Original Article

Adverse Cutaneous Drug Reactions - A Clinico-demographic Study in a Tertiary Care Teaching Hospital of the Kashmir Valley, India

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Abstract

Background: Adverse cutaneous drug reactions (ACDRs) are caused by a wide variety of agents. The aim was to study the incidence and clinico-demographic profile of ACDRs to identify any potential risk factors and compare the results with other studies.

Methods: A cross-sectional observational study was conducted over a period of one year from October 2012 to October 2013 in the out-patient department (OPD) of a tertiary care teaching hospital of the Kashmir valley in India and various ACDRs were recorded.

Results: The incidence of ACDRs was 0.16%. The mean age of patients was 39.36 ± 16.77 years. The male: female ratio was 0.97:1. The most frequently reported cutaneous reactions were with antimicrobials (57.33%) followed by NSAIDs (21.33%) and antiepileptic drugs (17.33%). Less common groups involved were steroids, antipsychotics and bisphosphonates (1.33% each). Fixed drug eruptions (FDEs) were the commonest (45.33%) followed by maculopapular (17.33%), photoallergic (8%), erythema multiforme (6.66%), Stevens-Johnson syndrome (5.33%) and lichenoid eruptions (4%). Less common patterns were urticaria, Drug Reaction with Eosinophilia and systemic symptoms (DRESS syndrome) and acneform eruptions (2.66% each) followed by angioedema, acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis and toxic epidermal necrolysis (1.33% each).

Conclusion: Physicians should have adequate knowledge of adverse drug reactions, especially of newer drugs which are increasing every year in order to minimize such events.

Keywords: Adverse drug reactions, adverse cutaneous drug reactions

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Introduction

Adverse Drug Reactions (ADRs) maybe said to be the inevitable price we pay for the benefits of modern drug therapy.[1] They are costly in terms of human illnesses caused as well as the economic terms and can undermine the doctor-patient relationship. Each class of drugs prescribed is associated with its own adverse reaction profile ranging from common and relatively benign reactions like mild gastrointestinal reactions to rare but potentially serious reactions. An adverse cutaneous drug reaction (ACDR) caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and encompass all adverse events related to drug eruption, regardless of etiology. The incidence of ACDRs in developed countries ranges from 1%–3% among inpatients,[2,3] whereas in developing countries such as India some studies peg it to 2%–5% of the inpatients.[4–7] However, there is lack of comprehensive data amongst outpatients. The present study was undertaken to assess the incidence and clinico-demographic profile of ACDRs among outpatients attending the Dermatology department of a tertiary care teaching hospital, to identify any potential risk factors and compare the results with other studies.

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Material and Methods

This hospital-based cross-sectional observational study was conducted over a period of one year from October 2012 to October 2013 in the dermatology outpatient department (OPD) of Sher-I-Kashmir Institute of Medical Sciences – Medical College Hospital, Srinagar, Kashmir, which is a tertiary care teaching hospital. The inclusion criteria in this study were patients of all age groups presenting to the dermatology OPD with suspected ACDRs. All self-reporting patients, patients referred from other departments of the hospital and patients referred from peripheral health care facilities were included. Written informed consent was taken from all patients included in the study. The exclusion criteria included reactions where drugs taken were not known, history of multiple drug intake, cutaneous lesions resembling drug reactions but on clinical examination appearing to be disease related (like viral exanthems, collagen vascular diseases) and drug reactions as a result of consumption of traditional preparations. Detailed history (culprit drug taken, incubation period of drug reaction, route of administration, purpose of drug intake, any pre-existing or co-morbid disease, past history of ADR, history of multiple drug intake), clinical examination (pattern of drug eruption, site of involvement , any extracutaneous manifestation) and review of any records available were done. Causality assessment was done using the Naranjo algorithm and ADRs were classified as definite, probable and possible. Based on modified Hartwigs and Siegel's scale, ADRs were graded from Level 1 to 7. Levels

1&2 were classified as mild ADRs, levels 3&4 as moderate and levels 5 to 7 as severe ADRs. Preventability was assessed using the Schumock and Thornton scale and ADRs were classified as definitely preventable, probably preventable and not preventable. Investigations like complete blood counts, blood sugar, liver and renal function tests were done for all patients. VDRL and HIV tests were done for patients when risk factors were present. Based on history and clinical examination, the ACDRs were analyzed for demographic parameters, types of ACDRs, classes of drugs and individual drugs causing ACDRs, any predisposing factors, systemic involvement and site of involvement. Descriptive statistics were used to analyze the data and the results were expressed as mean ± standard deviation and percentages.

