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Prevalence and Assessment of Adverse Drug Reactions in Mental Health Institute in a Tertiary Care Teaching Hospital: A 2 Years of Cross-Sectional Study

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Abstract
Introduction: *There are ample of psychotropic drugs in the market and their enormous use is seen day by day in psychiatric departments and peripheral institutions. The epidemiological data are limited regarding Adverse drug reaction (ADR) reporting due to these medications and its comparison with intensive monitoring studies in terms of causality, seriousness and preventability.*
Objectives: *To assess the prevalence and different spectrum of adverse drug reactions and to find out the causal relationship, severity and preventability.*
Material and Methods: *This is a cross sectional, hospital based study carried out in Dept. of Pharmacology in collaboration with Department of Psychiatry from 1st July 2014 to 30 th June 2016 in patients attending OPD/IPD in Dept. of Psychiatry in S.C.B. Medical College and Hospital, Cuttack, Odisha. Causality, Severity and Preventability of ADR due to medications were assessed. To predict the association of ADRs with different variables like age, gender and prescribed no of medications, assessment was done by binomial logistic regression method.*
Results: *Out of 289 no of patients reported with suspected ADRs, 168 (58.13%) were male and irrespective of gender maximum ADRs were reported in 20-29 yrs of age group. Total no of suspected ADRs reported were 410. Maximum no (33.56%) of patients were receiving three drugs, followed by 29.41% were on four drugs. Maximum were diagnosed as schizophrenia spectrum of disorders (35.29%) followed by Bipolar affective disorder 37(15.74%). Most common ADR observed was extra pyramidal syndrome (EPS) (20.24%). Frequently encountered drug causing ADRs was Olanzapine (22.43%). Among the ADRs 60.55% were of probable type, 61.09% of mild type in severity and regarding preventability, 87.64% were not preventable. There was no predictable significant association of age, gender and no of medications with suspected ADRs.*
Conclusion: *Our study shows EPS was the commonest ADR detected and Olanzapine was the commonest drug causing ADRs. Majority of ADRs were assessed as probable, severity was mild and not preventable.*
Keywords: *Adverse drug reaction, Psychotropic drugs, Prevalence, Extra pyramidal syndrome, Olanzapine, Schizophrenia.*

Introduction

According to W.H.O, Adverse Drug Reaction is defined as "Any response to a drug which is noxious, unintended and undesirable, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function"[1]. Psychotropic drugs, also sometimes called as psychoactive drugs, affect the central nervous system and can change in behavior pattern as well as perception. They substancially decrease the intensity of psychiatric symptoms such as delusions, hallucinations and depression and therefore enhance the mental well-being of psychiatric patients, but the diverse range of adverse effects induced by these drugs, tremendously worsens both the physical and mental well being which lead to non adherence to therapy[2]. ADRs in hospitalized psychiatric patients are not only common, but they also have a high rate of preventability[3-4]. In accordance to one study, 20.4% of reported ADRs over a 3-year period in a state psychiatric hospital were preventable[3]. Their study also found that psychiatric medications were responsible for 48.4% of ADRs. Preventable ADRs accounted for 13% of all ADRs in a psychiatric hospital and that atypical antipsychotics accounted for 37% of all ADRs according to another study[4]. There are reports of transfer of psychiatric patients to a medical hospital due to ADRs[5].

Pharmacovigilance in Psychiatry Department plays a crucial role in detecting ADRs and alerting Physicians to the possibility and circumstances of such events, thereby protecting the user population from the harm caused by medications which are avoidable[6]. In India, Pharmacovigilance activities still in nascent stage and there are limited studies available on the ADR profile of psychotropic drugs[7]. Clinicians' awareness about the adverse effects of psychotropic drugs and their preventability can foster rational and safe use of these sort of medications.

Objectives

This study was undertaken to assess

1. The pattern of different spectrum of suspected ADRs.
2. Clinico-demographic profile of suspeted ADRs.
3. To correlate with WHO-ART system organ classes involved.
4. To assess causality, severity and preventability of the generated ADRs

Materials and Methods

This is a Cross-sectional, Observational, Hospital based study conducted in Dept of Pharmacology in collaboration with Dept of Psychiatry S.C.B. Medical College and Hospital, Cuttack, Odisha from 1st July 2014 to 30th june 2016, for a period of 2 years. Consent was obtained either from patients or relatives.

Inclusion Criteria

Patients attending both indoor and outdoor in Dept of Psychiatry.

Age group from 10 – 70 years irrespective of sex.

In OPD, 25 consecutive cases and in IPD admitted cases (20 randomly selected cases from male and female ward) in 2 rotatory days / week excluding holidays.

