concomitant medication(s) were recorded based on ADR monitoring form drafted according to Central Drug Standard Control Organisation (CDSCO).[9] Reported ADRs were analyzed for causality by the 'World Health Organization - Uppsala Monitoring Centre (WHO - UMC) Scale' and for severity by 'modified Hartwig and Siegel Scale'.[10,11] ADRs were classified according the organ system affected using the 'Common Terminology Criteria for Adverse Events - Adverse Event by System Organ Class'.[12] Adverse events of causality lower than "possible" and those having similarity with disease symptomatology were not considered for analysis, to prevent ambiguity in results. Anonymity of participants and confidentiality of data was strictly maintained. Data was analyzed according to age and sex distribution, number and class of the psychopharmacological agents, system organ class affected by ADR and mental illness for which drug was prescribed. Simple proportions were used for analysis and the results expressed as percentages.

RESULTS

Out of the total 1200 patients screened for the study, 77 qualified the inclusion and exclusion criteria i.e. an overall incidence rate of 6.41%. From the 77 subjects, 92 ADRs were recorded. Males accounted for 59.74% (46) of the subjects. Maximum ADRs were reported in the age group of 31-40 years 31.16% (24), followed by 21-30 years 25.97% (20) as depicted in Table 1.

The commonest clinical diagnosis in the study subjects was schizophrenia and related psychoses (schizotypal and other delusional disorders), followed by depression. Nearly two-thirds of the subjects 63.63% (49) received more than 2 drugs, 28.57% (22) were on two drugs while 7.79% (6) patients received single drug. Mean number of psychotropic drugs per prescription received by the subjects was 3.05. A few subjects were taking concomitant medicines for other disorders such as hypertension, inflammatory bowel disease, rheumatoid arthritis, started before their psychotropic medication, or treatment for minor ailments like cough and cold or were prescribed vitamin supplements. In such cases, special attention was given to the medication history and only then suspected ADRs were attributed to the concerned psychotropic medicines.

Table 1: Age and sex distribution.

Age group	Male	Female	Male + Female
Upto 20 yrs	3	6	9
21-30	12	8	20
31-40	17	7	24
41-50	7	4	11
51-60	4	3	7
Above 60 yrs	3	3	6
Total	46	31	77

Table 2 enlists twenty-four different kinds of ADRs that were observed during the study. Tremor (13.04%) was the commonest ADR noted, closely followed by somnolence (11.95%) and constipation (9.78%). Some uncommon ADRs like tardive dyskinesia, oligomenorrhea, rabbit syndrome was also noted.

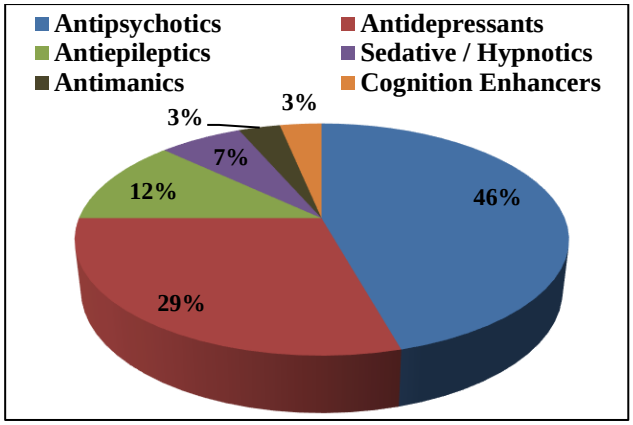

Figure 1: Percentage of ADRs by class of drug.

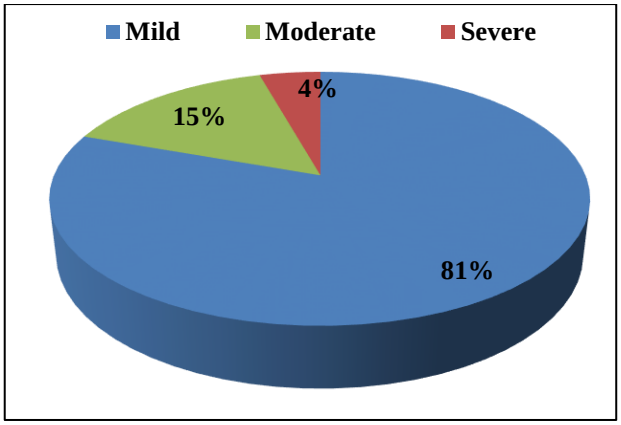

Figure 2: Severity of ADRs by percentage (using modified Hartwig and Siegel Scale).

