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A South Indian Journey on the Trivialized Healthcare Menace of Adverse Drug Reactions

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ABSTRACT

Introduction:
The primary objective is to encourage HCPs to report more ADRs by bringing out data on the incidence, rate and characteristics of ADRs, ADR-related hospital admissions and by exposing their impact on patient outcomes.

Materials and Methods:
This was a record-based retrospective cross-sectional analysis undertaken to investigate ADR monitoring and reporting in a tertiary care hospital. The databases from June 2016 to May 2020 were studied to assess the characteristics, causality, severity, and incidence rate of ADRs reported by the HCPs in accordance with the accepted criteria. The data was later analyzed using descriptive statistics.

Results:
A total of 775 ADRs were identified and reported, extending over 4 years. 72.9% of the hospitalized patients experienced an ADR, 27.09% visited due to ADRs and 0.12% had a fatal ADR. The incidence of ADRs was estimated to be 1.8 per 1000 patient days, with preventable ADR constituting 0.4 per 1000 patient days. Skin (60.38%) was the most common organ system affected typically with Anti-infectives (48.38%). After causality assessment 624 (80.51%) of the cases were classified as probable while 141 (18.19%) were possible. The majority (52.7%) of the reactions were moderate in severity.

Conclusion:
It is crucial to encourage all concerned HCPs to apprehend their role and responsibility in the identification, monitoring and reporting of suspected ADRs. Educational programs, periodic dissemination of data on the reported ADRs to the healthcare practitioners, and improvement of interactions between the physicians, nurses and pharmacists may be programs to implement.

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Introduction

No pharmaceutical moiety is entirely devoid of harmful and unintended effects and thus adverse drug reactions are a predestined outcome of drug therapy. The demand for prompt response augments the occurrence of adverse events which, when coupled with the patient's clinical condition and concomitant drugs, may lead to detrimental injury.

Adverse drug reaction (ADR) is an omnipresent public concern with its incidence in the Indian population falling between 1.8% and 25.1% and a hospital admission rate of 8% (1).

ADRs cause not only death and injury but also prolong the period of stay in hospitals with a consequent increase in healthcare expenditure and reduced patient satisfaction. As reported by Alomar MJ et al, ADR has caused a 2.38% increase in the length of hospital stay in critical care units (2).

It follows that practising clinicians must always consider adverse effects as part of their clinical diagnosis and in the overall context of patient management. It should always be borne in mind that, not only do drugs affect diseases-diseases affect drugs.

However, across the globe, under-reporting has been the biggest challenge in the spontaneous ADR reporting method and is ubiquitous even in developed nations with well-established surveillance systems (3).

This may be due to diverse reasons like heavy workload, fear of humiliation and litigation, the perception that reporting will not result in any improvement and inadequate expertise to rule out the occurrence of an adverse reaction (4).

In order to ensure the delivery of rational and judicious pharmacotherapy, it is fundamental for the healthcare team to be aware of the quantum and frequency of possible untoward risks.

An effective strategy to counteract this issue in a hospital set-up is to provide awareness about the existing monitoring system to the entire patient care team (5).

Hence, the present study aims to encourage the HCPs to report more ADRs by bringing out data on the incidence, rate and characteristics of ADRs, ADR-related hospital admissions and by exposing its severity and impact on patient outcomes.

Materials and Methods

Study design and setting

The study was conducted on the patients of Rajagiri Hospital, a 450 bedded multi-speciality tertiary care hospital in Aluva, Kerala, India. The study was a single-centered, cross-sectional study carried out for a period of 48 months from June 2016 to May 2020.

Inclusion criteria:

- All patients of either sex and of any age were either consulted in the outpatient department or admitted to the in-patient department during the study period.
- All patients who are presented to the hospital with an already developed ADR.
- All hospitalized patients who developed an adverse drug reaction during their clinical course.
- All ADRs due to allopathic medicines, vaccines, radiocontrast dyes and biologicals.

Exclusion criteria:

- Patients who developed an ADR due to intentional or accidental poisoning.
- ADR due to traditional, complementary medicines and medical consumables.
- Drug overdose and patients with drug abuse and intoxication.