Exclusion Criteria

Subjects unwilling to participate

- Suffering from any chronic & autoimmune disease
- Lactating and pregnant mothers.
- Patients started receiving treatment of more than 1 year.
- Patients with history of taking any other medications including modern medicine or indigenous medicine within 15 days.
- Smoker & alcoholics.
- Those who left hospital against medical advice.
- Doubtful / unlikely and unclassifiable type of ADRs.

Sampling Methods and Sample Collection: Convenient sampling method was used to obtain appropriate sample size.

10.2 % has been assumed as the proportion[8].

Minimum sample size determination procedure for estimating a population proportion was adopted here. The formula used for the purpose is as follows:

$$n = z^2_{1-\alpha/2}\, P(1-P)/d^2$$

Where n = Minimum sample size

$z^2_{1-\alpha/2}$ = value of the standard normal variant for $1-\alpha/2$ level of significance

P = Anticipated population proportion

$100(1-\alpha)\%$ = Confidence level

d= absolute precession required on either side of the population.

In this study following values of the above parameters have been considered keeping view of the frequency of availability of the cases in the study hospital.

i) Confidence level =$\mathbf{1}-\alpha$ =95%

ii) Anticipated population proportion P=10.2%

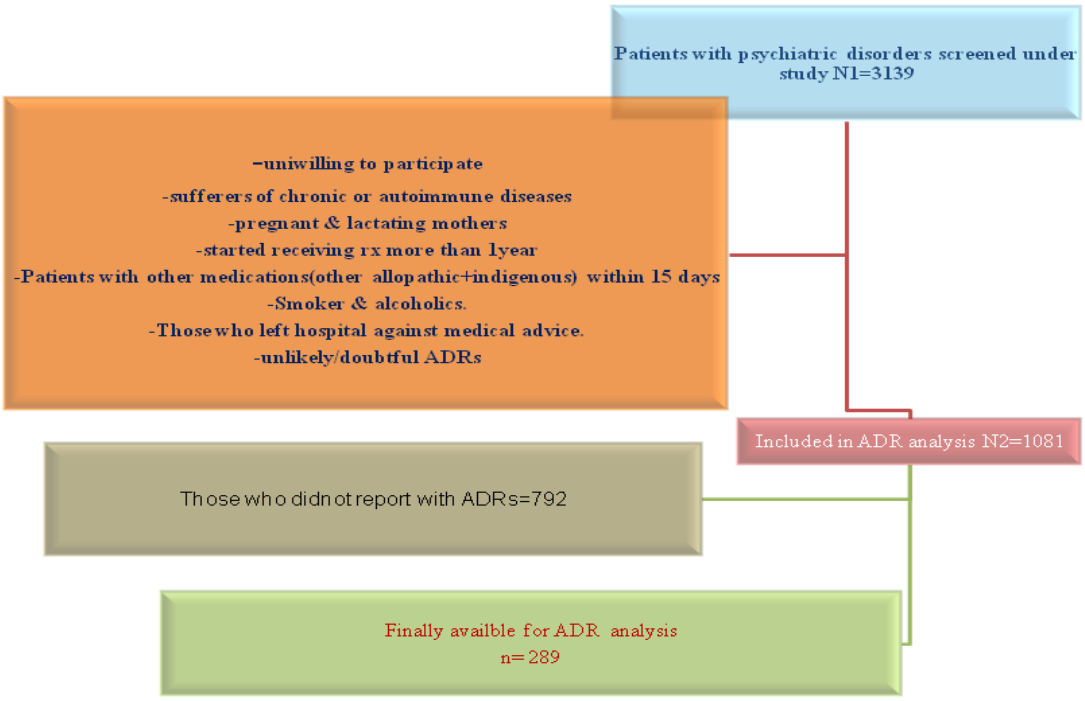
iii) Absolute precision d = 2% point

For these values of the input, the minimum sample size required was computed as 880. Assuming 10% follow up loss i.e. 88, the minimum sample size was computed as 968. Our sample size was taken as 1081.

Suspected ADRS were collected from patients as per inclusion criteria. Data entry into excel sheet and assessment of causality, severity and preventability was done in Department of Pharmacology. Drug interactions were analysed by using Medscape and Drugs.com drug interaction checker. Causality assesment was done by using WHO-UMC Scale, Preventability assessment by Schumock and Thornton scale [9] & Severity assessment by Hartwig's severity scale [10]. To establish the causality various libraries, databases like Pubmed, Cochrane, Embase and various text books were searched.

Statistical Analysis

Data was entered in Microsoft Excel and was imported to trial version of SPSS v 24. Normality of distribution was estimated by Shapiro–Wilk test *and* Kolmogorov–Smirnov test. Continuous data was summarized as mean ± standard deviation. Categorical variables were summarized as percentages. All continuous data were converted to binomial variables and binomial logistic regression was estimated to predict the association between the dependent variable (ADRs) vs independent variavles like (age, gender and no of medication) in the form of odd's ratio and confidence interval. $P < 0.05$ is considered as statistically significant. The results were presented in the form of text, tables, and figures.



