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STUDY OF THERAPEUTIC OUTCOME AND MONITORING OF ADVERSE DRUG REACTIONS (ADRS) IN PATIENTS COMING TO OUTDOOR PATIENT DEPARTMENT (OPD) OF DERMATOLOGY, VENEREOLOGY AND LEPROSY IN TERTIARY CARE HOSPITAL OF NORTHERN INDIA

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Keywords:

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ABSTRACT: Introduction: Cutaneous adverse drug reactions (CADRs) associated with significant morbidity and mortality are probably the most frequent of all manifestations of drug sensitivity. **Material and Methods:** It was a prospective observational study where newly diagnosed patients with ADRs reporting to OPD of Dermatology, K.G.M.U, Lucknow and satisfying inclusion criteria were enrolled. The various study tools used were the suspected ADR reporting form (CDSCO), Naranjo's causality scale, Modified Hartwig and Siegel severity scale and Dermatology Life Quality Index. **Results:** In a total of 124 patients recorded with CADRs, males (60.5%) were found more affected than females (39.5%). The most common age group found was 21-30 yrs (36.3%) followed by 31-40 yrs (25.8%) with a mean age ± SD 35.88 ± 13.87 range (18-78) years. The most common clinical pattern observed was Fixed Drug Eruption (FDE) (49.2%) followed by maculopapular rash (MPR) (36.3%). The incidence of Severe CADRs (SCADR) was 8.06%. Antimicrobial (50.8%) followed by unknown (17.7%), combinations (14.5%) and anti-epileptics (8.9%) were the most common drug groups suspected. On the severity scale, the majority of CADRs were moderately severe (70.9%). Causality assessment categorized most of the CADRs as probable (83.1%). The majority of FDE (39.3%) showed a small effect, MPR (33.3%) and SCADR (60%) showed an extremely large effect, other drug rashes (50%) showed a very large effect on the quality of life (QoL). The association of type of CADR with causality, severity and QoL was found statistically significant. (p-value <0.05). **Conclusion:** Prompt reporting and monitoring of ADRs is needed to timely manage and prevent them which may even progress to fatal scenarios.

INTRODUCTION: Adverse drug reactions (ADRs) are encountered as a major clinical problem that involves human suffering and increases the cost of health care.

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ADR is defined as 'a response occurring at drug doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modifications of physiological functions, which is noxious and unintended' [1].

ADRs are responsible for 5-11% of hospital admissions; of this 60-70 % are preventable [2]. CADR or toxidermia are commonly encountered skin manifestations among the ADRs. Various studies have reported CADRs to be the most frequent ADRs [3].

They are accountable for patients' adversity, hospital admission, economic burden and even death. Approximately 5 to 9% of all hospital costs have been related to ADRs [4]. A cutaneous adverse drug reaction (CADR) is defined as "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" [5]. The incidence of cutaneous ADRs in developed countries ranges from 1-3% whereas in developing countries it is 2-5% [6]. Cutaneous adverse drug reactions form an important clinical entity in dermatology practice and the clinical spectrum varies widely from a mild self-limiting exanthematous rash to severe life-threatening conditions. In India, less emphasis has been laid in this regard. Therefore, this study was undertaken. The primary objective of the study was to note & monitor ADRs in the form of recording the suspected ADR, grading according to severity scale, assessing causality, management and outcome and noting the suspected drug. The secondary objectives included collection of the data regarding the demographic profile, adverse drug reaction pattern and assessment of the quality of life in patients with adverse drug reactions coming to Outdoor Patient Department of Dermatology, Venereology & Leprosy, King George's Medical University (K.G.M.U), Lucknow.

MATERIALS AND METHODS: The present research work was conducted at the Department of Pharmacology & Therapeutics in collaboration with Department of Dermatology, Venereology & Leprosy, K.G.M.U. Lucknow. It was a prospective observational study of therapeutic outcome and monitoring of patients with cutaneous adverse drug reactions coming to OPD of Dermatology, Venereology & Leprosy, K.G.M.U. Lucknow. It was started only after the approval of Institutional Ethics Committee, K.G.M.U, Lucknow. (Ref code: 90th ECM II B-IMR-R/P6). Newly diagnosed patients with adverse drug reactions and satisfying inclusion criteria were enrolled only after taken written informed consent. The various study tools used were the suspected adverse drug reaction reporting form issued by Central Drugs Standard Control Organization (CDSCO) under Pharma-covigilance Programme of India (PvPI), Causality assessment done using Naranjo's causality assessment scale [7], Severity of ADRs assessed using severity assessment scale (Modified Hartwig and Siegel) [8]. The quality of life was assessed by the Dermatology Life Quality Index (DLQI) [9].

Inclusion and Exclusion Criteria:
Inclusion Criteria

- Newly diagnosed patients coming to OPD of Dermatology, Venereology & Leprosy, K.G.M.U, Lucknow.
- Patients with age more than 18 years.
- Patients of either sex.

Exclusion Criteria:

- Patients who were unwilling to participate and did not give consent in the study.
- Patients who were unable to give interview.
- Patients with incomplete medical records.
- Female patients who are pregnant.
- Terminally ill patients.
- Patients who are alcoholics, smokers, drug addicts, or having any psychotic illness.
- Patient with cardiac disease, cirrhosis, renal failure, diabetes, hypertension, carcinoma.

Data was entered in the Microsoft word excel sheet and analyzed. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean ± SD. P values less than 0.05 were considered statistically significant.

RESULTS:

Demographic Details: A total of 124 patients with cutaneous adverse drug reactions were enrolled. The total number of males in the study was 75 (60.5%) while females were 49 (39.5%). The age group ranged from 18 years to above 60 years. In the present study, the maximum number of cases fall in the age group of 21-30 yrs (36.3%) followed by 31-40 (25.8%). The mean age ± SD of the study population found was 35.88 ± 13.87 (18-78) years in **Table 1** and **Fig. 1**.