Table 2: ADRs with drugs implicated.

Type of ADR	Number of ADRs n (%)	Drugs implicated
Tremors	12 (13.04)	Haloperidol (5), Trifluoperazine (4), Olanzapine (2), Fluoxetine (1)
Somnolence	11 (11.95)	Escitalopram (3), Clonazepam (2), Olanzapine (2), Quetiapine (2), Divalproex (1), Lorazepam (1)
Constipation	9 (9.78)	Amitriptyline (3), Fluoxetine (2), Trifluoperazine (2), Aripiprazole (2)
Weight Gain	8 (8.69)	Olanzapine (5), Amitriptyline (1), Escitalopram (1), Trifluoperazine (1)
Dizziness	6 (6.52)	Diazepam (2), Carbamazepine (2), Amisulpiride (1), Clozapine (1)
Headache	5 (5.43)	Memantine (2), Valproate (1), Divalproex (1), Piracetam (1)
Palpitation	5 (5.43)	Risperidone (2), Fluoxetine (1), Sertraline (1), Clozapine (1)
Fatigue	4 (4.34)	Escitalopram (2), Carbamazepine (1), Clobazam (1)
Nausea	3 (3.26)	Lithium (2), Topiramate (1)
Cognitive Disturbance	3 (3.26)	Escitalopram (1), Valproate (1), Clonazepam (1)
Dry mouth	3 (3.26)	Amitriptyline (1), Sertraline (1), Trifluoperazine (1)
Anorexia	3 (3.26)	Topiramate (2), Paroxetine (1)
Orthostatic hypotension	3 (3.26)	Amitriptyline (1), Fluoxetine (1), Quetiapine (1)
Epigastric Discomfort	3 (3.26)	Paroxetine (2), Amitriptyline (1)
Reduced libido	2 (2.17)	Paroxetine (1), Amitriptyline (1)
Urinary hesitancy	2 (2.17)	Fluoxetine (1), Haloperidol (1)
EPSE	2 (2.17)	Haloperidol (1), Trifluoperazine (1)
Akathisia	2 (2.17)	Haloperidol (1), Trifluoperazine (1)
Tardive dyskinesia	1 (1.09)	Haloperidol (1)
Polyuria	1 (1.09)	Lithium (1)
Hypersalivation	1 (1.09)	Trifluoperazine (1)
Oligomenorrhea	1 (1.09)	Olanzapine (1)
Rabbit syndrome	1 (1.09)	Haloperidol (1)
Anxiety	1 (1.09)	Amisulpiride (1)
Total	n = 92	

The class of psychotropic agent most frequently suspected causing ADRs, was - antipsychotics 45.65% (typical = atypical, 22.82% each) followed by antidepressants 29.35% (SSRIs 20.65% and TCAs 8.69%) (Figure 1). Enlisted in Table 3 are the drugs incriminated in causing ADRs in descending order of frequency- trifluoperazine (11.96%) was the commonest (31.82% of ADRs), followed by olanzapine and haloperidol (10.53% each).

The most common organ system affected by the drug (Table 4) was the central nervous system (43 ADRs, 46.73%) followed by gastrointestinal gastrointestinal system (20.65%). On causality causality assessment using WHO-UMC scale, 66 ADRs (71.73%) turned out to be of "probable" category and 26 (28.26%) were of "possible" type. Rechallenge was not attempted for medical and

ethical reasons and hence none of the ADRs was labeled as "certain".

Table 3: Drugs suspected of causing ADRs.

