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Research Article

# A CLINICO-ETIOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTIONS AT TERTIARY CARE CENTER IN SOUTH INDIA

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**ABSTRACT**

**Objective:** The objective of the study was to study the most common aetiology, different clinical manifestations of adverse cutaneous drug reactions (ACDR), and to assess the association of morphological cutaneous pattern of ACDR and etiological group of drugs.

**Methods:** A cross-sectional, observational study was carried out at dermatological department of a large tertiary care center in Southern India. All clinically suspected ACDRs due to allopathic drugs, presented during two year period of all age groups and both sex were included in the study. A written informed consent was taken from patients and data were collected by means of pre-tested Performa including detailed clinical history, examination and relevant laboratory investigations. SPSS (Version 23.0) was used to obtain the results.

**Results:** About 46% were between age group of 19–40 years. Majority were female (54%). 59% had generalized lesions, 98% had cutaneous manifestations, and 30% had mucous involvement. Itching was the most common presenting feature (48%). However, only 6% patients were asymptomatic. Most common etiological group of drugs responsible for ACDRs are antibiotics (27%) and NSAIDs (19%) pointing toward its rampant use with and without prescription. Among the Antibiotics, Ciprofloxacin was noted to be the most common responsible for ACDR. Diclofenac was found be the most common NSAID followed by Ibuprofen and Ketorolac. Majority of ACDRs, that is, 72% comprised of probable ACDRsas per "Naranjo's algorithm." The most common type of lesions observed were plaques (30%), macules (20%), papules (7%), and edema (7%). A predominant pattern of correlation was noted between antibiotics and erythematous drug eruption, SJS, vasculitis, erythroderma, and AGEP. The most common clinical pattern of ACDR observed was Urticaria (19%), Fixed Drug Eruption (13%), Erythema Multiforme (9%), and Lichenoid drug eruption (8%).

**Conclusion:** The significance of this study was to study the profile of ACDR and to emphasize the awareness to the health-care providers on vigilant monitoring of ADRs and promptly reporting the same to prevent the occurrence of reactions in the vulnerable population. A systemic comprehensive monitoring and documentation of ADRs can curtail many untoward reactions in patient care and will lead to an effective drug administration. More studies are essential to create awareness of possible ACDR and to assist in the early recognition which, in turn, aids in the implementation of effective drug safety measures.

**Keywords:** Adverse, Cutaneous, Drug reactions.

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## INTRODUCTION

An "Adverse cutaneous drug reaction," that is, ACDR is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompasses all adverse events related to drug eruption, regardless of the etiology. ACDRs are the commonest reactions attributed by the drugs. These drug eruptions differ in their appearance, onset and severity. They may vary from mild nature pruritus or rash to severe and life-threatening conditions such as Stevens Johnson Syndrome or toxic epidermal necrolysis [1].

Improved treatment outcomes, extended treatment courses, longer patient survival, and polymedication have led to increased frequency and duration of exposure to drugs. Consequently, rise in drug sensitization is responsible for rise in incidence of drug reactions. Of all organs affected by drug reactions, the skin is most frequently involved [2]. The pattern of ACDRs and the drugs responsible for them keep changing from time to time because of new drugs being made available for therapy, changing prescription pattern, increased use of drugs for treatment of diseases, drug interactions due to multiple drug therapy and also due to a growing tendency for self-medication in the population. ACDRs are expensive in both social and economic terms with a significant impact on the doctor-patient relationship [3]. The world of ACDRs is wide and enigmatic and almost any non-inflammatory or inflammatory dermatosis can be mimicked. Thus, the aphorism – Anything you see, anything you think, and something that you do not even think of can be due to drugs. The clinical pattern of ACDR ranges from simple urticaria to extensive angioedema and exfoliative dermatitis.

