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Research Article

Adverse drug reactions in a tertiary care teaching hospital in India: analysis of spontaneously reported cases

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ABSTRACT

Background: Epidemiological data are limited regarding clinical characteristic of adverse drug reactions (ADRs) in India.
Aim: The aim was to assess ADRs with reference to the causative drugs, seriousness and their other clinical characteristics in Indian tertiary care teaching hospital.
Methods: A spontaneous reporting based ADR monitoring study was conducted over a period of 2 years. The World Health Organization (WHO) definition of an ADR and its seriousness was adopted. The organ system involvement was labeled by WHO-ADR terminology. ADRs were analyzed for causality by Naranjo's algorithm, preventability by modified Schumock and Thornton's criteria and types of reactions by Rawlins and Thompson classification. Subgroup analysis was performed between serious and non-serious reactions.
Results: Of the total of 135 reactions reported 111 reactions from 97 patients were included for analysis. The incidences of overall and serious ADRs were 0.25 and 0.06 per 1000 patients, respectively. The most commonly implicated organ systems were skin and appendages (52.25%). The major causative drug classes were antimicrobials (40.28%), central nervous system (23.61%) and autacoids (15.97%). About two-thirds of the reactions (65.77%) were classified as probable and one-tenth (8.10%) as preventable. The factors significantly associated with serious reactions were age group 40-60 years (odds ratio [OR]: 5.51), parenteral drugs (OR: 2.96), central and peripheral nervous system disorders (OR: 5.06), body as a whole - general disorders (OR: 9.05) and acute onset reactions (OR: 52.62).
Conclusion: Antimicrobials are common causative agents. Cohort study is recommended to confirm the risk factors of serious ADRs in Indian population.

Keywords: Pharmacovigilance, Adverse drug reaction monitoring, Serious reactions, Causative drugs, Antimicrobials

INTRODUCTION

Adverse drug reactions (ADRs) hold special importance in healthcare as they account for hospitalization, the economic burden, and mortality.[1,2] The female gender, elderly age group, multiple medications and the recent introduction of new drugs are important risk factors for ADRs.[3] Other important factors for their occurrence are race, pregnancy, breastfeeding, alcohol intake, and state of liver and kidney functions.[4] Antimicrobial drugs and analgesics are most frequently responsible for ADRs. However, their patterns and causative drugs can vary due to different prescribing habits, use of newer drugs and referral bias.[5,6] Many of these ADRs are preventable. Identification of it helps in achieving a substantial reduction in health care cost.[7]

India is a part of World Health Organization (WHO) program for the global monitoring of ADRs that depends on spontaneous reporting. It operates for all drugs throughout their life span. It is the most affordable system, which can identify serious reactions, rare ADRs as well as generate

early safety signals for new drugs. The spontaneous reporting system has resulted in many marketed drugs being withdrawn for the safety concerns.[8] The studies conducted in this field from India are scarce. Hence, this study is undertaken to analyze the causative drugs responsible for ADRs, its seriousness and other clinical patterns in a tertiary care teaching hospital.

METHODS

This spontaneously reporting based case-series study was started after prior approval from the institutional human ethics committee, GMERS Medical College, Gotri, Vadodara. Suspected ADR reporting form of Central Drug Standard Control Organization (CDSCO), India was used for the reporting of ADRs. The physicians were stimulated for the ADR reporting by periodic sensitization program, monthly reminder letters to each department, monthly analysis of reported ADRs and whenever possible one to one meeting and were asked to report all suspected ADRs.

All spontaneously reported ADRs to pharmacovigilance cell, GMERS Medical College, Gotri from January 2012 to December 2013 were evaluated. The reporting physician was contacted for the collection of any further information when it was necessary. The reported ADRs were evaluated based on inclusion and exclusion criteria. All suspected reactions following WHO's definition of ADR - "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy"[9] and showing "definite," "probable," and/or "possible" causal association with suspected drugs by Naranjo's algorithm were included.[10] Cases of drug poisoning, medication errors, doubtful causality, and ADR forms with insufficient information were excluded from the analysis.