Drug name	No of ADRs n (%)
Trifluoperazine	11 (11.96)
Olanzapine	10 (10.53)
Haloperidol	10 (10.53)
Amitriptyline	8 (8.69)
Escitalopram	7 (7.60)
Fluoxetine	6 (6.52)
Paroxetine	4 (4.34)
Lithium, Quetiapine, Carbamazepine, Topiramate, Clonazepam	3 (3.26) each
Valproate, Diazepam, Sertraline, Risperidone, Clozapine, Memantine, Amisulpiride, Divalproex, Aripiprazole	2 (2.17) each
Clobazam, Lorazepam, Piracetam	1 (1.09) each
Total	92

Table 4: Organ system affected by the ADR (by CTCAE - Adverse events by System Organ Class).

System affected	Type of ADR observed	Number of ADRs
Central and peripheral nervous system disorders	Tremors (12), Somnolence (11), Dizziness (6), Headache (5), Cognitive Disturbance (3), EPSE (2), Akathisia (2), Tardive Dyskinesia (1), Rabbit Syndrome (1)	43
Gastro-intestinal system disorders	Constipation (9), Nausea (3), Epigastric discomfort (3), Dry Mouth (3), Hypersalivation (1)	19
Metabolic and nutritional disorders	Weight gain (8), Anorexia (3)	11
Cardiovascular disorders	Palpitation (5), Orthostatic / Postural Hypotension (3)	8
General disorders	Fatigue (4)	4
Psychiatric disorders	Reduced Libido (2), Anxiety (1)	3
Urinary system disorders	Urinary Hesitancy (2), Polyuria (1)	3
Reproductive system disorders	Oligomenorrhea (1)	1
	Total	92

Assessment for severity of ADRs by modified Hartwig and Siegel scale revealed a large majority - 74 ADRs (80.43%) to be mild as shown in Figure 2. During the study period, none of the ADRs turned out to be fatal or life-threatening or required hospitalization for management.

DISCUSSION

The safety of any therapeutic agent is established during the period of drug development right from animal studies through clinical trials. Gathering data on safety continues throughout the life of a drug as there are differences in the setup of clinical trials and routine clinical practices. Relevance of this data and its application in current therapeutic practices is of utmost importance in strategically planning minimization of ADRs. Keeping the same view, this study is an attempt to bring out the ADR profile in psychiatry outpatient department of a tertiary care teaching hospital and the importance of ADR monitoring.

Monitoring of ADRs in psychiatry holds special place of importance. Psychiatry patients, who are generally dependent, are less likely to spontaneously report adverse reactions. The possible contributing reasons, which may be either on the part of patient or caregiver, could be failure to notice an adverse reaction, difficulty to establish proper communication, overlap of the problem with disease symptomatology, insufficient knowledge regarding ADRs or social neglect. Hence, the significance of active surveillance; which formed a part of the study methodology.

The overall incidence of ADRs (6.41%) in the current study closely matches to that of studies conducted by Solanke et al, (5.01%) and Prajapati et al, (8.68%).[13,14] A study conducted by Sengupta et al in Kolkata mentions that atleast 17.25% of their subjects reported ADRs.[15] Similar to other studies, the ADR pattern of present study shows male preponderance (59.74%), probably because of higher number of males attending psychiatry OPD which could be due to lack of awareness, social stigma particularly associated with females or male-dominance in society.[14,15] Studies conducted by Solanke et al, (44.27%) and Sharma et al, (38.8%) show otherwise.[13,16] More than 50% ADRs were seen in the age group of 21-40 yrs, which is working and productive; also correlates well with previous studies.[8,13,16] Some reasons could be prevalence of the disorder or better treatment seeking practices among the working age group or more attention to their health. The most commonly diagnosed condition was schizophrenia and related disorders, closely followed by mood disorders. This is reflected in the most frequently prescribed agents (viz. antipsychotics followed by antidepressants). Most commonly diagnosed conditions have a bearing on the class of drugs being prescribed, which in turn affects the pattern of ADRs depending on their safety profile.

