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RESEARCH ARTICLE

PREVALENCE AND CAUSALITY ASSESSMENT OF CUTANEOUS ADVERSE DRUG REACTIONS

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Abstract

Background: Cutaneous Adverse drug reactions (CADRs) are among the most frequent Adverse Drug Events (ADEs). Considering their impact on patient's lives and relatively high incidence, identifying the risks and monitoring of CADRs is of great clinical significance to prevent patient from unwanted exposure to drug toxicity.

Objective: To determine the prevalence of different types of CADR's and there causal relationship with the offending drug.

Material & methods: A prospective, observational and non-invasive study was carried out in Department of Dermatology at a Tertiary care hospital for duration of 6 months. Patients with 18 years or higher with visible skin lesions suspected to be drug related were included. Assessment was carried out by WHO, Naranjo's and Hartwig and Siegel's classification graded on a 3-point scale. Descriptive statistics were used to examine the normality of data and describe the analysis.

Results: A total of 95 cases of suspected Cutaneous ADRs were recorded from a total population of 10,000 patients, among which 90 cases were analyzed showing 34 cases (37.8%) males and 56 (62.2%) females. Maximum patients belonged to the age group of 21-30 years (34.4%). The total Prevalence was found to be 0.9%, in which the highest Prevalence was seen in females (0.56%). The most common CADR observed was Steroid induced acne (38.6%) and most common group of offending drugs were Topical corticosteroids (38.8%). According to WHO and Naranjo's scale most of the observed cases were classified as Probable (97.8%) and as per the Hartwig and Siegel's classification, 56 cases (62.2%) were Moderate in severity. One case (1.1%) was fatal.

Conclusions: A wide range of clinical spectrum of CADRs was observed. Out of which Steroid induced acne was the most common Cutaneous ADRs seen. Topical corticosteroids were the most common offending agent with highest Prevalence in females. Most of the cases were of Probable and Moderate in severity. Fatal case was observed with Toxic epidermal necrolysis. Further identification and reporting

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of CADR is essential in promoting drug safety and better patient care, among health care professionals and patients.

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Introduction:-

Adverse drug events (ADEs) are among the major challenges in modern medicine. Adverse drug reaction (ADR) has been defined in many ways. WHO defines ADR as any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, therapy of disease, or for the modification of physiological function.¹ A Cutaneous Adverse reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes, and it encompasses all adverse events related to drug eruption, regardless of the etiology.²

In India epidemiological studies estimated that ADRs are fourth to sixth leading cause of death.³ ADRs are one of the leading causes of morbidity and mortality, adding to overall healthcare cost. It is estimated that approximately 2.9–5.6% of all hospital admissions are caused by ADRs and as many as 35% of hospitalized patients experience an ADR during their hospital stay.⁴

Almost any medicine can induce skin reactions, and certain drug classes, such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptic drugs, have drug eruption rates approaching 1–5%.⁵ Most of the Cutaneous drug reactions are not serious but some are severe and potentially life-threatening. Serious reactions include Angioedema, Erythroderma, Stevens–Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN). Drug eruptions can also occur as a result of multi-organ involvement, as in Drug-induced Systemic lupus erythematosus. Drug reactions can be classified into immunologic and non-immunologic etiologies. The majority about 75–80% of adverse drug reactions are predictable & non-immunological in origin, the remaining 20–25% of adverse drug events are immune-mediated or unpredictable reactions. Skin reactions as a result of non-immunological causes are more common and include cumulative toxicity, overdose, photosensitivity, drug interactions, and metabolic alterations.⁶

Adverse drug reactions (ADRs) are a major cause of morbidity, hospital admission, and even death. Hence it is essential to recognize ADRs and to establish a causal relationship between the drug and the adverse event. It is desirable that ADRs should be objectively assessed and presented. Majority of CADR is diagnosed clinically. These reactions may differ with different classes of drugs. Generating data is essential to understand the pattern of CADR of different classes and generating information regarding offending drugs.³ Recognition of the offending drug enables early withdrawal and improved outcomes. This will help the doctors to ensure safe drug usage and be aware of offending drugs thereby reducing morbidity and mortality. Observational studies are tools to know the pattern of reactions and causative drugs.

Objectives:-

The objective of this study was to observe the types of Cutaneous Adverse drug reactions (CADRs) in the patients attending the Dermatology Department, Prevalence of Cutaneous Adverse drug reaction at Tertiary Care Hospital, to determine causal relationship with final outcome of CADR and to recognize the offending drug, to determine the severity index of the adverse reactions, prevent CADR and minimize hospitalization, to achieve a better treatment outcome and improve productivity and health.

