Section A-Research paper

Analysis of the Various Spectrum of Cutaneous Adverse Drug Reactions and Associated Factors in a Tertiary Care Teaching Hospital in Eastern India: A Cross-sectional Study

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Abstract

Incidences of cutaneous adverse drug reactions (CADRs) have showed increase in trend due to the indiscriminate and irrational use of medications and sometimes its life threatening as well. The objectives of the study were to identify different clinical spectrum of CADRs and to determine the causative agents, their severity and preventability. A cross sectional, descriptive study was conducted over a period of 1 year and 4 months from 1st of August 2019 to 31st November 2020, patients with various CADRs that reported to the Department of Dermatology were recorded. Causality, Preventability and Severity were assessed. A total of 322 patients were included in the study. Male preponderance (53.41%) was seen with maximum 22.67% in 18-35yrs age group and females (46.58%) showing maximum no 20.49% in 18-35 years age group. Analysis of patterns revealed that, Maculo Papular Rash (MPR) (29.50%) was the most common presentation among all CADRs followed by fixed drug eruption in 17.39%, SJS-TEN overlap syndrome in 13.04%, drug hypersensitivity syndrome (DHS) 7.76%, acneiform eruption 5.27%, Urticarial Vasculitis 4.03% comprised of majority of the cases. Most frequently involved drug classes were Antibacterial agents (28.74%) followed by non-steroidal anti-inflammatory agents [NSAIDs] (15.47%), Drugs acting on central nervous system (12.28%), Antiviral agents (11.05%) and Antitubercular drugs (7.86%). In accordance to WHO-UMC causality assessment scale classifies 55.12 % as probable, 40 % as possible and 4.87 % as definite. The most common suspected drug incriminated in various drug interactions is Antibacterial agents (27.92%) followed by NSAIDs (15.03%). Many of recorded CADRs (23%) cases were probably

preventable and simultaneously could reduce the burden of hospitalization in 79.18% moderate to severe CADR patients. Our intention is that the CADRs, as an added priority, should be properly identified, monitored, reported and use of high risk drugs and/or new drugs should be carefully prescribed. The awareness among the treating physicians should be created, so that the morbidity as well as mortality caused by CADRs should be minimised.
KEY WORDS

Causality Assessment; Pharmacovigilance; Preventability; Severity;

Introduction

The occurrence of cutaneous adverse drug reactions (CADRs) is quite high, accounting for 30 to 45% of all ADRs. This type of ADR is responsible for 2% of total hospital admissions.[1] Ensuring the safe use of medications is a major concern for various stakeholders such as prescribing physicians, pharmacists, nurses, regulatory authorities, pharmaceutical companies, and the public. Healthcare professionals have a responsibility to their patients, who may not be aware of medication-related problems. Unfortunately, poor awareness among healthcare professionals and patients, as well as a lack of widespread ADR monitoring centers, has led to low reporting rates in India. To address this issue, the National Pharmacovigilance Programme of India has been relaunched since 2011 to encourage ADR monitoring throughout the country, including through various AMCs in tertiary care centers.

Most adverse drug reactions (ADRs) are mild and resolve on their own. However, some reactions can be severe and even life-threatening, such as Steven Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), or the SJS-TEN overlap syndrome, which have been documented in medical literature.[2] Such severe reactions can result in extended hospital stays, additional expenses, and may even require discontinuation or alteration of the treatment plan.[3,4]

Several factors have been linked to an increased risk of cutaneous adverse drug reactions (CADRs), including being over the age of 60, being female, having obesity, having a compromised immune system, being pregnant, experiencing hepatic failure, or having renal insufficiency.[5] Some studies have identified anticonvulsants and antibiotics as the most common drug groups responsible for CADRs,[6,7] while others have pointed to non-steroidal anti-inflammatory drugs (NSAIDs).[8] With new drugs constantly being introduced to the market, the potential for adverse drug reactions is always present, causing concern for both patients and physicians. Having a thorough understanding of drugs and drug interactions that may contribute to the development of CADRs can aid physicians in selecting safer alternatives, ultimately benefiting society as a whole.

Early detection, assessment, monitoring and prevention of ADRs are vital enough to reduce distress to the patients, thus ameliorate public health. As per our knowledge, the studies related to CADRs in our region is very sparse. Hence, the present study was planned to assess the various spectrum of CADRs, suspected medications with the level of causal association as primary objectives and severity, preventability status as well as temporal relationship of CADRs with the culprit medications as secondary objectives.