The descending order of percentages of ADRs observed in our study was - tremors, somnolence, constipation, weight

gain. Tremor is reportedly the commonest in the studies of Prajapati et al, and Sengupta et al, while somnolence is the most frequently in studies of Solanke et al, and Sharma et al.[13-16] All these studies have documented weight gain as the second most common event. The relatively lower percentage of weight gain may be explained by lower use of antipsychotic polypharmacy, pre-counseling, or relatively lower use of atypical antipsychotics. Drug responsible for highest percentage of ADRs in our study was trifluoperazine, closely followed by olanzapine and haloperidol followed by amitriptyline. Solanke et al, Prajapati et al, and Sengupta et al, have observed olanzapine as the commonest suspected drug.[13-15] Many studies also mention haloperidol and amitriptyline among the most common incriminated drugs.[13-15] All these differences can be accounted for by differences in prescribing practices at various places.

By and large, majority of the authors have observed neurological, metabolic and gastrointestinal ADRs to psychotropic agents to be the commonest.[8,13-16] The present study also shows similar results. Most of the ADRs were mild in nature on the severity scale. Events which caused impairment in motor function were managed with corrective medication (such as trihexiphenidyl for EPSE or clonazepam for akathisia) or dose modification. Weight gain was managed by counseling for dietary habits and lifestyle changes. The suspected offending agent was withdrawn in rare cases, where the ADR was intolerable and replaced with another drug. None of the ADRs during study period resulted in death or required hospitalization; but some like tardive dyskinesia caused permanent disability.

On causality analysis, majority were found to be of probable category. Some adverse events in the study-somnolence, loss of appetite or palpitations to name a few, may be explained by underlying progression of disease, either directly or indirectly. These were included after meticulous inquiry, particularly for temporality of the reaction with drug intake. It was thought that erring on the side of caution is better to maximize safety of patients.

An important consideration is the socioeconomic background of patients attending the hospital who largely depend on free supply of medicines. A multi-centric study would be more helpful in generalizing the results as well as for comparisons between different regions. Also, a study of longer duration is warranted to allow for analysis based on duration of therapy, categorizing initial and follow up cases, analysing impact on management of co-morbid conditions. Given the limited availability of resources and setup, the study was not without limitations. Nevertheless, the pattern of ADRs according to demographic parameters, drug, disease, organ system would help physicians to identify patients at greater risk of ADRs.

Awareness among prescribers and consumers is one of the primary measures in prevention. It was observed during the study that awareness about ADR reporting among doctors, nurses and patients needs to be increased so as to improve the rate of spontaneous reports. It is worth mentioning a study conducted at a state psychiatric hospital in United States, which underlines the role of clinical pharmacists; where pharmacists also actively review all laboratory results and medication orders for indications that an ADR has occurred and help data entry into an internal online computer database.[17] Yet another study in UAE also fosters the role of clinical pharmacist.[8]

Building up of a database with combined efforts of pharmacologists and psychiatrists has been suggested by previous articles.[13,15] Involvement of nurses and pharmacists in medicines' monitoring has been described in the 'West Wales ADR Profile for Mental Health Medicines in Practice'.[18] A surveillance system involving various healthcare professionals with baseline and follow-up documentation of patients' health status can have a great impact on finding opportunities to reduce ADRs, decreasing drug related morbidity and rationalizing drug therapy.

The study provides an insight into pattern of adverse drug reactions in psychiatry outpatients of the hospital. It is prudent to communicate the drug-related side effects and adverse reactions to treating physicians as well as counsel patients (and caregivers) about them for anticipation and early detection to decrease preventable drug-related morbidity and healthcare costs. Similar studies conducted periodically can help to assess the changing ADR pattern as well as success of awareness and surveillance programmes. Implementation of initiatives adapted to suit the local needs and involvement of concerted efforts from all stakeholders in healthcare can go a long way in improving health outcomes.

CONCLUSION

The study provides an insight into pattern of adverse drug reactions in psychiatry outpatients of the hospital. It is prudent to communicate the drug-related side effects and adverse reactions to treating physicians as well as counsel patients (and caregivers) about them for anticipation and early detection to decrease preventable drug-related morbidity and healthcare costs. Similar studies conducted periodically can help to assess the changing ADR pattern as well as success of awareness and surveillance programmes. Implementation of initiatives adapted to suit the local needs and involvement of concerted efforts from all stakeholders in healthcare can go a long way in improving health outcomes.

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