TABLE 1: ASSOCIATION OF GENDER AND AGE OF THE STUDY POPULATION (N = 124)

Age group (yrs)	Total (N = 124)	Female (n = 49)		Male (n = 75)	
		No.	%	No.	%
≤20	8	4	8.2	4	5.3
21-30	45	20	40.8	25	33.3
31-40	32	13	26.5	19	25.3
41-50	22	8	16.3	14	18.7
51-60	11	4	8.2	7	9.3
>60	6	0	0.0	6	8.0
		x^2 =4.899 (d_f = 5); p = 0.428			
Mean age ± S. D. (Range)	35.88 ± 13.87 (18-78)	33.18 ± 11.04 (19-60)		37.64 ± 15.25 (18-78)	
		't' = 1.765; p = 0.080			

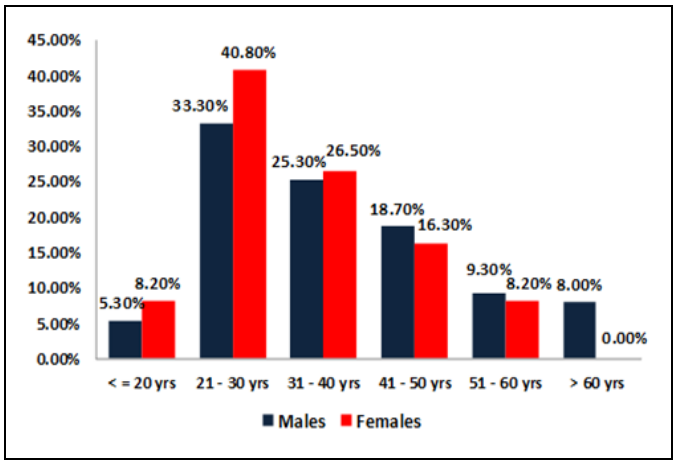

FIG. 1: ASSOCIATION OF GENDER AND AGE OF THE STUDY POPULATION (N = 124)

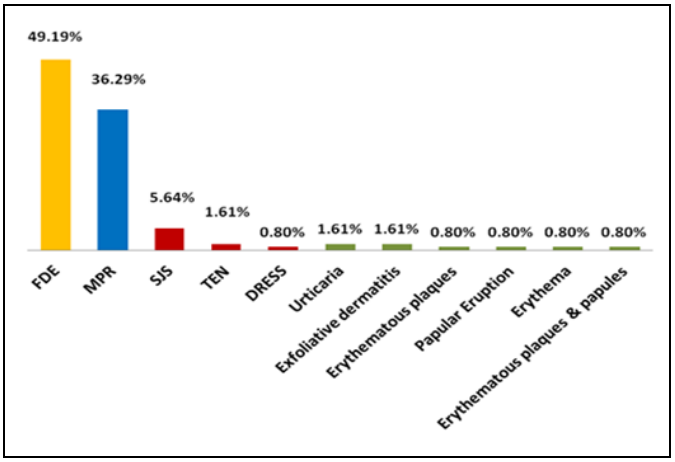

FIG. 2: DISTRIBUTION OF THE STUDY POPULATION ACCORDING TO TYPE OF CADR

Cutaneous Adverse Drug Reaction (CADR):

Types of CADR: Out of total 124 patients reported with cutaneous ADR, 61 cases were of Fixed Drug Eruption (FDE) constituting 49.2%, 45 cases of Maculopapular Rash (MPR) accounting for 36.3%, 10 cases of Severe cutaneous adverse drug reaction (SCADR) accounting for 8.1% and 8 cases were of other types of drug rash that constituted 6.5% of total cases. SCADR observed were 7 cases of Steven Johnson Syndrome (SJS), 2 cases of Toxic Epidermal Necrolysis (TEN) and 1 case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome with an incidence of 5.6%, 1.61%, 0.8% respectively. The other drug rash involved 2 cases of urticaria and 2 cases of exfoliative dermatitis with an incidence of 1.6% each and 1 case of erythematous plaque, 1 case of a papular eruption, 1 case of erythema, 1 case of erythematous papules and plaques with incidence of 0.8% each **Fig. 2** and **Table 2**.

TABLE 2: DISTRIBUTION OF THE STUDY POPULATION ACCORDING TO TYPE OF CADR

S. no.	Type of CADR	No. of cases	Percentage
1	Fixed Drug Eruption (FDE)*	61	49.19
2	Maculopapular rash (MR)	45	36.29
3	Severe cutaneous adverse drug reaction (SCADR):	10	8.06
	Steven Johnson syndrome	7	5.64
	Toxic Epidermal necrosis	2	0.61
	DRESS	1	0.80
4	Other drug rashes:		
	Urticaria	8	6.45
	Exfoliative Dermatitis	2	1.61
	Erythematous Plaques	2	1.61
	Papular Eruption	1	0.80
	Erythema	1	0.80
	Erythematous Plaque and Papules	1	0.80

*Bullous Fixed Drug Eruption (n=3) is to be mentioned

Drug Groups and Individual Drugs / Fixed-Dose Combination (FDC) Suspected to Cause CADR in the Study Population: Out of 124 CADR patient, antimicrobials were suspected for 63 cases (50.8%), unknown drugs 22 cases (17.7%), anti-epileptics 11 cases (8.9%), NSAID 3 cases (2.4%), anti-gout 2 cases (1.6%), homeopathic 2 cases (1.6%), antihistaminic 1 case (0.8%), proton pump inhibitor (PPI) 1 case (0.8%), ayurvedic 1 case (0.8%) and combination therapy for 18 cases (14.5%). The most common drug group found was of antimicrobials followed by unknown drug, combinations and anti-epileptics. Among the 63 cases implicated to antimicrobials, the fixed-dose combination of fluoroquinolones + imidazole was the most common group 55.6% (35/63) in which norfloxacin + tinidazole was accountable for maximum cases 28.6% (18/63) Antimicrobials along with NSAID 55.6% (6/18) was the most common medication observed among those patients who were reported with combinations of drug groups taken. Among anti-epileptics, hydantoin (phenytoin) was the most common group implicated 91% (10/11) **Table 3** and **Fig. 3**.