Results

The total number of patients reporting to the dermatology OPD during the study period (October 2012 to October 2013) was 48,238. A total of 92 ACDRs were reported during this one year period. The primary incidence of ACDRs reported was 0.19%. Seventeen cases were excluded from the study as 9 patients gave history of multiple drug intake, 3 patients could not recall the name of the drug taken, viral rash could not be excluded in 3, and 2 patients had taken traditional medications of unknown composition. A total of 75 ACDRs were included in the final analysis giving an incidence of 0.16%.

The mean age of patients developing ACDRs was 39.36 ± 16.77 years (range 2–75 years). The majority of them (21/75) were in the age group of 31–40 years followed by 17 patients in the age group 41–50. Eleven patients (14.66%) belonged to the pediatric age group. The mean age at presentation in males was 39.24 ± 18.36 years and in females was 39.47 ± 15.31 years. Males accounted for 49.33% (37) of ACDRs and females accounted for 50.66% (38). The male:female ratio was 0.97:1. Age and gender-wise distribution of patients reporting with Adverse Cutaneous Drug Reactions is summarized in Figure 1.

Route of drug administration was oral in 65 (86.66%), intramuscular in 8 (10.66%) and intravenous in 2 (2.66%) of the cases.

The time period (in days) for onset of drug reaction is shown in Figure 2.

Our patients had taken drugs mainly for infections, pain and neurological complaints.

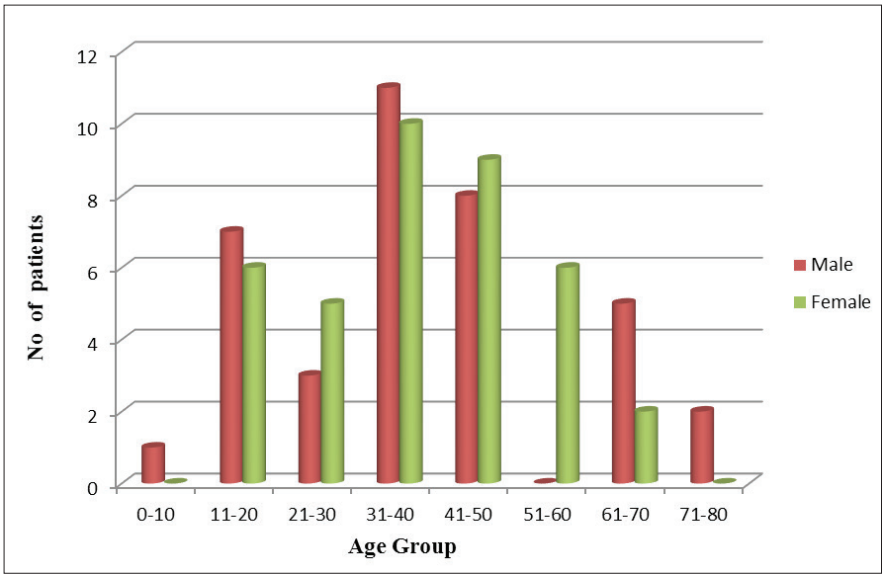

Figure 1. Age and gender-wise distribution of patients reporting with Adverse Cutaneous Drug Reactions.

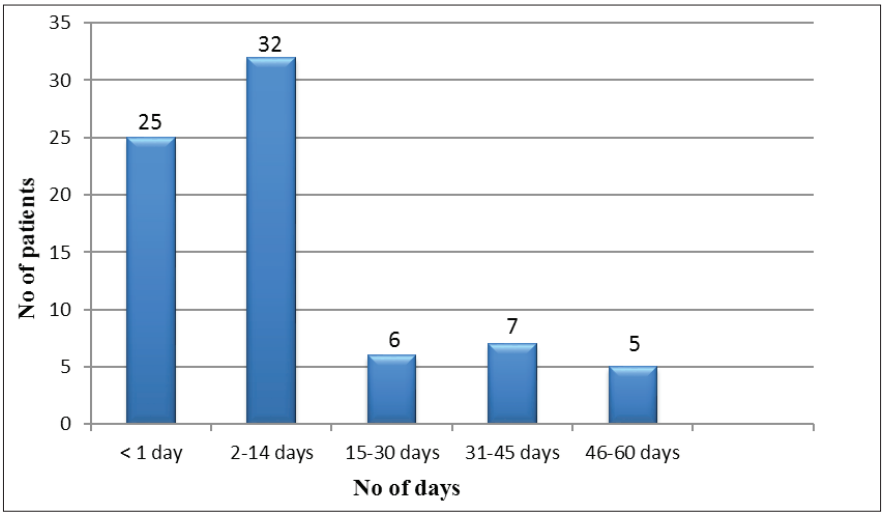

Figure 2. Time period (in days) for onset of drug reaction.