Results

Out of the total 1081 patients enrolled in our study, 289 (26.73%) patients reported with Suspected ADRs. Total no of suspected ADRS were 410 and total no of different spectrum of ADRS were 41. Male: Female ratio was 1.38:1 (Male = 58.13%) having mean age group 35.30±13.15 [median age group 35 (25-45)] in patients with ADRs while 35.29±13.26 [median age group 35 (25-45)] in patients without ADRs. No of medications in patients with ADRs were 3.00±1.13 [3 (2-4)] while no of medications in patients without ADRs were 2.98±1.12 [3 (2-4)] as shown in figure 3. In both genders maximum no of patients presented with ADRs wrere in 20-29 years of age group as shown in figure 1. Commonest clinical diagnosis was schizophrenia spectrum of disorders (35.29%) as depicted in figure 2. Most common class of medications causing ADRs were antipsychotics (60.97%) followed by antidepressants (14.39%) as shown in figure 4. Most common suspected causitive agents were Olanzepine (22.43%) followed by Haloperidol (18.04%) as shown in table 2. Common suspected ADRs were extrapyramidal side effects (20.24%) followed by edema and swelling (12.43%) as shown in table 1.. According to WHO-ART SOC system, maximum ADRs were neurological (41.95%). According to WHO-UMC causality assessment scale 60.55% probable and 39.45% possible as depicted in table 4. According to modified Hartwig scale, majority of ADRs are of mild type (61.09%) followed by moderate (34.86%) and severe (4.05%) as shown in table 4. According to Schumock and thronton scale, majority are not preventable (87.64%) as depicted in table 4. Table 5 showed binomial logistic regression analysis to predict the association of patients with suspected ADRs with age group, gender and no of medications. There was statistically significant association between them.

Figure 1: Age Specific Sex Distribution Pattern (n=289)

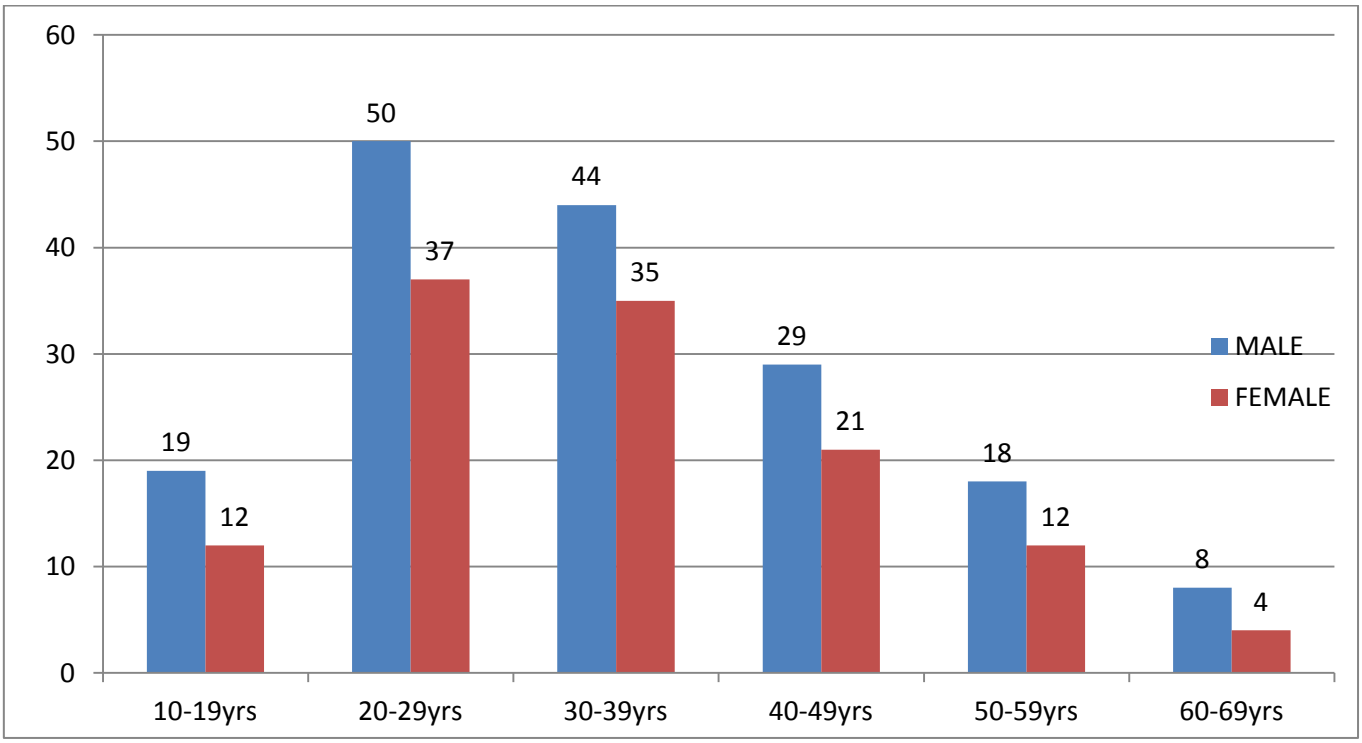


Figure 2: Patients Attending OPD & IPD For Different Indications among the cases with Suspected ADRs (n=289)