Materials and Methods:-

It was a prospective, observational, non-invasive study carried out at Out Patient and Inpatient Department of Dermatology at Osmania General Hospital, Hyderabad over a period of six months (January 2015–June 2015).

Inclusion criteria:-

- Patients of either sex as inpatients and outpatients attending Dermatology Department.
- Patients more than 18 years of age.
- All patients attending Dermatology department, presented with visible skin lesions suspected to be drug related included in the study.

Exclusion Criteria:-

- Patients less than 18 years of age.
- Patients without visible skin lesions.
- Patients who could not recall the name of the suspect medicines consumed.
- If lesions turned out to be disease related (e.g., viral exanthemas, rash of rickettsial infections, and collagen vascular disease,) on closer examination.
- Patients who reported to have consumed indigenous (ayurvedic and homeopathic) medicines were also excluded.
- Patients unable to respond to verbal questions.

Demographic data like patient name, age, sex, brief description of the suspected ADR, Information about the suspected drug were recorded in the case collection form. Each case was assessed for its causality using the WHO-UMC assessment scale⁷ and Naranjo's scale⁸ of which Unlikely, Conditional or Unassessable cases were excluded. The final diagnosis of CADR was based on history of drug exposure, clinical findings and under supervision of consultant Dermatologist. Severity of ADRs was evaluated by Hartwig and Siegel's classification graded on a 3-point scale.⁹

Results:-

During the study period, a total of 95 cases of suspected Cutaneous ADRs were recorded from a total population of 10,000 patients attended the Dermatology Department from January 2015 to June 2015, out of which 5 cases were excluded because the offending drug was not identified or the data was insufficient to make any analysis. The remaining 90 cases were analyzed, among which one case was fatal. Maximum patients belonged to the age group of 21-30(34.4%), followed by 18-20 age group (22.2%), 31-40 age group (20%), 41-50(13.3%), >50 age group(10%). The total prevalence was found to be 0.9 (90%), in which the highest prevalence was seen in females (P=0.56/56%) and the prevalence of males was found to be 0.34 (34%). Table 1 shows the description about the age distribution, gender distribution and prevalence of CADR. Figure 1(a) shows details of age distribution pattern of CADR encountered during the study. 34 cases (37.8%) were males and 56 cases (62.2%) were females showing Female predominance. Figure 1(b) shows sex distribution patterns seen during the study. Figure 1(c) shows the Prevalence rate of the CADR.

The most common pattern of Cutaneous ADR observed was Steroid induced acne (38.6%). The second common CADR seen was Fixed drug eruption (FDE) (13.3%) followed by Erythematous rash (11.1%), Toxic Epidermal Necrolysis (TEN) and Urticaria recording (7.5%). Among which one was fatal experienced from TEN. Steven Johnson Syndrome recorded (4.4%). About (3.3%) of Vasculitis and Erythema was observed. About (2.2%) were seen with Erythroderma, Photosensitivity reaction and Drug rash eosinophilic systemic syndrome (DRESS). Alopecia, Exfoliative Dermatitis, Infectious eczema dermatitis, and Acanthosis like-nigricans were identified in only about (1.1%). Table 2 and Figure 2 show details of the Clinical patterns of CADR encountered during our study.

The most common group of offending drugs responsible for Cutaneous ADRs were Topical corticosteroids (38.8%), among which Betamethasone recorded the highest incidence of CADR followed by Antibiotics (24.8%), among which Ciprofloxacin was the common offending drug seen followed by Metronidazole, Tetracycline, Amoxicillin, 1 case was seen with each of Cotrimoxazole, Ceftriaxone and Dapsone. Use of tetracycline in one patient was fatal. Use of Anti-epileptic drugs was seen in (15.4%), where Phenytoin recorded the highest number of ADRs. NSAIDs were seen in (10%), (3.3%) with Anti-tubercular drugs, Oral and Parental corticosteroids with (3.3%). Rare cases about (1.1%) were seen with Antifungal (Fluconazole), Opioid Analgesic (Tramadol), Angiotensin converting enzyme inhibitors (ACEI) (Captopril), and Non-nucleoside reverse transcriptase inhibitor (NNRTI) (Efavirenz). Table 3 and Figure 3 shows detail results of therapeutic drugs classes implicated in CADR encountered in this study.

Causality Assessment:-

90 cases of CADR were assessed as per WHO and Naranjo's Scale. According to Naranjo's Scale, most of the cases were Probable (97.8%) and (2.2%) showed a Definite score. According to WHO Scale (2.2%) scored Certain, remaining all (97.8%) were of Probable. Unlikely, conditional, unclassifiable were excluded from the study Table 4 and Figure 4 show details of Causality Assessment of CADR based on Naranjo's and WHO scale.