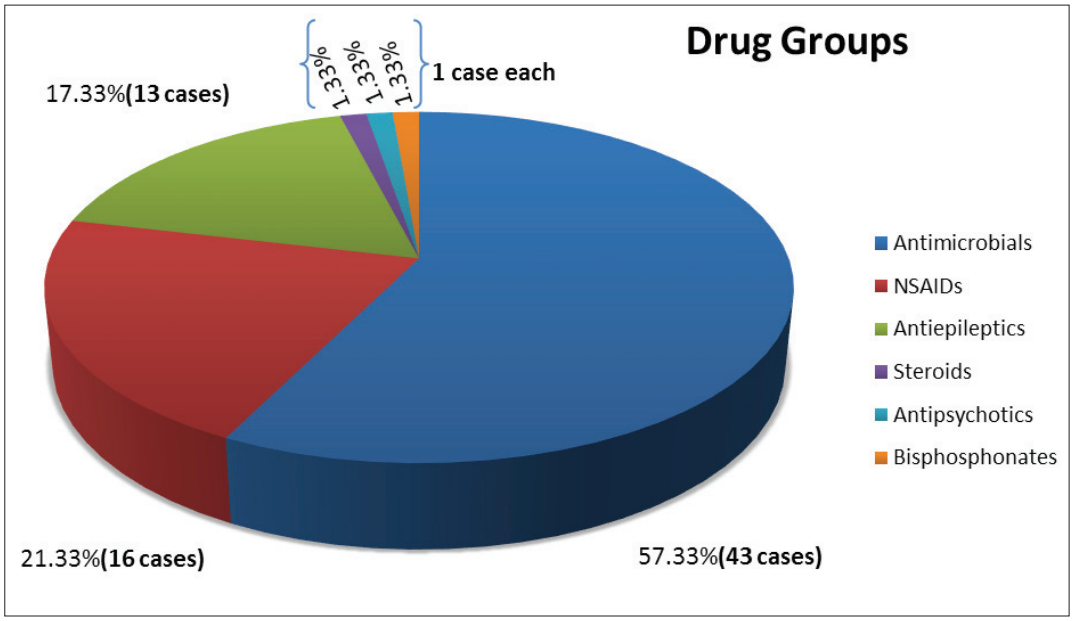

Figure 3. Different drug groups causing Adverse Cutaneous Drug Reactions.

The most frequently reported cutaneous reactions were with antimicrobials; 57.33% (43) followed by non-steroidal anti-inflammatory drugs (NSAIDs); 21.33% (16) and antiepileptic drugs (AEDs); 17.33% (13). Less common groups involved were steroids, antipsychotics and bisphosphonates; 1.33% each (1 patient each). Figure 3 shows different drug groups causing Adverse Cutaneous Drug Reactions.

Among antimicrobials, the most common offenders were quinolones (28). Among AEDs, it was mainly phenytoin (5) and carbamazepine (4) and among NSAIDs, it was mainly piroxicam (7) and acetic acid derivatives (diclofenac & aceclofenac, 7). The drug groups and individual drugs causing Adverse Cutaneous Drug Reactions are summarized in Table 1.

Fixed drug eruptions (FDEs) were the most common ACDRs accounting for 45.33% (34) followed by maculopapular; 17.33% (13), photoallergic reactions; 8% (6), erythema multiforme; 6.66% (5), Stevens-Johnson Syndrome (SJS); 5.33% (4) and lichenoid eruptions; 4% (3). Less common patterns were urticaria, Drug Reaction with Eosinophilia and systemic symptoms (DRESS syndrome) and acneform eruptions accounting for 2.66% each

Table 1. Drug groups and individual drugs causing Adverse Cutaneous Drug Reactions.

