EVIDENCE BASED MEDICINE

Key Words: adverse drug reactions, psychotropic medications, intensive monitoring, spontaneous reporting, short and long term safety

A Prospective Surveillance of Pharmacovigilance of Psychotropic Medicines in a Developing Country

By Jisha Myalil Lucca, Madhan Ramesh, Gurumurthy Parthasarathi, Dushad Ram

ABSTRACT ~ ***Aims/objectives:*** *Psychotropic drugs are associated with significant short-term and long-term safety issues which may affect patients' mental health, physical health and cost of care.* ***Experimental designs:*** *This was a prospective study conducted in psychiatry department of a tertiary care hospital. Study included patients of any age and either sex who presented with psychiatric illness as diagnosed by ICD-10 and were receiving at least one psychotropic agent. The study involved both intensive and spontaneous reporting methods to identify ADRs. Causality, Severity, Preventability of reported ADR was assessed using standard scales.* ***Principle observation:*** *Of 4321 patients reviewed, 1630 patients met study criteria, 990 ADRs were identified from 613 patients at an overall incidence rate of 37.6%. Antidepressants were the commonest group of agents implicated in ADRs (42%) followed by Antipsychotics (41%). Escitalopram (15.9%) and Olanzapine (12.1%) were the most commonly implicated medications. Most commonly involved system organ class was Gastrointestinal system (22.7%) followed by Central and peripheral nervous system (17.8%). Dry mouth (10.2%), weight gain (8.18%) and tremors (5.85%) were the commonly reported ADRs. Female gender ($p = 0.002$), Co-morbid conditions ($p = 0.001$) and drug- drug interactions ($p = 0.000$) were found as risk factors in developing ADRs in psychiatry patients.* ***Conclusion:*** *Patients receiving psychotropic medicines need routine monitoring to ensure their safety and adherence.* Psychopharmacology Bulletin. *2016;46(1):54–66.*

Introduction

The introduction of first generation neuroleptic prompted large changes in the field of psychiatry, leading to a medical and pharmacological understanding of mental illness followed by the identification Extrapyramidal symptoms (EPS).[1,2] The correlation between the development of extrapyramidal symptoms and the improvement of psychotic symptoms led to the idea that side-effects were unavoidable. In the early 1990s new classes of antidepressants [selective serotonin

Drs. Lucca, Ramesh, Parthasarathi, JSS College of Pharmacy, JSS University, SS Nagara, Mysore – 570 015, Karnataka, India. Dr. Ram, JSS Medical College and Hospital, Ramanuja road, Mysore, Karnataka, India.

To whom correspondence should be addressed: Dr. Jisha M. Lucca, Lecturer, Department of Pharmacy Practice, JSS College of Pharmacy, JSS University, SS Nagara, Mysore – 570 015, India. Mobile: 9620970917; Office: +91 821 2 548353/56; Fax: +91 821 4 253628.

reuptake inhibitors (SNRIs)] and second generation antipsychotics (SGAs) were introduced into the market.[3] With the advent of these new treatment options, entirely a new concerns regarding different patterns of adverse drug reactions and drug interactions have arised.[4] The safety and efficacy of these newer class of drugs have been established through a large number of randomized clinical trials.[5] However most of the clinical trials of psychotropics are conducted in "ideal" conditions, patients are selected according to stringent criteria and comorbid medical conditions are usually excluded. These trials are often short-term, lasting only for a few weeks or months.[6] By contrast, the patients encounter in routine clinical practice is often having more complex presentations and comorbid medical illnesses, and they remain under care of a psychiatrist for longer periods of time.[7] Also patients do not respond to initial drug therapy, may require several trials of different medications and combination of various drugs, which can increase the risk of adverse effects or drug interactions.[8–11] In this context, ADRs that were not noticed in a trial become more apparent, and the burden of managing them falls on the practicing healthcare professionals.