As different drugs cause different types of cutaneous reactions, a more detailed description of cutaneous eruptions is necessary to know the prognostic factors. ACDRs, like any other drug reactions, are influenced by various factors such as gender, age, underlying diseases, immune status, genes, environmental factors, and history of allergy. The incidence and prevalence of ACDRs may vary in different geographical regions due to difference in disease prevalence, pattern of drug use, and genetic and environmental factors. Effective monitoring of ACDRs, both hospital-based and population-based, forms an integral part of ADR monitoring programs as well as part of pharmacovigilance, not only to generate valid data but also to identify and assess predisposing/underlying risk factors and to evaluate treatment outcome. However, reporting and documentation of ACDRs is not being effectively organized and implemented in Indian population, and systematic epidemiological studies for the same seem to be inadequate. Population-based epidemiological studies are cumbersome and time consuming

and hence difficult to organize compared to hospital-based studies. However, in the last few years, a few studies in the Indian population have been reported mainly from major hospitals. Since existing data regarding ACDRs is rather limited, inconsistent and even conflicting, more studies may be required to generate valid data and hence the present study was taken up to Study the commonest etiology, different clinical manifestations of adverse cutaneous drug reactions (ACDR) and assess the association of morphological cutaneous pattern of ACDR and etiological group of drug.

## METHODS

A cross-sectional, observational study was carried out at dermatological department of a large tertiary care center in Southern India. Sample size was calculated based on the time period of two years. All ACDRs presented during this period and fulfilling the criteria of inclusion criteria were included in the study. Patients of all age groups and sex with clinically suspected ACDRs due to allopathic drugs only, with documented evidence of having taken the suspected drug and giving written informed consent were the inclusion criteria. A written informed consent was taken from patients in a language the patient understands, and data was collected by means of pre-tested Performa including detailed clinical history, examination and relevant laboratory investigations. The casualty assessment of drug reaction was calculated according to the "Naranjo's algorithm" [4] as- doubtful, probable, possible and definite adverse drug reaction. The Naranjo Algorithm is a questionnaire designed by Naranjo *et al.* for determining the likelihood of whether the adverse drug reaction is actually due to the drug rather than the result of other factors. The probability of ACDR is divided as definite, possible and probable. The Naranjo score was obtained after answering pre-designed set of ten questions present in the Naranjo algorithm. A score of 9 and above was considered as a definite ACDR, score of 5-8 was considered as a probable ACDR and score of 1–4 was considered as a possible. ACDRMaster charts and graphs were prepared using MS-Excel 2007 and data were processed on SPSS (Version 23.0) to find frequency of variables.

## RESULTS

Basic parameters of ACDR among study participants are shown in Table 1. Itching was the most common presenting feature seen along with other symptoms comprising of about 48% of cases. However, only 6% patients were asymptomatic. According to this study, the most common etiological group of drugs responsible for ACDRs is antibiotics (27%), NSAIDs (19%), antihypertensives (8%), antiepileptics (7%), and antipyretics (6%) followed by antifungals (5%) (Fig. 1). The class of drugs responsible for lesser number of drug reactions in this study was antitubercular drugs, antivirals, antihelminthics, antihistamines, and antipsychotics. Whereas, class of drugs causing least cases of ACDRs was antacids, antigout, antithyroid, hypoglycemic, immunosuppresses, OC pills, and Steroids. Among the class of drugs causing ACDR, Antibiotics and NSAIDs caused significantly higher percentage of drug reactions (Fig. 1) pointing toward its rampant use with and without prescription. Among the Antibiotics, ciprofloxacin was noted to be the most common one responsible for acdr. other antibiotics significantly noted were amoxicillin, ceftriaxone, Cotrimoxazole, dapsone, minocycline, ofloxacin, and penicillin. Whereas, other antibiotics noted were cefadroxil, cefixime, cefuroxime, cephalexin, doxycycline, erythromycin, gentamicin, norfloxacin, and roxithromycin. After antibiotics, NSAIDs were the most common class of drugs responsible for ACDR. Diclofenac was found be the most common NSAID followed by Ibuprofen and Ketorolac (Table 3). Other drugs noted were acetaminophen, indomethacin, mefenamic acid, naproxen, and nimesulide.