Material and Methods

In collaboration with the Department of Dermatology, the Department of Pharmacology conducted a cross-sectional study at a tertiary care teaching hospital in eastern India over a period of 16 months, from August 1, 2019, to November 31, 2020. Institutional ethics committee approval was obtained before initiating the research. The study included all suspected cases of cutaneous adverse drug reactions (CADRs), regardless of age and gender, who visited the Dermatology department as either outpatients or inpatients (self-presenting or referred from other departments/hospitals). The study excluded reactions categorized as unlikely, unclassifiable, or doubtful, where suspected drugs or drug groups could not be identified, patients receiving traditional or indigenous medicines, cases with other known causes of cutaneous allergic reactions, and those who refused to disclose details of their CADRs or had CADRs caused by locally applied drugs.

The principal investigator visited the outpatient and inpatient department of Dermatology including referral from inpatient set up of other departments during the study period. The findings suggestive of CADRs were assessed by proper history taking, clinical examination by in charge dermatologists and review of previous prescriptions if available. The details of the demographic data (age, gender, residency, socioeconomic status, number of comorbidities, previous history of drug allergy, whether with prescription drug intake or over-the-counter drug intake, total number of medications per patient), indications for drug intake, various spectrum of CADRs and the suspected drugs, time period between intake and onset of symptoms were noted in the individual case record form through active surveillance. The socioeconomic status of the patients were classified based on Per capita monthly income by Modified BG Prasad socioeconomic classification scale, revised in 2016 [9]. All patients with CADRs were followed up till the recovery. ADR letters were circulated to all clinical departments, requesting them to report any adverse drug reactions encountered. Causality, preventability and severity were assessed by WHO-UMC Causality Assessment Scale[10], modified Schumock and Thornton scale [11] and modified Hartwig and Siegel scale[12] respectively.

Data analysis was done by percentage calculation, pie charts and bar diagrams with the help of Microsoft excel 2013. Normality of distribution was estimated by Shapiro–Wilk test. Continuous data (normally distributed) was summarized as mean ± standard deviation. Continuous data (not normally distributed) was summarized as median (IQR) with SPSS v16. Categorical variables were summarized as percentages. Association between the variables and the severity was assessed by chi square test. Among the variables, socioeconomic status was assessed by modified BG prasad classification and finally divided into binary variables as easy assessment (≤Lower middle class and > middle class). Incidence in percentage was estimated number of patients diagnosed as CADR by the concerned dermatologists (as numerator) and total number of outpatients and inpatients in dermatology department during the study period as denominator and has to be multiplied with 100. Association between severity and variables was assessed using chi square test.

Convenience sampling method (nonprobability) was adopted for identifying patients and gathering of data. A total of 495 patients with Suspected ADRs during the study period were

assessed, of which 322 were suspected to be CADRs. All 322 cases were selected for study after exclusion.

Results

Among the total of 322 CADRs identified, the following observations and results were obtained. The maximum number of CADRs were observed in the patients of age group of 18-34 years among both gender groups followed by 35-64 years group among both gender groups. Median (IQR) age of the patients was 32 (22-46) with minimum of 5 months to maximum of 80 years. Slight male preponderance was observed with male to female ratio of 1.14:1. Majority of the patients (75.46%) were resident of rural area and having socio-ecomic status of lower middle to lower group (81.98%). At least 38.5% of patients were having either one or two comorbidities. Among all patients, 7.76% had a history of similar sort of drug allergies in the past. CADRs were associated more commonly (72.67%) with prescribed drugs as compared to over-the-counter drugs. Median (IQR) no of medication intake per patient was 3 (3-4) [mean±sd = 3.85±1.39] with minimum of two to maximum of eight medications. Polypharmacy (intake of ≥4 medications) was observed in 40.36% of patients as depicted in table 1.

The indications of medication/s intake in the occurrence of CADRs were depicted in Figure 1. Medications prescribed for infectious diseases/septicemia (23.91%) including HIV AIDS and tuberculosis/Multi Drug Resistant tuberculosis (16.14%) catered the majority (40.05%) of the patients.