Moreover, clinical development of most of the drugs happens in the developed countries, mainly in the west. Hence the efficacy and safety data available may not be applicable to Indian population due to the reasons like, difference in the prescribing practice, pharmaceutical preparation, and genetic variables.[6] Studies on the adverse drug reaction of psychotropic medications are plentiful in number,[11–20] but are carried out for short period of time (1–6 months). There is paucity of information on long term safety of psychotropic's medication, Also studies determining the predictors of ADRs to psychotropic agents and estimating the cost involved in the management of ADR are lacking. In the absence of much needed information on risk-benefit ratio on psychotropic agents, the process of therapeutic decision-making to maximize the clinical effectiveness, minimize the ADRs and provide a cost benefit treatment is difficult. Therefore, this study aims to asses both short-term and long-term safety and tolerability of psychotropic agents in general and to study the preventability and predictors of ADRs and also the cost incurred in the management of ADRs in local psychiatric population.

Materials and Methods

Study Settings and Population

This study was carried out in a tertiary care teaching hospital located in the South Indian state of Karnataka over a period of three year from April 1, 2012 to March 30, 2015. Patients of any age presented with

psychiatric illness as diagnosed by ICD-10 who were either admitted to psychiatry ward or treated on outpatient basis and receiving at least single psychotropic agent were included in the study. Patients were excluded from the study if they appeared intoxicated with drugs or alcohol or deemed actively psychotic by the psychiatrist. Patients presenting for the first time (index visit) and receiving other than allopathic drugs were also excluded from the study.

Ethical Considerations

The study protocol was reviewed and approved by Institutional Human Ethical Committee of Jagadguru Sri Shivarathreeshwara College of Pharmacy, Mysore and also administrative approval was obtained from the JSS hospital authority prior to the commencement of study.

Data Collection Procedure

This prospective study adopted both spontaneous reporting and active surveillance pharmacovigilance methodology simultaneously.

Spontaneous Reporting

Adverse drug reaction reports were accepted from all the healthcare professionals of psychiatric department irrespective of their status and types of services offered. A pre designed suitable "ADR notification form" was made available at both outpatient and inpatient unit of the psychiatric department. This was prepared based on a format similar to the national pharmacovigilance program of India (PVPI). This notification form contained only the basic and essential information. Psychiatrists, nurses and other health care professionals were asked to fill in the notification form, when they encountered suspected ADRs. Apart from notification form, other modes of reporting such as telephonic reporting, direct access, referral of patients and personal meeting were adopted to ease the reporting of "suspected" ADRs. The reporter was not required to prove cause and effect prior to the reporting of "suspected" adverse drug reaction. Once the suspected ADR was reported, patients' medical records were reviewed and also patients and or healthcare professionals were interviewed as needed to collect all the necessary and relevant data pertaining to the "suspected" ADR.

Intensive Monitoring

All the patients admitted to the psychiatric ward were intensively monitored on daily basis from the day of admission to till the day of discharge.

While, the out patients were randomly reviewed on their visits to the outpatient department (OPD) to detect any new symptoms that might be associated with the use of medicine. Any adverse event noted by the study pharmacist was brought to the notice of the concerned psychiatrist and the adverse outcome was labeled as adverse drug reaction only after discussing with the consultant. In case of any difference of opinion with respect to the suspected reaction, treating psychiatrist's opinion was considered as final. All the information required for the assessment of identified ADRs was gathered using various patient information sources and standard drug information resources. All the collected data such as patients' details, medication details, event details and other relevant data were documented in a suitably designed data collection forms. All the patients were followed regularly during their onsite visits for identification and documentation of both short-term and long-term ADRs. The follow up process consisted of patents interview and chart review.

Statistical Analysis

Predictors of each of short-term and long-term ADRs were determined at a p value < 0.05 by investigating the effect of age, gender, co morbid medical condition, type of patients, allergic condition, medication adherence, total number of drugs prescribed and pDDI. Multivariate regression analysis was used to evaluate the influence of theses predictors on development of ADRs. Also the predictors of ADRs inpatient and outpatient were determined at a p value < 0.05 by multivariate regression analysis. All the statistical analysis were performed by using Statistical Package for Social Sciences (SPSS) V21.0 software.