Drug groups	Individual drugs involved (number and percentages)	Total
Antimicrobials	Quinolones (28; 37.33%) Ofloxacin (13; 17.33%), Ciprofloxacin (9; 12%), Sparfloxacin (3; 4%), Levofloxacin (2; 2.66%), Norfloxacin (1; 1.33%)	43 (57.33%)
	Cephalosporins (5; 6.66%) Cefpodoxime (2; 2.66%), Cefixime (2; 2.66%), Ceftriaxone (1; 1.33%)	
	Sulphonamides (4; 5.33%) Sulfasalazine (2; 2.66%), Cotrimoxazole (2; 2.66%)	
	Amoxycillin (2; 2.66%) Antitubercular (2; 2.66%) Lincomycin (1; 1.33%) Nitrofurantoin (1; 1.33%)	
Non-steroidal anti-inflammatory drugs (NSAIDs)	Piroxicam (7; 9.33%), Diclofenac (4; 5.33%), Aceclofenac (3; 4%), Etoricoxib (1; 1.33%), Nimesulide (1; 1.33%)	16 (21.33%)
Antiepileptics	Phenytoin (5; 6.66%), Carbamazepine (4; 5.33%), Levetiracetam (2; 2.66%), Lamotrigine (1; 1.33%), Phenobarbitone (1; 1.33%)	13 (17.33%)
Corticosteroids	Prednisolone (1; 1.33%)	1 (1.33%)
Antipsychotics	Prochlorperazine (1; 1.33%)	1 (1.33%)
Bisphosphonates	Zolendronic Acid (1; 1.33%)	1 (1.33%)
		75 (100%)

Table 2. Types of Adverse Cutaneous Drug Reactions and their causative agents.

Types of ACDRs	Causative Drugs (numbers)	Total
FDEs	Ofloxacin (12), Piroxicam (6), Ciprofloxacin (6), Diclofenac (3), Aceclofenac (2), Etoricoxib (1), Cefixime (1), Prochlorperazine (1), Norfloxacin (1), Cotrimoxazole (1)	34 (45.33%)
Maculopapular	Phenytoin (3), Carbamazepine (1), Lamotrigene (1), Phenobarbitone (1), Nimesulide (1), Amoxycillin (1), Ciprofloxacin (1), Levofloxacin (1), Cefpodoxime (1), Lincomycin (1), Zolendronic acid (1)	13 (17.33%)
Photoallergic	Sparfloxacin (3), Sufasalazine (2), Antitubercular (1)	6 (8%)
Erythema Multiforme	Amoxycillin (1), Ciprofloxacin (1), Levofloxacin (1), Cefpodoxime (1), Levetiracetam (1)	5 (6.66%)
SJS	Phenytoin (1), Carbamazepine (1), Cefexime (1), Ofloxacin (1)	4 (5.33%)
Lichenoid Eruptions	Carbamazepine (1), Ceftriaxone (1), Antitubercular (1)	3 (4%)
Urticaria	Piroxicam (1), Aceclofenac (1)	2 (2.66%)
DRESS Syndrome	Phenytoin (1), Leviteracetam (1)	2 (2.66%)
Acneform Eruptions	Prednisolone (1), Nitrofurantoin (1)	2 (2.66%)
TEN	Diclofenac (1)	1 (1.33%)
Exfoliative dermatitis	Carbamezepine (1)	1 (1.33%)
Angioedema	Ciprofloxacin (1)	1 (1.33%)
AGEP	Cotrimoxazole (1)	1 (1.33%)
		75 (100%)

ACDRs= adverse cutaneous drug reactions; FDEs = fixed drug eruptions; SJS = Stevens-Johnson Syndrome; DRESS Syndrome = Drug Reaction with Eosinophila and Systemic Symptoms; AGEP = acute generalized exanthematous pustulosis; TEN = toxic epidermal necrolysis.

(2 patients each) followed by angioedema, acute generalized exanthematous pustulosis (AGEP), exfoliative dermatitis and toxic epidermal necrolysis (TEN); 1.33% each (1 patient each). The types of Adverse Cutaneous Drug Reactions and their causative agents are listed in Table 2.

FDEs were most commonly induced by antimicrobials; 61.76% (21) and NSAIDs; 35.29% (12). Maculopapular rashes were mainly caused by AEDs; 46.15% (6) and antimicrobials; 38.46% (5).

Site of involvement was cutaneous in 37 (49.33%), both cutaneous and mucosal in 35 (46.66%) and only mucosal in 3 (4%) of patients.