Analysis of patterns revealed that, Maculo Papular Rash (MPR) ± Pruritus ± Erythema was the most common presentation among all CADRs, accounting for 29.50% of cases, followed by fixed drug eruption in 17.39%, SJS-TEN overlap syndrome in 13.04%, drug hypersensitivity syndrome (DHS) 7.76%, acneiform eruption 5.27%, urticarial vasculitis 4.03% comprised of majority of the cases (as shown in table 2).

The most common suspected drug incriminated in various drug interactions is Antibacterial agents (27.92%) followed by non-steroidal anti-inflammatory agents (15.03%) and antiviral agents (12.64%). But, if the total antimicrobial agents were concerned (antibacterial including antitubercular and antileprotic agents), they were responsible for majority (62.76%) of CADRs. (as highlighted in table 3). Of these, cases of SJS-TEN overlap syndrome, Drug induced hypersensitivity syndrome, erythema multiforme, DRESS, Erythroderma, Papulo-vesicular bullous eruption, angioedema, acute generalized exanthematous pustulosis, two cases of severe erythematous maculo popular rash with pruritus (morbilliform eruption), one case of severe fixed drug eruption involving genitalia were life threatening, which represented the severe form of CADRs (29.50%) among the study population.

The agents most commonly associated with MPR ± pruritus ± erythema was Nevirapine followed by first line antitubercular drugs (Rifampicin + Isoniazid + Pyrazinamide + Ethambutol). The agents most commonly associated with fixed drug eruption were fluoroquinolone antimicrobial agents like Ofloxacin, ciprofloxacin and norfloxacin as depicted in table no 4.The time period between the intake of medications and onset of symptoms of various spectrum of frequently encountered CADRs with respect to

commencement of the drug therapy varied from minimum median of 1 day for FDE and UV to maximum median of 15 days for DHS as depicted in table 5. These was no significant association between the variables and the severity as depicted in table no 6.

According to the final causality assessment, 4.87% patients were classified under the category of certain, as rechallenge data was available, 55.12% were probably associated as only dechallenge data was available and 40% as having possible association with the drug, as dechallenge data was not available as shown in figure 2. In accordance to severity assessment scale, 20.83% were mild, 64.58% were moderate and 14.58% were severe. According to preventability scale, 5.66% were definitely preventable and 71.33% were not preventable (As depicted in figure 2). There were no reported deaths during the study period due to CADRs.

Discussions

The incidence observed in our study (1.02%) was slightly higher than that reported in a previous study conducted by Thakkar et al (0.45%), but in contrast to the findings of another study by Ghosh et al (2.85%)[13,14]"Our study revealed a modest male predominance (male: female = 1.14:1), which is consistent with the findings of studies conducted by Patel et al. and Jha et al.[14,16], but in contrast to studies conducted by Thakkar et al. and Pudukadan et al. [13,17]. History of drug reaction was present in 7.76% of patients, which was in contrast to another research conducted by Agrawal A et al, where 18.8% of patients has the previous history of similar sort of drug reaction[18]. In our study, polypharmacy (i.e., more than five drugs per patient) was noticed in 78 (24.22%) of cases which was in contrast 7.06%, 68% and 93.1% cases in research carried out independently by Modi A et al , Sriram S et al and Jose J et al respectively[19-21]. Among the enrolled patients, the presence of comorbidities (38.5%) was observed along with polypharmacy. Two other independent studies conducted in India by Sriram et al. and Jose et al. highlighted that comorbid conditions (42% and 52.1% respectively) were the major predisposing factors associated with the development of CADRs [20,21].

Most of the patients (40.05%) in the current study took medications for septicemia and HIV with or without Tuberculosis/multidrug resistant tuberculosis. But, Aggarwal A et al (36.88%) and Saha A et al (41.5%) highlighted fever was the most common cause of drug administration [18,22]. We might think that CADRs were frequently noticed in patients with septicemia, because probably this condition needs personalized polypharmacy.

