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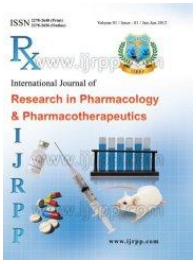

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Evaluation of pattern, predictability, severity and preventability of adverse drug reactions in the department of psychiatry at a tertiary care hospital in bengaluru – a five years experience

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ABSTRACT

Objective

Psychotropics are known to cause number of adverse drug reactions (ADRs) which often results in either nonadherence or discontinuation of therapy. Present study aimed to analyze the pattern as well as causality, preventability, severity and predictability of occurrence of ADRs in psychiatry.

Materials and Methods

This retrospective cohort study was conducted to analyze the ADRs reported spontaneously from the Department of Psychiatry at a tertiary care hospital, Bengaluru to the ADR monitoring centre, Bangalore Medical College & Research Institute. Causality of ADR was assessed by WHO-ADR probability scale, preventability was assessed using Modified Schumock & Thornton scale and severity was assessed using Hartwig and Siegel criteria. Beer's criterion was used to identify the potentially inappropriate drugs among elderly that caused ADRs. Descriptive statistics was used for analysis.

Results

40.7% of ADRs were observed among patients aged between 31-40 years. Higher frequencies of ADRs were noted among patients diagnosed with depression (34.5%), followed by schizophrenia (28.3%). Central Nervous System (58%) was affected predominantly. Headache (12.3) was the most commonly observed ADR followed by dystonia (11.1%) and drowsiness (9.9%). Patients receiving antidepressants (48%) and antipsychotics (37%) experienced more ADRs. Fluoxetine (17%) accounted for majority of ADRs followed by risperidone (12.3%). 85% of the ADRs were of 'probable' causality and predominantly predictable (95.1%). 9% of the ADRs were definitely preventable. 44% of ADRs required additional medical treatment. 96.3% of patients recovered completely.

Conclusions

5% of ADRs were severe, no mortality was noted which highlights the appropriate management of ADRs at our centre. Regular intensive monitoring of ADRs in psychiatry outpatient department will help to improve to the quality of care.

Keywords: Adverse drug reactions, Causality, Psychiatry, Preventability, Severity

INTRODUCTION

Pharmacovigilance is defined as "the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any drug related problem". [1] It is highly essential in India, as there is inadequate safety related data for psychotropics. India seems to rate below 1% in ADR reporting, as against the world rate of 5%. [2]

Patients with psychiatric disorders are often managed with pharmacotherapy. Standard treatment guidelines recommend prolonged therapy due to relapsing nature of the disease that often results in variety of ADRs. Hence, it is important to identify and report ADRs in psychiatry.

Majority of the ADRs related studies reported in Europe from 1995 to 2008, implicated psychotropic drugs. [3] Thomas et al. noted that psychotropics were responsible for 48.4% of all ADRs at a psychiatric hospital of United States over a period of 3 years. [4] The well-known AMSP (Arzneimittelsicherheit in der Psychiatrie) study concluded that the incidence of severe ADRs among psychiatric inpatients were about 1.5%. [5] All these reports emphasize the importance of ADR monitoring among patients on psychotropics.

Polypharmacy is often practiced in psychiatry as many patients may not respond to initial monotherapy, which in-turn increases the risk of encountering ADRs. Owing to the long term management of psychiatric disorders, new ADRs that were not noted during clinical trials could be encountered in clinical practice. Psychotropics directly affect central nervous system and produces undesirable behavioural changes, at times which can be life threatening. Hence, it becomes the responsibility of treating psychiatrists to identify such reactions and report them.

Growing concern among healthcare personnel over drug safety and better patient outcome has stressed the importance of pharmacovigilance. Spontaneous reporting system is the core of data generation in pharmacovigilance. Hence, the present study was taken up to analyse the ADRs reported from the Department of Psychiatry of a tertiary care teaching hospital, Bengaluru.