Study procedure

The study is executed as a record-based retrospective survey. Details of all reported ADRs during the period of study are gathered from the Department of clinical pharmacology.

The data collected after reviewing the submitted ADR reporting form are as follows: Patient demographics, the reason for hospitalization, previous history of drug allergy, details of the suspected drug and observed reaction, date and time of onset of reaction, concomitant illness and therapy. The data were analyzed in MS Excel employing descriptive statistics (Figure .1).

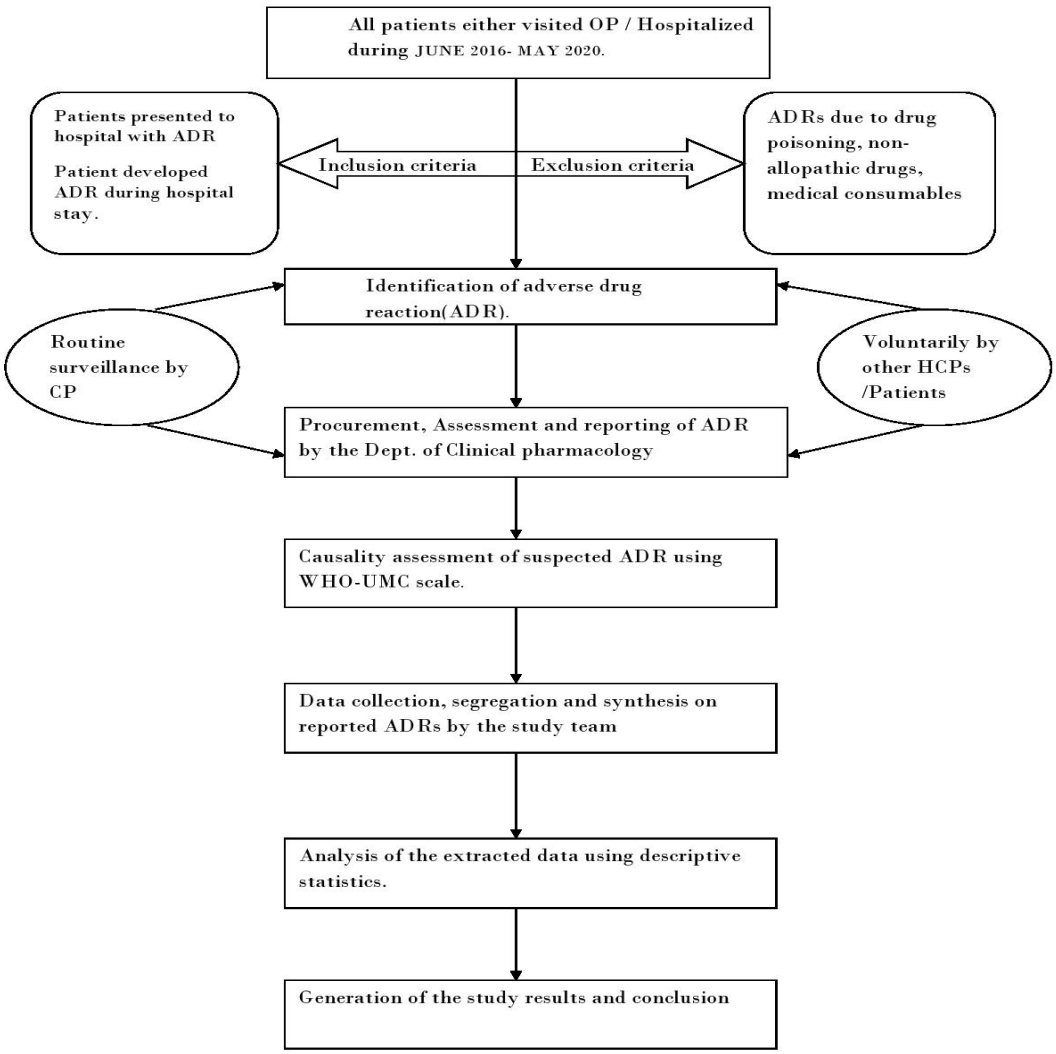

Fig 1: Methodology adopted for monitoring ADR in our hospital **OP- Out-Patient, CP- Clinical Pharmacist, WHO-UMC- World Health Organization-Uppsala Monitoring Centre, HCPs- Health Care Professionals

Results

Distribution of ADRs in the hospital

During the study period of four years, a total of 775 ADRs were identified and reported. 68(8.77%) of ADRs were from the outpatient department. 707(91.22%) ADRs were identified of a total of 95,619 inpatients, 142(20.08%) were of admissions due to ADRs and 565(79.91%) were of patient experienced ADRs during the hospital stay. The incidence of ADRs was estimated to be 1.65 per 1000 patient days.