Result

Total 1630 patients met the study criteria and were included in the study. Of which 43.3% (n = 708) were inpatients and 56.6% (n = 922) were outpatients. A total of 1199 patients were followed at least once during the study period. Among the 1011 ADRs that were either detected or reported from 630 patients, only 990 ADRs from 613 patients were considered for further analysis, 21 ADRs from 17 patients were excluded owing to the lack of information. The overall incidence of ADR was found to be 37.6% and the average number of ADRs in a patient was 1.6 (range 1 to 8). The incidence of ADR was high in outpatients [n = 397 (43%)], female gender [n = 353 (43.4%)], patients receiving 3–4 drugs [n = 220 (43.1%)], presence of co morbid medical condition [n = 152 (48.4%)] and in patients with behavioral and emotional disorders with onset usually occurring in childhood and

adolescence (F90–F99) [n = 3 (75%)]. The incidence of ADR based on patient characteristics is presented in Table 1. A total of 688 (69.4%) ADRs were detected by active surveillance, while 302 (30.5%) ADRs were spontaneously reported by the psychiatrist, postgraduate medical students and the nursing staff of the psychiatric department. One half of the patients experienced one ADR while 24.6% and 15.8% patients developed two ADRs and three or more ADRs respectively.

Of the total 990 ADRs, long-term and short-term ADRs accounted for 14.7% (n = 146) and 85.25% (n = 844) respectively, weight gain (15%), menstrual irregularity (8.2%), tardive dyskinesia (5.4%) were the commonly observed long-term ADRs while dry mouth (11.9%) weight gain (6.8%), tremors (6.7%) and increased sweating (6.3%) were the commonly observed short-term ADRs. The long-term and short-term ADRs are presented in the Table 2. Anatomical class of medication frequently implicated in ADRs was drugs acting on the nervous system (N) [n = 952 (96.2%)]. Psycholeptics (N05) [n = 454 (45.8%)] and psychoanaleptics (N06) [n = 418 (42.2%)] were the therapeutic classes of drugs commonly implicated in ADRs. Anatomical and therapeutic class of medications implicated in ADRs is presented in the Table 3.

One half of the ADRs were 'probable' in their casual relationship, as assessed by WHO probability Scale. 76.7% adverse reactions were predictable, and preventable reactions accounted for 18.8%. One half (n = 495) of the ADRs belonged to 'Level 1' in their severity category (Table 4).

Multivariate regression analysis identified female gender, presence of comorbid medical conditions and presence of drug-drug interaction as the predictors of both short-term and long-term ADRs. Predictors of short-term and long-term ADRs and their clinical significance are given in Table 5.

Of the total ADRs, 24% of the ADRs incurred cost in the management of ADRs. Total cost incurred in the management of 238 ADRs was Rs. 114731.00/- Average cost incurred per ADR was Rs. 482.06 INR (range: Rs. 10–Rs. 7846/-). Of the total direct cost incurred in the management of ADRs, bed charge accounted for Rs. 75460.00 followed by medication cost (Rs. 24791.00). The total direct cost incurred in the management of ADRs is presented in Table 6.

Discussion

The incidence of ADR was found to be 37.6%, which is consistent with the literature that report the incidence of ADRs in the varying range of 3.6%–91%.[15–21] Average number of ADR/patient was 1.6 (range:1–8). Highest number of ADRs identified in single patient was eight and was observed in different points of time of her 45 days hospital stay.

TABLE 1

Incidence of ADRs Based on Patient Characteristics

CHARACTERISTICS	NUMBER OF PATIENTS (N = 1630)	NUMBER OF PATIENTS WITH ADR (N = 613)	INCIDENCE	NUMBER OF ADRs (N = 990)	PERCENTAGE OF ADRs
Category					
Inpatients	708	216	30.5	353	35.6
Out patients	922	397	43.1	637	64.3
Gender					
Male	818	260	31.7	416	42
Female	812	353	43.4	574	57.9
Age (years)					
Pediatrics	90	29	32.2	51	5.1
Adults					
19–29	443	177	39.9	291	29.4
30–39	486	177	36.4	285	28.9
40–49	338	129	38.1	216	21.8
50–59	154	55	35.7	83	8.4
Geriatrics	119	46	38.7	64	6.4
Number of Medications					
1–2	618	234	37.8	347	35.1
3–4	511	220	43.1	349	35.3
⩾ 5	501	159	31.7	294	29.7
Co-Morbid conditions					
Absent	1316	461	35.1	763	77.1
Present	314	152	48.4	227	22.9
Allergy					
Absent	1620	609	37.5	986	99.5
Present	10	4	40	4	0.4
Medication Adherence					
Adherent	1178	443	37.6	718	72.5
Non adherent	452	170	37.6	272	27.4
Diseases condition (ICD 10 chapter 5 categories)*					
F01–F09	44	27	61.3	29	2.9
F10–F19	187	30	16	43	4.3
F20–F29	227	102	44.9	169	17.1
F30–F39	834	306	36.6	517	52.2
F40–F49	244	104	42.6	165	16.7
F50–F59	51	22	43.1	35	3.5
F60–F69	18	9	50	16	1.6
F70–F79	19	9	47.3	12	1.2
F80–F89	2	1	50	1	0.1
F90–F99	4	3	75	3	0.3