MATERIALS & METHODS

This retrospective cohort study was carried out from 2012 to mid-2016 to analyze the ADRs reported spontaneously from the Department of Psychiatry at a tertiary care Hospital, Bengaluru to the ADR monitoring centre of Bengaluru. Patient demographics, clinical & drug data, details of ADRs, onset time, causal drug details, outcome and severity were collected as per Central Drug Standard Control Organization (CDSCO) adverse drug event reporting form.

Assessment tools

Causality of ADR was assessed by WHO-ADR probability scale and preventability was assessed by using Modified Schumock & Thornton scale. [6, 7] Severity of each ADR was assessed using Hartwig and Siegel Scale. [8] Predictability was categorized as Type A and B ADRs. [9] Beer's criteria was use to identify the potentially inappropriate drugs among elderly that led to ADRs. [10]

Definition

An Adverse drug reaction (ADR) is defined by World health organization (WHO) as an "any response by a drug which is noxious, unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy in turns it may give such hazards effect for a fatal life." [11]

Statistical analysis

Descriptive statistics like percentage, ratio was used for analysis. Continuous parametric variables were presented as mean+SD and non parametric variables were presented as median and interquartile range. Microsoft Office Excel 2007 was used for analysis.

Ethics

The study protocol was assessed and approved by the Institutional Ethics Committee. Confidentiality of data was maintained.

Results

A total of 81 ADRs were reported spontaneously. Male preponderance 53 (65.4%) was detected. Patients aged between 22-77 years were affected the most with mean age of 40.53 +9.53 years. Majority of ADRs were noted among patients aged between 31-40 years (40.7%) followed by 41-50 years (27.1%). Least number (2.5%) of ADRs was observed among patients aged between 51-60 years.

Psychotropics caused a broad spectrum (33 different types) of ADRs affecting patients with different psychiatric disorders involving all major organ systems. (Table 1, 2)

Antidepressants (48%) were the commonly implicated drugs, of which selective serotonin reuptake inhibitors (SSRIs) [28.4%], especially Fluoxetine (17.2%) contributed for maximum ADRs. Fluoxetine was mostly responsible for diarrhoea (3.7%), headache (3.7%) and insomnia (3.7%). Dystonia (2.5%) was observed with risperidone. ADRs affecting the gastrointestinal tract (GIT) were noted commonly with antidepressants (85.7%). Ophthalmic ADRs were commonly seen with antipsychotics (75%). Weight gain was noted exclusively with olanzapine (100%).

Table 1: Disease wise distribution of ADRs (n=81)

Diagnosis	Number of ADRs	Frequency (%)
Depression	28	28.3
Schizophrenia	23	19.8
Bipolar affective disorder	10	12.3
Obsessive compulsive disorder	6	7.4
Social Anxiety Disorder	5	6.2
Acute Psychosis	4	4.9
Generalised Anxiety Disorder	3	3.7
Alcohol withdrawal syndrome	1	1.2
Somatoform disorder	1	1.2
Panic attacks	1	1.2

Table 2: Organ-system wise distribution of ADRs (n=81)

Systems involved	ADRs	Frequency (%)
Central Nervous System (n=41)	Headache	10 (12.3)
	Dystonia	09 (11.1)
	Drowsiness	08 (9.9)
	Insomnia	04 (4.9)
	Dyskinesia	03 (3.7)
	Somnolence	02 (2.5)
	Tremor	01 (1.2)
	Agitation	01 (1.2)
	Oculogyric crisis	01 (1.2)
	Akathisia	01 (1.2)
	Perioral tremor	01 (1.2)
	Neuroleptic Malignant Syndrome	01 (1.2)
Metabolic System (n=8)	Hypothyroidism	02 (2.5)
	Weight gain	03 (3.7)
	Hyponatremia	01 (1.2)
	Galactorrhoea	02 (2.5)
Anticholinergic System (n=3)	Dry mouth	02 (2.5)
	Urinary retention	01 (1.2)
Ophthalmological System (n=4)	Visual blurring	02 (2.5)
	Diplopia	02 (2.5)
	Anorexia	05 (2.5)
	Diarrhoea	04 (2.5)