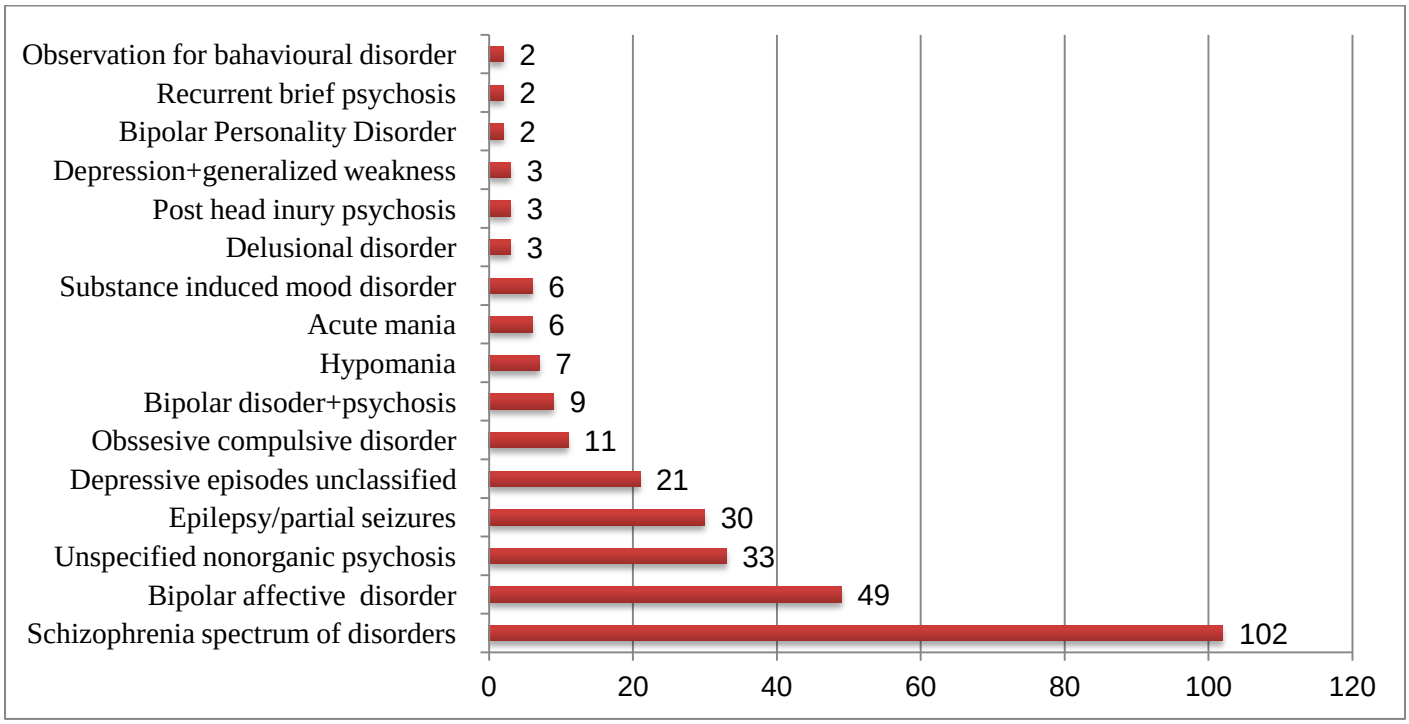


Figure 3: Numbers of Persons with ADRS on Numbers of Drugs (N=289)