Data were collected in a case record form for the demographics, diagnosis, adverse drug event, incubation period for the development of reactions, outcome, severity of event, relevant investigations, causative drugs with dosage, route, frequency and duration of administration, dechallenge (withdrawal of the suspected drugs after the reaction) and its outcome, rechallenge (reintroduction of the suspected drugs after the recovery from the reactions) and its outcome, concomitant medications and polypharmacy. Suspected drugs were coded according to WHO-anatomical therapeutic chemical classification.[11] The organ system involvement for ADR was labeled per WHO-ADR terminology.[12] ADRs were classified in to three categories for the onset of reactions: acute those occurring within 1 hr of administration of suspected drugs, subacute those occurring within 1-24 hrs of administration of suspected drugs and latent those developed after 2 days of administration of suspected drugs. ADRs were also categorized into two types - augmented (A) and bizarre (B) as per Rawlins and Thompson classification.[13] The preventability of the reactions was assessed according to Schumock and Thornton's criteria modified by Lau *et al*. ADRs were categorized into three

preventable categories - definite, probable and not preventable reactions.[14] The seriousness of reactions was evaluated according to WHO criteria.[9] The subgroup analysis was done between serious and non-serious reactions for the gender, age groups, route of administration of suspected drugs, causative drug groups, organ system involvement, onset of ADR, type of reaction and preventability.

Statistical analysis

The data were extracted in Excel sheet using a structured format. The age group, gender, diagnosis, drugs, organ system involved, types, onset of reactions, outcome, causality, seriousness, and preventability were presented in proportions. The mean (95% confidence interval [CI]) was used for age. Fisher's exact test/Chi-square test was used to find an association between serious and non-serious ADRs for different variables and their odds ratio (OR) (95% CI) was calculated. All the statistical analysis was performed through Graph Pad Prism 6.0 version software (GraphPad Software Inc. USA). $p<0.05$ was considered as statistically significant.

RESULTS

A total of 389,070 patients (190,436 males and 198,634 females) had attended outpatient/admitted to the GMERS General Hospital from January 2012 to December 2013. During the study period, a total of 135 ADRs from 120 patients were reported. Of 135 reactions, 24 reactions from 23 patients were excluded for the doubtful causality by Naranjo's algorithm. A total of 111 reactions from 97 patients were included for the analysis. A total of 23 ADRs (20.72%) from 22 patients were reported as serious reactions.

Characteristics of the patients

The mean age of the patients was 40 (95% CI: 36.69, 43.37) years. The youngest patient was a 1-year-old male child, and the eldest was 72-year-old male. The age group distribution for 0-20, 21-39, 40-60 and >60 years was 8 (8.25%), 43 (44.33%), 36 (37.11%), and 10 (10.31%) percent, respectively. The females (53.61%) experienced higher reactions than males (46.39%). The male:female ratio was 1:1.15.

ADRs

The incidence of overall ADRs was 0.25/1000 patients. The incidence of a serious reaction was 0.06/1000 patients. The incidences for males and females were 0.24/1000 patients and 0.26/1000 patients, respectively. A total of 42 different types of ADRs from 13 organ systems were reported. As shown in Table 1, the commonly involved organ systems were skin and appendages 58 (52.25%) followed by gastro-intestinal system 16 (14.41%) and central and peripheral nervous system 14 (12.61%). The commonly reported

Table 1: Organ system involvement (SOC) and types of observed ADRs as per WHO-ART classification.

Organ system involvement (SOC)	Types of observed ADRs	n (%)
Skin and appendages disorders	Maculopapular rash (22), urticaria (6), FDE (6), contact dermatitis (5), acneform eruption (4), angioedema (3), erythema multiformis (3), SJS (2), urticaria with angioedema (2), erythroderma (1), dermographism (1), palmoplanter exfoliation (1), photosensitivity (1), peeling of skin (1)	58 (52.25)
Gastro-intestinal system disorders	Diarrhoea (5), oral ulcer (3), nausea (2), vomiting (2), gastritis (2), constipation (1), dryness of mouth (1)	16 (14.41)
Central and peripheral nervous system disorders	Extrapyramidal symptoms (6), giddiness (2), sedation (2), insomnia (1), tremor (1), phenytoin toxicity (1), meningitis (1)	14 (12.61)
Body as a whole - general disorders	Immediate hypersensitivity (3), anaphylaxis (1), pedal edema (1)	06 (5.41)
Metabolic and nutritional disorders	Weight gain (5)	05 (4.50)
Reproductive disorders, female	Menstrual irregularity (2), galactorrhoea (1)	03 (2.70)
Respiratory system disorders	Dry cough (2)	02 (1.80)
Psychiatric disorders	Erectile dysfunction (1), pschiatric symptoms (1)	02 (1.80)
Urinary system disorders	Unilateral facial oedema (1)	01 (0.90)
Liver and biliary system disorders	Hepatitis (1)	01 (0.90)
Vision disorders	Acute myopia with angle closure glaucoma (1)	01 (0.90)
Cardiovascular disorders, general	Hypertension (1)	01 (0.90)
Heart rate and rhythm disorders	Ventricular premature contraction (1)	01 (0.90)