In the present study, the percentage of assessment of ACDR at initial contact according to Naranjo algorithm noted was as follows; majority of ACDRs, that is, 72% comprised probable ACDRs, whereas possible ACDRs were 28%. None of the ACDR was definite as drug re-challenge test is not included in this study. The most common type of lesions observed were plaques (30%), macules (20%), papules (7%), and edema (7%) (Table 2). Macules were predominantly present in ACDRs due to antibiotics followed by antihelminthic, antihypertensives, and antipsychotics. Whereas, plaques were mostly associated with ACDR due to NSAIDs, antihypertensives, antibiotics, and antipyretics. Papules were associated predominantly with ACDRs due to antibiotics, OC pills, and steroids (Fig. 2). A drug can cause any of the clinical patterns of ACDR. In this study, a correlation between the etiological class of drug and clinical pattern of ACDR was studied in the study subjects who meet the inclusion criteria. A predominant pattern of correlation was noted between antibiotics and erythematous drug eruption, SJS, vasculitis, erythroderma, and AGEP (Fig. 3).

NSAIDs were seen to cause FDEs, urticaria, SJS and vasculitis. Whereas, antihypertensives were mostly associated with urticarial drug reaction patterns and fixed drug eruption (FDE). Antitubercular drugs mostly lead to urticarial reactions and lichenoid drug eruptions. Antiepileptics were associated with erythema multiforme, FDE, urticaria, and SJS patterns of ACDR. ACDRs can present in numerous clinical patterns ranging from mild drug reactions such as acneiform eruptions to life-threatening severe drug reaction patterns such as Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). In this study, the most common clinical pattern of ACDR observed was Urticaria (19%), Fixed Drug Eruption (13%), Erythema Multiforme (9%), and Lichenoid drug eruption (8%). Whereas, other reactions less frequently observed were erythematous drug eruption, maculopapular rash.

**Table 1: Basic parameters of ACDR among study participants**

| | Frequency | Percentage |
|---|---|---|
| Age category | | |
| 0–2 years | 7 | 7.00 |
| 13–18 years | 10 | 10.00 |
| 19–40 years | 46 | 46.00 |
| Above 40 years | 37 | 37.00 |
| Sex | | |
| Female | 54 | 54.00 |
| Male | 46 | 46.00 |
| Extent of lesions | | |
| Generalized | 59 | 59.00 |
| Localized | 41 | 41.00 |
| Cutaneous involvement | | |
| Yes | 98 | 98.00 |
| No | 2 | 2.00 |
| Mucous involvement | | |
| Yes | 30 | 30.00 |
| No | 70 | 70.00 |
| Assessment of ACDR (Naranjo algorithm) | | |
| Possible | 28 | 28.00 |
| Probable | 72 | 72.00 |
| Symptoms | | |
| Asymptomatic | 6 | 6.00 |
| Fever | 15 | 15.00 |
| Itching | 48 | 48.00 |
| Pain | 25 | 25.00 |
| Swelling | 6 | 6.00 |
| Total | 100 | 100.00 |

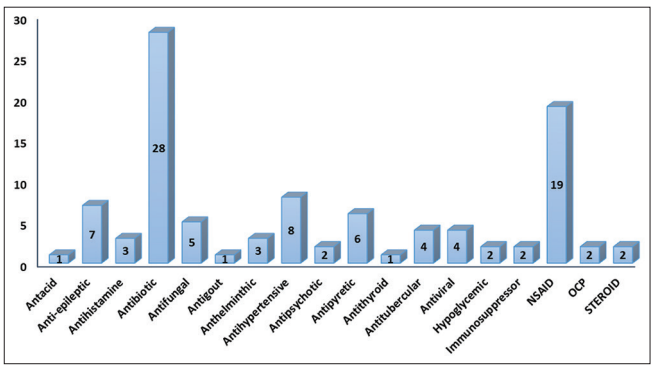


**Fig. 1: Distribution of various variety of drugs causing ACDR**

## DISCUSSION

Adverse reactions to drugs are common in everyday medical practice. The side effects of a drug cannot be avoided. The incidence and clinical pattern of drug eruption depends on the choice and frequency with which different drugs are used. Drug reaction can occur to any prescribed, or over the counter medications and herbal preparations. Majority of ACDRs are diagnosed clinically. Recognition of the offending drug enables early withdrawal and improved outcomes. Observational studies are tools to know the pattern of reactions and causative drugs. Even in spite of a large data base on cutaneous adverse drug reactions, there continues to be a constant need for newer updates so as to develop a greater insight into these disorders.

