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PATTERN, CAUSALITY ASSESSMENT AND SEVERITY OF SUSPECTED ADVERSE DRUG REACTIONS REPORTED AT TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT: Background: Present study was conducted to evaluate pattern, causal association and severity of suspected Adverse Drug Reactions (ADRs) at a tertiary care teaching hospital in western India. **Materials & Method:** Spontaneous collection of suspected ADRs was done over a period of one year. Demographic data, suspected drug group/s, causal association, severity & preventability scale from the reported ADRs were analysed. **Results:** 150 suspected ADR reports were collected. Adult patients (14-50 years) experienced 109 (72.66 %) ADRs followed by elderly patients (>50 years) experienced 29 (19.33%) ADRs and paediatric patients (<14 years) experienced 12(8%) ADRs. On the causality scale 62.67% were probable ADRs and on severity scale 63% were moderately severe ADRs. According to MeDRA classification of ADR, Skin and subcutaneous tissue disorders were most common (47.67%), followed by Gastrointestinal disorders (23 %) and Nervous system disorders (13.95%). ADRs were most commonly seen due to antimicrobial drugs (44.3%) followed by Non steroidal anti-inflammatory drugs (NSAIDs) (17.8%). **Conclusion:** Our study findings showed underreporting in spontaneous ADR reporting system. Continuous efforts through training, sensitization & awareness programmes of all the stakeholders of health care system should be done to improve ADR reporting.

INTRODUCTION: The incidence of adverse drug reaction (ADR) has been raised drastically because of mushrooming of new drugs that occurred in health care practice, especially in last decade [1]. According to WHO, ADR is any response to a drug that is noxious and unintended, and that occurs at doses used in man for the prophylaxis, diagnosis or therapy of disease or for modification of physiological function [2].

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While Pharmacovigilance encompasses science and activities related to detecting, assessing, understanding and preventing adverse effects or any other drug-related problem [3]. Drug therapy can act as a double-edged sword in the management of ailments. Rational drug use can make a remarkable improvement in morbidity and mortality. In contrast, irrational drug usage, polypharmacy and drug interactions are major responsible factors for adverse drug reactions, increased in-hospital stay, and a remarkable increase in the cost of therapy.

Pharmacovigilance aims to foster rational drug therapy to maximize the health care outcome through early detection, treatment, prevention of adverse drug reactions and associated health care burden. ADR is a major concern for the patient too,

and it has been found that it is the core reason for the reduction in patient compliance. If ADR has been effectively communicated before therapy, there will be a definite improvement in patient compliance [4]. Further to this, the data collected by ADR reporting will be very useful for the future decision of the therapeutic status of the drug as well as the selection of drug treatment for health illnesses [5].

Pharmacovigilance's official functioning has been initiated in India through "Pharmacovigilance Programme of India" (PvPI) by Govt. of India in 2010. The headquarter of this program was shifted to Indian Pharmacopoeia Commission (IPC) in 2011 as a national coordinating center (NCC) in Ghaziabad [1]. There is an improvement in the reporting of ADRs because of tireless efforts of national coordinating center and peripheral ADR monitoring centres [6]. It was also reflected in the reporting number. In 2020-21, the total number of ADR reporting was 52, 810 [7]. These data were effectively evaluated and utilized by NCC, and recommendations were made to the Central Drug Standard & Control Organization (CDSCO) for the necessary regulatory measures. Even though the graph of the ADR reporting is on an increasing trend year by year, the actual percentage of ADR reporting is far from the expected (only 1% Vs expected 5-6%) [8, 9].

Amidst many measures, the most important measure is to enhance the awareness of health care professionals about the importance of ADR reporting. This will improve the outcome of therapy and reduce the health care-associated economic burden to society. Considering all these, the present study evaluated the pattern, causal association, and severity of suspected adverse drug reactions (ADRs) in western India's tertiary care teaching hospital.

METHODS: This research work was conducted after the approval (IAEC no-19/2019; dated 25/10/2019) of the institutional ethics committee, GMERS medical college, Gandhinagar, Gujarat, India. Suspected ADRs were collected over one year through spontaneous reporting from all the clinical specialties of tertiary care teaching hospitals. All the spontaneously reported suspected ADRs (N=150) by health care professionals (including intern doctors) in the outpatient department (OPD) as well as in patient department (IPD) were evaluated.