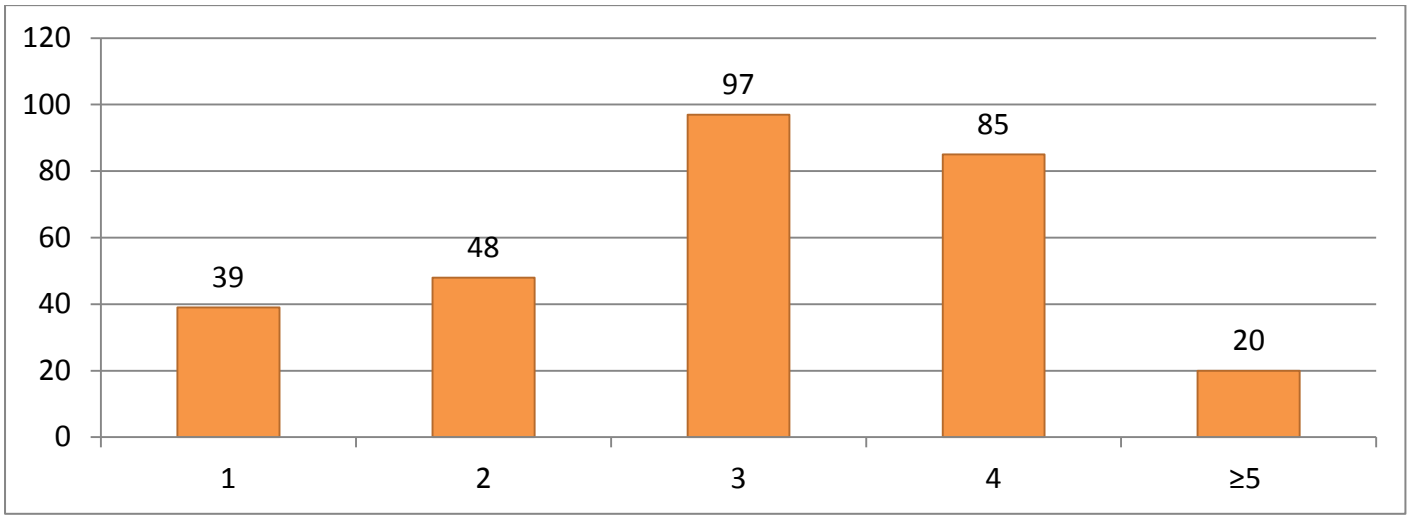


Table 1: WHO-ART SOC Code Suspected Adverse Drug Reactions (n=410)

WHO-ART SOC CODE-SUSPECTED ADVERSE DRUG REACTIONS (No of occurrences) [6]	Total no of occurrences	Percentage of occurances
NEUROLOGICAL DISORDERS (0400)- Extra Pyramidal Side effects (83), Tremor (41), lethargy (8), Slurring of speech (7), Acute dystonia (6), Ataxia (5), Akathisia (5), Gidiness (4), Light headedness (3), Headache (3)	172	41.95%
METABOLIC AND NUTRITIONAL DISORDER (0800)-Edema/swelling of limb and/or face (51), Weight gain (12), Impaired glucose tolerance (4)	68	16.58%
GASTROINTESTINAL SYSTEM DISORDER (0600)- Sialorrhea (17), Nausea/vomiting (12), Dyspepsia (7), Constipation (6), Decreased appetite (3), Increased appetite (3) Dry mouth (2), Diarrhoea (2),	57	13.90%
PSYCHIATRIC DISORDER (0500)- Sedation (22), Agitation (5), Insomnia (4), Irritability (4),	38	9.26%
SKIN AND APPENDAGES DISORDERS (0100)- Skin Rash±Pruritus (14), Sjs-Ten (7), Mpdr (6), Lichenification (2), Alopecia (2)	35	8.53%

URINARTY TRACT DISORDERS (1300)- Urinary Incontinence (4)**,** Nephropathy (3),	12	2.92%
REPRODUCTIVE DISORDERS (1400)- Decreased libido (5), Amenorrhoea (4)	09	2.34%
ENDOCRINE DISORDERS (900)- Hyperprolactinemia (3), Hypothyroidism (2)	05	1.21%
BODY AS A WHOLE GENERAL DISORDERS(1810)- Generalized weakness (6)	08	1.95%
CARDIOVASCULAR DISORDERS (100)- Palpitation (03)**,** Postural hypotension (2)	05	1.21%
HEMATOLOGICAL()- Agranulocytisis (2)	02	0.48%