Gastro Intestinal System (n=14)	Gastritis	03 (2.5)
	Constipation	01 (1.2)
	Vomiting	01 (1.2)
Dermatological System (n=4)	Maculopapular rash	02 (2.5)
	Diffuse Alopecia	01 (1.2)
	Desquamative erythematous rash	01 (1.2)
Autonomic nervous System (n=3)	Sialorrhoea	03 (3.7)
Cardio Vascular System (n=2)	Hypertension	01 (1.2)
	Postural hypotension	01 (1.2)
Haematopoietic System (n=1)	Thrombocytopenia	01 (1.2)
Musculoskeletal System (n=1)	Arthralgia	01 (1.2)

Table 3: Different drug classes implicated in ADRs (n=81)

Name of the group	Causative drug class	Causative drug	Frequency (%)
Antidepressants (n=39)	Selective Serotonin Reuptake Inhibitors (n=23)	Fluoxetine	14 (17.2)
		Escitalopram	05 (6.1)
		Paroxetine	04 (4.9)
	Tricyclic Antidepressants (n=14)	Amitriptyline	09 (9.9)
		Imipramine	05 (6.1)
	Serotonin Noradrenalin Reuptake Inhibitors (n=1)	Venlafaxine	01 (1.2)
	Newer Antidepressant (n=1)	Mitrazapine	01 (1.2)
Antipsychotic (n=30)	Atypical Antipsychotic (n=21)	Risperidone	09 (12.3)
		Clozapine	06 (6.1)
		Olanzapine	05 (4.9)
		Aripiprazole	01 (1.2)
	Typical Antipsychotic (n=9)	Haloperidol	05 (7.4)
		Chlorpromazine	02 (2.5)
		Zuclopenthioxol	01 (1.2)
		Fluphenazine	01 (1.2)
Antiepileptics (n=4)	Older Antiepileptics (n=4)	Carbamazepine	03 (3.7)
		Sodium Valproate	01 (1.2)
Benzodiazepine (n=2)	Short acting (n=2)	Lorazepam	01 (1.2)
		Clonazepam	01 (1.2)
Anti-maniac (n=3)	Lithium		03 (3.7)
Anticholinergics (n=2)	Trihexyphenidyl		02 (2.5)
Anti-tubercular (n=1)	First generation	Isoniazid	01 (1.2)

Table 4: Clinical Spectrum of ADRs related to commonly implicated drugs (n=81)

Name of the drug	ADRs	Frequency (%)
Fluoxetine (n=14)	Postural hypotension	1 (1.2)
	Diarrhoea	3 (3.7)
	Headache	3 (3.7)
	Drowsiness	2 (2.5)
	Insomnia	3 (3.7)
	Gastritis	1 (1.2)
	Anorexia	1 (1.2)
	Diplopia	1 (1.2)
	Tremor	1 (1.2)
	Sialorrhoea	1 (1.2)
Risperidone (n=09)	Dystonia	2 (2.5)
	Gastritis	1 (1.2)
	Tardive dyskinesia	1 (1.2)
	Galactorrhoea	1 (1.2)

	Dyslipidemia	1 (1.2)
	Drowsiness	1 (1.2)
	Urinary retention	1 (1.2)
Amitriptyline (n=09)	Headache	3 (3.7)
	Anorexia	1 (1.2)
	Visual blurring	1 (1.2)
	Diarrhoea	1 (1.2)

WHO-ADR probability scale indicates 85% of ADRs were of 'probable' causality and 15% were possible. Elderly patients experienced only 7 ADRs (8.6%), of which 6 (7.4%) ADRs resulted from the drugs which should have been avoided in elderly and the other 1 (1.2%) ADR was due to the drug that required caution in elderly (Table-5).