Extracutaneous manifestations in the form of fever, malaise, organomegaly and lymphadenopathy were seen in 15 (20%) of the cases. Eosinophilia was seen in two patients.

Causality assessment as per the Naranjo algorithm showed that 61 ADRs were probable, 10 were possible and 4 were definite.

On evaluation of severity of ADRs based on modified Hartwig & Siegels scale, 66 ADRs were moderately severe, 8 were mild and 1 was severe. A total of 51, 15, 5, 3, and 1 ADRs came under level 3, 4(b), 2, 1, and 5, respectively.

According to the Schumock and Thornton scale, 52 ADRs were not preventable, 17 were definitely preventable and 6 were probably preventable.

Ten out of 75 had past history of drug reactions out of which eight had consumed the same drugs with similar reaction pattern in the past and two had reactions to different drugs.

In this study, there were eight patients with hypertension, one with diabetes mellitus, one with both hypertension and diabetes, three with rheumatoid arthritis, one with hypothyroidism, one with depression, one with sarcoidosis and two with infantile hemiparesis

No cutaneous reactions resulted in mortality and complications were not seen with any of the drug reactions.

Discussion

A low incidence rate of 0.16% was reported in this study. Studies done in outpatient settings are limited and have reported different incidence rates. Chatterjee *et al*.[8] reported an incidence of 2.6% whereas Saha *et al*.[9] reported an incidence of 0.28%. Despite all these studies being conducted in tertiary care hospitals among outpatients, differences in incidence rates in various regions are difficult to explain and may be due to pharmacogenetic variations between different populations, level of awareness of drug related events and free access to health care facilities. Incidence rates on the other hand among inpatients are reported on the higher side, ranging between 2%–5%.[4–7] This is probably due to use of multiple drugs among hospitalized patients, use of drugs with more potential to cause ADRs, more severe illness and underlying comorbid factors among inpatients. In the present study, the low incidence rate may also be due to exclusion of 17 patients of the original 92 subjects due to multiple drug intake, failure to recall names of drugs and use of traditional preparations.

The mean age of patients developing ACDRs was 39.36 ± 16.77 years. A South Indian study[7] showed similar results reporting mean age as 37.06 ± 30.12 years. Both males and females showed equal preponderance to ACDRs with male: female ratio of 0.97:1, which has been reported to be similar (0.96:1) in another study.[9] This study has a lower male:female ratio as compared to other studies[10,11] done outside India where the ratio of male:female was 1:1.18. Some studies have shown a male preponderance[12] whereas some have shown female preponderance.[8] These differences may be due to different health care seeking patterns in various regions. All ages were involved in ACDRs (range 2–75) which is similar to other studies.[12,13]

The most frequently reported cutaneous reactions were with antimicrobials (57.33%), NSAIDs (21.33%) and AEDs (17.33%). A similar pattern has also been reported by a Chandigarh study.[12] Antimicrobials have been implicated as main offenders in other

studies.[6,7,14,15] Quinolones (28) were the most common antimicrobials causing ACDRs in our study. Inbaraj *et al.*[16] also reported this group as the common antimicrobial involved. Quinolones are favorite drugs of choice prescribed by physicians, as well as dispensed by local chemists and as self-medication for gastrointestinal infections which is probably the reason for this group being predominant in our study. Many other studies have reported cotrimoxazole.[7,17,18]

Predominance of sulfonamides has been reported from a multicenter analysis from Italy and a 6-year study from Chandigarh, India.[12,14] Cotrimoxazole is available in many hospital supplies of India and is also a cheap antimicrobial. This may account for its being a more commonly implicated drug in other studies. Only two patients reported with ACDRs to cotrimoxazole in this study. In our setting, patients purchase drugs mainly from local pharmacies and prescribing cotrimoxazole is not a common practice.

Piroxicam (7) followed by diclofenac (4) and aceclofenac (3) were the most common drugs among NSAIDs in this study. Chattopadhyay *et al.*[19] reported diclofenac followed by ibuprofen, Hiware S *et al*.[18] reported ibuprofen and diclofenac, Ghosh *et al*.[20] reported salicylates and ibuprofen whereas Saha *et al*.[9] reported paracetamol and diclofenac among NSAIDs causing ACDRs. These differences shown by various studies reflect the different prescribing patterns of drugs in various settings for pain and fever, use of certain favorite drugs by physicians and local chemists as well as self-medication by patients.

