IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 11 Ser.8 (November. 2022), PP 34-40
www.iosrjournals.org

Spectrum of Cutaneous Adverse Drug Reactions (CADR) in Tertiary care teaching hospital in Andhra Pradesh

Radha Puppala[1], Vijaya LakshmiPanthalla[2], K. Penchalaiah[3]
[1](Postgraduate, Department of Dermatology Venereology and Leprosy, Kurnool medical College, India
[2]Designated Associate Professor, Department of Dermatology Venereology and Leprosy, Kurnool medical College, India, [3]Professorand Head of the Department of Dermatology Venereology and Leprosy, Kurnool medical College, India)

Abstract:
Background: *Cutaneous adverse drug reactions form a diverse spectrum which require prompt clinical recognition and early treatment initiation to reduce mortality and morbidity. Timely withdrawal of the offending drug plays a significant role in controlling these reactions. Various studies in literature have published different clinico- epidemiological data depending upon the geographical location of the study population. Through this study, we intend to evaluate the clinico-epidemiological factors pertaining to cutaneous adverse drug reactions in our region.*
Materials And Methods: *This prospective observational study was conducted in a tertiary care Government General Hospital, Kurnool, Andhra Pradesh from September 2020 to October 2022. Our study included 50 cases who presented to our outpatient and emergency departments with clinical presentation of cutaneous adverse drug reactions. Epidemiological data, chief complaints, clinical features, probable offending agent and causal association using Naranjo's scale of various drug reactions were recorded and the data was subjected to descriptive analysis.*
Results: *We had slight male predominance of cases, male: female ratio being 1.27:1 and most common age group predisposed to reactions was 40-60 years. 10% of cases had history of atopy. 76% of the cases were non severe cutaneous drug reactions comprising of drug induced exanthematous rash (30%), urticaria/ angioedema (6%), Fixed Drug Eruption (24%) and others (lichenoid reaction, etc). Severe cutaneous adverse drug reaction (Erythema Multiforme/ Stevens Johnson syndrome/ Toxic Epidermal Necrolysis/ DRESS/AGEP/ Exfoliative dermatitis) comprised of 34 % of total cases. Antimicrobials (Amoxicillin) were the most common inciting factors in our series (30%) followed by non-steroidal anti-inflammatory drugs (26%).*
Conclusion: *Through this study we emphasize that early recognition of diverse spectrum of cutaneous drug reactions, timely withdrawal of offending agent and initiation of supportive treatment wherever necessary is highly essential to curtail the mortality and morbidity. Patient education plays a crucial role in controlling the recurrences.*
Key Word*: Cutaneous, Adverse, Drug reaction, Steven Johnsons syndrome, Toxic Epidermal Necrolysis, Lichenoid reaction, Erythema multiforme.*
Abbreviations*: SCAR- Severe Cutaneous Adverse Reaction, CADR- Cutaneous Adverse Drug Reaction, DRESS- Drug Rash with Eosinophilia and Systemic Symptoms, AGEP- Acute Generalized Exanthematous Pustulosis, SCORTEN- SCORe of Toxic Epidermal Necrolysis, SJS/TEN- Steven Johnsons Syndrome/ Toxic Epidermal Necrolysis, EMF- Erythema Multiforme.*

Date of Submission: 19-11-2022 Date of Acceptance: 03-12-2022

I. Introduction

CADR is defined by WHO as a response that is noxious and unintended, occurring at doses normally used for prophylaxis, diagnosis and therapy of disease. Skin is the most common organ system to be affected by drug reactions[1,2]. Cutaneous manifestations have an incidence rate of 10-30 % among all adverse drug reactions[3]. A high index of clinical suspicion, detailed and thorough clinical history which includes temporal correlation of drug intake and onset of skin manifestations, recurrence with intake of structurally similar drugs is mandatory so as to not confuse with inflammatory disorders. Early recognition and withdrawal of causative drug is essential so as to diminish mortality and morbidity[1,4]. Drug reactions can be immunologically or non-immunologically mediated, and one drug may cause more than one type of reaction depending upon underlying genetic, HLA, immunological, metabolic factors and associated co-morbidities of the individual[1]. They range from benign, self-limiting to severe life-threatening reactions, referred to as Severe Cutaneous Adverse

Reactions (SCAR)[5]. With the current trends of polypharmacy, establishing the causality is very challenging in most cases, gold standard test being the drug rechallenge, however at times this can lead to severe manifestations and is to be attempted only when the concerned drug is essential and irreplaceable therapeutically[1,2]. Our study aims to find the epidemiology, clinical pattern and potential cause of various cutaneous adverse drug reactions in our geographic location.