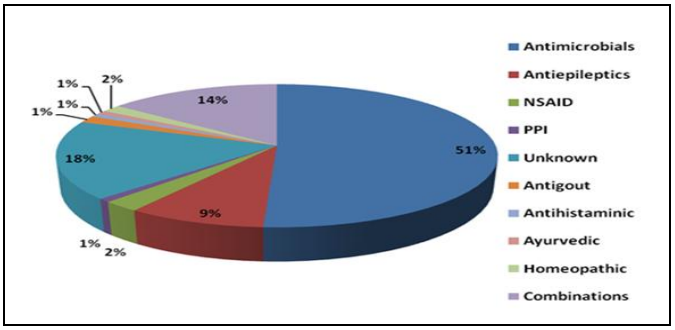

FIG. 3: DRUG GROUPS SUSPECTED TO CAUSE CADR

TABLE 3: DRUG GROUPS AND INDIVIDUAL DRUGS / FDC SUSPECTED TO CAUSE CADR

Drug groups	Drugs (Individual / FDC)		Cases (Out of 124)	%
Antimicrobials	Fluoroquinolones + Imidazole	Ofloxacin + ornidazole	6	4.8
		Norfloxacin + Metronidazole	1	0.8
		Norfloxacin + Tinidazole	18	14.5
		Ciprofloxacin + Tinidazole	6	4.8
		Levofloxacin + Ornidazole	1	0.8
		Ofloxacin + Tinidazole	3	2.4
	Fluoroquinolones	Ciprofloxacin	4	3.2
		Levofloxacin	2	1.6
		Ofloxacin	1	0.8
	Imidazole	Metronidazole	1	0.8
		Ornidazole	2	1.6
		Secinidazole	1	0.8
	Cephalosporins	Cefoperazone - Sulbactum	1	0.8
		Cefixime	3	2.4
		Ceftriaxone	2	1.6
		Cefadroxil	1	0.8
	Carbapenem + Lincosamide	Meropenem + Clindamycin	1	0.8
	Cephalosporin + Fluoroquinolone	Cefixime + Ofloxacin	1	0.8
	Penicillin + Lincosamide	Piperacillin + Clindamycin	1	0.8
	Antitubercular	Isoniazid + Rifampicin + Pyrazinamide + Ethambutol	4	3.2
	Antifungal	Itraconazole	1	0.8
		Oral & topical antifungals	1	0.8
	Antileprotic	Dapsone	1	0.8
		Total (Antimicrobial)	63	50.8
Antiepileptic	Hydantoin	Phenytoin	10	8.1
NSAID	Para aminophenol derivative	Paracetamol	1	0.8
	Acetic acid derivative	Diclofenac	2	1.6
		Total (NSAID)	3	2.4
PPI	Proton pump inhibitor	Pantaprazole	1	0.8
Unknown			22	17.7
Anti-gout		Allopurinol	2	1.6
Antihistaminic	Second Generation	Levocetrizine	1	0.8
Ayurvedic			1	0.8
Homeopathic			2	1.6
Combinations			18	14.5

Type of CADR and Suspected Drug Groups / Individual Drugs, FDC: In the present study, it was observed antimicrobials 55.7% (34/61) followed by 55.7% (34/61) followed by unknown 23% (14/61) as the most common drug groups suspected to cause FDE. Bullous form of FDE was reported in 5% cases (3/61). Antimicrobial, unknown and combinations were the suspected drug groups for each case of bullous FDE respectively. Similarly, antimicrobials 53.3% (24/45) were the most common drug group suspected to cause MPR which was followed by anti-epileptics 15.6% (7/45). Maximum cases of SCADR were implicated to combinations and unknown 30% (3/10) each followed by anti-microbials 20% (2/10). Anti-epileptics and anti-gout accounted for 10% (1/10) each. In cases reported with other drug rash, antimicrobials and anti-epileptics 37.5% (3/8) each was the most common suspected drug group found. Further, individual drugs / FDC suspected to cause a particular type of CADR were observed as in **Table 4**, **Table 5** and **Fig. 4**.

TABLE 4: ASSOCIATION OF TYPE OF CADR WITH THE SUSPECTED DRUG GROUPS

Drug Groups	Total (N=124)	FDE (n=61)		MPR (n = 45)		SCADR (n = 10)		Oth (n = 8)	
		No.	%	No.	%	No.	%	No.	%
Antimicrobials	63	34	55.7	24	53.3	2	20.0	3	37.5
Antiepileptic	11	0	0.0	7	15.6	1	10.0	3	37.5
NSAID	3	2	3.3	1	2.2	0	0.0	0	0.0
PPI	1	0	0.0	1	2.2	0	0.0	0	0.0
Unknown	22	14	23.0	4	8.9	3	30.0	1	12.5
Anti-gout	2	0	0.0	1	2.2	1	10.0	0	0.0
Antihistaminic	1	1	1.6	0	0.0	0	0.0	0	0.0
Ayurvedic	1	1	1.6	0	0.0	0	0.0	0	0.0
Homeopathic	2	2	3.3	0	0.0	0	0.0	0	0.0
Combination	18	7	11.5	7	15.6	3	30.0	1	12.5

$\chi^2=35.660(d_f = 27)$; p=0.123

TABLE 5: TYPE OF CADR AND THE SUSPECTED MEDICATION

Type of CADR	Suspected drug groups with individual drugs/FDC	Percent
FDE	Antimicrobials	55.7
	Ofloxacin + ornidazole (3)	
	Norfloxacin + Metronidazole (1)	
	Norfloxacin + Tinidazole (14)	
	Ciprofloxacin + Tinidazole (4)	
	Levofloxacin + Ornidazole (1)	
	Metronidazole (1)	
	Ornidazole (2)	
	Ciprofloxacin (4)	
	Ofloxacin (1)	
	Levofloxacin (2)	
	Cefixime + ofloxacin (1)	23
	Unknown (14)	3.3
	NSAID [Diclofenac (2)]	1.6
	Antihistaminic [Levocetrizine (1)]	3.3
	Homeopathic (2)	1.6
	Ayurvedic (1)	11.5
	Combination (7)	(out of 61)
MPR	Antimicrobials	53.3
	Ofloxacin + ornidazole (3)	
	Norfloxacin + Tinidazole (4)	
	Ciprofloxacin + Tinidazole (2)	
	Ofloxacin + Tinidazole (3)	
	Antitubercular (2)	

	Cefoperazone - Sulbactum (1)	
	Cefixime (3)	
	Ceftriaxone (2)	
	Cefadroxil (1)	
	Meropenem + clindamycin (1)	
	Piperacillin + clindamycin (1)	
	Antifungal [Itraconazole (1)]	
	Antiepileptic [Phenytoin (7)]	15.6
	Antigout [Allopurinol (1)]	2.2
	PPI [Pantoprazole (1)]	2.2
	NSAID [paracetamol (1)]	2.2
	Unknown (4)	8.9
	Combination (7)	15.6 (out of 45)
SCADR		
SJS	Antimicrobial [Secinidazole (1)]	10%
	Antiepileptic [Phenytoin (1)]	10%
	Unknown (3)	30%
	Combinations (2)	20%
	Anti-gout [Allopurinol (1)]	10%
TEN	Combination (1)	10%
DRESS	Anti-leprotic [Dapsone (1)]	10% (out of 10)
OTHER DRUG RASH		
Urticaria	Antimicrobial [Anti-tubercular (2)]	25%
Exfoliative Dermatitis	Antiepileptic	
	Phenytoin (1)	12.5%
	Lamotrigine (1)	12.5%
Erythematous Plaques Papular Eruption	Antiepileptic [Phenytoin (1)]	12.5%
Erythema	Combination (1)	12.5%
Erythematous Papules & Plaques	Antimicrobial [Anti-fungal (1)]	12.5%
	Unknown (1)	12.5% (out of 8)

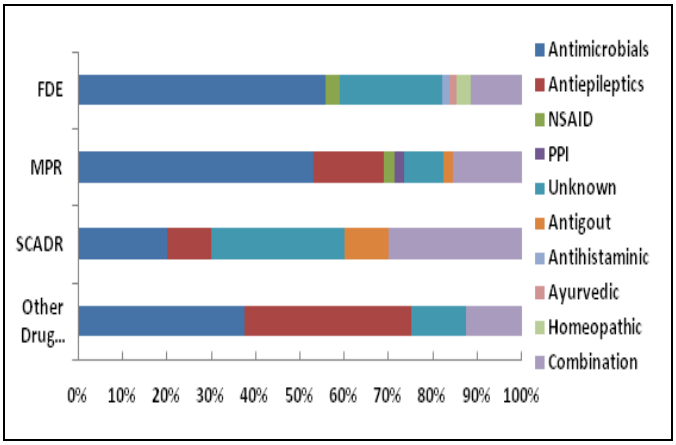

FIG. 4: ASSOCIATION OF TYPE OF CADR WITH THE SUSPECTED DRUG GROUP

Causality of Cutaneous Adverse Drug Reaction: As per Naranjo's Algorithm 83.1% of the CADRs were categorized as "probable" with score ranging from 5 – 8 whereas 16.9% of the CADRs were categorized as "possible" with score ranging from 1 – 4 with the mean score ± SD [Range: 6.85 ± 1.45 (3-8)] **Table 7**, **Fig. 5**.