Phenytoin (5) and carbamazepine (4) were common AEDs implicated which has been found to be similar in other studies.[7,8,12] Other AEDs involved were phenobarbitone (1), lamotrigene (1), and leviteracetam (2). Of the two patients developing ACDRs to levetiracetam, both initially had DRESS syndrome secondary to phenytoin. Withdrawal of phenytoin resulted in resolution of symptoms in both patients initially. Levetiracetam as an alternate AED was started by the neurologist. After starting levetiracetam, one patient again developed DRESS Syndrome after a gap of 30 days and another developed erythema multiforme like lesions after a period of two weeks. Levetiracetam is a newer AED which is structurally and pharmacologically unrelated to other AEDs. Only few cases of levetiractam induced ACDRs have been reported in the literature. Gómez-Zorrilla *et al*.[21] in 2012 reported a patient presenting with DRESS Syndrome who took no medications other than levetiracetam. Hall and Fromm[22] reported DRESS Syndrome in a patient who was on both phenytoin and levetiracetam. Although levetiracetam is usually well tolerated, clinicians should be aware of its potential to cause DRESS syndrome. Cross-sensitivity to AEDs is more commonly encountered with aromatic AEDs like phenytoin, phenobarbital, carbamazepine, oxcarbazepine and lamotrigine. A case of levetiracetam induced angioedema in a patient with previous anticonvulsant hypersensitivity reaction to phenytoin and lamotrigine has been reported.[23]

FDEs (45.33%) were the most common morphological pattern observed in our study followed by maculopapular (17.33%). A study conducted in South India[7] and Gujarat[13] also reported FDEs as the most common type of ACDR. Most of the other studies[12,24,25] have reported maculopapular rashes as the most common morphological pattern. Urticarias have been commonly reported by Chaterjee *et al*.[8]

The majority of FDEs were caused by quinolones, mainly ofloxacin (13), which has also been reported by an earlier study.[16] Quinolones were a common cause of morbilliform rash and photosensitivity in a Gujarat-based study.[13] Others[26,27,28] have reported sulphonamides as common agents causing FDEs.

Maculopapular rashes were mainly attributed to AEDs (46.15%) and antimicrobials (38.46%). AEDs were the most common cause of maculopapular rash reported by Sharma *et al*.[12]

A single case of TEN was reported which was caused by diclofenac. Other severe ACDRs like SJS, DRESS syndrome and exfoliative dermatitis were seven in number and were caused by phenytoin (3), carbamazepine (2), cefixime (1), and ciprofloxacin (1).

Extracutaneous involvement was seen in SJS, TEN, DRESS syndrome and exfoliative dermatitis.

In conclusion, more studies need to be conducted in order to assess the magnitude of ACDRs in outpatients. Self-medication and medications prescribed by local chemists is a continuing problem in developing countries such as India. The main limitation of this study was that drug rechallenge was not done due to ethical reasons as patients report to this hospital from far flung areas and follow up after rechallenge could not have been ascertained. Positive rechallenge makes the drug reaction certain and adds reliability and reduces false positive cases. Long-term follow up and monitoring of patients could not be done. Minor drug reactions and self-limiting cases often go underreported by patients and some physicians, thereby not reflecting on the true incidence of drug reactions in the population. Moreover, drug reactions caused by topical drugs were not included in the study, further underestimating the true incidence.

Despite these limitations, this study shows that health care providers should realize the importance of reporting every drug reaction they face. The patterns of ACDRs are changing every year due to emergence of newer drugs. Physicians should have an adequate knowledge of ADRs, especially of newer drugs in order to minimize such events**.**