*Organic, including symptomatic, mental disorders (F01–F09), Mental and behavioral disorders due to psychoactive substance use (F10–F19), Schizophrenia, schizotypal and delusional disorders (F20–F29) Mood [affective] disorders (F30–F39), Neurotic, stress-related and somatoform disorders (F40–F49), Behavioural syndromes associated with physiological disturbances and physical factors (F50–F59), Disorders of adult personality and behavior (F60–F69), Mental retardation (F70–F79), Disorders of psychological development (F80–F89), Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90–F99).

TABLE 2

Long-term and Short-term ADRs

LONG-TERM ADRS (N = 146)	SHORT-TERM ADRS (N = 844)
Weight increased [0408] (22), Menstrual disorders [0657] (12), Dyskinesia Tardive [1065] (8), Amenorrhea [0636] (6), Lactation non puerperal [0652] (5), Psychosis [0193] (5), Acne [0001] (5), Libido decreased [0184] (4), Hyperkinesias [0114] (4), Manic reactions [0184] (4), Alopecia [0002] (4), Gastritis [0291] (4), Urinary incontinence [0156] (4), Edema peripheral [0401] (4), Myalgia [0073] (3), Amnesia [0164] (3), Extrapyramidal disorders [0106] (3), Abdominal pain [0268] (3), Diabetes [0371] (2), Saliva increased [0222] (2), Gum hyperplasia [0296] (2), Hyper lipidaemia [1338] (2), Hypoaesthesia [0117] (2), Depression [0172] (2), Anemia [0544] (2), Fatigue [0729] (2), Impotence [0182] (2), Hyper triglyceredemia [1338] (1), Vaginal discomfort [1505] (1), Dyskinesia [1102] (1), Dystonia [0068] (1), Speech disorders [0150] (1), Tremors [0154] (1), Dreaming abnormal [1243] (1), Dyspepsia [0279] (1), Sweating increased [0043] (2), Fixed eruption [1249] (1), Arthralgia [0063] (1), Osteoporosis [0076] (1), Polyuria [0613] (1), Pancytopenia [0566] (1), Ejaculation premature [1230] (1), Hypotension [0212] (1), Hypertension [0210] (1), Bradycardia [0208] (1), Hypothyroidism [0417] (1), Taste loss [0266] (1), Epistasis [0515] (1)	Mouth dry [0218] (101), Weight increased [0408] (59), Tremors [0154] (57), Sweating increased [0043] (54), Hypotension postural [0213] (48), Constipation [0204] (44), Dizziness [0101] (30), Somnolence [0197] (27), Fatigue [0729] (26), Dystonia [0068] (18), Speech disorders [0150] (18), Thrombophlebitis [0466] (18), Gastritis [0291] (17), Appetite increased [0168] (16), Saliva increased [0222] (14), Headache [0109] (14), Anorexia [0165] (11), Taste loss [0266] (11), Yawning [0201] (10), Vomiting [0228] (10), Insomnia [0183] (10), Polyuria [0613] (10), Lactation non puerperal [0652] (10), Amenorrhea [0636] (9), Psychosis [0193] (9), Dreaming abnormal [1243] (9), Abdominal pain [0268] (9), Menstrual disorders [0657] (8), Myalgia [0073] (7), Dyspepsia [0279] (7), Hyperkinesias [0114] (7), Libido decreased [0184] (7), Delirium [0099] (6), Weight decreased [0407] (6), Hypertension [0210] (6), Hypotension [0212] (5), Tinnitus [0264] (5), Falls [1444] (5), Polydypsia [1606] (4), Acne [0001] (4), Alopecia [0002] (4), Hypoaesthesias [0117] (4), Nausea [0308] (4), Diarrhea [0205] (3), Depression [0172] (3), Hallucinations [0179] (3), Prurities [0024] (3), Impotence [0182] (3), Ejaculation premature [1230] (3), Tachycardia [0224] (3), Thrombocytopenia [0594] (2), Rash [0027] (2), Stomatitis ulcerative [0328] (2), Agitation [0163] (2), Amnesia [0164] (2), Ataxia [0088] (2), Hyponatremia [0392] (2), Manic reactions [0186] (2), Halitosis [1810] (2), Facial edema [0602] (2), Fever [0725] (2), Vision blurred [0257] (2), Urine flow decreased [1780] (2), Extra pyramidal disorders [0106] (2), Flatulence [0285] (1), Tooth ache [1376] (1), Oculogyric crisis [0132] (1), Paraethesia [0137] (1), Stupor [0151] (1), Incontinence [0156] (1), Anxiety [0166] (1), Nervousness [0188] (1), Concentration impaired [1127] (1), Hyper amonimea [1113] (1), Rash maculopapular [0030] (1), Skin discoloration [0036] (1), Edema peripheral [0401] (1), Pain [0730] (1), Urinary incontinence [0156] (1), Arthralgia [0063] (1), Palpitations [0221] (1), Diplopia [0241] (1), Gingival bleeding [0930] (1), Epistaxis [0515] (1)