TABLE 6: NARANJOS CAUSALITY SCALE

S. no.	Naranjo's causality Scale	No. of cases	Percentage
1	Doubtful (<1)	0	0.0
2	Possible (1-4)	21	16.9
3	Probable (5-8)	103	83.1
4	Definite (>8)	0	0.0

Mean score ± S. D. [Range: 6.85 ± 1.45 (3-8)]

Majority of cases with FDE (68.9%), MPR (95.6%) and all the cases with SCADR and Other drug rash were observed to be of probable category. The p-value of 0.001 shows the association was statistically significant **Fig. 6** and **Table 7**.

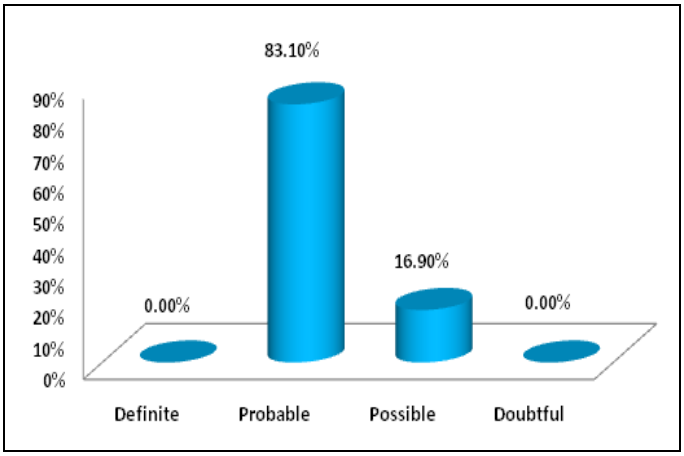

FIG. 5: NARANJO'S CAUSALITY SCALE

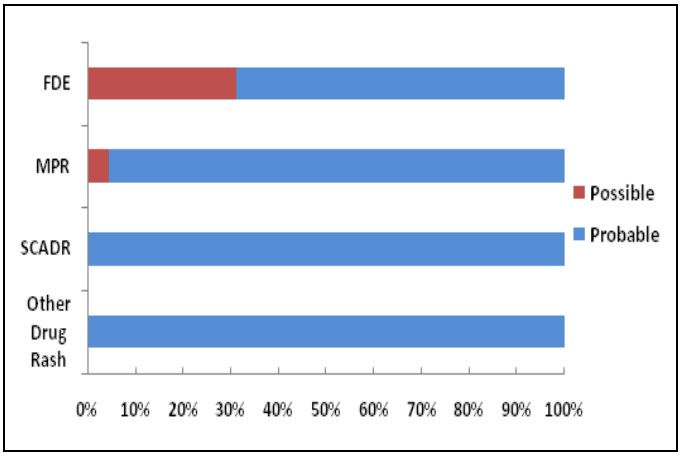

FIG. 6: ASSOCIATION OF TYPE OF CADR WITH NARANJO'S CAUSALITY SCALE

TABLE 7: ASSOCIATION OF TYPE OF CADR WITH NARANJOS CAUSALITY SCALE

Causality (Naranjo scale)	Total (N=124)	FDE (n = 61)		MPR (n = 45)		SCADR (n = 10)		Oth (n = 8)	
		No.	%	No.	%	No.	%	No.	%
Possible (1-4 score)	21	19	31.1	2	4.4	0	0.0	0	0.0
Probable (5-8 score)	103	42	68.9	43	95.6	10	100.0	8	100.0

x^2=17.420(df=3); p=0.001; *Other drug rash

Severity of Cutaneous Adverse Drug Reaction: Modified Hartwig and Siegel Scale, which is a standard scale for severity assessment was used to assess the severity of CADRs. It was observed that out of 124 CADR reported, 26 cases (20.9%) were mild, 88 cases (70.9%) were moderate and 10 cases (8.06%) were of severe grade **Table 8** and **Fig. 7**. Association of type of CADR with severity grade was also observed and found to be statistically significant with p-value <0.001 **Table 9** and **Fig. 8**.

TABLE 8: MODIFIED HARTWIG's AND SEIGEL's SEVERITY SCALE

S. no.	Modified Hartwig's and Seigel's Severity Scale	No. of cases	Percentage
1	Mild Level 1-0/26 Level 2-26/26 (100%)	26	20.9
2	Moderate Level 3-85/88 (96.6%) Level 4(a)-2/88 (2.3%) Level 4(b)-1/88 (1.1)	88	70.9
3	Severe Level 5-10/10 (100.0%) Level 6-0/10 Level 7-0/10	10	8.06