By year, analysis of reported ADRs is shown in Table no: 1. A significant increase in the number of ADRs reported during the final year of study may be accounted for increased surveillance of ADRs, as more number of clinical pharmacists are employed by the hospital, to strengthen the ADR monitoring practices.

Table 1: Yearly Distribution of ADRs in Inpatient department

Year distribution	Total patient days n=426598	Total inpatient n=95619	Total ADR n=707
JUNE 2016-MAY 2017	90829	20253	81(11.45%)
JUNE 2017-MAY 2018	107916	24044	110(15.55%)
JUNE 2018-MAY 2019	119227	26101	139(19.66%)
JUNE 2019-MAY 2020	108626	25221	377(53.32%)

Percentage of hospital admissions due to ADR

A total of 210(27.09%) patients visited due to ADR during the 4 years of study. Of these, 68(9%) cases were in the outpatient department and 142(18%) were in the inpatient department. The majority of ADRs (75.75%) in the outpatient department were related to dermatological reactions. Coming to the reporting tendencies, a total of 51.09% of ADR were reported by clinical pharmacists followed by physicians (47.09%) and (1.86%) nurses respectively (Fig.2).

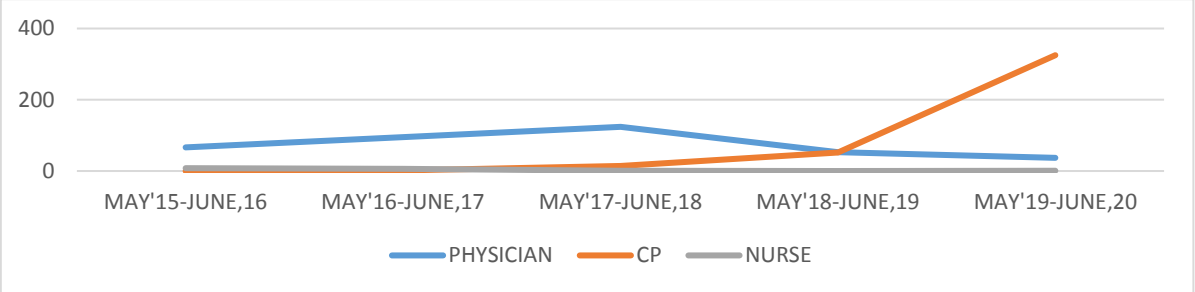

Fig 2: The contribution of each HCPs during each individual year of study

Demographic details of the study population

The majority of adverse drug reactions were reported in males (52.64%) than females (47.35%) and gender imbalance was stable over time. The male: female ratio was 1.11:1. Of the reported reactions, about 40.38% were in people 60 years of age or older and more than 51% were in people between 19-59 years. The youngest patient was an 11-month female child, and the eldest was a 93-year-old female. Most of the ADRs occurred in all age groups due to antibiotics. Paediatrics tended to have more ADRs from anti-epileptics and adults patients (19-59yrs) tended to have ADRs due to water-balance drugs, musculoskeletal drugs or cardiovascular agents. 20 of 775 (2.58%) patients were affected by more than one ADR of which 55% were elderly patients aged more than 60 years. Forty per cent of patients affected by more than one ADR belonged to the adults group (18-59 years) (Table no: 2).