Table 5: Spectrum of ADRs among Elderly (n=81)

Potentially Inappropriate Medications (Beer's criteria) (age>60 years)	ADRs	Drug class	Causative drug	Frequency (%)
Drugs to be avoided (n=6)	Urinary retention	Tricyclic Antidepressant	Amitriptyline	1 (1.2)
	Tremor	Atypical Antipsychotic	Risperidone	1 (1.2)
	Sialorrhoea	Atypical Antipsychotic	Risperidone	1 (1.2)
	Dystonia	Atypical Antipsychotic	Risperidone	1 (1.2)
	Anorexia	Tricyclic Antidepressant	Amitriptyline	1 (1.2)
	Dry Mouth	Tricyclic Antidepressant	Imipramine	1 (1.2)
Drugs require caution (n=1)	Hyponatremia	Antiepileptic	Carbamazepine	1 (1.2)

Potentially inappropriate prescribing was observed with atypical antipsychotics (50%) and tricyclic antidepressants (50%). Risperidone (50%) was the commonly implicated drug in elderly for development of ADRs. Out of 81 ADRs, only 9% ADRs were severe, while 50% of ADRs were of moderate severity and 41% cases were of mild severity. Among severe ADRs, 50% cases required hospitalisation. Life threatening ADRs was observed in 12.5% cases. Permanent damage was seen in 37.5% cases with tardive dyskinesia. Severe ADRs were noted commonly with antipsychotics (75%). Tardive dyskinesia was noted more commonly (66% vs 33%) with atypical antipsychotics than typical antipsychotics (Table-6).

Table-6: Profile of Severe ADRs (n=81)

Causes of Severe ADRs	ADRs	Causative Drugs	Frequency (%)
Hospitalisation (n=4)	Psychosis	Isoniazid	1 (1.2)
	Neuroleptic malignant syndrome	Haloperidol	1 (1.2)
	Dystonia	Chlorpromazine	1 (1.2)
	Desquamative Erythematous Rash	Amitriptyline	1 (1.2)
Life threatening (n=1)	Neuroleptic malignant syndrome	Haloperidol	1 (1.2)
Permanent damage (n=3)	Tardive Dyskinesia	Risperidone	1 (1.2)
	Tardive Dyskinesia	Aripiprazole	1 (1.2)
	Tardive Dyskinesia	Haloperidol	1 (1.2)

Preventability scale indicates 74% of the ADRs were not preventable while 9% of ADRs were definitely preventable. Antipsychotics (57%) were responsible for majority of definitely preventable ADRs.

Out of 81 ADRs, 95.1 % were predictable ADRs (Type-A), whereas only 4.9 % were unpredictable (Type-B). Unpredictable ADRs was seen commonly with Antidepressants (50%) [Amitriptyline induced rash (25%) and escitalopram induced arthralgia (25%)]. Unpredictable ADRs frequently manifested cutaneously (75%) like, amitriptyline induced rash (25%), carbamazepine induced rash (25%) and lithium induced rash (25%). In 52% of cases ADRs were managed by reducing the doses of causative drugs while 44% cases required additional medical therapy. In 36% cases causative drug was withdrawn. Therapy was unchanged in 12% cases. 96.7% of cases recovered completely while in 3.7% cases patients recovered with sequelae. 3 (3.6%) out of 81 ADRs were of rare variety like, clozapine induced thrombocytopenia (1.2%), escitalopram induced arthralgia (1.2%) and risperidone induced perioral tremor (1.2%).

DISCUSSION

ADRs are a significant predictor of drug adherence and better patient outcome especially, in psychiatry where therapy requires prolonged administration of drugs.