SOC: System-organ classification, ADR: Adverse drug reaction, WHO-ART: World Health Organization-adverse drug reaction terminology, FDE: Fixed drug eruption, SJS: Stevens–Johnson syndrome

ADRs were maculopapular rash (22), fixed drug eruptions (FDEs) (6), urticaria (6) and extrapyramidal symptoms (6).

Causative drugs

Total number of suspected drugs was 144 (average 1.17 drugs per reaction). The most common route of administration for suspected drugs was oral 116 (80.56%), followed by intramuscular 19 (13.19%) and topical 7 (4.86%). As shown in Figure 1, major suspect drug systems were antimicrobials (40.28%), central nervous system (23.61%), and autacoids (15.97%). As shown in Table 2, commonly suspected pharmacology groups were non-steroidal anti-inflammatory drugs (NSAIDs) (14.58%), β-lactams (12.5%) and fluoroquinolones (9.72%). Commonly implicated drugs were diclofenac (11) and ciprofloxacin (9).

On subgroup analysis, antimicrobials and NSAIDs mainly caused cutaneous reactions. Antipsychotic drug mainly caused extrapyramidal symptoms and weight gain. The most common reactions observed with diclofenac, ciprofloxacin and amoxicillin was maculopapular rash (Table 3). The distribution of polypharmacy and reactions are presented in Table 4.

Single drug was suspected in 64 patients. The commonly offending classes of drugs were antimicrobials (31.25%), central nervous system (28.12%) and autacoids (10.94%). The common offenders were amoxicillin (7.81%), ciprofloxacin (6.25%) and risperidone (6.25%) in a single drug suspected cases.
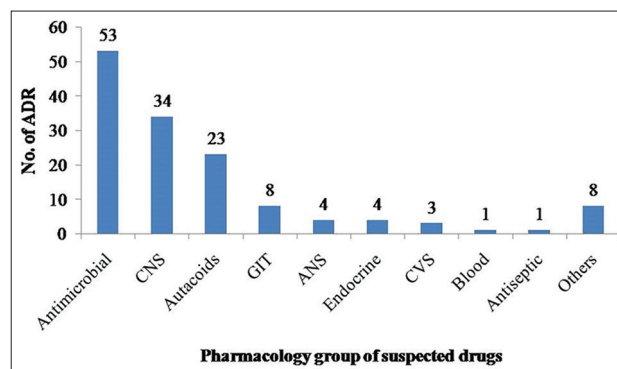

Figure 1: Pharmacology groups of suspected drugs.

Incubation period, onset of reactions, co-morbid conditions and history of allergic disorders

The incubation period varied from 2-3 mins to 6 months. The onset distributions of ADRs for acute, subacute and latent reactions were 5 (4.50%), 52 (46.85%) and 52 (46.85%), respectively. The co-morbid conditions were cardiovascular diseases (6), diabetes mellitus (2), rheumatoid arthritis (1), epilepsy (1), anemia (1), hepatic dysfunction (1), polymenorrhagia (1) and pregnancy (1). The history of atopy and food allergy was present in one patient each.

Outcome of reactions

The withdrawal of suspected drugs (dechallenge) was performed in 92 (82.88) ADRs. A total 79 (85.87%) reactions were improved after dechallenge. A total of 86 (77.48%)

Table 2: Causative drugs for suspected ADRs.