Table 2: Demographics profile of the study population

ATC Classification	**Number (n=775) %**
Alimentary tract and metabolism (A)	24 (3.09%)
Blood and blood forming organs (B)	20 (2.58%)
Cardiovascular system (C)	94 (12.12%)
Genito-urinary system and sex hormones (G)	4 (0.51%)
Systemic hormonal preparations, excluding sex hormones and insulins (H)	25 (3.22%)
Anti-infectives for systemic use (J)	375 (48.38%)
Antineoplastic and immuno-modulating agents (L)	37 (4.77%)
Musculo-skeletal system (M)	91 (11.74%)
Nervous system (N)	69 (8.90%)
Respiratory system (R)	18 (2.32%)
Sensory organs (S)	5 (0.64%)
Various(V)	13 (1.67%)

Management of ADR

Most of the ADRs (n=751, 96.9%) were managed by the withdrawal of the offending drugs. In 23 (2.96%) patients, the offending drug was rechallenged. The reappearance of reaction was found in 15 (1.93%), while in the remaining 8 (1.03%) cases, it didn't reappear. (Figure .3)

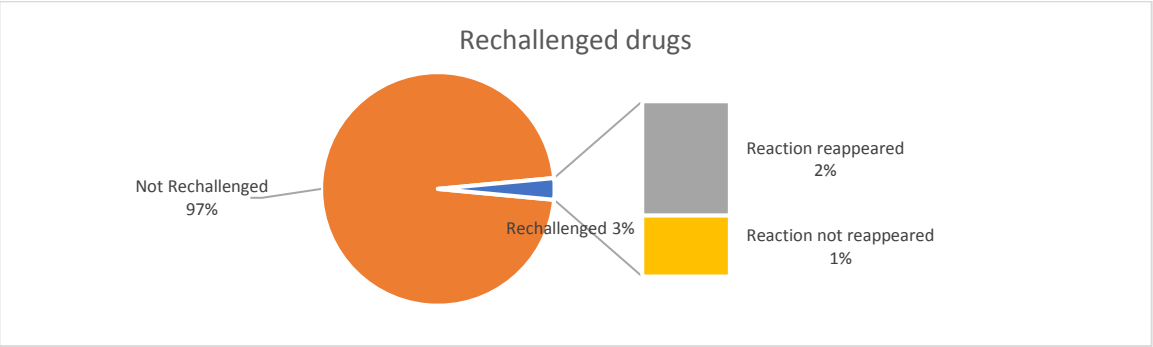

Fig 3: Percentage of rechallenged drugs

Percentage of ADR requiring medical/ surgical intervention

The patients who required medical/ surgical intervention were 439 (56.64%) ADRs. Surgical intervention was done in only 1 case (0.22%).

Cardiopulmonary resuscitation (CPR) was done in 0.12% of cases. Due to a lack of surveillance, treatment details for 320 (72.89%) cases were unknown. No intervention was attempted in 335 (43.22%) cases. The most commonly used drug classes were antihistamines and corticosteroids which predominated pheniramine maleate (25.21%) and hydrocortisone (8.40%) respectively.

Drug-Drug Interactions (DDI) - induced ADRs

Around 145 ADRs were reported with concurrent medication history and the remaining were unknown/not reported. The ADR might be considered to arise from a drug-drug interaction in 17 cases (2.19%). Of these 17 ADRs, the majority were haematological reactions such as hematuria, sudural haemorrhage (Table.4).

Table 4: ADRs associated with (DDIs)

Drug – Drug Interactions (DDIs)	**Effects**	**Number (n=17) %**
Heparin + Aspirin/clopidogrel	Hematuria, thrombocytopenia	4(23.52%)
Heparin + Reteplase	Multiple ecchymosis	1(5.88%)
Enoxaparin + Aspirin	Blood loss anemia	1(5.88%)
Aspirin + Ticagrelor	Decreased hemoglobin	1(5.88%)
Aspirin + Clopidogrel	Swelling of hand	1(5.88%)
Tirofibatin + Aspirin/clopidogrel	hematuria	1(5.88%)
Isoniazid + Rifampicin	Altered Serum transaminase	1(5.88%)
Rifampicin + Isoniazide/pyrazinamide	Altered Serum transaminase	1(5.88%)
Pyrazinamide + Rifampicin	Altered Serum transaminase	1(5.88%)
Salbutamol + Budesonise/formeterol	Tremor and palpitation	1(5.88%)
Levetiracetam + Lorazepam	Aggressive behaviour	1(5.88%)
Haloperidol + Clobazam	Hyponatremia	1(5.88%)
Haloperidol + Levetiracetam/levodopa-carbidopa	Extrapyramidal activity	1(5.88%)
Midazolam + Levetiracetam	Bradycardia	1(5.88%)

Causality assessment using the WHO scale

The causality of ADRs was done using the WHO-UMC causality assessment scale and classified accordingly.