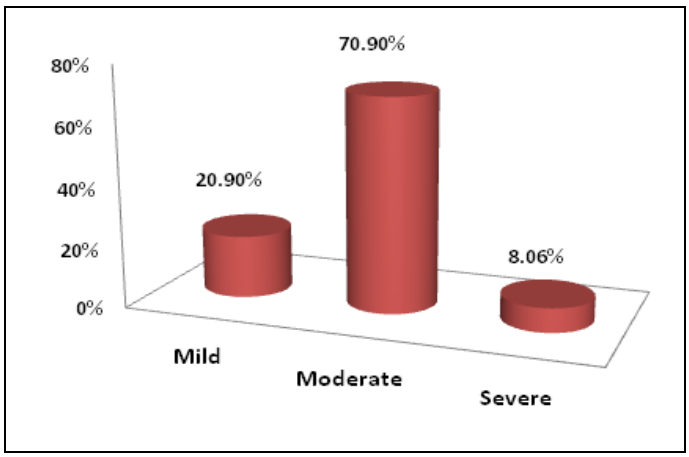

FIG. 7: MODIFIED HARTWIG'S AND SEIGEL'S SEVERITY SCALE

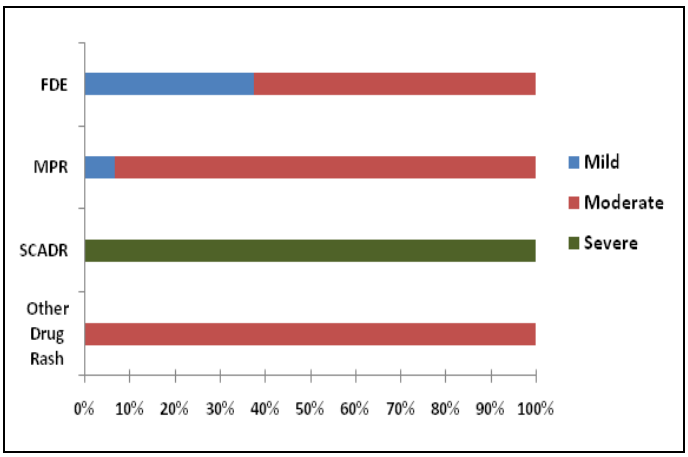

FIG. 8: ASSOCIATION OF TYPE OF CADR WITH MODIFIED HARTWIG'S AND SEIGEL'S SEVERITY SCALE

TABLE 9: ASSOCIATION OF TYPE OF CADR WITH MODIFIED HARTWIG'S AND SEIGEL'S SEVERITY SCALE

Severity (Hartwig scale)	Total (N=124)	FDE (n=61)		MPR (n=41)		SCADR (n=10)		Oth* (n=8)	
		No.	%	No.	%	No.	%	No.	%
Mild	26	23	37.7	3	6.7	0	0.0	0	0.0
Moderate	88	38	62.3	42	93.3	0	0	8	100.0
Severe	10	0	0.0	0	0.0	10	100.0	0	0.0

χ^2=142 (df=6); p<0.001;*Other drug rash

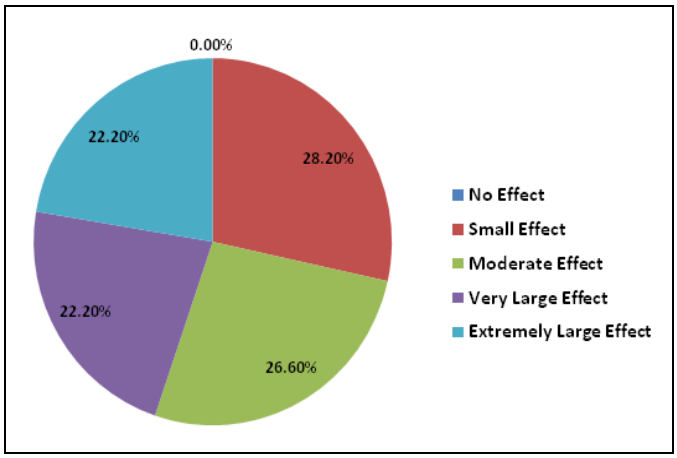

FIG. 9: DERMATOLOGY LIFE QUALITY INDEX IN PATIENTS OF CADR

TABLE 10: DERMATOLOGY LIFE QUALITY INDEX IN PATIENTS OF CADR

S. no.	Dermatology life quality index	No. of cases	Percentage
1	No effect (0-1)	0	0.0
2	Small effect (2-5)	35	28.2
3	Moderate effect (6-10)	33	26.6
4	Very large effect (11-20)	28	22.6
5	Extremely large effect (21-30)	28	22.6

Quality of Life in CADR Patients: The Quality of life in CADR patients was assessed using the Dermatology Life Quality Index (DLQI) score. It was observed that out of 124 CADR reported, 35 cases (28.2%) showed a small effect, 33 cases (26.6%) showed moderate effect and very large effect and extremely large effect were shown by 28 Cases (22.6%) each **Table 10** and **Fig. 9**.

Association of Dermatology Life Quality Index with Type of CADR: It was observed that maximum number of cases of FDE showed small effect 39.3% (24/61) followed by moderate effect 34.4% (21/61) on their quality of life. In MPR cases, maximum patients 33.3% (15/45) showed extreme large effect followed by equal distribution 22.2% (10/45) of other DLQI grades on their quality of life. Similarly, the extreme large effect was observed in maximum cases 60% (6/10) of SCADR followed by a very large effect shown by 40% (4/10) cases. In cases with other drug rashes, a very large effect on the quality of life predominated with 50% (4/8) followed by a moderate effect, observed in 25% (2/8). The association observed was statistically significant with p-value 0.001 **Table 12** and **Fig. 10**.

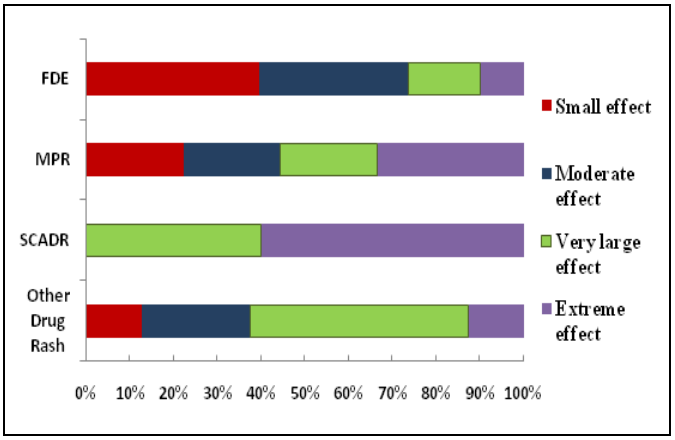

FIG. 10: DERMATOLOGY LIFE QUALITY INDEX AND TYPE OF CADR

TABLE 11: DERMATOLOGY LIFE QUALITY INDEX AND TYPE OF CADR

DLQI grade	Total (N = 124)	FDE (n = 61)		MPR (n = 45)		SCADR (n = 10)		Oth* (n = 8)	
		No.	%	No.	%	No.	%	No.	%
Small effect (2-5)	35	24	39.3	10	22.2	0	0.0	1	12.5
Moderate effect (6-10)	33	21	34.4	10	22.2	0	0.0	2	25.0
V. large effect (11-20)	28	10	16.4	10	22.2	4	40.0	4	50.0
Extreme effect (21-30)	28	6	9.8	15	33.3	6	60.0	1	12.5

χ^2=29.461(d_f = 9); p=0.001;*Other drug rash

Management and Outcome of CADRs: In the present study, 124 patients were reported with CADR.

Seriousness of the Reaction: 115 CADR cases required intervention to prevent permanent damage, 9 cases were of hospitalization.

Time of Reporting: Out of 124 CADRs, 114 cases were continuing at the time of reporting while 10 had recovered with Sequelae.

Time Relationship of CADR with Suspected Drug Therapy: Maximum cases 72.6% (90/124) of CADR reported within 1 week of starting drug therapy. Among these, the majority of CADR 61.1% (55/90) were observed within 24 h of therapy. Others were observed within 1 month to more than 1 year of therapy. The essential step in the management of all CADRs was the withdrawal of the offending drug. In mild to moderate cases anti-histaminics and steroids (oral/topical) either alone or in combination were advised. The majority of the patients reported with FDE recovered in 1 to 2 weeks while most of the patients reported with MPR and other drug rash showed recovery in almost 1 month with some extended up to 2 months. Hospitalized 2 cases of TEN and 3 cases of SJS were kept under constant monitoring and intensive medical care [maintenance of fluid-electrolyte balance, administration of steroids (systemic/topical for surface lesions), high protein diet] with the withdrawal of the offending drug and were followed for the outcome. These patients showed gradual improvement in a period of time and took almost 3 to 4 months to recover. Out of 7 cases of SJS, 4 cases were strictly advised prompt withdrawal of offending drug and steroids and protein diet and regularly followed up. Recovery was observed in these patients in about a month.