Severity Index:-

Severity of CADR was assessed as per the Hartwig and Siegel's classification graded on a 3-point scale. The results of assessment of the severity index revealed that most of the cases were Moderate in severity accounting for (62.2%), followed by Mild with (26.7%) and (10%) were identified as Severe. One case (1.1%) was fatal. Table 5 and Figure 5 show the details of Severity Assessment of CADR encountered during the study period.

TABLE 1:- AGE, SEX AND PREVALENCE OF CADR

Age group	Males	Total no. of ADRs = 90	Total population 10,000	Females	Total no. of ADRs = 90	Total population 10,000	Total	Total no. of ADRs = 90	Total population 10,000
		% in Males	Prevalence (P)		% in Females	Prevalence (P)		% in Total	Prevalence (P)
18-20	6	17.64%	0.06	14	25%	0.14	20	22.2%	0.20
21-30	9	26.48%	0.09	22	39.28%	0.22	31	34.4%	0.31
31-40	9	26.48%	0.09	9	16.07%	0.09	18	20%	0.18
41-50	5	14.7%	0.05	7	12.5%	0.07	12	13.3%	0.12
>50	5	14.7%	0.05	4	7.15%	0.04	9	10%	0.09
Total	34	38%	P = 0.34 or 34%	56	62%	P = 0.56 or 56%	90	100%	P= 0.9 or 90%

TABLE 2:- CLINICAL PATTERNS OF CADR

Clinical type	Frequency	Percentage
Steroid induced acne	34	38.6%
Fixed Drug Eruption (FDE)	12	13.3%
Erythematous rash	10	11.1%
Toxic Epidermal Necrolysis(TEN)	7	7.5%
Urticaria	7	7.5%
Steven Johnson syndrome(SJS)	4	4.4%
Vasculitis	3	3.3%
Erythema multiforme(EMF)	3	3.3%
Erythroderma	2	2.2%
Drug Rash Eosinophilic Systemic Syndrome(DRESS)	2	2.2%
Photosensitivity reaction	2	2.2%
Eczema dermatitis	1	1.1%
Exfoliative dermatitis	1	1.1%
Alopecia	1	1.1%
Acanthosis like nigricans	1	1.1%

TABLE 3:- DRUGS RESPONSIBLE FOR CADRs

Drug name	Individual group	No. of cases	Total no. of cases	Percentages
Topical corticosteroids	Betamethasone	24	35	38.3%
	Mometasone	10		
	Clobetasol	1		
Antibiotics	Ciprofloxacin	7	22	24.8%
	Metronidazole	6		
	Tetracycline	4		
	Amoxicillin	2		
	Cotrimoxazole	1		
	Ceftriaxone	1		
	Dapsone	1		
Antiepileptic	Carbamazepine	2	14	15.4%
	Phenytoin	12		
NSAIDS	Diclofenac sodium	4	9	10%
	Naproxen	2		
	Aspirin	2		
	Ibuprofen	1		
Antitubercular	Isoniazid	1	3	3.3%
	Rifampicin	2		
Oral corticosteroids	Prednisolone (oral)	2	3	3.3%
	Hydrocortisone (IV)	1		
Opioid Analgesic	Tramadol	1	1	1.1%
Antifungal drugs	Fluconazole	1	1	1.1%
Angiotensin converting enzyme inhibitor (ACEI)	Captopril	1	1	1.1%
Non nucleoside reverse transcriptase inhibitor (NNRI)	Efavirenz	1	1	1.1%

TABLE 4:- CAUSALITY ASSESSMENT OF CADRs (WHO AND NARANJO'S SCALE)

Type of reaction	WHO SCALE		NARANJO SCALE			
	No. of cases	Percentage	No. of cases	Score		%
Definite	2	2.2%	2	+10		2.2%
Probable	88	97.8%	88	No of cases	Score	97.8%
				40	+6	
				44	+7	
				4	+8	
Possible	0	0%	0	0		0%

TABLE 5:- SEVERITY INDEX OF CADRs (HARTWIG AND SIEGEL'S SEVERITY ASSESSMENT SCALE)

Severity index	No. of cases	Percentage
Mild	24	26.7%
Moderate	56	62.2%
Severe	9	10%
Fatal	1	1.1%