II. Material And Methods

This prospective, observational study was conducted in Department of Dermatology, Venereology and Leprosy of Government General Hospital, Kurnool, Andhra Pradesh from September 2020 to October 2022. All patients who presented to our out-patient clinic and emergency clinic with clinical features of drug reactions were included. We had a total of 50 patients of both genders and all age groups who presented within study period with drug reactions and were included in our study.

Study Design: Prospective longitudinal observational study.

Study Location: This study was conducted in a tertiary care teaching hospital in the Department of Dermatology, Venereology and Leprosy of Government General Hospital, Budhawarpet, Kurnool, Andhra Pradesh, India.

Study Duration: September 2020 to October 2022, 2 years and 2 months.

Sample size: 50 patients.

Subjects & selection method:After obtaining permission from our institutional ethical committee, all the consecutive cases who presented to out-patient clinic and emergency departments of our hospital with clinical features of drug reactions during the period of study were included. Aims of our study were to study various epidemiological factors associated with cutaneous adverse drug reactions, to assess the varied clinical presentations and predominant symptoms and to determine causal association in all cases using Naranjo's adverse reaction probability scale. Using this data we intended to find out the most common offending agent.

Inclusion criteria:

All clinically suspected cases of drug reactions, who presented to our Outpatient and Emergency departments during the period of study were included after obtaining informed consent.

Exclusion criteria:

Patients

1.Who refused informed consent.

2. Who had inflammatory, infective or connective tissue disorders which mimicked drug reactions.

3. Those cases wherein there is a doubtful causal association between drug intake and onset of reaction.

4. Subjects who could not give detailed clinical history were excluded from our study.

Procedure methodology

After obtaining informed consent from the patient or the attender, a proforma containing questionnaire regarding detailed clinical history and epidemiological data was used to obtain relevant history and socio-demographic epidemiological data. This was followed by laboratory investigations such as complete blood picture with differential count, erythrocyte sedimentation rate, peripheral blood smear, serum electrolytes, absolute eosinophil count, liver function tests, renal function tests, complete urine analysis, random blood sugar in all cases.Specific investigations like D- dimer, fibrin degradation products, radiological investigations like chest x ray and ultrasound abdomen were performed only in severe drug reactions. Blood culture, swabs for microbiology, ASO titre, Tzanck smear, viral markers and ANA profile were additionally performed in clinically suspicious cases, to rule out infective or connective tissue disorders that mimic drug reactions.

Cases of severe cutaneous adverse reactions were admitted in our hospital for stabilization, intensive care and management and those with mild reactions were managed on an outpatient basis. RegiSCAR criteria was used to define DRESS and SCORTEN system was used for prognostication in SJS/TEN. All patients were counselled regarding the cause, possible recurrence and advised caution in relation to the use of same or structurally related drugs in future.

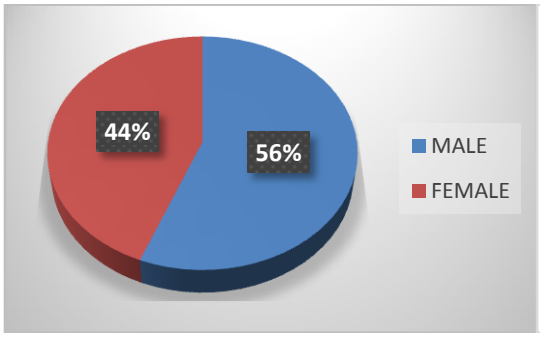
Assessment of causality between drug intake and adverse cutaneous manifestation was performed using Naranjo's adverse drug reaction probability scale which uses a standard set of 10 questions to generate a score from -4 to+13 for every case. Depending upon the score generated, the reaction can be classified as definite (>9), probable (5-8), possible (1-4) or doubtful (<1). Doubtful causal association were excluded from our study.