Management of a hospitalized case of DRESS involved prompt discontinuation of the offending drug, systemic steroids with supportive care and intensive monitoring. 3 cases of maculopapular rash were found hospitalized. Their management also involved the withdrawal of offending drugs, steroids (oral/topical) and antihistaminics. They recovered in a month's period. 6 cases who developed CADR under anti-tubercular treatment (ATT) [4 cases were on only ATT while the other 2 were taking polytherapy] were advised to stop all the medications, treated for CADR and then to restart the ATT with individual drugs one by one. After the CADR improved, rechallenge was done by the respective authority with the administration of single ATT drug and monitoring for the CADR. The rechallenge with ethambutol, isoniazid and rifampicin was found negative.

DISCUSSION:

Demographic Characteristics: Gender wise distribution of total of 124 patients reported, 60.5% (75) were males and 39.5% (49) were females. Males were found to be more affected than females in our study. This finding is in close approximation to studies done by Agrawal A *et al*., [10] 58.1% (93) males, 41.9% (67) females), Modi A *et al*., [11] (55.2 % males, 44.8% females), Dhanani JG et al., [12] (54% males, 46% females), T N *et al*., [13] (77.7% of males, 2.3% females) and Joshi DB *et al*., [14] (54% males, 46% females). Similar to present study previous studies also indicate that males seem to be more susceptible than females for developing CADRs. In contrast some other studies Amrinder R *et al*., [15], Inbaraj SD *et al*., [16] have shown females more involved than males whereas another study, Thakkar S *et al*., [17] has shown the equal incidence of CADRs in males and females. Age-wise distribution in the present study showed the maximum number of patients were in the age group of 21-30 yrs (36.3%) followed by 31-40 yrs (25.8%). Similar finding was observed in studies conducted by Agrawal A *et al*., [10] (26.3% in the age group of 21-30 yrs followed by 20.6% in age group 31-40 yrs), B Raghu Kiran *et al*., [18] (45% in the age group of 21-30 yrs followed by 25% in age group 31-40 yrs), Sharma R *et al*., [19] (30.6% in the age group of 21-30 yrs followed by 26% age group 31-40 yrs, Joshi DB *et al*., [14] (31.4% in the age group of 21-30 yrs followed by 22.9% in age group 31-40 yrs). Varghese B *et al*., [20] also found the majority of patients in the age group < = 30 yrs (29.3%). Our and these previously reported studies are in parallel agreement to describe the most common age group of patients suffering from cutaneous ADR. In contrast, a study conducted by Amrinder R *et al*., [15] found the maximum number of patients in the age group of 31-40 yrs (25%) followed by age group 21-30 yrs (21%). A study conducted by Qayoom S *et al*., [21] showed a majority of patients belonging to age group 31-40 yrs (28%) followed by 41-50 yrs (22.7%). In our study, the mean age of patients with cutaneous ADR was 35.88 ± 13.87. The mean age of the patient-reported by Joshi DB *et al*., [14] was 35.26 ± 15.13 years (for both male and female respectively), Qayoom S *et al*., [21] were 39.36 ± 16.77, Sharma R *et al*., [19] was 33.26 years, Agrawal A *et al*., [10] were 30.06 years, Varghese B *et al*., [20] were 43.5 yrs. The above-quoted first three

studies are in somewhat agreement with our finding while the other two studies show variability.

Pattern of Cutaneous Adverse Drug Reaction: Distribution of cutaneous ADR showed various types of morphological patterns in the study population. Fixed drug eruption (FDE), Maculopapular rash (MPR), urticaria, exfoliative dermatitis, papular eruption, plaques, erythema, exfoliation, and severe cutaneous ADR were the different types of drug reactions observed in the present study. Fixed drug eruption was the most common clinical pattern observed followed by maculopapular rash.

Fixed Drug Eruption (FDE): In the present study, out of total of 124 patients reported with cutaneous ADR, 61 cases were of fixed drug eruption where more males were affected than females in a ratio of 1.65:1. The more common age group in which FDE seen was 21-30 yrs followed by 31-40 yrs. FDE constituted 49.2% (61/124) and was the most common clinical pattern recorded in our study.Similarly, previous reports by Qayoom S *et al*., [21] Beniwal R *et al*., [22] Amrinder R *et al*., [15] Sharma R *et al*., [19] Agrawal A *et al*., [10] B Raghu Kiran *et al*., [18] T N *et al*., [13] has observed FDE as the most common cutaneous ADR with incidence of 45.33% (34/75), 41% (82/200), 33.3% (40/120), 33.3% (50/150), 28.7% (46/160), 18% (18/100), 66.7% (60/90) in their studies respectively. From these previous study reports, it can be understood that some of the north Indian, as well as some of the south Indian studies, record similar findings that may rule out the regional difference.

Maculopapular Rash (MPR): We observed that out of total of 124 patients reported with cutaneous ADR, 45 cases were of Maculopapular Rash where more males were affected than females in a ratio of 1.56:1. The more common age group in which MPR seen was 31-40 yrs followed by 21-30 yrs. MPR constituted 36.3% (45/124) and was the second most common clinical pattern recorded in our study. On similar lines, Amrinder R *et al*., [15], Agrawal A *et al*., [10], T N *et al*., [13], Qayoom S *et al*., [21] recorded MPR as the second most common cutaneous ADR with the incidence of 30.8% (37/120), 26.3 % (42/160), 22.2% (20/90), 17.33% (13/75) respectively in their studies. Previous reports by Qayoom S *et al*., [21], Amrinder R *et al*., [15], Agrawal A *et al*., [10] and T N *et al*., [13], study done in Kashmir, Punjab, Madhya Pradesh and Chennai respectively recorded fixed drug eruption and maculopapular rash as the most and the second most common cutaneous ADR in their respective studies which is similar to our study that was conducted in Uttar Pradesh. The diversity of study locations presenting with similar findings somewhat indicates the consistency of the finding.