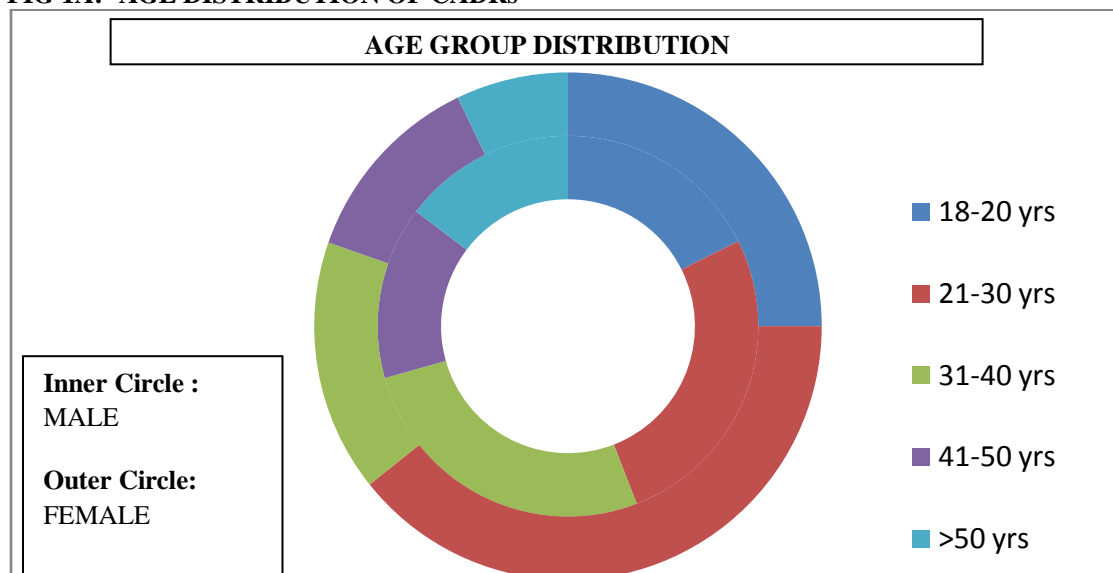
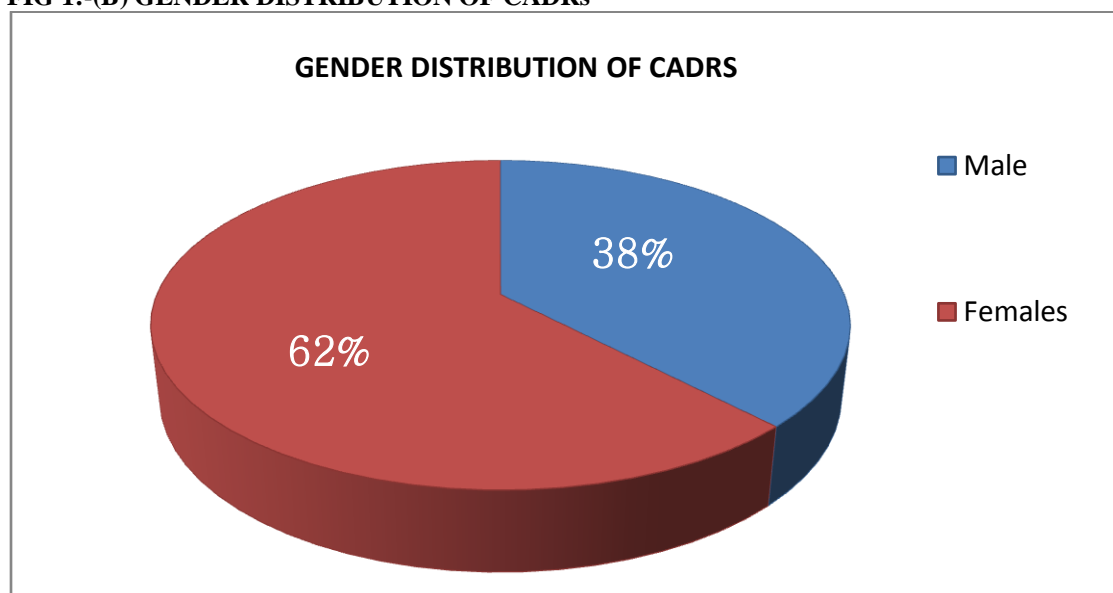
FIG 1A:- AGE DISTRIBUTION OF CADRs**FIG 1:-(B) GENDER DISTRIBUTION OF CADRs**