In a study done by Sangeetha Raja *et al.* on pattern of adverse drug reactions in a tertiary care teaching hospital found that there was an insignificant increase in prevalence among female (52.5%) than male (47.5%) [5], and similar results were found in a study by Saravanan *et al.* [6] which were consistent with the results of this study, that is, ACDRs were seen 54% in females and 46% in males. In this study, majority of ACDRs, that is, 46% were observed in the adult population group from age 19 years to 40 years which was almost similar to 42% seen in a study by Syed Hussain *et al.* [7].

In another study by Patel *et al.*, the major suspect group of drugs responsible for ACDRs were antimicrobials (45.46%), NSAIDs (20.87%), antiepileptics (14.57%), and corticosteroids (3.87%). The commonly implicated drugs were Sulfa (13.32%), β-lactams (8.96%), Carbamazepine (6.65%), Phenytoin (6.46%), Fluoroquinolones (5.12%), Ibuprofen (4.71%), Nitroimidazole (4.17%), Antituberculars (2.81%), Diclofenac (2.32%), and Aspirin (2.26%). Whereas in the same study the most common clinical patterns of ACDRs seen were Maculopapular rash (32.39%), FDEs (20.13%), and urticaria (17.49%) [8]. In this study, the most common clinical pattern of ACDR

**Table 2: Clinical pattern and morphology of ACDR among study participants**

| | Frequency | Percentage |
|---|---|---|
| Clinical pattern of ACDR | | |
| Acneiform drug eruption | 6 | 6.00 |
| AGEP | 7 | 7.00 |
| Angioedema | 7 | 7.00 |
| Bullous drug eruption | 2 | 2.00 |
| EM | 9 | 9.00 |
| Erythematous drug eruption | 7 | 7.00 |
| Erythroderma | 5 | 5.00 |
| FDE | 13 | 13.00 |
| Lichenoid drug eruption | 8 | 8.00 |
| Maculopapular rash | 7 | 7.00 |
| SJS | 5 | 5.00 |
| Ten | 2 | 2.00 |
| Urticaria | 19 | 19.00 |
| Vasculitis | 3 | 3.00 |
| Morphology | | |
| Bullae | 5 | 5.00 |
| Erosion | 6 | 6.00 |
| Macule | 20 | 20.00 |
| Maculopapular | 6 | 6.00 |
| Edema | 7 | 7.00 |
| Papule | 7 | 7.00 |
| Patch | 2 | 2.00 |
| Plaque | 30 | 30.00 |
| Pustules | 6 | 6.00 |
| Scales | 5 | 5.00 |
| Vesicles | 6 | 6.00 |
| Total | 100 | 100.00 |

**Table 3: Antibiotics and NSAIDS causing ACDR among study participants**

| | Frequency | Percentage |
|---|---|---|
| Antibiotics causing ACDR | | |
| Amoxicillin | 2 | 2.00 |
| Cefadroxil | 1 | 1.00 |
| Cefixime | 1 | 1.00 |
| Ceftriaxone | 2 | 2.00 |
| Cefuroxime | 1 | 1.00 |
| Cephalexin | 1 | 1.00 |
| Ciprofloxacin | 3 | 3.00 |
| Cotrimoxazole | 2 | 2.00 |
| Dapsone | 2 | 2.00 |
| Doxycycline | 1 | 1.00 |
| Erythromycin | 1 | 1.00 |
| Gentamicin | 1 | 1.00 |
| Minocycline | 2 | 2.00 |
| Norfloxacin | 1 | 1.00 |
| Ofloxacin | 2 | 2.00 |
| Penicillin | 2 | 2.00 |
| Roxithromycin | 1 | 1.00 |
| NSAIDS causing ACDR | | |
| Acetaminophen | 1 | 1.00 |
| Diclofenac | 4 | 4.00 |
| Ibuprofen | 3 | 3.00 |
| Indomethacin | 2 | 2.00 |
| Ketorolac | 3 | 3.00 |
| Mefenamic acid | 1 | 1.00 |
| Naproxen | 2 | 2.00 |
| Nimesulide | 1 | 1.00 |