Data of spontaneously reported ADRs were collected from health care professionals, and they were carefully evaluated. Demographic details of patients, duration & details of suspected adverse reaction, suspected agent(s) along with indications for which they were prescribed, other co-prescribed agents, self-medications, laboratory parameters, de-challenge, re-challenge and the outcome were reported in suspected ADR reporting form.

MeDRA (Medical Dictionary for Regulatory Activities) coding system was utilized for system organ classification of suspected adverse drug reactions [10]. The causal association was done by using Naranjo's causality assessment scale [11]. According to this scale, ADRs were classified into definite (if score >9), probable (score in between 5-8), possible (score in between 1-4), and doubtful (if 0 or less than it). Modified Hartwig and Siegel scales were used to assess the severity of suspected ADRs [12]. Based on this scale, suspected ADRs were categorized into mild, moderate, and severe based on the duration of hospitalization, the requirement of change in the medication and if any disability occurred or not due to ADR. Data was entered in Microsoft Excel version 2010 and the results were analyzed using descriptive statistics. Results were presented in table, pie chart and bar diagram. Throughout the research, confidentiality of study participants was maintained.

RESULTS AND DISCUSSION: Pharmacovigilance programme of India (PvPI) has monitored adverse drug reactions across the country since 2010, and total 395 adverse drug reaction monitoring centers (AMCs) have been recognized in India [13]. Although most health care professionals are sensitized about Pharmacovigilance, the practice of spontaneous ADR reporting is highly underrated.

For the present study, total 150 ADR forms were evaluated. The analysis of ADR forms revealed that patients aged 14 to 50 years experienced 109 (72.66 %) ADRs, elderly patients (>50 years age) experienced 19.33 %, and pediatric patients (< 14 years age) experienced 8% ADRs. Concerning

patient gender, 51% of female experienced ADR. Age is one of the important risk factors for the occurrence of ADR[14]. Previous studies showed that high incidence of ADR reporting in paediatric and old age patients may be due to age-related changes in pharmacokinetics and pharmacodynamics of drugs.

In contrast, we have found the maximum number of ADR reported in adult patients. This finding can be attributed to the age-related changes in pharmacokinetic and pharmacodynamic of drug responses, co-morbid conditions, and polypharmacy [15-17].

Our study also showed that the female gender reported more ADRs than males, similar to other studies. An increased number of drugs prescribed to females is a possible explanation. Other probable factors include differences in weight, body mass index, fat composition, and hormonal changes in different phases (menstruation, pregnancy, lactation, menopause) [18].

System Organ Class Analysis: According to MeDRA classification of ADR, as shown in **Table 1**, skin and subcutaneous tissue disorders were the most affected system with 47.67% of all ADRs reported, followed by Gastrointestinal disorders (23 %), nervous system disorders (13.95 %) and General disorders and administration site conditions (5.81 %). Similar findings were observed by Jung IY *et al*. Dermatitis was the most common preferred term (16.28 %), followed by vomiting (11.63%) and pruritus (10. 47 %). Patients are more cautious about skin-related issues, leading to frequent hospital visits [19].

TABLE 1: CLASSIFICATION OF ADR ACCORDING TO MEDRA

S. no.	Medra SOC	SOC case	PT	PT no.	PT (%)
1	Skin and subcutenous tissue disorder	82	Dermatitis	28	16.28
			Pruritus	18	10.47
			Rash	14	8.14
			Urticaria	9	5.23
			Angiooedema	6	3.49
			Fixed drug eruption	3	1.74
			Skin discoloration	2	1.16
			Dry skin	1	0.58
			Erythema multiformae	1	0.58
2	Gastrointestinal disorders	40	Vomiting	20	11.63
			Gastritis	7	4.07
			Constipation	6	3.49
			Abdominal pain	4	2.33
			Salivary hypersecretion	2	1.16
			Diarrhoea	1	0.58
3	Nervous system disorders	24	Tremor	13	7.56
			Headache	6	3.49
			Dizziness	3	1.74
			Dysarthria	1	0.58
			Tardive dyskinesia	1	0.58
4	General disorders and administration site conditions	10	Pain	5	2.91
			Swelling	3	1.74
			Pyrexia	2	1.16
5	Musculoskeletal and connective tissue disorders	4	Restlessness	3	1.74
			Muscle rigidity	1	0.58
6	Reproductive system and breast disorders	4	Breast pain	2	1.16
			Genital ulcer`	1	0.58
			Male sexual dysfunction	1	0.58
7	Metabolism and nutrition disorders	3	Weight increased	2	1.16
			Decreased appetite	1	0.58
8	Respiratory, thoracic and mediastinal disorder	2	Dyspnoea	2	1.16
9	Renal and urinary disorders	2	Urinary retention	2	1.16
10	Vascular disorders	1	Orthostatic hypotension	1	0.58