FIG 1(C):- PREVALENCE RATE OF CADRs

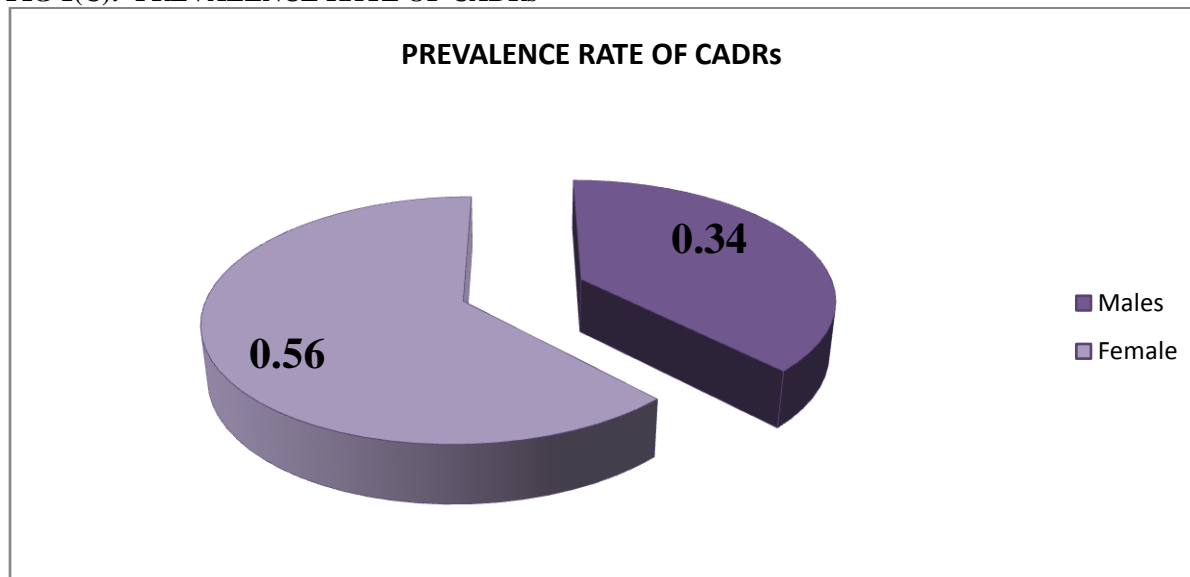


FIG 2:- CLINICAL PATTERNS OF CADRs