In the present study, commonest encountered CADR was MPR. Similar finding was observed in studies conducted by Thakkar S et al, Jha N et al and Modi A et al [13,16,19], but in contrast to studies carried out by Pudukadan et al , Agrawal A et al and Sharma R et al (where FDE was most frequently encountered in both the studies) [17,18,23]. In our study, 42 cases of Stevens–Johnson syndrome were identified, which was highest among the very severe life threating CADRs. This was much higher than other studies carried out by Modi A et al and Gohel D et al respectively [19,24]. Death of two patients due to cutaneous adverse events had occurred.1st case was due to SJS-TEN with body surface area >80% where suspected drugs were both cefixime and fixed dose combination of ciprofloxacin and tinidazole. The 2nd reported death is due to papulo vesicular bullous lesion where suspected drugs were ciprofloxacin and metronidazole.

In the current study, antimicrobial agents (62.76%), particularly antibiotics (54.34%), and NSAIDs (15.03%) were the drug classes most implicated in CADRs, which was consistent with earlier studies by Sharma R et al.[23], Patel TK et al.[25], and Sebastian J et al.[26] On the other hand, Modi A et al.'s[19] study found that the most frequently encountered group was antiretroviral drugs (ARV), followed by NSAIDs, which was in contrast to our findings. Cephalosporins (8.59%) followed by fluoroquinolones (7.87%) were the most implicated groups among antibiotics. The majority of CADRs (approximately 60% = MPR + FDE + SJS-TEN) were reported within a median of one to four days, similar to Agrawal A et al.'s[18] study, where about 45.6% of patients developed symptoms within 2-5 days of drug intake. However, these findings contrasted with Modi A et al.'s[19] study, where the temporal relationship was seven days.

According to the WHO-UMC causality evaluation criteria, only 19 instances (4.87%) in the current study demonstrated a definite causal relationship, whereas the remainder were categorised as probable/likely (n=215; 55.12%) or possible (n=156; 40%). Many Indian research carried out by Gohel D et al, Krishna J et al, Shah SP et al [24,27,28] depicted that probable relationship is more than possible, but Modi A et al[19] found the reverse. Out of the different categories of CADRs, a certain relationship could be established in a small percentage of cases. Specifically, in the MPR group, there was a definite relationship in 10 out of 95 cases, in the FDE group, 6 out of 56 cases had a clear relationship, in the DHS group, only 2 out of 25 cases had a confirmed relationship, and in the case of red man syndrome, only 1 out of 5 cases had a discernible relationship. This was determined based on factors such as successful rechallenge, a reasonable response to withdrawal, or a recent history of similar events. Contrary to the findings of Ziqi Yan et al.'s[29] study, which showed that elderly people with multiple comorbidities and taking multiple medications were at a higher risk of experiencing severe adverse drug reactions (ADRs), our study did not reveal any significant association between the severity of ADRs and the variables.

Our study revealed that 28.66% of CADRs were preventable, similar to the findings of a study by Bates DW et al.[30] who reported 5.66% as definitely preventable, consistent with Dartnell JGA's study[31] which showed 23% as probably preventable. This was due to the failure to take necessary precautionary measures or conduct laboratory tests when administering drugs to patients. The remaining 71.33% were deemed probably not preventable. Our study's findings were comparable to those of studies conducted in the United States[30] and Germany[32], which showed that 28% and 28.5% of ADRs, respectively, were preventable. However, these results differed from another Indian study by Modi A et al.[19], which found that 88.90% of ADRs were not preventable, and only 11.10% were preventable. In line with a study from Australia[33], 5.5% of ADRs were found to be definitely preventable, which was consistent with our study's results.

Hartwig's severity scale[12] was used for severity assessment in our study, where any adverse reaction was considered serious (14.58%) if the patient outcome fell within various categories such as death, life-threatening, hospitalization, disability, birth defect, or required intervention to prevent permanent damage. Adverse reactions were considered moderate (64.58%) when the offending agent was either held or changed, an antidote was given, or the patient stayed in the hospital for at least one day. Mild adverse reactions (20.83%) were

identified when there was no need to change the offending drug, or if it needed to be discontinued, no antidotes were given. Simillar results were observed in two indian studies conducted independently by Modi A et al[19] and Padmavathi et al[34], where Most of the CADRs were of moderately severe in nature. Immediately after identification of the CADR, dechallenge of the offending drug was done in most of the cases and then appropriate measures were taken to treat patients appropriately. Severe cases were managed with caution and closely monitored until discharge from hospital.