TABLE 3

Anatomical and Therapeutic Class of Medication Implicated in ADRs

ANATOMICAL CLASS [CODE] (NUMBER OF ADRs)	THERAPEUTICAL CLASS [CODE]	NUMBER OF ADRs (%)
Nervous system [N] [n = 952 (96.2)]	Psycholeptics [N05]	454 (45.8)
	Psychoanaleptics [N06]	418 (42.2)
	Antiepileptics [N03]	68 (6.8)
	Analgesics [N02]	1 (0.1)
	Anti-parkinson drugs [N04]	1 (0.1)
	Other nervous system drugs [N07]	1 (0.1)
Anti infectives for systemic use [J] [n = 13 (1.3)]	Antimycobacterials [J04]	6 (0.6)
	Antibacterials for systemic use [J01]	6 (0.6)
	Antivirals for systemic use [J05]	1 (0.1)
Dermatologicals [D] [n = 12 (1.2)]	Corticosteroids, dermatological preparation [D07]	11 (1.1)
	Anti-Acne preparations [D10]	1 (0.1)
Cardiovascular system [C] [n = 6 (0.6)]	Calcium channel blockers [C08]	2 (0.2)
	Agents acting on the rennin angiotensin system [C09]	2 (0.2)
	Lipid modifying agents [C10]	2 (0.2)
Alimentary tract and metabolism [A] [n = 4 (0.4)]	Antiemetics and antinauseants [A04]	2 (0.2)
	Stomatological preparations [A01]	1 (0.1)
	Drugs for functional gastrointestinal disorders [A03]	1 (0.1)
Genitourinary system and sex hormones [G] [n = 1 (0.1)]	Urologicals [G04]	1 (0.1)
Antiparasitic products, insecticides and repellents [P] [n = 1 (0.1)]	Antiprotozoals [P01]	1 (0.1)
Blood and blood forming organs [B] [n = 1 (0.1)]	Anti anemic preparations [B03]	1 (0.1)

TABLE 4

Predictability, Preventability, Severity and Seriousness of Reported ADRs

ASSESSMENT	CATEGORY	NUMBER OF ADRs (%)
Predictability	Predictable	760 (76.7)
	Not predictable	230 (23.2)
Preventability	Not preventable	804 (81.2)
	Probably preventable	169 (17.1)
	Definitely preventable	17 (1.7)
Severity	Level 1	495 (50)
	Level 2	263 (26.5)
	Level 3	179 (18.1)
	Level 4a	20 (2.0)
	Level 4b	30 (3.0)
	Level 5	2 (0.2)
	Level 6	1 (0.1)
Seriousness	Serious	53 (5.3)
	Non Serious	937 (94.6)