Statistical analysis

The collected clinico- epidemiological data was tabulated and subjected to descriptive analysis. SPSS 21.0 was used to tabulate and analyze the data. Tables and graphs were generated accordingly. The results were presented as frequency and percentages and compared with the data from the available published literature.

III. Result

Total sample size of our study was 50 cases, of which 28 (56%) were males and 22 (44%) were female patients. Male: female ratio was 1.27:1. We had majority of subjects (20 cases) between 40 and 60 years of age which comprised 40% of total cases.



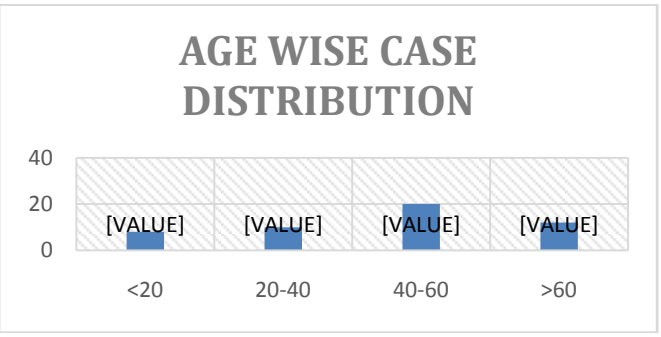


Diagram 1: Distribution of cases based on gender. **Diagram 2:**Age wise distribution of cases.

Most of our cases had history of developing symptoms of cutaneous drug reactions within a month of drug administration for varying causes. Very few patients developed symptoms within 24 hours and beyond one month. Lag period between the drug intake and development of symptoms was noted and was found less than 24 hours for urticaria and angioedema, around 2 to 6 days for fixed drug eruption and AGEP, and approximately 2 weeks for SJS/TEN. Lichenoid drug reaction, exanthematous drug eruption, erythema multiforme, DRESS, acneiform eruption and others developed within varying period of 1 to 3 weeks after drug consumption.

Itching (80%) followed by burning sensation and pain (16%) accompanying cutaneous eruption were the predominant clinical complaints. Febrile and flu like prodrome was recorded only in 15% cases.

Most common agent provoking cutaneous drug reaction in our series was antimicrobials (30%) accounting for 15 cases.This was closely followed by non-steroidal analgesics and antipyretics causing reactions in 13 cases (26%) and antiepileptics such as Phenytoin being responsible for 6% (3) of cases. Amoxycillin was the commonest culprit among the penicillin group followed by fluroquinolones and lastly by cephalosporins. Among NSAIDS group Diclofenac was the offending drug in most cases followed by Ibuprofen and Paracetamol. Phenytoin was single most common cause among anticonvulsants causing a variety of drug reactions.

Clinical presentation wise, maculopapular exanthematous rash encompassed majority of cases (30%), followed by fixed drug eruption (24%), SJS/TEN (20%) and others (lichenoid reactions, AGEP, DRESS) 10%. We had limited cases of exfoliative dermatitis (8%), urticaria (6%) and 1 case erythema multiforme majus (2%). All of our cases had cutaneous involvement involving trunk, face and extremities. Mucosal involvement was recorded in 32 % (16) of subjects. Facial and pedal edemawere seen mostly associated with DRESS and in 6% of subjects.