Causality and severity assessment

The Causality assessment, according to Naranjo's algorithm, is shown in **Fig. 1**, 62.67 % ADRs were classified as 'probable' and 36.67 % ADRs as 'possible.

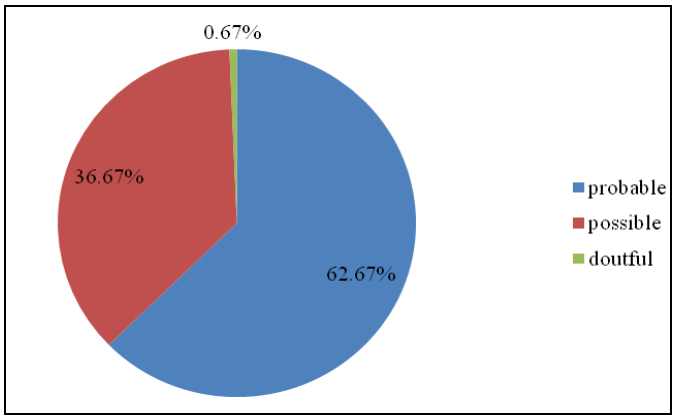

FIG. 1: CAUSALITY ASSESSMENT OF REPORTED ADR ACCORDING TO NARANJO'S SCALE

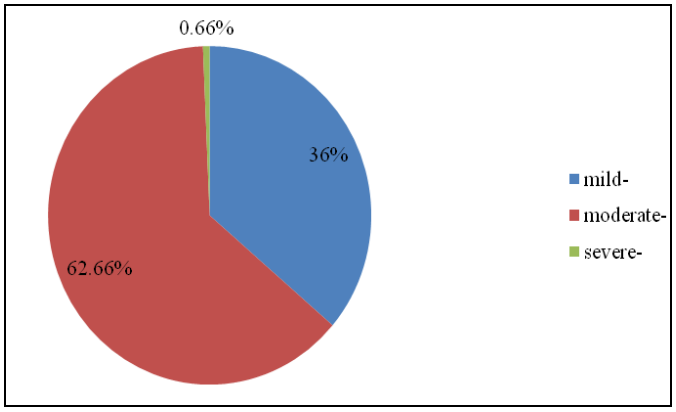

FIG. 2: SEVERITY ASSESSMENT OF REPORTED ADR ACCORDING TO MODIFIED HARTWIG AND SIEGEL SCALE

Main reason for probable category being common is health care professionals who confirmed first for any cause of ADR and responsible drug for ADR clinically along with laboratory parameters, and then they sent us ADR information [28]. The severity assessment according to modified Hartwig and Siegel scale as shown in **Fig. 2**, with majority being classified as moderate (62.66 %) followed by mild (36 %) and severe (0.67 %) adverse drug reactions. This result is in line with several other studies [25].

Drug Class Analysis: Antimicrobials were the most common group of drugs responsible for ADR reports (82, 44.3%) followed by analgesics (33, 17.8%) and drugs acting on the central nervous system fulfilled (40, 21.62 %) of ADR reports **Fig. 3**.

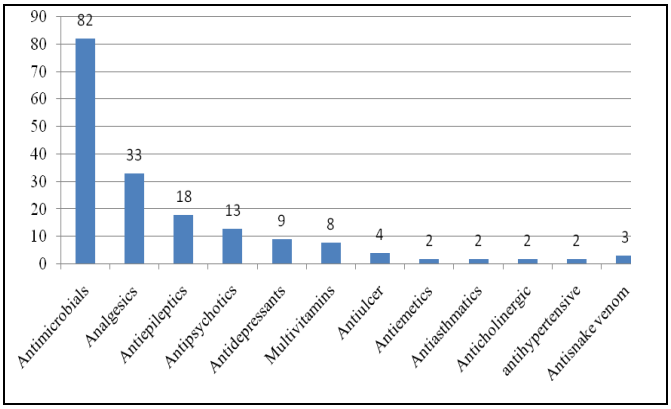

FIG. 3: DRUG ANALYSIS (185 DRUGS/150 ADR FORMS)