Group	n (%)	Drugs	n (%)
Antimicrobial	58 (40.28)	CNS	34 (23.61)
β-lactam antibiotics	18 (12.5)	Antipsychotic	22 (15.28)
Amoxycillin	07 (4.86)	Olanzapine	07 (4.86)
Ceftriaxone	03 (2.08)	Risperidone	07 (4.86)
Fluroquinolones	14 (9.72)	Antidepressant	06 (4.16)
Ciprofloxacine	09 (6.25)	Escitalopram	02 (1.39)
Antitubercular drugs	10 (6.94)	Amitryptilline	02 (1.39)
Nitroimidazoles	06 (4.16)	Antiepileptic drugs	03 (2.08)
Chloroquine	05 (3.47)	Opioids	02 (1.39)
Cotrimoxazole	03 (2.08)	Benzodiazepines	01 (0.69)
Other antibiotics	03 (2.08)	Other	29 (20.14)
Autacoides	23 (15.97)	Anti-ulcer	03 (2.08)
NSAIDs	21 (14.58)	Anti-diarrheal	03 (2.08)
Diclofenac	11 (7.64)	Anticholinergic	03 (2.08)
Ibuprofen	04 (2.78)	Antihypertensive	03 (2.08)
Nimesulide	03 (2.08)	Multivitamin	03 (2.08)
		Total	144 (100)

ADR: Adverse drug reaction, CNS: Central nervous system, NASIDS: Non-steroidal anti-inflammatory drugs

Table 3: Commonly suspected drugs and their patterns of reactions.

Drugs	WHO-ATC code	Number of ADR	ADRs (n)
Diclofenac	M01AB05	11	Maculopapular rash (3), FDEs (1), erythroderma (1), angioedema (1), urticaria with angioedema (1), generalized itching (1), urticaria (1), SJS (1), oral ulcer (1)
Ciprofloxacine	J01MA02	09	Maculopapular rash (3), urticaria (2), urticaria with angioedema (1), bullous fixed drug eruptions (1), SJS (1), oral ulcer (1)
Amoxycillin	J01CA04	07	Maculopapular rash (3), diarrhea (2), erythema multiforme major (1), peeling of skin (1)
Olanzapine	N05AH03	07	Weight gain (3), extrapyramidal symptoms (1), giddiness (1), unilateral facial edema (1), acneform eruptions (1)
Risperidone	N05AX08	07	Extrapyramidal symptoms (3), menstrual irregularity (2), weight gain (1), galactorrhea (1)
Chloroquine	P01BA01	05	Maculopapular rash (3), SJS (1), photosensitivity (1)

WHO-ATC: World Health Organization-anatomical therapeutic classification, ADR: Adverse drug reaction, SJS: Stevens-Johnson syndrome, FDE: Fixed drug eruption

Table 4: Polypharmacy and ADRs.

Polypharmacy	n (%)
1	21 (18.92)
2-4	57 (51.35)
5-7	26 (23.42)
>7	07 (6.31)
Total	111 (100)

ADR: Adverse drug reaction

were recovered/recovering at the time of the last assessment. The rechallenge was not performed in any patients. No fatal outcome was observed in this study (Table 5).

Serious versus non-serious reactions

Almost 20% reported reactions belonged to serious category. The reasons for the seriousness were: requirement of intervention to prevent permanent impairment/damage (11), hospitalization-initial or prolonged (7), life-threatening (4) and disability (1). The commonly observed serious ADRs were extrapyramidal symptoms (4) and immediate type of hypersensitivity reactions (3). The skin was the most commonly involved system in serious ADRs. Antimicrobial agents were the common offenders for serious reactions. They mainly caused cutaneous reactions. The comparisons of different variables between serious and non-serious reactions are presented in Table 6. The age group 41-60 yrs

(OR: 5.51 [1.97, 15.42]), parenteral drugs (OR: 2.96 [1.26, 6.92]), central and peripheral nervous system disorders

Table 5: Outcome of reactions.

Outcome	n (%)
After dechallenge/dose alteration	
Improved	79 (85.87)
Not improved	01 (1.09)
Unknown	12 (13.04)
Final outcome	
Fatal	00 (0.00)
Recovered	35 (31.53)
Recovering	51 (45.95)
Continuing	15 (13.51)
Unknown	10 (9.01)

(OR: 5.06 [1.56, 16.43]), body as a whole - general disorders (OR: 9.05 [1.54, 53.10]) and acute onset reactions within 1 hr (OR: 52.62 [2.78, 994.21]) were significantly associated with serious reactions. The age group 21-40 (OR: 0.28 [0.09, 0.86]) and gastrointestinal system disorders (OR: 0.09 [0.01, 1.62]) were significantly associated with non-serious reactions. The distribution of gender, causative drug groups, preventable reactions and types of ADR did not differ between serious and non-serious reactions.