Male preponderance (65.4%) was observed in the present study. About 55-60% of patients attending psychiatry outpatient department in the study centre were males which might have contributed to this result. Most common age group reporting ADRs was 31-40 years (40.7%) followed by 41-50 years and only 8.6% of ADRs was observed among elderly. G Waldemar et al evaluated the influence of age on ADRs due to psychopharmacological treatment at Switzerland and concluded that differences in doses of drugs could be an important determinant for differential distribution of ADRs among various age groups. Young patients received higher doses that were associated with higher frequency of ADRs. His observations clearly demonstrated that physicians tend to reduce the doses as the age increases. [12]

In the current study, majority (30%) of ADRs were noted in patients with depressive disorders. Sridhar SB et al from UAE reported 24% of ADRs among patients with depression. [13] An epidemiological survey conducted in India reported 15.9% as overall prevalence of depression which justifies the higher utilisation of antidepressants in the present study. [14] Antidepressants (48.1%) followed by antipsychotics (37%) were the most commonly implicated drugs leading to ADRs in the present study. Sharma T et al from Jammu & Kashmir, India on ADRs Monitoring in Psychiatry also found that antidepressants (45%) were responsible for majority of ADRs. [15] SSRIs were frequently implicated antidepressants causing wide spectrum of ADRs in the present study. Zou C et al reported that higher utilization of SSRIs could be due to their rapid onset of action, good tolerability and superior efficacy as maintenance therapy in depressive disorders. [16]

National Institute for Clinical Excellence (NICE) guideline recommends SSRIs as the first line therapy in the management of depressive disorders.[17] Effect of SSRIs on 5HT-3&4 receptors in gastrointestinal tract and post synaptic 5HT-2 receptor in spinal cord, production of nitric oxide and sleep architecture might contribute for majority of its ADRs.

Present study showed that CNS (48.3%) was commonly affected by ADRs followed by GIT (17.3%). Sridhar SB et al from UAE also reported 29.5% of CNS and 23% of GIT adverse effects. [14] Serotonin and dopamine influence huge array of brain functions, including sleep, cognition, sensory perception and motor activity. [18] Antidepressants and antipsychotics produce their therapeutic effects by modulating either seretonergic or dopaminergic pathways. Hence ADRs affecting CNS could be predominantly noted in the present study.

Fluoxetine is known to have higher affinity towards serotonin (5HT-3 and 4) receptors, resulting in increased gut motility that might have contributed to diarrhoea noted in 3.7% of the patients. Olanzapine was frequently associated with weight gain. Olanzapine is known to produce blockade of 5HT-2c, H1 and β3- adrenergic receptors receptor leading to higher levels of ghrelin and leptin which is associated with increased appetite and weight gain. [19] Tardive dyskinesia was noted commonly with atypical antipsychotics (risperidone and aripiprazole). Proposed hypothesis for tardive dyskinesia are D2 receptor super sensitivity, oxidative stress created from chronic antipsychotic use, dysfunctional striatal gamma amino butyric acid (GABA) input to motor

neurons and lower expression of serotonin (5HT-2A) receptors. [20] Aripiprazole is known to have highest affinity for dopamine (D-2) receptor leading to long term suppression followed by up-regulation of dopamine (D-2) receptors resulting in tardive dyskinesia. [21] A recent cohort study also reported increased incidence of tardive dyskinesia with atypical antipsychotics. [22] This data suggests that risk of tardive dyskinesia persists with atypical antipsychotics also. Long term and greater utilisation of atypical antipsychotics could be responsible for higher incidence of tardive dyskinesia in the present study.

Causality assessment of ADRs in this study showed around 85% as probable and around 15% as possible with no cases as certain because rechallenge of causative drug was not attempted. S.Taruna et al from Jammu & Kashmir, India noted 81% of the ADRs to be of "probable" causality. [15] In the current study 9.9% of ADRs were termed as severe which is higher compared to the AMSP study where upto 1.5% of psychiatric inpatients experienced severe ADRs. [5] Severe ADRs were noted commonly with antipsychotics. Permanent damage like slurring of speech and difficulty in chewing was also documented. This highlights the importance of individualisation (emphasis on age & gender) of pharmacotherapy especially while using antipsychotics. Identification of the predisposing factors, use of alternative drugs and strict monitoring of patients might help the clinicians to minimise potentially life threatening ADRs.