Figure 4: Association of Drug Class with ADRS

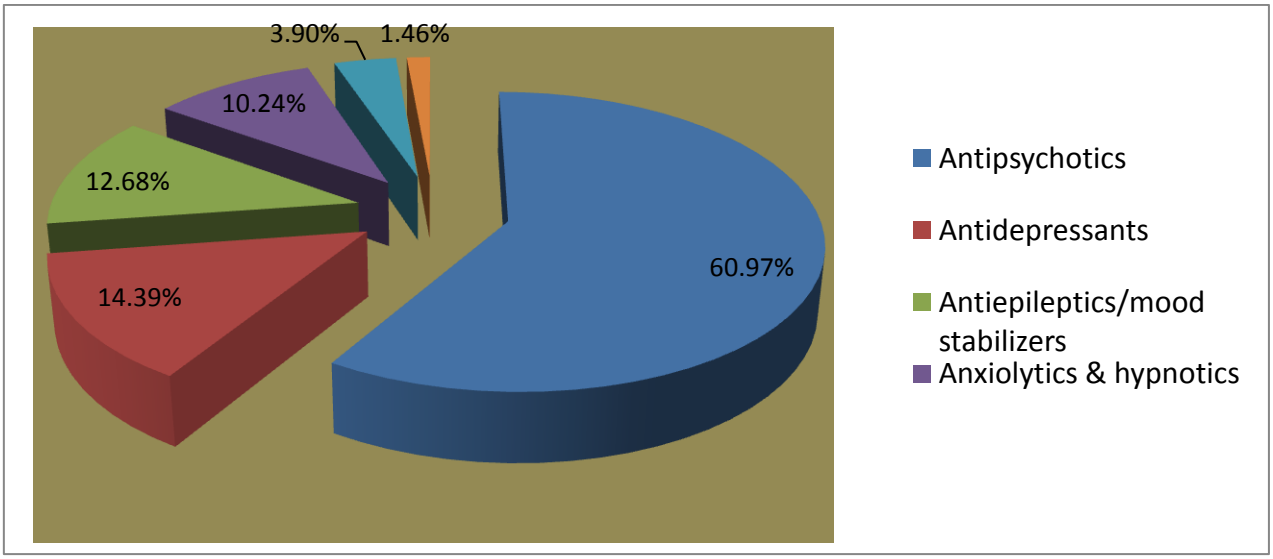


Table 2: Frequency of Prescribing Pattern of Different Neuropsychiatric Drugs in Patients with Suspected ADRS

Drugs pescribed	Frecuency	No (% of all ADRs)	Drugs pescribed	Frecuency	No (% of all ADRs)
Olanzapine	116	92 (22.43%)	Oxcarbamazepine	09	03 (0.73%)
Haloperidol	98	75 (18.29%)	Fluvoxamine	18	14 (3.41%)
Nitrazepam	82	08 (1.95%)	Chloropromazine	09	06 (1.46%)
Procyclidine	57	00 (0.00%)	Quetiapine	17	11 (2.46%)
Risperidone	48	33 (8.04%)	Sertralin	10	07 (1.70%)
Promethazine	44	06 (1.46%)	Fluoxetine	11	07 (1.70%)
Clonazepam	47	12 (2.92%)	Escitalopram	08	02 (0.48%)
Valproate	36	16 (3.90%)	Topiramate	05	03 (0.73%)
Trihexyphenidyl	38	03 (0.73%)	Amitryptiline+Chlordiazepoxide	12	08 (1.95%)
Divalproex sodium	17	06 (1.46%)	Levateracetam	04	03 (0.73%)
Phenytoin	16	10 (2.43%)	Lamotrigine	04	04 (0.97%)
Lithium	16	10 (2.43%)	Duloxetine	06	04 (0.97%)
Clozapine	22	20 (4.87%)	Risperidone+trihexyphenidyl	06	03 (0.73%)
Amisulpiride	14	08 (1.95%)	Dotheiapin	05	03 (0.73%)
Lorazepam	13	12 (2.92%)	Mirtazapine	03	03 (0.73%)
Thioridazone	11	07 (1.70%)	Loxapine	03	02 (0.48%)
Carbamazepine	12	06 (1.46%)	Aripiprazole	02	02 (0.48%)
			Trifluperazine	02	02 (0.48%)

Table 3: Drugs Commonly Implicated In Adverse Drug Reactions **(n=410)** with their frequency of use