Assessment of ADRs

The causality distributions of "definite," "probable" and "possible" categories were 2 (1.80%), 73 (65.77%) and 36 (32.43%), respectively. As per Schumock and Thorton preventability criteria "definitely preventable," "probably

Table 6: Comparison of serious and non-serious reactions.

Variables	Serious	Non-serious	OR (95% CI)	p value
Gender				
Male	13 (59.09)	32 (42.67)	1.94 (0.74, 5.10)	0.2648
Female	09 (40.91)	43 (57.33)	-	-
Age groups				
0-20	00 (00.00)	08 (10.67)	0.17 (0.01, 3.18)	0.1921
21-40	05 (22.72)	38 (50.66)	0.28 (0.09, 0.86)	0.0276
41-60	15 (68.18)	21 (28.00)	5.51 (1.97, 15.42)	0.0015
>60	02 (9.10)	08 (10.67)	0.84 (0.16, 4.27)	1.0000
Route of administration				
Parenteral	13 (39.39)	20 (18.02)	2.96 (1.26, 6.92)	0.0198
Oral	20 (60.61)	91 (81.98)	-	-
Causative drug groups				
Antimicrobial	13 (39.39)	45 (40.54)	0.35 (0.15, 0.83)	0.9061
CNS	11 (33.33)	23 (20.72)	1.91 (0.81, 4.51)	0.2061
Autacoids	03 (09.09)	20 (18.02)	0.45 (0.13, 1.64)	0.2855
Gastrointestinal tract	03 (09.09)	05 (04.50)	2.12 (0.48, 9.39)	0.3843
Organ system involvement (SOC)				
Skin and appendages	08 (34.78)	50 (56.88)	0.40 (0.16, 1.05)	0.0991
Gastro-intestinal system	00 (00.00)	16 (18.18)	0.09 (0.00, 1.62)	0.0395
CNS and PNS	07 (30.43)	07 (07.95)	5.06 (1.56, 16.43)	0.0111
Body as a whole - general	04 (17.39)	02 (02.72)	9.05 (1.54, 53.10)	0.0163
Onset of ADR				
Acute (<1 hr)	05 (21.74)	00 (00.00)	52.62 (2.78, 994.21)	0.0003
Sub-acute (1-24 hrs)	09 (39.13)	43 (48.86)	0.67 (0.26, 1.72)	0.5497
Latent (>2 days)	09 (39.13)	43 (48.86)	0.67 (0.26, 1.72)	0.4889
Preventability assessment				
Preventable	03 (13.04)	06 (06.82)	2.05 (0.47, 8.91)	0.3896
Not preventable	20 (86.96)	82 (93.18)	-	-
Type of ADR				
Augmented (A)	11 (47.83)	38 (43.18)	1.20 (0.48, 3.03)	0.8143
Bizarre (B)	12 (52.17)	50 (56.82)	-	-

p value by Fisher's exact test/Chi-square test. OR: Odds ratio, CI: Confidence interval, SOC: System organ classification, CNS: Central nervous system, PNS: Peripheral nervous system, ADR: Adverse drug reaction

preventable" and "not preventable" categories were 8 (7.20%), 1 (0.90%) and 102 (91.90%), respectively. Reasons for the preventability were: inappropriate drug for the patient's clinical condition (7), history of allergy or previous reactions to the drug (1) and required therapeutic drug monitoring was not performed (1). The six out of seven instances of inappropriate drug selection belonged to antimicrobials. Type A - augmented and Type B - bizarre category reactions were 49 (44.14%) and 62 (55.86%) respectively.