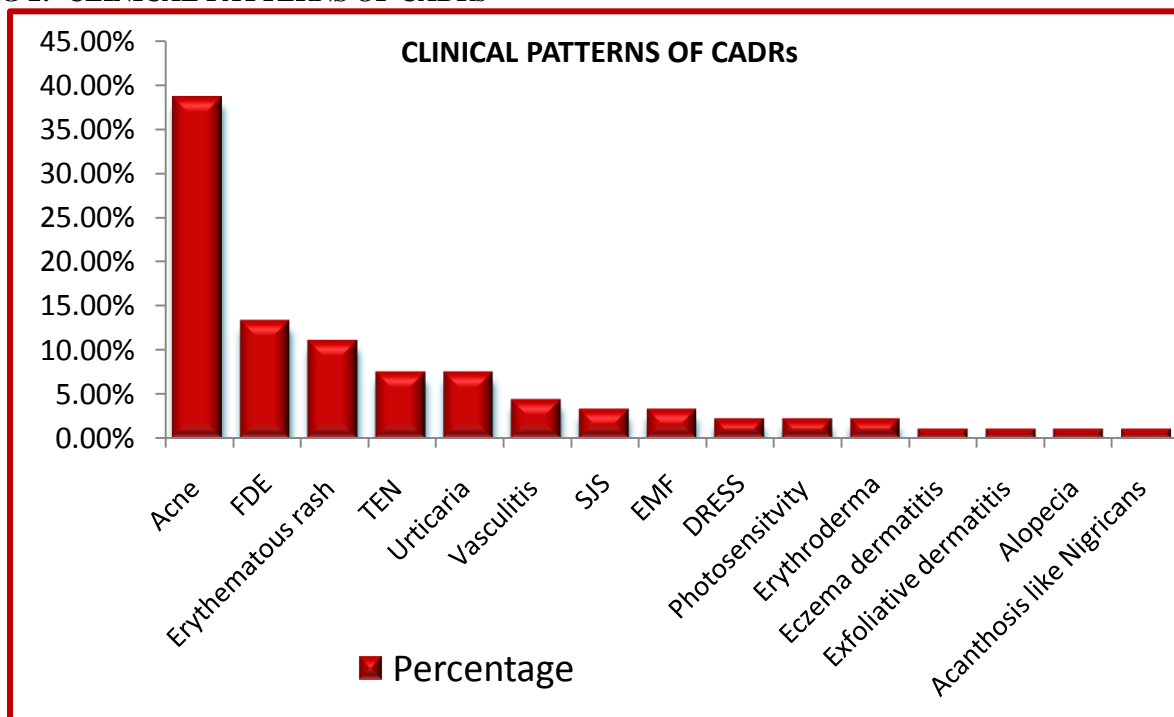


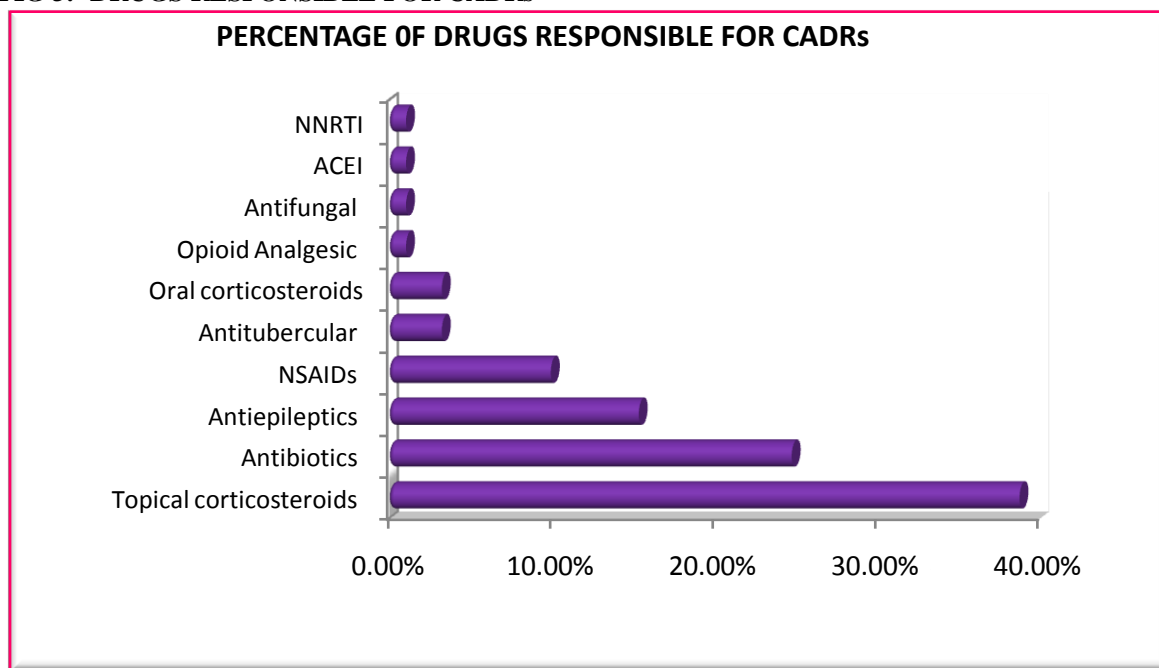
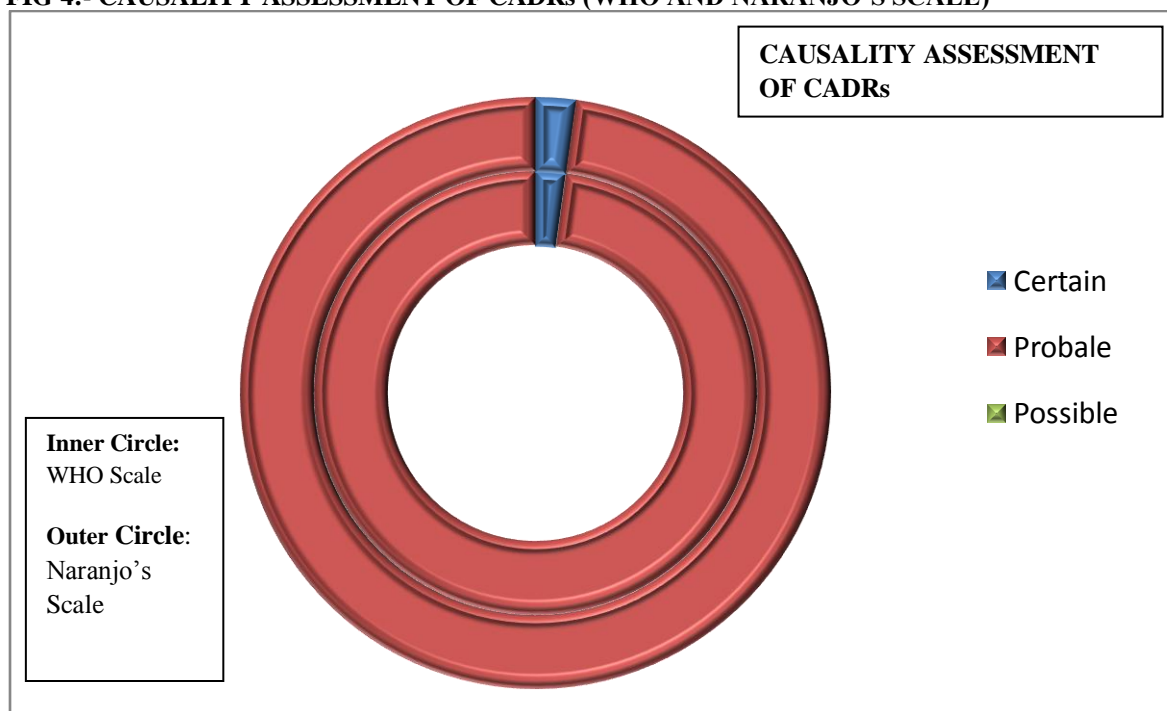