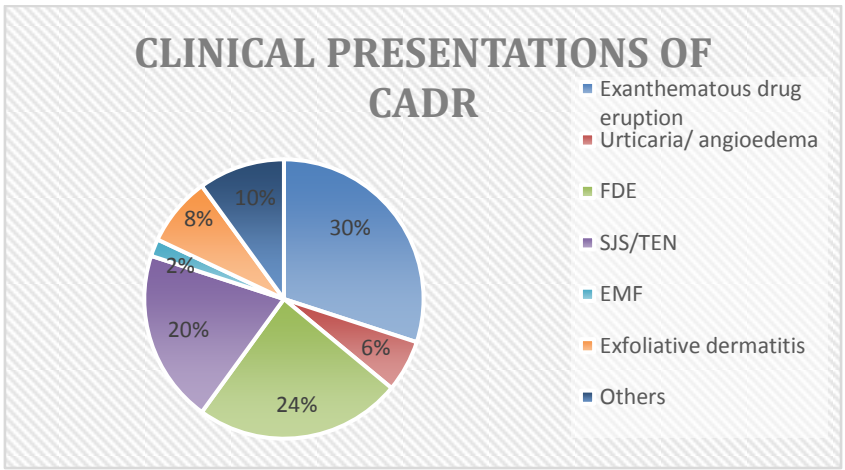


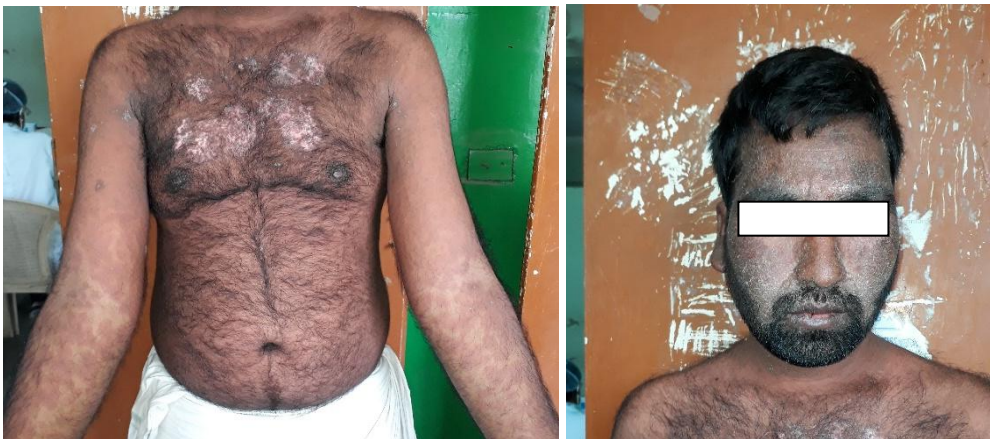
Diagram 3: Distribution of cutaneous adverse drug reactions based on various clinical presentations.

In our series, cases of severe cutaneous adverse reactions (SCAR) were fewer as compared to non-SCAR cutaneous drug reactions. SCAR group comprised of AGEP, SJS/TEN, EMF major, DRESS and drug

induced exfoliative dermatitis/ erythroderma which accounted for 17 cases (34%) whereas non-SCAR group comprised of remaining 66% cases (33 subjects). Antiepileptics were the most common agents causing SCAR. None of the patients had a prior personal nor family history of SCAR. In 5 patients there was history of atopy and bronchial asthma, which accounted for 10% of total subjects. We had recorded no deaths among any patients admitted for SCAR.

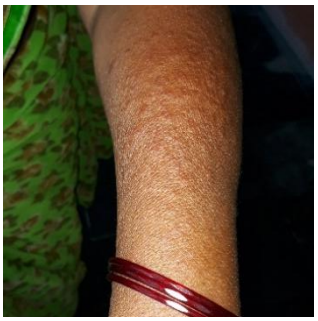
Naranjo's scale was assessed in all patients to find the causality association and 70 % (35) of the subjects fell into ''probable" category followed by 18% (9) of patients in "possible" category and only 12% cases (6) in "definite" category. Majority of cases in definite category were fixed drug eruptions.

All patients were thoroughly clinically assessed andgeneral condition was stabilized in required cases. Suspicious drug or polypharmacy withdrawal was done in all cases. None of our cases were subjected to dose reduction nor drug rechallenge test, rather the suspected drug was replaced with structurally unrelated drug of similar efficacy if deemed therapeutically essential. All subjects and attenders were educated regarding the probable cause of their condition, possibility of recurrences and a short list of cross-reacting drugs were handed over at discharge.