8.4% of the ADRs among elderly were due to utilisation of potentially inappropriate medications. Prescribers should avoid psychotropics with anticholinergic properties like tricyclic antidepressants among elderly, as they are known to increase the risk of urinary retention and dry mouth in them. Instead, SSRIs that are devoid of these effects could be better alternatives. Electrolyte abnormalities are commonly seen in geriatric population. So, drugs like carbamazepine which is known to cause hyponatremia should be avoided. Regular monitoring of serum electrolytes and use of other antiepileptics like valproic acid could be beneficial.

Preventability assessment showed 9% of reported ADRs were definitely preventable. Venlafaxine induced hypertension could have been prevented by close monitoring of the dose escalations. Dystonia induced by typical antipsychotics could have been prevented by choosing alternative antipsychotic that are devoid of these effects. Lithium induced hypothyroidism could have been prevented by regular screening. Courtney A. Iuppa concluded that preventable ADRs were more common with antipsychotics as noted in the present study. [23] Many complex multi-dimensional intervention strategies like, simultaneous use central anticholinergics with typical antipsychotics, fish liver oil with clozapine, close monitoring of serum levels for optimizing the doses of lithium have been suggested to prevent ADRs induced by psychotropics. [24]

4.9% of cases were noted to be unpredictable (amitriptyline induced maculopapular rash, carbamazepine induced diffuse erythematous rash, lithium induced maculopapular rash and escitalopram induced arthralgia), as the pharmacological properties of these drugs could not explain the cause of ADRs which constituted majority of unpredictable ADRs in current study.

52% cases ADRs were managed by reducing the doses of the causative drugs, while in 36% of the cases causative drug was withdrawn. 44% of the patients required additional treatment like, trihexyphenidyl to manage dystonia, oculogyric crisis and perioral tremor due to antipsychotics, propranolol to reduce akathisia due to antipsychotics, dantrolene sodium to manage patients with neuroleptic malignant syndrome, vit-E (ability to elevate super oxide dismutase level, which in turn reduces oxidative stress) for patients with tardive dyskinesia.

Some infrequently reported ADRs like olanzapine induced oculogyric crisis, risperidone induced perioral tremor and escitalopram induced arthralgia were of particular interest in our study. Oculogyric crisis is an acute dystonic reaction resulting from dopamine inhibition by typical antipsychotics in the striatum. Olanzapine induced oculogyric crisis was managed with intravenous benztropine and diphenhydramine. Perioral tremor is a hyper-cholinergic state resulting from blockade of dopaminergic neurons by typical antipsychotics. This was treated with central anticholinergic trihexyphenidyl and initiating olanzapine instead of risperidone as it has less antimuscarinic property.

This study is relevant to any facility with psychiatric patients, but data from this study may not be generalized to other psychiatric hospitals due to

differences in patient population, formulary considerations, and the academic nature of this hospital. The main limitation of our study is that, it was conducted in one hospital and there is likely to be variation among various hospitals because of local population characteristics. Though retrospective design is acceptable for pharmacovigilance study, a prospective study with larger sample size would have helped to analyse the predictors of ADRs. This study relied on data from spontaneous reporting of ADRs. Underreporting is noted to be one of the drawbacks of spontaneous reporting.

CONCLUSIONS

The present study provides a comprehensive profile of the ADRs which are encountered frequently in psychiatry department along with some rare events (clozapine induced thrombocytopenia, escitalopram induced arthralgia and risperidone induced perioral tremor). Majority of the ADRs reported during the study were moderate in severity with most of the patients recovering completely after drug withdrawal or dose alteration. Though 5% of ADRs were severe, because of appropriate and timely intervention no mortality was reported. The study emphasizes the importance of monitoring and reporting of ADRs. Regular intensive monitoring of ADRs in psychiatry might help in early detection of ADRs, leading to improvement in the quality of care, reduction of treatment cost and consequently enhancing the drug adherence.

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