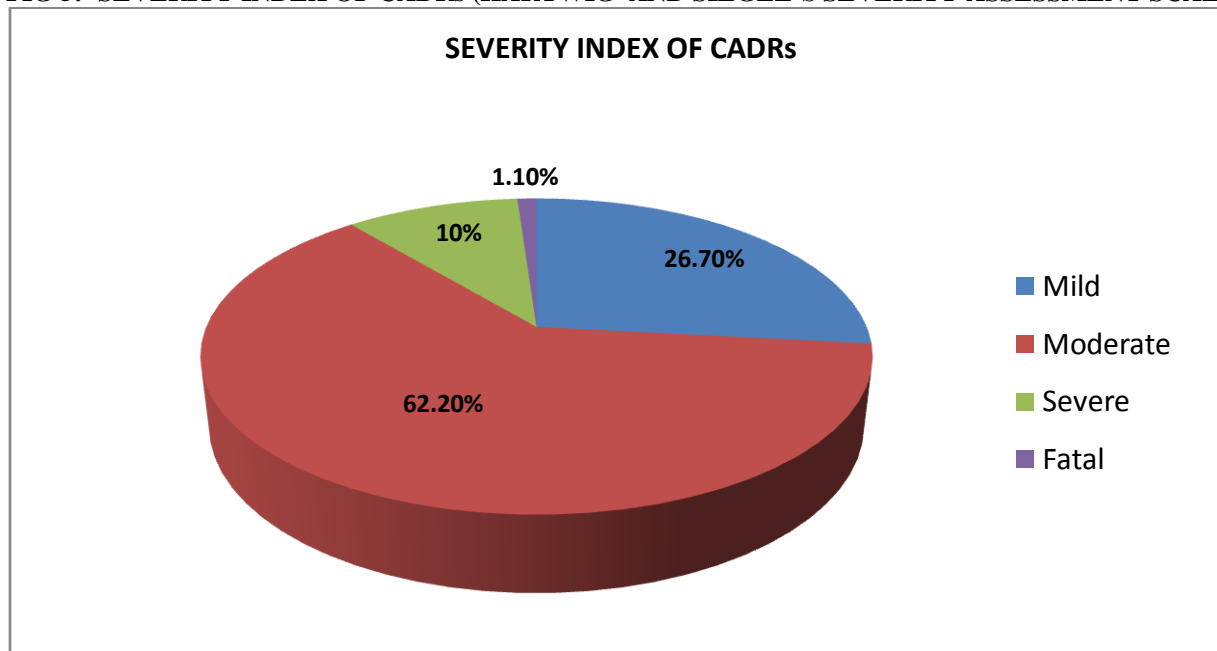
FIG 3:- DRUGS RESPONSIBLE FOR CADRs**FIG 4:- CAUSALITY ASSESSMENT OF CADRs (WHO AND NARANJO'S SCALE)**