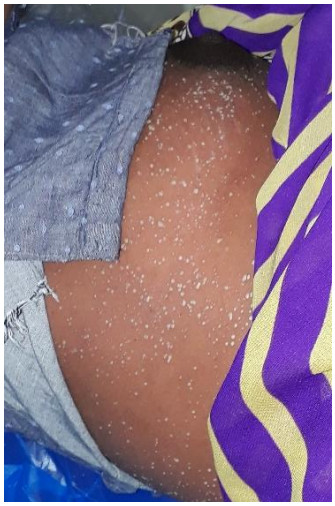


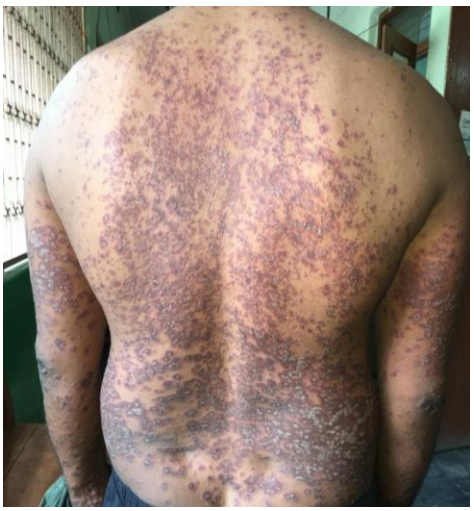
Case1: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) with facial edema.

Case2: Toxic Epidermal Necrolysis **Case 3**: Bullous FDE



Case 4: Drug induced maculo-papular rash





Case 5: Acute Generalized Exanthematous Pustulosis **Case 6:** Lichenoid drug eruption.

IV. Discussion

Our study comprised of 28 males and 22 female patients resulting in slight male predominance of cases with male: female being 1.27:1. This is in concordance with studies conducted by Jha et al.[2] (1.3:1), Patel and Marfatia et al.[6] (1.27:1) and Rajendran et al.[7](1.2:1). Whereas other studies by Pudukadan and Thappa[8] showed female predominance of cases. There was no association between occupation, socioeconomic status nor urban/rural residence of the patient with predisposition to drug reactions in our study.

Maximum number of cases (40%) in our study were clustered between 40 to 60 years age group range. This was similar to findings by Rajendran et al.[7](38.4%) and Patel and Marfatia[6] (30%). This can be explained by the prevailing polypharmacy in adult population due to various co-morbidities and chronic lifestyle diseases. Next most common age group where reactions were predominant was elderly patients of more than 60 years. Declining immune response or immunological senescence to haptens generated as byproducts of various drug metabolism could be the reason why elderly patients haven't shown peak incidence despite polypharmaceutical usage[1,6,7].

Personal and family history of bronchial asthma, allergic rhinitis and atopic dermatitis was noted in 10% (5 cases) in our study. This was comparable to studies by Jha et al.[2](12%) and Inbaraj et al.[9](7%). Whereas lower andhigher percentage of atopic history was recorded by Rajendran et al.[7](5%) and Al-Raaie and Banodkar[10] (21%) respectively.

Most common clinical presentation of cutaneous adverse drug reaction in our study was exanthematous maculo-papular rash, which was seen in 30% cases, this was followed by fixed drug eruption (24%) cases. Maculopapular drug rash was the most common presentation in studies by Rajendran et al.[7] (31.5%), Saha et al.[11] (30 %), Noel et al.[12] (35%) and Choon and Lai et al.[13] (42.3%). Pudukadan and Thappa[8] noted fixed drug eruptions to be most common whereas Chatterjee et al.[14] and Al- Raaie et al.[10] found drug induced urticaria to be the most common clinical presentation in their respective studies. This inter-study variation could be due to variable genetic factors of the study population, and also variation in local drug availability and prescriptions.