ADRs	Name of drugs	ADRs	Name of Drug
EPS (83)	Haloperidol (59), Olanzapine (14), Risperidone (6), Trifluperazine (2)	Acute Dystonia (6)	Haloperidol (6)
Edema / Swelling (51)	Olanzapine (45), Quetiapine (2), Amitryptiline (2)	Constipation (8)	Olanzapine (4), Mirtazapine (1), Clozapine (1), Amisulpiride (1), Aripiprazole (1)
Tremor (41)	Haloperidol (3), Risperidone (15), Olanzapine (11), Clozapine (4), Chlorpromazine (3), Lithium (3)	Slurring of speech (8)	Nitrazepam (2), Haloperidol (3), Lithium (2), Fluvoxamine (1)
Lightheadedness (3)	Nitazepam (1), Clonazepam (1), Dothiepin (1)	Ataxia (6)	Valproate (2), Carbamazepine (1), Topiramate (1), Lithium (1)
Sialorrohoea (17)	Clozapine (13), Risperidone (4)	Dyspepsia (7)	Fluvoxamine (3), Duloxetine (2)
Skin rash (17)	Valproate (6), Carbamazepine (4), Lamotrigine (4), Oxcarbamazine (1), Divalproate (1)	Generalized weakness (8)	Amitryptiline (3), Escitalopram (2), Topiramate (2), Levateracetam (1)
Nausea/Vomit (13)	Valproate(5), Flavoxamine (2), Sertraline(2), Divalproate (2), Aripiprazole (1), Topiramate (1)	Akathisia (5)	Haloperidol (2), Olanzapine (1), Risperidone (1), Thioridazine (1)
MPDR (6)	Phenytoin (6)	Agitation (5)	Risperidone (2), Amisulpiride (1), Fluoxetine(1) , Loxapine (1)
SJS-TEN (7)	Phenytoin (3), Carbamazepine (2), Levateracetam (2)	Decreased libido (8)	Amisulpiride (2), Risperodone(2), Fluoxetine (1), Thioridazine (1), Chloropromazine (1), Sertraline (1)
Impaired Glucose Tolerance (4)	Olanzepine (2), Quetiapine (2)	Lethargy (8)	Clonazepam (2), Fluvoxamine (4)
Gidiness (4)	Risperidone (1), Sertraline (1), Loxapine (2)	Hyperprolactinemia (3)	Amisulpiride (3)
Insomnia(5)	Sertraline (2), Amisulpiride (2), Fluvoxamine (1)	Headache (4)	Sertraline(1), Fluoxetine(1),Fluvoxamine(1)
Amenorrhoea (4)	Haloperidol (2), Olanzepine (2)	Postural hypotension (2)	Risperidone (2)
Nephropathy (3)	Lithium (3)	Urinary incontinence (5)	Olanzepine(2), Quetiapine (2),Thioridazine(1)
Sedation (23)	Lorazepam (12), Nitrazepam (5), Amitryptiline (1), Quetiapine (2), Dothiepin (1), Clonazepam (1),Thioridazine (1)	Dry mouth (5)	Olanzepine (1), Chloropromazine (1), Mirtazapine (1), Dotheiapin (1), Amitryptiline+Chlordiazepoxide (1)
Increased appetite (3)	Olanzepine (1), Quetiapine (1)	Alopecia (3)	Valproate (3)
Lichenification (2)	Carbamazepine (1), Phenytoin (1)	Dizziness (4)	Fluoxetine (1), Fluvoxamine (1), Oxcarbamazine (1), Thioridazine (1)
Decreased appetite (4)	Divalproate (2), Duloxetine (1),Fluoxetine (1)	Diarrhoea(2)	Olanzepine (1)
Hypothyroidism (2)	Lithium (1)	Irritability (5)	Clonazepam (4), Fluoxetine (1)
Palpitation (3)	Sertraline (2), Chlorpromazine (1)	Weight gain (13)	Olanzapine (7), Quetiapine (2), Amitryptiline (1),Mirtazapine (1)
Agranulocytosis(2)	Clozapine (2)		

Table 4: Causality, Severity and Preventability Assessment

	Number	Percentage
Causality Assessment by WHO-UMC Scale		
Certain	0	0
Probable	248	60.55
Possible	162	39.45
Severity by Modified Hartiwig ANS Siegel Scale		
Mild	251	61.09
Moderate	146	35.63
Severe	13	3.27
Preventibility By Schumock and Thronton Scale		
Definitely preventable	0	0
Probably preventable	50	12.36
Not preventable	360	87.64

Table 5: Parameter Estimates For Binomial Logistic Regression Analysis

					Unadjusted odd's ratio				**Adjusted odd's ratio**			
			ADRs				95% Confidence Interval for Exp(B)				95% Confidence Interval for Exp(B)	
ADR[a]			Present	Absent	Sig.	Exp(B)	Lower Bound	Upper Bound	Sig.	Exp(B)	Lower Bound	Upper Bound
Present	Age group	<=40yrs	197	532	.758	1.047	.784	1.397	.730	1.052	.787	1.407
		>40yrs	92	260								
	Gender	Male	167	448	.720	1.051	.800	1.380	.711	1.053	.802	1.383
		Female	122	344								
	No of medications / person	2-Jan	87	244	.824	.967	.722	1.297	.793	.961	.716	1.291
		>=3	202	548								
a. The reference category is: absent.												

Discussions

Incidence of ADRs found in our study (26.73%) was similar to a study conducted by Shah *et al, that* had found 32.80% of patients in psychiatric in-patient setting, reported ADRs[11]. Incidence of ADRs found in our study was in contrast to study in two psychiatric hospitals in Germany where it was 60.7% whereas another study by Sridhar SB et al it was 10.2% in OPD patients.[12,8]. A study conducted in Brazil in 2001 showed that 219 suspected ADRs of psychoactive medications and antidepressants were the commonest groups responsible for the ADRs[13]. In our study antipsychotics were responsible for most of the ADRs.

There were more male patients who developed ADRs on administration of psychotropic agents that is similar to the findings of previous studies [14,15]. Our finding contrasts with few studies where more female developed ADRs than male[16,17]. The most common age group in which these ADRs were observed was in the 20-29 years (30.54%). Although ADRs are known to be frequently occurring in the geriatric age group, only 4.36% patients from the age group > 60 years attending our Mental health institute showed ADRs.