Causality was probable in 624(80.51%), possible in 141 (18.19%) and certain/ definite in 10 (1.29%) patients. Only one fatal ADR was reported during the study.

Predictability and Preventability Assessment of the Reported ADR

On analysing the predictability (using the Schumock- Thornton scale) and preventability of ADRs, the incidence of preventable ADRs was found to be 0.4 per 1000 patient days.

159(20.51%) of the total ADRs were both predictable and preventable, of these, 42.13% were definitely preventable and 57.86% were probably preventable. The majority of ADRs (69.97%) were predictable but not preventable (Table. 5).

Table 5: Predictability and Preventability assessment

Predictability - Preventability assessment	**Number (n=775)%**
Non predictable, not preventable	61(7.88%)
Non predictable, preventable	14(1.8%)
Predicatable, definitely preventable	67(8.6%)
Predictable, not preventable	541(69.8%)
Predictable, probably preventable	92(11.8%)

Severity Assessment of ADR

The WHO severity assessment of the ADRs was done using the Modified Hartwig and Siegel scale. It showed that 339(43.74%) ADRs were mild in nature, 409(52.77%) were moderate and 27 (3.4%) were severe. The intervention in serious ADRs included dialysis and surgery (Table. 6).

Table 6: Severity Assessment of ADR

Severity (n=775) %		
Mild		339 (43.7%)
Moderate		409 (52.7%)
Severe	Life threatening	3 (11.1%)
	Death	1 (3.7%)
	Hospitalization prolonged	15 (55.5%)
	Required intervention	8 (29.6%)

Discussion

The study proceeds retrospectively in a lengthier time course of 48 months from June 2016 to May 2020. This has given us ample time and opportunity to study and demonstrate the trend in the occurrence, identification, assessment and reporting of adverse effects resulting from the medical management of patients.

Furthermore, the firm establishment of the Department of clinical pharmacology guided by a clinical pharmacologist, wherein a sufficient number of CPs are directed to actively introspect the entire medication management system, has indubitably, favoured the process.

As far as we are aware from the literature, our study is the first in south India to explore the incidence of errors over such a lengthier period of 48 months.

Coming to the findings, the incidence of adverse drug reaction in the present study was estimated to be 1.8 per 1000 patient days of which preventable ADR constituted 0.4 per 1000 patient days. On comparing the global data on ADR rates, this is indeed a lesser figure. It may be either due to under-reporting tendencies or failure on the part of HCPs to identify/diagnose an ADR. However, active surveillance by the hospital pharmacovigilance department may also account for the low incidence rate.

Many researchers have substantiated that the incidence of ADRs is rising worldwide, but are under-reported. It includes a Brazilian study performed in a pediatric hospital over 4042 patient days and recorded an incidence of 8 (6). Another prospective cohort study intensively followed up all admissions to the internal medicine ward of the hospital and found an incidence rate of 10.1% over four months (7). A striking finding was observed in active surveillance for 3 months conducted in multiple intensive care units of the US and identified an ADR rate of 72.6 per 1000

patient days (8). Varying rates across the globe affirms that a much higher number of events occur daily but only a trivial fraction protrudes from the submerged iceberg. More stringent measures have to be adopted to bring out the actual incidence and execute productive corrective and preventive actions. Along with the hospitalized patients, the study inclusion criteria comprises outpatients (OP), who have approached the hospital with clinical manifestations or symptoms of adverse drug events which were subsequently confirmed by the physician.

The credibility of the data may be limited primarily because we do not have an active monitoring system in the outpatient department. Secondly, reporting rates depend on how a healthcare professional identifies an adverse drug reaction when a patient approaches him. Hence, we did not calculate the incidence for out-patient ADRs. Instead, the frequency (n) of outpatient ADRs was estimated as 71, with a major chunk constituted by dermatological reactions. 9.1 % of the total ADRs reported in the hospital during the study period were by the outpatient department.