TABLE 5

Predictors of Short-term and Long-term ADRs

	SHORT-TERM ADRs		LONG-TERM ADRs	
CHARACTERISTICS	ODDS RATIO (CI*)	P VALUE[a]	ODDS RATIO (CI*)	P VALUE
Age (years)				
⩽ 18	1 (Reference)			
19–29	1.627 (0.950–2.786)	0.076	0.751 (0.313–1.801)	0.521
30–39	1.277 (0.744–2.190)	0.375	0.927 (0.394–2.181)	0.862
40–49	1.019 (0.583–1.780)	0.948	1.446 (0.616–3.394)	0.397
50–59	1.292 (0.698–2.392)	0.414	0.506 (0.169–1.515)	0.224
⩾ 60	1.198 (0.628–2.283)	0.584	0.817 (0.286–2.332)	0.706
Sex				
Male	1 (Reference)			
Female	1.42 (1.13–1.8)	0.002	1.49 (1.01–2.19)	0.046
Category				
Inpatients	0.464 (0.330–0.651)	0.000	0.735 (0.424–1.274)	0.273
Out patients	1 (Reference)			
Co morbidity				
Absent	1 (Reference)			
Present	1.592 (1.208–2.098)	0.001	1.688 (1.088–2.618)	0.019
Number of drugs				
1–2	1 (Reference)			
3 to 4	1.191 (0.892–1.589)	0.236	1.352 (0.837–2.182)	0.218
⩾ 5	1.135 (0.746–1.725)	0.555	1.050 (0.521–2.117)	0.891
Medication adherence				
Absent	1 (Reference)			
Present	1.019 (0.795–1.304)	0.884	1.204 (0.783–1.853)	0.398
Allergy				
Absent	1 (Reference)			
Present	1.565 (0.403–6.080)	0.517	0.000 (0.000)	0.999
Drug-drug Interaction				
Absent	1 (Reference)			
Present	2.565 (2.032–3.239)	0.000	1.610 (1.086–2.387)	0.018

*CI, 95% confidence interval. [a]P value < 0.05 is considered as significant.

Incidence of ADRs in the outpatients (43.1%) was higher than the inpatients (30.5%). This result perhaps may be due to reasons that most of the patients were discharged within 2 weeks of their hospital admission, while majority of the psychotropic agents are expected to show their action after 2 weeks. Moreover, long-term side effects could not be detected within such short duration of hospital stay. ADRs in the inpatient settings were predominantly severe (EPS, thrombophlebitis) and required interventions, while in outpatients setting ADRs were observed to be mild and self-limiting (dry mouth, sedation). Central nervous system (CNS) and vascular disorders were the most commonly affected system organ class in inpatients; whereas in outpatients, it was gastrointestinal system disorders followed by metabolic and nutritional disorders.

TABLE 6

Direct Cost Involved in the Management of ADRs

TYPE OF DIRECT COST	NUMBER OF ADR (%) (n = 238)[a]	COST IN RS. (% COST)
Medicine Cost	226 (94.95)	24791.00 (21.6)
Lab Investigation	21 (8.82)	11050.00 (9.6)
Hospital Bed Charge	53 (22.2)	75460.00 (65.7)
Other charges[b]	41 (17.2)	3430.00 (2.9)
Total cost		114731.00

[a]⩾ 2 parameters may be involved in the management of an ADR. [b]Administration charges, nursing charges, medical devices.

It is well-reported that ADRs are more common in females.[22–24] This study showed no discrepancy to the results of the previously published studies. The explanation for a higher risk in females may be multi-causal including gender-related differences in pharmacokinetics, pharmacodynamics, pharmacogenetics, immunological and hormonal factors as well as diversity in the use of medications (contraceptives) by women compared with men. The study didn't observe any diversity in severity and type of ADRs in different age groups. One of the reasons could be that psychiatrists possibly consider the special requirements of elderly and pediatric patients and monitor them more intensively, prescribe lower dosages or avoid high-risk drugs and dangerous combinations thus reduces the risks of ADRs in these patients.

Majority of the ADRs were reported by active surveillance. However, the rate of spontaneous reporting was higher (30.5%) in this study when compared to other Indian studies (1.8–12.5%).[25–27] The reason for increased reporting rate in our study might be perhaps due to the existence of well established ADR monitoring and reporting system in the study site. Health care professionals (HCPs), especially psychiatrists, reported the majority of the ADRs. psychologists, medical interns, nurses and student nurses also reported ADRs in hospitalized patients. Surprisingly, consumers also have reported very few ADRs. It was observed that spontaneous reporting by the HCPs was majorly to those ADRs that were moderate to severe and rare reaction.