References

1. Nolan L, O'Malley K. Adverse drug reactions in the elderly. *Br J Hosp Med*. 1989; **41:** 446 – 457.
2. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001; **137:** 765 – 770.
3. Craig KS, Edward WC, Anthony AG. Cutaneous drug reactions. *Pharmacol Rev*. 2001; **53:** 357 – 379.
4. Noel MV, Sushma M, Guido S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care centre. *Indian J Pharmacol*. 2004; **36:** 292 – 295.
5. Uppal R, Jhag R, Malhotra S. Adverse drug reactions among in patients in a north Indian referral hospital. *Natl Med J India*. 2000; **13:** 16 – 18.
6. Jhaj R, Uppal R, Malhotra S, Bhargava VK. Cutaneous adverse drug reactions in in-patients in a tertiary care hospital. *Indian J Dermatol Venereal Leprol*. 1999; **65:** 14 – 17.
7. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care centre in South India. *Indian J Dermatol Venereal Leprol*. 2004; **70:** 20 – 24.
8. Chatterjee S, Ghosh AP, Barbhuiya J, Dey SK. Adverse cutaneous drug reactions: a one-year survey at a dermatology outpatient clinic of a tertiary care hospital. *Indian J Pharmacol.* 2006; **38:** 429 – 431.
9. Saha A, Das NK, Hazra A, Gharami RC, Chowdhury SN, Datta PK. Cutaneous adverse drug reaction profile in a tertiary care outpatient setting in Eastern India. *Indian J Pharmacol*. 2012; **44:** 792 – 797.
10. Puavilai S, Timpatanapong P. Prospective study of cutaneous drug reactions. *J Med Assoc Thai*. 1989; **72:** 167 – 171.
11. Kacalak-Rzepka A, Klimowicz A, Bielecka-Grzela S, Zaluga E, Maleszka R, Fabiañczyk H. Retrospective analysis of adverse cutaneous drug reactions in patients hospitalized in Department of Dermatology and Venereology of Pomeranian Medical University in 1996-

2006. *Ann Acad Med Stetin*. 2008; **54:** 52 – 58.
12. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents - a 6-year series from Chandigarh, India. *J Postgrad Med.* 2001; **47:** 95.
13. Raksha MP, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. *Indian J Dermatol Venereol Leprol*. 2008; **74:** 80.
14. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol*. 1999; **48:** 839 – 846.
15. Kauppinen K, Stubb S. Drug eruptions: causative agents and clinical types. *Acta Dermatol Venereol (Stock)*. 1984; **64:** 320 – 324.
16. S D I, M M, N S M, Amutha A, I GJ, Rahman F. Pharmacovigilance of the cutaneous drug reactions in outpatients of dermatology department at a tertiary care hospital. *J Clin Diagn Res*. 2012; **6(10):** 1688 – 1691.
17. Nandha R, Gupta A, Hashmi A. Cutaneous adverse drug reactions in a tertiary care teaching hospital: a North Indian perspective. *Int J Appl Basic Med Res*. 2011; **1:** 50 – 53.
18. Hiware S, Shrivastava M, Mishra D, Mukhi J, Puppalwar G. Evaluation of cutaneous drug reactions in patients visiting outpatient departments of Indira Gandhi Government Medical College and Hospital (IGGMC and H), Nagpur. *Indian J Dermatol*. 2013; **58:** 18 – 21.
19. Chattopadhyay C, Chakrabarti N. A cross-sectional study of cutaneous drug reactions in a private dental college and government medical college in eastern India. *Niger J Clin Pract*. 2012; **15:** 194 – 198.
20. Ghosh S, Leelavathi D, Padma GM Rao. Study and evaluation of the various cutaneous adverse drug reactions in *Kasturba* Hospital, Manipal. *Indian J Pharma Sci.* 2006; **68:** 212.
21. Gómez-Zorrilla S, Ferraz AV, Pedrós C, Lemus M, Peña C. Levetiracetam-induced drug reaction with eosinophilia and systemic symptoms syndrome. *Ann Pharmacother*. 2012; **46(7–8):** e20.
22. Hall DJ, Fromm JS. Drug reaction with eosinophilia and systemic symptoms syndrome in a patient taking phenytoin and levetiracetam: a case report. *J Med Case Rep*. 2013; **7:** 2.
23. Alkhotani A, McLachlan RS**.** Levetiracetam induced angioedema in a patient with previous anticonvulsant hypersensitivity reaction to phenytoin and lamotrigine. *Seizure.* 2012; **21(5):** 407 – 408.
24. Mani MZ, Mathew M. A study of 218 drug eruptions. *Indian J Dermatol Venereol Leprol.* 1983; **49:** 109 – 117
25. Kaur S, Kumar B, Ravikiran TN, Hedge P, Chaudhury RR. A study of cutaneous drug eruptions. *Bulletin PGI*. 1980; **14:** 73 – 79.
26. Mehta TK, Marquis L, Shelty JN. A study of 70 cases of drug eruptions. *Indian J Dermatol Venereol Leprol.* 1971; **37:** 1 – 5.
27. Kauppinen K. Cutaneous reaction of drugs. *Acta Derm Venereol*. 1972; **52(Suppl 68):** 1 – 89.
28. Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol*. 1998; **37:** 833 – 838.