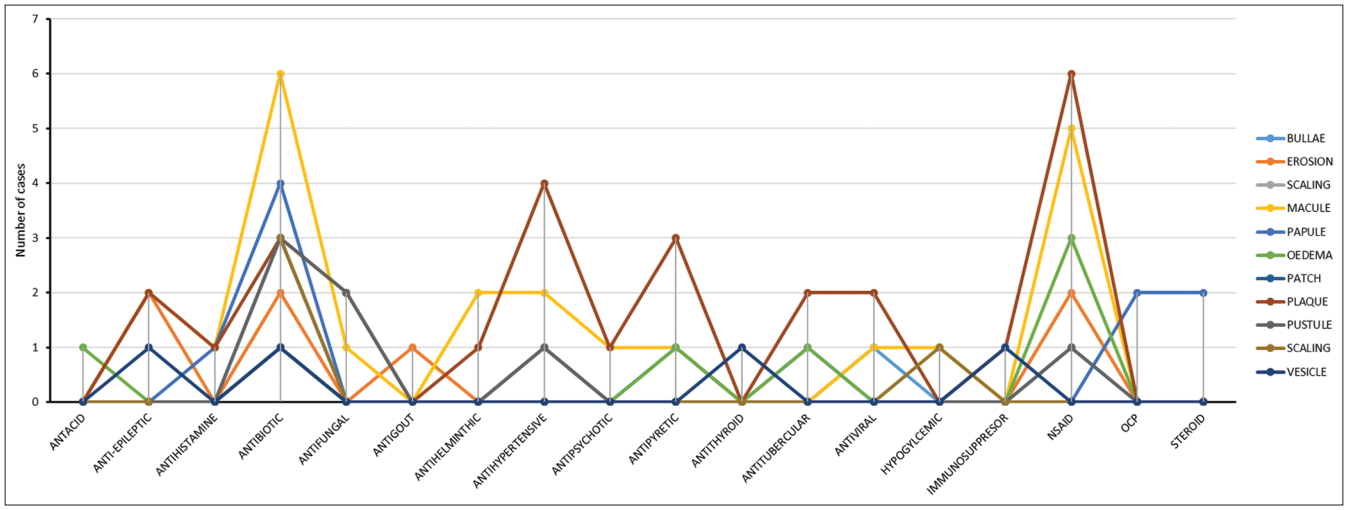


**Fig. 2: Distribution of class of drugs and morphological pattern**

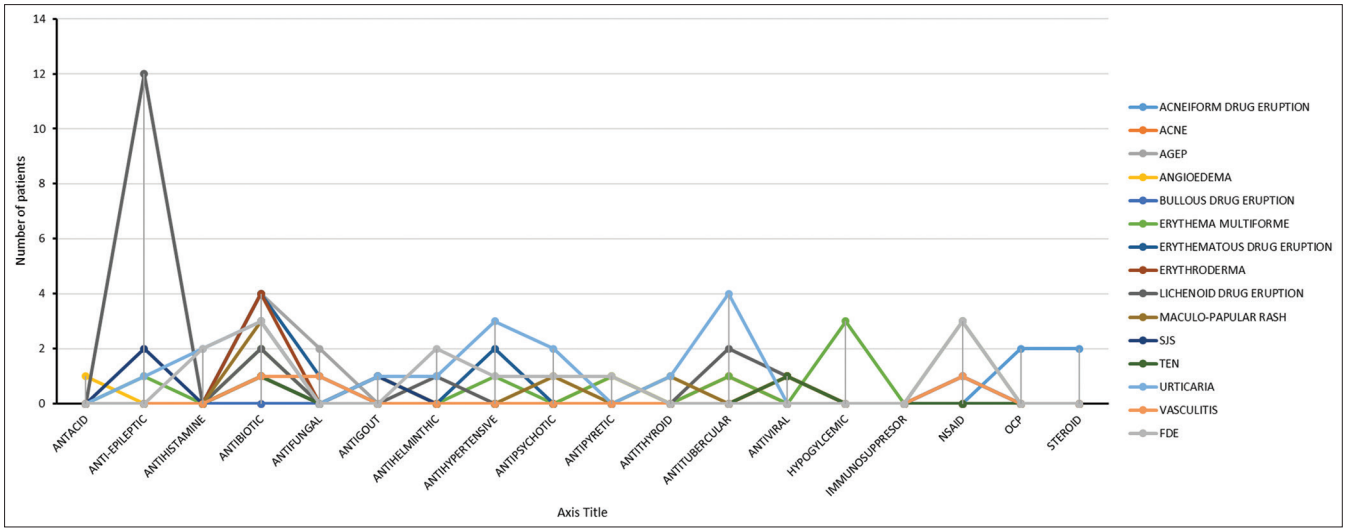


**Fig. 3: Distribution of class of drugs and ACDR**

observed was Urticaria (19%), Fixed Drug Eruption, that is, FDE (13%), Erythema multiforme (9%), and lichenoid drug eruption (8%). Other reactions less frequently observed were erythematous drug eruption, maculopapular rash.

The most common etiological group of drugs responsible for ACDRs in this study is Antibiotics (27%), NSAIDs (19%), Antihypertensives (8%), Antiepileptics (7%), and Antipyretics (6%) followed by Antifungals (5%) which is similar to a study conducted by Nilesh Mahatme *et al*. that stated that largest number of ACDR were associated with the use of antimicrobial agents (48%), followed by NSAIDs, and antihypertensives (8%) [9]. In this study, antibiotics are the major causative drugs of ACDR that coincides with the reported literature [10-15]. A large study done in Italy also reported that antimicrobials were the most common cause of ACDRs [13]. The previous studies in India also have shown that Antimicrobials are the major causative agents for ACDRs [16]. This could be attributed to the widespread use and self-medication of antibiotics these days. The class of drugs responsible for lesser number of drug reactions in this study was antitubercular drugs, antivirals, antihelminthic, antihistamines, and antipsychotics. Whereas, class of drugs causing least cases of ACDRs was antacids, antigout, antithyroid, hypoglycemics, immunosupressors, OC pills, and steroids.