Drugs acting on nervous system was the most common (96%) anatomical class of medication implicated in ADRs and this observation is comparable with other studies.[28,29] ADRs due to psychotropic medications (94%) were far more common than non psychotropic medications (6%). This finding was similar to the results of Luppa et al.[13] study, while it contradicts with the findings of study conducted by Michele et al.[12] wherein non psychiatric medications were responsible for 53% of ADRs, which is much higher than the finding of our study. Among the non psychotropic drugs anti-infective for the systemic use was

commonly implicated in causing ADRs, This finding differ from the finding of the other studies[12,13] wherein, cardiovascular drugs reported to be most commonly implicated non psychiatric drugs. This disparity could be due to differences in the disease prevalence and prescribing pattern of medications in the study settings.

The nature of both long-term and short-term ADRs observed in our study were in consistent with the finding of the other studies.[30–32] Majority of the long term ADRs belonged to the system organ class metabolic and nutritional disorders. Weight gain was the most commonly observed long term ADR and olanzapine was the most risky agents.

The preventability of reported ADRs accounted for 18.7%. The drug class frequently associated with preventable ADRs was antipsychotics. These findings contradict with other published studies[12,13] wherein lithium was reported to be commonly associated with preventable ADRs. In 65.5% of cases drug-drug interactions was determined to be the source of preventable ADRs, only few patients had the history of allergy or documented previous ADR to the suspected drug. Also ADRs were preventable as result of preventive measures were not prescribed or administer for the patients. The ADRs were also preventable due to the reason that in few cases, dose and route of the suspected drug is inappropriate due to patient age and body weight.

The average direct cost incurred per ADR was 482.06 INR (8.3 US$) which is low compared to other Indian studies, that reported the cost involved in the management of ADRs between US$ 15 and US$ 115.[32–37] The probable reasons may be that, these studies were carried out in inpatient setting, while in our study majority of patients were from outpatient setting. The cost difference could also be due to the difference in the study settings. The cost of treatment generally varies from hospital to hospital depending on the level of sophistication and type of hospital. Usually the charity trusts hospitals charge lower fees than private corporate hospitals. Thus, results of the present study might reflect the economic burden of ADRs in similar types of hospitals across the country. The parameters that were considered for the direct cost involved in the management of ADRs include cost of medicines, bed charges, laboratory investigations and others charges like nursing fee and registration charges. As our study site is a non government funded charitable hospital consultation is free of cost therefore we are not considered the consultation charges. It was found that hospital bed charges were the major contributor of total expenses (INR 75460). However, in Thiyagu[38] et al. study higher charges in managing the adverse reactions were accounted for laboratory investigations. This disparity probably due to reason that major portion of the reported ADRs in Thiyagu et al study were hepatocellular damage. A total of 223 patients incurred some cost in managing

their ADRs. This study observed that there was a wide variation in the cost incurred in the management of ADRs that rages between Rs 10 to Rs.7846/-. It was observed that as the severity of ADRs increased, the cost incurred in the management of ADRs also increased.

Presence of co morbid condition and drug-drug interaction and female gender were identified as risk factor for long-term and short-term ADRs in psychiatry. Adequately powered, prospective randomized controlled studies are needed to assess long term safety concerns. Until such studies have been carried out, clinicians are urged to exercise caution in using these drugs and rely on the traditional means of carefully assessing and monitoring patients.

Conclusion

The study finding suggested that one-third of patients with mental disorders developed ADRs. Also, ADRs cause a significant health and economic burden to patients with mental illness. As considerable number of ADRs were preventable, it is important to develop and implement strategies to overcome such adverse consequence in future. Intense monitoring of patients especially those received multiple medications for early detection and prevention of potential DDIs may result in improved therapeutic outcomes and decreased unnecessary healthcare expenditure.

Authors' Contributions

Authors one and two contributed significantly towards the conception, design, analysis and interpretation of data and also drafting the article or revising it critically for important intellectual content. Author three and four contributed in interpretation of data, drafting the article, revising it critically for important intellectual content and final approval of the version to be published. ✤

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