A contrasting finding was observed in a cross-sectional study of 7 months conducted in the outpatient and multiple inpatient departments of a north Indian hospital. This study which involved all adverse drug reactions reported by physicians in the hospital identified that more than 90% of the ADRs were reported from the outpatient department (9).

This signifies that higher reporting can be expected if the scope of ADR management mechanisms in the IP wards were extended to the outpatient department also.

Many unfortunate events of hospitalization due to adverse drug reactions occur worldwide. In fact, a vast majority of these could have been avoided if patients were given adequate medication counselling at the time of outpatient visit or inpatient discharge either by the prescriber, nurse, pharmacist or clinical pharmacist.

We have found in our study that 0.13% of hospital admissions were due to ADRs. Besides, 18% of the study population (142 out of 755) were hospitalized with ADR as the reason for admission. Most of the extracted literature showed a higher rate may be due to the variations in study population, duration or methodology (9-12). Whatsoever the figure is disturbing as these are unfortunate events which have resulted in avoidable physical and emotional burdens for the patients. Fortunately, in our system we have clinical pharmacy and nursing services directed at training IP discharge patients and other HCPs on the relevance of this issue, which could be one reason behind reduced ADR-related hospitalization.

The credibility of the data, particularly in a retrospective study, depends on the reporter of adverse drug reaction.

Analysing the pattern of ADR reporting, we observed that physicians were the major reporters during the first three years of the study. This was dramatically taken over by clinical pharmacists with their last year's reporting exceeding 10 fold of physician's contribution. This may be due to the changes in hospital policies which endorsed daily intensive ward-based monitoring of adverse drug reactions by clinical pharmacists in the hospital. Subsequently, there was a steep rise in total reporting from 81 ADRs being reported in the first year of study to 377 ADRs in the final year by CPs. One study assessing physicians' contribution towards ADR reporting is worth discussing. It is a questionnaire-based study conducted in Kuwait in which participating physicians admitted that even though the majority (75%) have encountered an ADR during their daily practice, only 34% have officially reported it to the concerned centres (13,14). The same may be the case with most tertiary care hospitals.

Although clinicians are detecting ADRs and taking appropriate corrective actions, these are not documented due to their busy work schedules or some other reasons. Most of the patients in our analysis fall under the adult category, closely followed by elderly adults (61-70 years).

One notable factor is that the range for the former group (19-60 years) is much higher than that for the latter even though both showed comparable distributions. Whilst most of the ADRs in paediatrics were either mild or moderate, severe ADRs were found more in the elderly than in adults. Findings in most of the studies reaffirm that increased

age is definitely an independent risk factor for ADR (15,16). On par with it, paediatrics are another highly vulnerable group for ADR but are rendered less attention. In our study, infants and paediatrics constituted only 4% and 5% of the population respectively. Lower rates in most of the studies may be due to the usual pattern of inpatient distribution which often predominates adults (17). The study findings remind us that the severity and consequences of medication-related adverse events are pronounced differently in different age groups. Young healthy people without co-morbidities may recover quicker than a neonate or elderly person with organ failure or immunodeficiency. Therefore, age-specific therapy monitoring has to be established and practised by clinicians with special emphasis on multi-organ damage, high-alert drugs and polypharmacy.

Considering the drug classes involved, we used WHO-ATC classification to categorize the involved drugs (21). Antiinfectives (J) were the most frequently involved (48.38%) followed by cardiovascular drugs (C) and musculoskeletal agents (M).

Most of the investigations relating to adverse drug reactions have identified Antiinfectives as the most widely involved drug group, which adds credibility to our finding (15,22-25). Irrational use of Anti-infectives for non-indicated conditions as well as inappropriately continuing the antimicrobial therapy without timely discontinuation or switching to a lesser potent agent may also lead to ADRs. Apart from assuring better pharmacotherapy, antimicrobial stewardship programs in hospitals can also reduce adverse events due to these agents, if executed constructively. Cutaneous eruption and erythema predominated the drug reaction list in our study as well as in the comparators. Perhaps it may be because a vast majority of ADRs by antibiotics occurred after the administration of test doses for hypersensitivity testing.