Among the antibiotics, ciprofloxacin was noted to be the most common one responsible for ACDR. However, in studies done in other parts of India, cotrimoxazole continues to be commonly incriminated antimicrobial [17,18]. This could be attributed to the widespread use of β-lactam antibiotics in our setup or different trends in the use of antimicrobials in various regions. Anyhow, the use of Cotrimoxazole has declined in the recent past; hence, the offender has given place for other antimicrobials.

A predominant pattern of correlation was noted between antibiotics and erythematous drug eruption, SJS, vasculitis, erythroderma, and AGEP. After antibiotics, NSAIDs were the next common class of drugs responsible for ACDR. Diclofenac was found be the most common NSAID followed by Ibuprofen and ketorolac. Other drugs noted were acetaminophen, indomethacin, mefenamic acid, naproxen, and nimesulide. NSAIDs were seen to cause FDEs, Urticaria, SJS and vasculitis in a study done in India. ACDR rate for NSAIDs ranges from 0.3% to 0.69% [19]. Ibuprofen, Diclofenac, and Aspirin are the most common causative agents and produce few severe reactions. Considering their widespread use, the risk of severe CADRs seems minimal. One Indian study on NSAIDs reports CADRs (50.29%) as the most common ACDR; ibuprofen (51.19%) and diclofenac (27.08%) were the commonly implicated drugs [20]. However, studies abroad observed Mefenamic acid [21], Naproxen [15], and Paracetamol [22] as common agents.