Table 2 shows antimicrobials involved in ADR. Out of 82 antimicrobial agents, drug groups are fluoroquinolones (27,14.6%) and nitroimidazoles (14, 7.6%) were two classes most commonly implicated in reports followed by cephalosporins (13, 7%), penicillins (9, 4.9%), antitubercular drugs (8,4.3%), antimalarial drugs (4,2.2%) cotrimoxazole (2, 1.1%), macrolides (2, 1.1%) & antifungal agents (2, 1.1%). The other group of drugs represented fewer than 3 % of ADR. Out of 63 suspected ADRs due to 82 antimicrobial agents, 52 (63.41%) belonged to dermatology while 16 (19.51%) belonged to the gastrointestinal system. Amidst these 63 suspected ADRs, the male to female ratio was 1.03%. The range of duration of suspected ADRs due to antimicrobials was less than one day to 10 days.

TABLE 2: ANTIMICROBIALS INVOLVED IN ADVERSE DRUG REACTIONS

S. no.	Antimicrobial drug group	Total (N=82)	(%)
1	Fluroquinolones	27	32.9
2	Nitroimidazole	14	17.1
3	Cephalosporin	13	15.9
4	Penicillin	9	11.0
5	Cotrimaxazole	2	2.4
6	Macrolide	2	2.4
7	Antifungal	2	2.4
8	Aminoglycoside	1	1.2
9	Antitubercular	8	9.8
10	Antimalarial	4	4.9

In the present study, antimicrobials were the most commonly reported group responsible for the occurrence of suspected ADRs. In one study conducted at an Indian tertiary care hospital, antimicrobials were responsible for 40.9% of ADRs and an Australian tertiary center reported that antimicrobials were related to 25% of ADRs [19-21]. It is likely that Antimicrobial agents are the most commonly prescribed medication worldwide, and their usage is continuously increasing [22-24].

Among all antimicrobials, fluoroquinolones were top reported drug group, followed by nitroimidazole and cephalosporins, as they were the most prescribed antimicrobial agents at our hospital. NSAIDs were the second most responsible for ADRs because conventional usage is a popular prescription pattern all over India [28].

Jung IY *et al.* 2017 reported that fluoroquinolones were the second most frequent cause of ADRs among antimicrobials, accounting for 16% of cases [19]. Two studies found that third-generation cephalosporins were more responsible compared to other generations cephalosporins [29, 30]. In the present study, ceftriaxone was the only cephalosporin responsible for the occurrence of ADRs. It has been suggested that there is no other available cephalosporin in hospitalized patients in the present institute.

We reported approximately 12 to 13 suspected ADR forms per month. Hence, the total numbers of reported suspected ADR forms were 150 in a span of one year. This result suggests that the ADR reporting rate is low in this study, while dikshit *et al.* and Jose *et al* show that the average ADR reporting is 28 and 34 per month, respectively [31, 32]. Low ADR reporting may be due to overburdened or inattention toward ADR reporting by doctors and nursing staff. Negligence towards mild and common ADRs to report and lack of guidelines also contribute to under-reporting ADRs. Due to limited manpower and the absence of a database of drug prescriptions, it was impossible to find out the actual incidence of ADRs to drugs as there was no denominator. The authors observed only frequently responsible drugs for ADRs. They also could not apply the preventability of ADR. Despite some limitations in the study, data obtained from this research will be useful for clinicians regarding proper drug selection and limiting the unnecessary use of AMA and NSAIDs. It also reflects the need to carefully measure safety, monitoring, preventability, and treatment of adverse drug reactions of drugs [33]. The pattern of ADRs reported in our hospital provides data of ADRs due to frequent drugs used at our hospital. It will be helpful to clinicians for optimum and safe use of these drugs. Hence, continuous efforts are required for the safety assessment of drugs.

CONCLUSION: Insignificant ADR reporting observed in the spontaneous ADR reporting system is a major concern. Continuous efforts like training, sensitization, and collaboration of health care professionals are required for up-gradation in ADR reporting.

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