Although there is substantial evidence that drug-drug interactions contribute to the occurrence of ADR it is difficult to estimate the real incidence, particularly in an observational study.

Most of the studies suggest that even if they occur in insignificant proportions, a considerable number of ADRs due to drug interactions can have long-lasting sequel on the patients and healthcare team. We analysed our data set to find out the chances for any drug-drug interaction and observed 2.19% (n=17) cases to have administered one or more drug(s) during the hospital stay, which may have probable interaction with the offending drug and resulted in the same reaction. To compare, we conducted a detailed literature search and one study by a Croatian agency for medicinal products and medical devices has interesting conclusions.

They explored their database for spontaneous ADR reporting and deduced that 53 out of 94 potential drug interactions during the three years resulted in Serious ADRs and Antiplatelet, anticoagulants, and NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) were the culprits in most (28).

This is in line with our findings where 52.9% of ADRs due to drug-drug interactions were caused by haematological agents. Another 3-month study executed in the internal medicine department of a Romanian hospital to follow up on the DDIs causing adverse drug reactions revealed that 4.62% of patients with potential DDIs and 3.61% of the total number of patients developed ADRs (29).

Altogether, these data substantiates that DDIs are a potential cause of ADR and a reduced number of these events in various studies may be due to deficiencies in the identification, monitoring and reporting practices. The causality of reported ADRs was done by the clinical pharmacologist using the WHO-UMC causality assessment scale. Approximately 81% of ADRs were found to be probable and 18% to be possible. Only 1.2% of the drugs were certain to have caused the ADR. In point of fact, interpretations from standard causality assessment tools vary significantly from findings based on clinical experience.

The four cardinal principles of causality which include drug dechallenge, rechallenge, temporal association and plausibility do not necessarily have to be observed in all the cases for an adverse event to be certain or probable caused by the suspected drug. While in our case, 98% of cases had a drug dechallenge and 2.9% had a rechallenge but

only 1.2% of the ADRs belonged to the category 'Certain'. Furthermore, over 60% of the rechallenged cases in which an adverse reaction reappeared, were probable in causality assessment. This may be due to the effects of concomitant drugs or concurrent illness which were not statistically evaluated in our descriptive mode of study. Similarly, there were events which were definitely caused by the suspected drug but drugs were not dechallenged, probably due to the less serious nature of the reaction.

For instance, urine discolouration is caused by rifampicin in a patient with active pulmonary tuberculosis. Assumptions are thus considerably influenced by the professional experience of the HCP and the clinical condition of the patient.

The preventability of ADRs was assessed using the Modified Schumock and Thornton scale and was estimated to be 22.4% in our data. Among them, 7.84% were definitely preventable and 14.56% were probably preventable.

Preventable ADRs remind us that if routine monitoring and detection are intensified, it could have avoided a considerable number of drug-related adverse events. It also signifies the need of rendering vigorous attention to this neglected aspect of drug therapy. A 12-month study conducted in a multispecialty teaching hospital to develop an ADR reporting system also identified a similar rate of 22.3% (22). Possibility for an ADR to be the reason for patient complaints shall always be an integral criterion for making clinical judgement. ADR detection and reporting has to be adopted as a "Just-culture" practice in any healthcare setup. A higher ADR rate was reported by multiple studies with preventability ranging from 40-60% (21,23,24). A lower number of preventable ADRs (22%) in our study may be due to a fully functional department of Pharmacovigilance in our hospital, which in turn might have identified anticipable adverse events at the earliest and prevented them from manifesting into adverse drug reactions.

Conclusion

Adverse drug reactions, in many instances, have been demonstrated to result in dysrhythmic healthcare delivery across the globe. Our study points out that there is an immediate need for streamlining the hospital-based ADR monitoring and reporting strategies, to counteract the issue of underreporting and for optimizing patient safety. Uninterrupted and smooth functioning of an ADR surveillance system requires continuous simulation. Hence it is necessary to develop a positive attitude towards pharmacovigilance and associated disciplines among physicians, nurses, and clinical/ hospital pharmacists so that ADR reporting can be integrated into daily clinical practice.

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