In this study, antiepileptics were associated with erythema multiforme, FDE, urticaria and SJS patterns of ACDR. The common antiepileptics implicated for ACDR were carbamazepine and phenytoin which is consistent with the study carried by Patel *et al*. [8] and other studies abroad [11,12,15].According to the study by Tejas, maculopapular rash and SJS/TEN are common with antiepileptics. Whereas urticaria and FDE are rare, which is in contrast to this study. Other studies from Asia show Carbamazepine as most common offending drug for SJS/TEN [11,12,23]. Antiepileptics are also implicated with SJS/TEN in the western population. The EuroSCAR study in the European population suggests Carbamazepine (relative-risk [RR]:33), Phenytoin (RR: 26), Phenobarbitone (RR:17), and Lamotrigine (RR>14) as important causative antiepileptics for SJS/TEN [24]. Antiepileptics show high severe to non-severe case ratio compared with antimicrobials and NSAIDs. One of the possible reasons may be because of the Pharmacogenetic basis for Carbamazepine induced-SJS/TEN. The association with HLA-B*1502 alleles with Carbamazepine induced-SJS/TEN is detected in the Indian and other Asian populations, but not in Caucasians [25]. The presence of HLA A*3101 is associated with Carbamazepine-induced hypersensitivity reactions including SJS/TEN in patients of Northern European ancestry [26]. Cross-reactivity of Carbamazepine is observed with Phenytoin, Oxcarbazepine, and Lamotrigine [27,28]. Majority of the cutaneous reactions occur within six weeks of initiation of therapy with phenytoin or carbamazepine [29]. Caution is required during the initial period of therapy. This study reports allopurinol induced-SJS/TEN in a low frequency when compared with other Asian studies [11-12]. HLA B*5801 is associated with severe CADRs with allopurinol in Korean, Chinese, and Thai descent [30].

In this study, the most common clinical pattern of ACDR observed was Urticaria (19%), Fixed Drug Eruption, that is, FDE (13%), Erythema multiforme (9%) and lichenoid drug eruption (8%). Whereas other reactions less frequently observed were erythematous drug eruption, maculopapular rash. In a study conducted by Mahatme *et al*. majority of ACDRs comprised urticaria (30%), followed by fixed drug eruption (FDE), that is, 24% and acute generalized exanthematous pustulosis (AGEP) was the least in occurrence (2%) [9]. Whereas in a study conducted by Patel *et al*. Maculopapular rash (32.39%), FDEs (20.13%), and urticaria (17.49%) were the commonly reported ACDRs [8,31].

In this study, 100 ACDRs were reported to the pharmacovigilance committee of India, and the suspected attributable drugs leading to ACDR were withdrawn for the management and were treated according to their severity after ruling out the other possible differential diagnosis clinically, under the guidance of senior consultants. Each patient was given a drug reaction "Alert card" on which the suspected drug causing ACDR was mentioned and the patient was educated regarding

informing the physicians about their drug allergy profile in the future to prevent severe drug reaction events. The casualty assessment of the reported ACDRs according to the Naranjo's scale revealed that no reactions were certain and most of them were probable with a lesser number of possible ADRs. This data are in correlation with the study of Jose *et al*. [32] and of Syed Hussain *et al*. [7] the data were subjected to descriptive analysis. Since it is an observational study, no statistical test was conducted.

The present study indicates that the pattern and spectrum of ACDRs were almost similar to those observed in other studies with little difference in morphological patterns and individual causative drugs. Our study has provided baseline information about the proportion of ACDR in our practice and their clinical patterns and morphological distributions while emphasizing on the most commonly attributed drugs in relation to ACDR. It emphasizes the need for more extensive ADR monitoring in the hospital and will be useful in generating more data about ADR. The significance of this study is to spread awareness to the health-care providers on vigilant monitoring of ACDRs and promptly reporting the same to prevent the recurrence of reactions in the vulnerable population. Although the present study has some limitations as it is an observational study for a short duration and involved small study population, still this study would help to collect more data regarding the pattern of ACDRs in tertiary health centers and increase awareness for further pharmacovigilance studies.

## CONCLUSION

The significance of this study is to emphasize the awareness to the health-care providers on vigilant monitoring of ADRs and promptly reporting the same so as to prevent the occurrence of reactions in the vulnerable population. Frequent pharmacovigilance programs should be initiated to sensitize the doctors on importance of reporting the ADRs. Above all, proper counseling for the patient to inform about their previous drug allergy if any, to the treating physician and also should be emphasized to avoid self-medications. A systemic comprehensive monitoring and documentation of ADRs can curtail many untoward reactions in patient care and will lead to an effective drug administration. More studies are essential to create awareness of possible ACDR and to assist in the early recognition which, in turn, aids in the implementation of effective drug safety measures.

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## AUTHORS CONTRIBUTION

All authors have contributed to preparation of manuscript.

## CONFLICT OF INTEREST

Nil.

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