Severe Cutaneous Adverse Drug Reaction (SCADR): In our study, out of total of 124 patients reported with cutaneous ADR, 10 cases were of severe cutaneous adverse drug reaction with an incidence of 8.06%. The incidence of 5.6% (7/124) cases of SJS observed in the present study is comparable to finding in the studies conducted by Kumari M. Nithya *et al*., [23] , Amrinder R *et al*., [15] and Qayoom S *et al*., [21] where 5.71% (4/70), 5.8% and 5.33% (4/75) incidence of SJS were recorded. We observed 9 patients out of 124 presented with SJS/TEN that accounted for a total incidence of 7.21%. This finding is in parallel agreement with the study conducted by Beniwal R *et al*., [22] where 7% (14/200) incidence of SJS/TEN has been reported. On similar lines, Patel T *et al*., [24] recorded incidence of 6.84% (251/3671) cases of SJS/TEN in their study. The incidence of DRESS reported was 0.8%, 1 patients out of total 124 in the present study. Amrinder R *et al*., [15] and Thakkar S *et al*., [17] observed 0.83% (1/120) and 0.6% (1/171) incidence in their study. These studies hold similarities to finding in our study. The incidence of SCADR reported in our study is 8.06% which includes Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). A study conducted by Agrawal A *et al*., [10] observed 7.6% (12/160) incidence which lies close to finding in our study. Amrinder R *et al*., [15] and Qayoom S *et al*., [21], who recorded 9.2% (11/120) and 9.3% (7/75) incidence respectively in their studies also show resemblance to the finding in our study.

In contrast, a study conducted by Joshi DB *et al*., [14] has reported a higher incidence of 20% (7/35) SCADR. A much higher occurrence of 36.7% (144/362) SCADR has been recorded in the study done by Choon SE and Choon SE and Lai NM [25]. The finding of these previous reports indicates that

distribution of SCADR (SJS + TEN + DRESS) among the different populations can vary in a wider range as depicted by Malaysian study conducted by Choon SE and Lai NM [25] compared to other studies conducted on Indian population and this may be attributable to epidemiological differences.

Other Drug Rash: The other clinical patterns reported in our study were exfoliative dermatitis, urticaria, erythematous plaques, papular eruption, papules & plaques, and erythema. The incidence of exfoliative dermatitis observed in our study was 1.6% (2/124) which is in sync with the studies conducted by Agrawal A *et al*., [10], Qayoom S *et al*., [21] and Kumari M. Nithya *et al*., [23] where the incidence found was 1.3% (2/160), 1.33% (1/75) and 2.85% (2/75) respectively. 1.6% (2/124) incidence of urticaria was reported in the present study. This finding is similar to finding recorded in studies conducted by T *et al*., [26] Kumari M. Nithya *et al*., [23] and Joshi DB *et al*., [14] where incidence found was 1.11% (1/90), 2.85% (2/70) and 2.86% (1/35) respectively. The other clinical patterns of CADR, erythematous plaques, papular eruption, erythema, erythematous plaques & papules reported in our study showed an incidence of 0.8% (1/124) each.

Suspected Drug Groups and Drugs Causing CADR: Antimicrobials were the most common suspected drug group observed in our study with the incidence of 50.8% (63/124). Similarly, Kumari M. Nithya *et al*., [23] Modi A *et al*., [11] Beniwal R *et al*., [22], Sharma R *et al*., [19] Agrawal A *et al*., [10] Amrinder R *et al*., [15] Jha N *et al*., [27] and Qayoom S *et al*., [21] reported antimicrobials as the most common suspected drug group with incidence of 48.6%, 46%, 40.5%, 40%, 37.5%, 37.5%, 64.73% and 57.33% respectively in their studies. A systematic review on cutaneous adverse drug reactions conducted by Patel TK *et al*., [24] reported anti-microbials as the major causative drug group (45.46%) in their analysis of data from various studies done in the Indian population. This finding is highly suggestive of findings reported in our study.

Among antimicrobials, Fluoroquinolones + Imidazole (FDC) (35/63) was the most commonly involved, followed by Quinolones and Cephalosporins (7/63 each) and Imidazole (4/63). Studies conducted by Beniwal R *et al*., [22] and Qayoom *et al*., [21] have reported quinolones as the most commonly involved antimicrobial in their studies. Our study also reports fluoroquinolones as majorly implicated drugs (FDC as well as alone) among anti-microbials. After antimicrobials, unknown drugs (17.7%), the combination of drug groups (14.5%) followed by anti-epileptics (8.9%) were reported to be commonly associated with CADR occurrence in the present study. We observed unknown drug group as the second most common association. Only few studies as done by Sebastian R *et al*., [28] and Joshi DB *et al*., [14] has shown an unknown drug association with incidence of 3% and 2.86% respectively which is significantly low than that found in our study. Incidence of combinations responsible for CADR has been observed as 10% and 8.57% in studies conducted By Amrinder R *et al*., [15] and Joshi DB *et al*., [14] respectively.

This finding in these studies is comparable to finding in our study. Incidence of 9.66% and 12.5% anti-epileptics association with CADR observed in studies conducted by Modi A *et al*., [22] and Agrawal A *et al*., [10] respectively was found comparable with an incidence of 8.9% reported in our study. Phenytoin was the most common antiepileptic found in our study which is a similar finding seen in studies conducted by Agrawal A *et al*., [10] and Qayoom *et al*., [21]. Though we observed a lower incidence of 2.4% of NSAIDS as suspected drug group which has been reported as one of the common offending agents by Beniwal R *et al*., [22] and Hiware S *et al*., [29] in cases with combinations, NSAIDs was found the most commonly involved group (10/18) in our study. Other suspected drug groups observed in the present study were anti-gout (1.6%), PPI and Antihistamines (0.8% each), homeopathic (1.6%) and Ayurvedic (0.8%). Anti-tubercular (3.2%), antifungal (1.6%), anti-leprotic (0.8%) were the other antimicrobial groups reported in our study.

Association of Suspected Drug Groups/Drugs with Type of CADR: We observed most of the FDE cases (55.7%) were associated with antimicrobials where fluoroquinolones + imidazole (FDC) (23/61) were found maximally involved followed by fluoroquinolones alone (7/61), imidazole alone (3/61), and 1 case of cephalosporin

+ fluoroquinolone. Similarly, Vora RV *et al*., [30] and Jhaj R *et al*., [31] also reported antimicrobials as the most common drug group suspected in their studies with an incidence of 44.07% and 80.6% respectively. The second most common drug group observed was unknown accounting for (14/61) followed by combinations (7/61). NSAIDs (diclofenac), homeopathic with 2 cases (2/61) each and antihistaminic (levocetirizine), ayurvedic with 1 case (1/61) each were found associated with FDE.3 cases of bullous FDE were reported in our study. One case was found associated with norfloxacin + tinidazole (FDC) and the other two to combinations and unknown group respectively. Daulatabadkar B *et al*., [32] reported a case of generalized FDE where the patient received ofloxacin-ornidazole followed by amoxicillin-clavulanic acid. This finding is comparable to finding observed in the present study.