Most of our cases were benign, non-severe cutaneous adverse reactions which accounted for 66% of total cases whereas SCAR accounted for 34% of total cases. This is in concordance with SCAR incidence by Saha et al.[11] and Choon and Lai et al.[13] which are 32% and 39% respectively. In contrast, studies by Rajendran et al.[7] and Sasidharanpillai et al.[15] recorded lower rates of SCAR around 13%. This variation in incidence of SCAR can be pharmaco-genetically related and also differ due to early recognition and withdrawal of suspected

drug thus halting the severity of drug reaction and preventing progression into SCAR. No family history of past history of SCAR have been recorded in or study population. Anticonvulsants were the chief culprits leading to SCAR in our patients and many studies such as Rajendran et al.[7], Noel MV et al.[12], Sasidharanpillai et al.[15] and Patel TK et al.[16] have reported similar scenario. Phenytoin was the common offending antiepileptic whereas fluroquinolones were the most common antimicrobial agents resulting in SJS/TEN.

Antimicrobial agents formed the overall most common cause for cutaneous drug reactions in our study population (30%). This is consistent with findings by Rajendran et al.[7] (30%), Jha et al.[2](64%), Chatterjee at al.[14] (34 %) and Mahatme and Narasimharao[18] (48%). Among the Penicillin category, Amoxicillin wasfound to be the commonest offending agent in our study, responsible for 14% of cases similar to Rajendran S et al.[7] who also reported amoxicillinto be the most common offending antimicrobial (13%). Jha et al.[2] found cephalosporins and Saha et al.[11] reported sulphonamides to be the most common reaction causing antimicrobials. Al- Raaie et al.[10] found non-steroidal analgesics and Noel et al.[12] found antiepileptics to be the most common offending agents causing reactions in their respective studies. This variation in chief offending agents can be explained by different patterns of drug prescriptions, local drug availability and population metabolic pharmacogenetics.

Itching (80%) was the predominant symptom associated with cutaneous eruption in our study population followed by burning sensation (16%). Rajendran et al.[7] reported a similar symptom profile among his study population wherein 88% of cases had pruritis and 20% of subjects complained of burning sensation.

Mucosal involvement was seen in 16 cases (32%) which is in concordance with findings by Rajendran et al.[7] (31%) and Jha et al.2 (27.25%). While Inbaraj SD et al.[9] recorded lower rates of mucosal erosions at 5%. All cases had skin involvement due to drug reactions in our study.

Offending drug	Our study	Rajendran S et al.[7]	Al-Raaie et al.[10]	Chatterjee et al.[14]
Antimicrobials	30%	30%	29%	34%
NSAIDS	26%	8%	29%	21.5%
Antiepileptics	6%	18%	8%	32.8%
Others(ATT, ART,etc)	38%	44%	34%	11.5%

Table 1: Comparison of frequency of cutaneous drug reactions due to various offending drugs.

	Our study %	Rajendran et al.[7] %	Saha et al.[11] %	Chatterjee et al.[14] %	Jha et al.[2] %
Exanthematous drug eruption	30	31.5	30.1	25.4	42.6
Urticaria/ angioedema	6	8.8	5.6	27.2	30.2
FDE	24	13.4	24.5	25.2	9.3
SJS/TEN	20	6.9	24.5	1.6	2.3
EMF	2	6.5	-	2.57	3.5
Exfoliative dermatitis	8	0.9	7.5	-	0.77
Others	10	32	-	18	11.3

Table2: Comparison of various clinical presentations of cutaneous adverse drug reactions

Limitations: Due to onset of COVID 19 pandemic and government imposed social and mobility restrictions, we had fewer number of cases during our study period. The exact prevalence of cutaneous adverse drug reactions in the community could not be assessed as most patients with mild variety of drug reaction do not get referred to our tertiary care teaching hospital as they are managed at primary or community health centers. Drug rechallenge was not attempted due to fear of manifestation of severe reaction. Long term follow ups and recurrence data could not be collected due to limited study period.