DISCUSSION

In this study, the overall incidence of ADRs was 0.25 per 1000 patients, which included reports from both outpatients and inpatients. The observed incidence is low as compared to previous studies.[7,15-18] They could not be directly compared with this study as reported incidences in these studies were mainly based on inpatients only or related to specific wards or intensive monitoring. Jose and Rao based on the data of spontaneous reporting observed the incidence of 1.14% for inpatients and 0.012% for the outpatients.[19]

In this study, demographic data showed slightly high incidence of ADRs in females. Female gender is considered important risk factors for ADRs.[3,4] Other Indian spontaneous reporting studies had also observed high percentage of ADRs in female.[15,16,20] However, Jose and Rao observed similar incidence of 0.15% for both genders.[19] The adults showed high frequency of reactions, which is in concurrent with the studies by Venkatesan et al.,[17] Rajkannan et al.[18] and Rao et al.[20] but differed from Ramesh et al.[15] and Arulmani et al.[16] showing high incidence in elderly.

In the present study, most commonly involved system was skin. A similar trend was reported in previous studies.[16,19,21] The other most commonly reported system in the literature is a gastrointestinal tract.[15,17,18,20] In our study, gastrointestinal tract was second most commonly involved system. In one Indian study, gastrointestinal reactions occurred most commonly during hospitalization while cutaneous reactions most commonly accounted for hospitalization.[7] The most commonly identified ADR was rash, as reported earlier.[16,19,21] Other studies reported vomiting and hypokalemia as common reactions.[18] The most common serious reaction was extrapyramidal symptoms in this study that is in contrast with the previous studies showing pancytopenia[15] and Stevens–Johnson syndrome (SJS).[21] In line with the previous study, most reactions had subacute and latent onset.[18]

The major causative drug class was antimicrobials. This finding is concurrent with many epidemiological studies.[7,16,18,20-22] The cardiovascular drugs[15] and antineoplastic agents[19] are also reported in the literature. In this study, antimicrobials were most commonly reported class for the drug allergies as observed earlier.[23] They are reported as most frequent cause of serious cutaneous reactions like SJS in India.[24] In concurrent with the previous study, commonly

observed antimicrobial groups were β-lactam antibiotics and fluoroquinolones.[25] β-lactams are the commonest cause of drug allergies in most epidemiological studies on ADRs.[23] The cross-reactivity is also frequent among them. Skin tests, specific immunoglobulin E assays and cellular tests in negative patients can facilitate confirmation of its allergy.[23] Among antimicrobials, ciprofloxacin was the most commonly implicated drug in this study. Fluoroquinolones can cause both immediate and non-immediate type of reactions.[23] High degree of cross-reactivity among fluoroquinolones is observed in the literature.[26] Skin tests lack sensitivity and specificity for fluoroquinolones.[23] Other studies reported amoxicillin,[16,19] ceftriaxone[18] and cotrimoxazole[22] as most commonly implicated antimicrobials. In this study, we found that amoxicillin was the most frequent among single drug suspects.

The most common pharmacology group was NSAIDs and implicated drug was diclofenac in this study. Other studies had reported salbutamol[18] and phenytoin[19] as most commonly suspected drug for ADRs. Diclofenac was suspected in almost all types of common cutaneous reactions including rashes, FDEs, urticaria, angioedema, and itching. It also accounted for serious cutaneous reactions like erythroderma and SJS. Skin prick and intradermal tests are not reliable for diclofenac. There is a possibility of cross-reactivity with other phenylacetic acids such as aceclofenac and fenoclofenac.[27] The cutaneous reactions are reported with all NSAIDs irrespective of their chemical group. They affect 0.3% of the general population.[28] However, not a single case of gastrointestinal system disorder was reported with diclofenac. This may be because of spontaneous reporting nature of this study and physicians may have felt that gastrointestinal symptoms are not worth to report.

Among central nervous system drugs, antipsychotics were commonly identified drug group. Among them, olanzapine and risperidone were the commonly identified drugs. Olanzapine most commonly involved in weight gain while risperidone caused extrapyramidal symptoms that are in line with the previous study.[29] One Indian study observed olanzapine and haloperidol as most common offending drugs among psychiatric outpatients.[30] The difference for common antipsychotics may be due to the difference in utilization pattern of drugs. In our hospital, atypical antipsychotics are preferred over typical ones.

The distribution of causative drugs among overall cases and single drug suspected cases showed similar trends for common causative classes and drugs. The antimicrobials, central nervous system drugs, and autacoids were common agents in both groups. However, antimicrobials (31.25% vs. 40.28%) and autacoids (10.94% vs. 15.97%) showed low frequency while central nervous system drugs (28.12% vs. 23.61%) showed high frequency in single drug suspected cases as compared to overall cases. This may be because of less frequency of co-prescriptions with central nervous system drugs than antimicrobials and NSAIDs. Second,

it is also easier to identify the characteristic ADRs of antipsychotics and antidepressant agents.