Further, we observed 53.3% cases of MPR were implicated to antimicrobials where fluoroquinolones + imidazole (FDC) (12/45) were the major drugs involved followed by cephalosporins (7/45), anti-tubercular (2/45), antifungal (itraconazole) (1/45) and 1 case (1/45) each of lincosamide with carbapenem and lincosamide with penicillin. 15.6% cases each of anti-epileptics and combinations were reported. Among anti-epileptics, phenytoin was the suspected drug found to be associated with MPR cases (7/45). Antigout (allopurinol), PPI (pantoprazole), NSAID (paracetamol) with 1 case (1/45) each was found associated with MPR. Antimicrobials (quinolones, cephalosporins), anticonvulsants (phenytoin), anti-tuberculars, NSAIDS and allopurinol association with MPR have been reported by Doshi BR, Manjunathswamy BS [33]. We also observed a similar association in our study.

Out of the 10 cases of SCADR observed in our study, 7 cases were of SJS, 2 cases of TEN and 1 case of DRESS. 3 cases of SJS were found associated with unknown drugs, 2 with combinations, 1 with antiepileptic (phenytoin) and 1 with antimicrobial (secinidazole). Sharma VK *et al*., [34] reported reported anticonvulsants (35.08%) with phenytoin most common drugs associated with SJS/TEN. Similarly, Sasidharanpillai S *et al*., [35] recorded anticonvulsants (46.5%) with phenytoin as the major drug associated with SCADR. In the present study also the only case of SJS implicated to anti-epileptics was found associated with phenytoin. We observed 1 case of TEN was associated with anti-gout (allopurinol) while other with combinations. Similar to our finding, Banerjee B and and Chowdhury SK [36] have reported a case of TEN associated with allopurinol. A case of DRESS reported in our study was found associated with anti-leprotic (dapsone). Vinod KV *et al*., [37] have reported a case of DRESS associated with dapsone which is similar to our finding. Balaji O *et al*., [38] also reported a case of dapsone induced DRESS.

In other drug rash cases, we observed 2 cases of urticaria associated with anti- tuberculars, 1 case of exfoliative dermatitis/erythroderma with phenytoin and the other with lamotrigine where both of these drugs belong to the antiepileptic drug class. K. Venkateswarlu *et al*., [39] has reported a case of exfoliative dermatitis associated with phenytoin and César A *et al*., [40] has reported lamotrigine association with erythroderma, findings similar to our study. Phenytoin was also recorded with 1 case of erythematous plaques. 1 case of erythema, 1 case of papular eruption and 1 case of erythematous papules & plaques were found associated with antifungals (oral + topicals) combination and unknown group drugs respectively. Out of 4 cases implicated to anti-tuberculars, we observed 2 cases of MPR and 2 cases of urticaria. 2 cases of combinations where anti-tuberculars were taken by the patient also presented with maculopapular rash. Association of morbilliform rash (34 cases) and urticaria (4 cases) with antituberculars has been reported by Tan WC *et al*., [41] in their study. Sinha K *et al*., [42] observed 8.45% cases on anti-tubercular treatment presented with allergic skin reactions. These findings in previous reports are comparable to finding in our study.

Causality of Cutaneous Adverse Drug Reactions (CADRs): In our study, Naranjo's Algorithm was used as the causality assessment tool. Of the 124 CADRs reported, the majority (83.1%) were categorized as “probable” and the rest 16.9% were “possible” Qayoom S *et al*., [21] and Sharma R *et al*., [19] observed most of the CADRs had probable association on naranjos causality with an incidence of 81.3% and 77.3% in their study.

The finding of these reports lies in parallel agreement with the finding in the present study. Similarly, studies conducted by Beniwal R *et al*., [22] and T N *et al*., [13] showed probable association as the most common with an incidence of 69% and 66.7% respectively. A high incidence of probable association (98.3%) compared to our study was observed in a study study conducted by Inbaraj SD *et al*., [16]. In contrast, Modi A *et al*., [22] reported possible (54.61%) as a more common association than probable (45.38%) as per naranjos assessment. It was observed that the majority of cases with FDE (68.9%), MPR (95.6%) and all the cases with SCADR and Other drug rash belonged to probable category. This association was found statistically significant in our study.

Severity of Cutaneous Adverse Drug Reaction: In the present study severity assessment was done using Modified Hartwig and Siegel Scale. It was observed that out of 124 CADR reported, the majority of cases (70.9%) were moderately severe followed by mild severity (20.9%). 8.06% were of severe grade. Studies conducted by Beniwal R *et al*., [22] and Modi A *et al*., [11] also reported a similar finding where moderately severe was the most common association with CADR found in their studies with an incidence of 78%, 81.2% respectively. Patel NH *et al*., [43] also reported moderately severe (82%) as the most common association with CADR. Agrawal A *et al*., [10] and Beniwal R *et al*., [22] observed 12.5% and 16% severe cases in their studies which were seen as higher incidence than observed in our study. Majority cases of FDE and MPR and all cases of other drug rash were moderately severe whereas all cases of SCADR were of severe category. This association of severity assessment with the type of CADR was found to be statistically significant.

Quality of Life (QoL): On assessing Quality of life in CADR patients using Dermatology Life Quality Index (DLQI) score, we observed that out of 124 CADR reported, 35 cases (28.2%) showed small effect, 33 cases (26.6%) showed moderate effect and very large effect and extremely large effect were shown by 28 cases (22.6%) each. We observed that the effect on the quality of life was varying with the type of CADR occurred. In FDE cases small effect (39.3%) on QoL predominated followed by moderate effect (34.4%). In MPR cases, extreme effect (33.3%) on QoL was predominant whereas all other grades were in equal proportion (22.2% each). In SCADR (including SJS, TEN and DRESS) majority of cases were observed with extreme effect (60%) followed by a very large effect (40%) on QoL. In other drug rash cases (including exfoliative dermatitis, erythema, papular eruption, plaques, plaques & papules and urticarial) very large effect (50%) was predominant followed by moderate effect (25%), G CR *et al*., [44] reported higher DLQI score for exfoliative dermatitis, DRESS and SJS and lower for FDE, the finding which is similar to finding in our study. Varghese B *et al*., [20] reported a very large effect (46.6%) on QoL followed by extreme large effect (41.4%) where majority of patients presented with MPR followed by acute urticaria which is comparable to finding in our study.

CONCLUSION: It can be concluded that proper monitoring, constant watch, and immediate reporting is of immense importance with increasing rates of adverse drug reactions which produces detrimental effects on the body and adds to the economic burden and significantly degrades the quality of life. Vigilance is the only way to assess and timely manage the adverse reaction which if progresses can be even life-threatening. In this regard, government national, international, health care professional and individual itself can associate to strengthen the reporting of adverse drug reactions, pharmacovigilance networks, to provide better patient care.

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LIMITATION: The duration of the study with a smaller sample size was one of the major limitations, though the result value can't be ignored. For causality assessment, except for antitubercular cases, rechallenge was not done which excluded any of the cutaneous adverse drug reactions to be categorized as definite. Recall bias cannot be ignored.

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CONFLICTS OF INTEREST: None declared

ETHICAL APPROVAL: The study was approved by the Institutional Ethics Committee, K.G.M.U, Lucknow (Ref. Code 90th ECM II B-IMR-R/P6).

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