V. Conclusion

Our study showed slight male predominance with 20- 40 years being most common age range. Non-severe cutaneous adverse reactions of varied clinical picture formed majority of cases as compared to severe cutaneous adverse reactions. Itchy maculo-papular exanthematous rash was the most common overall clinical presentation. Most of our cases were associated with indiscriminate antimicrobial usage followed by non-steroidal analgesic consumption. Through this study we emphasize that early recognition of diverse spectrum of cutaneous drug reactions, timely withdrawal of offending agent and initiation of supportive treatment wherever necessary is highly essential to cut back the mortality and morbidity. Patient education regarding the cause of their condition, chances of recurrence with reusageof same and cross- reacting drugs plays a significant role in reduction of incidence of adverse drug reactions.

References

[1]. Lalit Kumar Gupta, Manisha Balai. Drug reactions. IADVL textbook of Dermatology,Venereology and Leprosy. Bhalani publishing house; 5th Ed. 2022; p2985-3028.
[2]. Jha N, Alexander E, Kanish B, Badyal DK. A study of cutaneous adverse drug reactions in a tertiary care center in punjab. Indian Dermatol Online J 2018;9:299‑303
[3]. Arulmani R, Rajendran AD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. Br J Clin Pharmacol 2007;65:210-6.
[4]. Sharma R, Dogra D, Dogra N. A study of cutaneous adverse drug reactions at a tertiary center in Jammu, India. Indian Dermatol Online J. 2015 May-Jun;6(3):168-71. doi: 10.4103/2229-5178.156384. PMID: 26009710; PMCID: PMC4439744.
[5]. Anant K, Chaukimath S. P, Ajit J, Leela H. A Study of Cutaneous Adverse Drug Reactions; Clinical/Morphological Pattern and Causative Agents Reported in an ADR Monitoring Centre in a Tertiary Care Hospital of North Karnataka. Biomed Pharmacol J 2020;13(3).
[6]. Patel RM, Marfatia YS. Clinical study of cutaneous drug eruption in 200 patients. Indian J Dermatol Venereol Leprol 2008;74:74‑80.
[7]. Rajendran L, Thyvalappil A, Sridharan R, Ajayakumar S, Deep S, Divakaran B. A study of cutaneous adverse drug reactions in a tertiary care center in South India. Clin Dermatol Rev 2021;5:173-7.
[8]. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. Indian J Dermatol Venereol Leprol 2004;70:20‑4.
[9]. Inbaraj SD, Muniappan M, Muthiah NS, Amutha A, Glory J, Rahman F. Pharmacovigilance of the cutaneous drug reactions in outpatients of dermatology department at a tertiary care hospital. J Clin Diagn Res 2012;6:1688‑91.
[10]. Al‑Raaie F, Banodkar DD. Epidemiological study of cutaneous adverse drug reactions in oman. Oman Med J 2008;23:21‑7.
[11]. Saha A, Das NK, Hazra A, Gharami RC, Chowdhury SN, Datta PK. Cutaneous adverse drug reaction profile in a tertiary care out patient setting in eastern India. Indian J Pharmacol 2012;44:792‑7.
[12]. Noel MV, Sushma M, Gudio S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care center. Indian J Pharmacol 2004;36:292‑5.
[13]. Choon SE, Lai NM. An epidemiological and clinical analysis of cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. Indian J Dermatol Venereol Leprol 2012;78:734‑9.
[14]. 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;38:429‑31.
[15]. Sasidharanpillai S, Riyaz N, Khader A, Rajan U, Binitha MP, Sureshan DN. Severe cutaneous adverse drug reactions: A clinicoepidemiological study. Indian J Dermatol 2015;60:102.
[16]. Patel TK, Thakkar SH, Sharma D. Cutaneous adverse drug reactions in Indian population: A systematic review. Indian Dermatol Online J 2014;5:S76‑86
[17]. Mahatme N, Narasimharao R. A study of clinical patterns and causative agents of adverse cutaneous drug reactions. Indian J Drugs Dermatol 2016;2:13‑8.

Radha Puppala, et. al. "Spectrum of Cutaneous Adverse Drug Reactions (CADR) in Tertiary care teaching hospital in Andhra Pradesh." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(11), 2022, pp. 34-40.