Total 20% reactions were of serious in nature in our study which is lower than 52% by Doshi et al.[7] However, commonly observed reasons for seriousness like requirement of intervention and initiation or prolongations of hospitalization were in line with Doshi et al.[7] We observed cutaneous reactions as most frequent serious ADR. This is in contrast to the previous study showing acute renal failure.[31] In this study, factors associated with serious ADRs were age group 41-60 years, parenteral route drugs, central and peripheral nervous system disorders, body as a whole - general disorders and acute onset reactions within 1 hr. Zopf et al. had observed raised temperature, low erythrocyte levels, low thrombocyte levels, a high number of drugs and female gender as independent predictors for ADRs associated with hospitalization.[32] In line with our study, one spontaneous reporting study from UK found no difference between males and females for serious ADRs. However, their reporting were highest in the fifth and sixth decades and was appeared to decline in the ninth decade.[33] The factors for serious ADRs require cautious interpretation due to spontaneous nature of this study. Trends of reporting in French pharmacovigilance database suggest that ADR reports represent both serious and non-serious reactions during the 1st year of marketing of new drug. Later on practitioners know the main ADRs and prefer to report serious ADRs.[34] Large scale cohort study with intensive monitoring is required to confirm the risk factors for seriousness of reactions in Indian population.

The withdrawal of suspected drugs was required in almost 80% cases, and the majority of them showed improvement at the time of the last assessment. Dechallenge was not performed in remaining cases due to therapeutic reasons. For the ethical reasons rechallenge was not performed in any case.

In causality assessment, almost 65% reactions belonged to "probable" category. This was in line with the previous studies.[16,18] Almost 30% cases belonged to "possible" category. In most cases, it was because of multiple drug suspects. This may be because of high frequency of polypharmacy. Almost one-fourth patients who developed ADRs were on more than five drugs. The multiple medications are important risk factors for drug interactions and ADRs.[35] Each additional medication taken by the patient's multiplies the hazard of an ADR occurrence by 1.14 (95% CI 1.09, 1.20).[2] In this study, a total of one-tenth of the reported ADRs was preventable, which is lower than literature suggesting its rate of 15-37% in Indian studies.[7,18,19] This suggests rational selection of drugs as per indications in majority of cases. The main reason for the preventability was an inappropriate use of antimicrobial agents. This together with polypharmacy highlights an important area for improvising the drug utilization. This can be minimized by increasing awareness among physicians. Majority reactions in our study belonged to Type B. This finding is in contrast to previous studies.[17-19]

This study has many limitations. There is a possibility of underreporting due to spontaneous nature of the study. One important factor is physicians' lack of interest for reporting and documentation of well-established drug-ADR pair. No ADR with a new drug was observed in this study. One reason may be because of Government setup of this study and physicians usually prescribe from the hospital pharmacy. Secondly, it may be because of Weber effect where peak of ADR reporting occurs during the initial period of post-marketing phase.[36] We also observed similar findings in other spontaneous reporting studies from Government or public charity hospitals across India. CDSCO should actively involve private hospitals/ practitioners to have more data about the newer drugs. Our study represents the data of tertiary care teaching Government hospital. This may not be applicable to private hospitals and other levels of health care systems. The preventability assessment was based on the judgment of pharmacologists. Skin allergen tests and oral drug provocations were not performed in patients of cutaneous allergic reactions with multiple drug suspects to identify the culprit and safer alternatives.

CONCLUSION

In our set up, the efficiency of spontaneously reporting system to detect overall and serious reactions was 0.25 and 0.06/1000 cases, respectively. Adults and females experienced more ADRs. The commonly observed organ systems in ADRs were skin and appendages and gastro-intestinal system. Central and peripheral nervous system disorders and body as a whole - general disorder were associated with serious reactions. The commonly implicated pharmacology groups were NSAIDs, β-lactams and fluoroquinolones. The most implicated class for a serious reaction was antimicrobials. Requirement of intervention and initiation or prolongation of hospitalization were common reasons for seriousness. Irrational use of antimicrobials is common reason for the preventable ADRs.

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