FIG 5:- SEVERITY INDEX OF CADRs (HARTWIG AND SIEGEL'S SEVERITY ASSESSMENT SCALE)

Discussion:-

A Prospective, Observational and non-invasive study was carried out for a period of 6 months recording 95 cases, from a total population of 10, 000 patients attended the Dermatology Department, out of which 5 cases were excluded because the offending drug was not identified or the data was insufficient to make any analysis. The remaining 90 cases were analyzed, among which one case was fatal. Of the 90 cases, 34(37.8%) were males and 56 (62.2%) were females contributing to female preponderance, which was similar to that of studies reported in the literature by **Ruchika Nandha, et al (2011)¹⁰**, **V Sudershan et al (2011)¹¹**, **Saraswoti neupane and Surya Raj Sharma (2012)¹²**, **Akram Ahmed et al (2012)¹³**, **Mahmood Farshchian et al (2015).¹⁴** Unlike in study of **Shalini Chawla et al (2011)¹⁵** and **Tejas K Patel, Sejal H Thakkar, DC Sharma- Review (2015)¹⁶** which showed male preponderance.

In our study, highest percentage of CADR was recorded in the age group of 21- 30 showing (34.4%) which is in accordance with studies reported by **Shalini Chawla et al (2011)¹⁵** where the mean age of patients who experienced CADR was 32, and **V Sudershan et al (2011)¹⁷** reported higher incidence in adult age group of 21-30 years. Adverse drug reactions reported in our study showed maximum incidence with the application of Topical corticosteroids (38.8%), followed by Antibiotics (24.8%), among which Ciprofloxacin was the common offending drug. (15.4%) were seen in patients who administered Anti-epileptic drugs where Phenytoin recorded the highest number of ADRs. NSAID was about (10%). Antitubercular, Oral and Parenteral corticosteroids were the offending agent recording (3.3%). Rare cases (1.1%) were seen in patients taken Antifungal agents, Opioid Analgesic, Angiotensin converting enzyme inhibitors (ACEI), and Non-nucleoside reverse transcriptase inhibitor (NNRTI). Studies carried out by **Bharani Kalpana R, et al (2014)¹⁸** have reported that oral Antimicrobials, Injectable Antimicrobials, NSAID's and Topical Steroids (Betnovate) were the leading cause of ADRs .All the other literature articles showed the highest offending drug to be Antimicrobials accounting for nearly 50% of the cases, followed by NSAIDs, Antiepileptic.

The common clinical pattern of Cutaneous ADR observed in our study was Steroid induced acne recording about (38.6%). The second common CADR was seen is Fixed drug eruption (FDE) with about (13.3%) followed by Erythematous rash that showed (11.1%), Toxic Epidermal Necrolysis (TEN) and Urticaria recording (7.5%).in which 1 was fatal with TEN wherein similar mortality with TEN was seen in the study of **Saraswoti neupane and Surya Raj Sharma (2012)¹²** Steven Johnson Syndrome (SJS) were identified in (4.4%). About (3.3%) of Vasculitis and Erythema was observed, (2.2%) were seen with Erythroderma, Photosensitivity reaction and Drug rash

eosinophilic systemic syndrome (DRESS). Rare cases about (1.1%) was seen in Alopecia, Exfoliative Dermatitis, Infectious eczema dermatitis, and Acanthosis like nigricans. Unlike in other studies Fixed drug eruption was the highest recorded clinical pattern of ADR by **Saraswoti neupane and Surya Raj Sharma (2012)**¹². Some studies have observed urticaria and exanthematous rash as offending agents by **Karamsad Suthar J.V1 and Desai S.V (2011)**¹⁹ recording both about 31.42%, whereas studies by **Balpande K.G., et.al (2013)**²⁰ recorded (32.75%) and (26.72%) respectively. Acute urticaria was the most common clinical presentation (59.2%) in the study by **Mahmood Farshchian et al (2015)**¹⁴

According to Causality assessment as per the Naranjo's scale, (2.2%) scored Definite, Remaining all about (97.8%) scored Probable and as per the WHO scale (2.2%) scored Certain, rest all (97.8%) were of Probable. Unlikely, conditional, unclassifiable were excluded from the study. Most of the studies showed the same assessment data giving high incidence of Probable cases about (55.89%) reported by **Mena Shrivastava et al (2011)**²¹, and about (90.62%) as reported by **Palanisamy S, Arul Kumaran KSG, Rajasekaran A (2009)**²² and about (78.26%) reported by **Himangshu Mahato et al (2014)**²³

The results of assessment of the severity index revealed most cases with Moderate about (62.2%), followed by Mild about (26.6%). (10%) were identified as Severe. One case (1.1%) was fatal which was similarly seen in the study by **Saraswoti neupane and Surya Raj Sharma (2012)**¹² In our study all the cases were Type B (Bizarre type) which was similarly seen in the study by **Karamsad Suthar J. and Desai S.V (2011)**¹⁹ where 100% ACDRs were Type B (Bizarre immunological allergic drug reaction).

Conclusion:-

Clinical patterns and the drugs causing ADR are remarkably similar to those observed in other studies except for minor variations. A wide clinical spectrum of Cutaneous ADRs ranging from Steroid induced acne to Fixed Drug Eruption (FDE), Erythematous rashes, serious Toxic Epidermal Necrolysis (TEN), Urticaria, Steven Johnson Syndrome (SJS) and Drug Rash Eosinophilic Systemic Syndrome (DRESS) was observed. Out of which Steroid induced acne was the most common Cutaneous ADRs seen. Topical corticosteroids were the most common and among which Betamethasone was offending agent causing Cutaneous ADRs. The study demonstrated the causal relationship that was established using WHO and Naranjo's algorithm. It was evaluated that majority of the cases assessed were "probable", with few cases of "certain". Analysis revealed the severity of Cutaneous ADR that showed majority of the cases as moderate followed by mild and severe. Fatal case was seen with TEN. These variations may be explained by the differences in drug usage patterns and short duration of the study. The aim of the study was achieved by assessing the prevalence, causality and severity assessment, offending drugs involved in CADR and clinical patterns recorded during the course of study. This helps in prevention and early detection of CADR and can be used as a guide to healthcare professionals to communicate more effectively regarding the management of such conditions.

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Conflict of Interest:-

I and the other co authors have no conflict of interest to declare.

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