The medication classes most frequently associated with ADRs in our study were antipsychotics (60.97%) (mostly atypical or second generation antipsychotics) followed by antidepressants (14.39%) and mood stabilizers 12.68% (including the antiepileptics used for mood stabilization). According to study by Thomas et al, antiepileptics and second-generation (atypical) antipsychotics were the common causes of ADRs[3]. Segregation

was done on the basis of disease diagnosed [Figure-2] and the distribution of data according to suspected ADRs is shown in Table 1. Drugs use pattern in prescriptions are tabulated in Table 3.

Extrapyramidal symptoms, edema, swelling and weight gain were found to be the most common adverse effect induced by psychotropic agents according to our study [Table 1, Table 3]. The second generation anti-psychotics Olanzapine, Quetiapine and among anti depressants Amitryptiline are known to cause weight gain. A direct link between cytokines and increase in body mass index (BMI) following Olanzapine therapy has also been described[18]. Olanzapine also impairs glucose regulation and causes dyslipi-demia which leads to increase in body fat [19, 20]. Increase in serum leptin level was also attributed as a cause of weight gain in patients treated with second generation antipsychotics[21]. Second generation anti-psychotics Olanzapine and Clozapine have low propensity of extra pyramidal side effects compared to conventional anti-psychotics like Haloperidol. However they also induce tremors, akasthisia and tardive dyskinesia[22]. According to our study few cases of tremors are reported due to Olanzapine, Clozapine, Risperidone as shown in Table-3.

Regarding causality assessment, our study had no "certain" cases on WHO causality assessment scale since the suspected ADRs were mostly of mild to moderate severity [Table-4] and hence did not require withdrawal of therapy as well as patients were on multiple medications which is in contrast to another study by Sridhar et al which mentioned 14.3% were of certain type[8]. In our study, in cases where dechallenge was done, rechallenge was not attempted with the offending drug while in the Brazilian study, 24 cases were found to be "definite" after rechallenge was attempted[13]. Regarding severity assessment, mild and moderate type were maximum in our study which was similar to study by Sridhar et al[8] and Afkat A et al[23]. None of these studies found suspected ADRs to be severe whereas in our study 3.27% ADRs were found to be severe which is a matter of concern. Our study had 9 (3.27%) cases of life threatening "severe" category ADRs [Table-4] , while in the Brazilian study 12 cases were found to be life threatening "severe" category ADRs[13]. Regarding preventability assessment, our study had 50 (12.36%) cases of "preventable" ADRs [Table-4] while according to another study, 12 ADRs were found to be "preventable" [24]. In our study maximum ADRs were not preventable [360 (87.64%)]. This finding corresponds with that of Nithya *et al*. reported that all the ADRs to psychotropic drugs were not preventable[25]; while In another study by Lahon *et al*. mentioned a good number of the ADRs were probably preventable.[26]

Age, gender, number of drugs received or polypharmacy and race are the predisposing factors of ADRs[27] According to our study there was no significant association of suspected ADRs with different variables like age group, gender and no of medication [Table-5] which is similar to studies by Sridhar SB et al [gender (P = 0.06), age (P = 0.36), prescribed number of medications (P = 0.51)][8] and by Afkat A et al [age (p=0.8) or sex (p=0.6)][23]. Another study conducted by Kasper *et al.* identified that age and male gender as the predictors of tardive dyskinesia in patients with schizophrenia.[28]

Limitations of our study

As this was a cross sectional study and was done in 2 days per week in OPD and 1day per week in IPD (male & female in alternate week), it might have possible that we had missed a lots of cases which might have a great impact on final results. We had not taken diet and few other confounding factors into account which might have influenced the occurence of ADRs. Apart from routine haematological and biochemical reports, we could not generally order tests like ECG screening of patients, Therapeutic Drug Monitoring of psychotropic drugs (except Lithium in selected cases). One of the important aspect is that we coul dnot assess the adherance of the patients to psychotropic medications.

Conclusion

The prevalence of ADRs in our study population was high (26.73%). Most of them (61.09%) were mild in nature followed by 35.63% of moderate severity and 3.27% severe ADRs which led to discontinue the treatment. The present study adds to the existing data on the prevalence and severity of ADRs following psychotropic medications from the other centers and create awareness among our health care professionals about the importance of active surveillance studies. The knowledge about the possible ADRs and their severity will help the health care professionals to be vigilant about preventing, early detection, treating and alleviating the adverse health effects due to ADRs, thereby reducing the risk of morbidity and mortality caused by ADRs. Hence it may improve the quality of care, curtailing the treatment cost and augmentation of medication adherence pattern among patients.

Declarations

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Conflict of interest: None declared.

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