Conclusion

The majority of CADRs in the current research developed within an average of seven days of therapy in the 3.36% of patients in whom they occurred. Antimicrobial agents and NSAIDs were the pharmacological classes most frequently linked to CADRs. CADRs affect patient morbidity and mortality, which is a serious public health problem. The quality of life of patients can be significantly compromised by hospitalisation and increased financial load, both of which may be avoidable in some circumstances. Additionally, CADRs can lead to nonadherence to prescribed therapy and eventual treatment failure. Unnecessary polypharmacy and prescribing drugs with cross-reactivity pose a common medicolegal hazard. Therefore, it is crucial to assess the clinical spectrum of various CADRs, identify the culprit medication and their temporal relationship. Engaging pharmacologists and clinical pharmacists can enhance patient care, promote drug safety and aid in the prevention, early identification, and detection of CADRs.

Table 1: Demographic and clinical attributes of enrolled patients (N=322)

Demographic attributes		Number	Percentage (%)
Age group	0-<18YRS	51	15.83
	18-<35YRS	139	43.16
	35-<65YRS	106	32.91
	>65YRS	26	8.07
Gender	Men	172	53.41
	Women	150	46.58
BMI	<18.5	69	21.42
	18.5-22.9	127	39.44
	23-24.9	74	22.98
	>=25	52	16.14
Residency	Urban/Semiurban	79	24.53
	Rural	243	75.46
Socioeconomic status	<lower middle class	264	81.98
	>middle class	58	18.01
Number of comorbidities	Nil	198	61.49
	One	108	33.54
	Two	16	4.96
Previous history of drug allergy	Yes	25	7.76
	No	297	92.23

Prescribed drugs	Yes	234	72.67
	No	88	27.33
No of medication intake	two	16	4.96
	Three	176	54.65
	Four	52	16.14
	≥Five	78	24.22
Departments from where CADRs reported	Dermatology (Directly)	143	44.40
	From Other Departments to Dermatology	179	55.59
Area of involvement	Generalized	107	33.22
	Localized	215	66.77

Table 2: Frequency of presentation of Different spectrum of CADRs

Serial No	CADR type	No of Patients (N=322)	Serial No	CADR type	No of Patients (N=322)
1	Maculo Papular Rash (MPR) ± Pruritus ± Erythema	95 (29.50)	13	*DRESS	05 (1.55%)
2	Fixed Drug Eruption (FDE)	56 (17.39%)	14	Erythroderma	04 (1.24%)
3	SJS-TEN Overlap Syndrome	42 (13.04%)	15	Papulo-vescicular bullos eruption	04 (1.24%)
4	Drug Hypersensitivity Syndrome (DHS)	25 (7.76%)	16	Angioedema	03 (0.93%)
5	Acneiform Skin Eruption (AFE)	17 (5.27%)	17	Oral ulcer	03 (0.93%)
6	Urticarial Vasculitis (UV)	13 (4.03%)	18	Ecchymotic patch and purpuric rash	03 (0.93%)
7	Generalized Pruritus	10 (3.10%)	20	Psoriatic form of drug reaction	02 (0.62%)
8	Nail Discoloration	10 (3.10%)	21	Injection site edema & skin exfoliation	02 (0.62%)
9	Erythema Multiforme	08 (2.48%)	22	Retinoid dermatitis	01 (0.31%)

10	Lichenification	07 (2.17%)	23	Multiple blisters on foot and hand	01 (0.31%)
11	Red Man Syndrome	05 (1.55%)	24	**Agep	01 (0.31%)
12	Phototoxicity	05 (1.55%)			

*DRESS: Drug reaction with eosinophilia and systemic symptoms, **AGEP: Acute generalized exanthematous pustulosis

Table 3: Percentage of Different Classes of medications Incrimated in Various Drug Reactions

Serial No	Medication classes (Total no of medications N=419)	Medications incrimated in various drug reactions	
1.	Antibacterials excluding antitubercular agents (117) (27.92%) Antibacterials including antitubercular agents (149) (35.56%) Antibacterials including antitubercular and antileprotic agents 175 (54.34%)	Cephalosporins (36) = Cefixime (13), Ceftriaxone ± Sulbactam (12), Cefopodoxime (6), Cefuroxime (3), Cefoperazone (2) Fluoroquinolones (33) = Ofloxacin (13), Ciprofloxacin (12), Norfloxacin (4), Levofloxacin (3), Gatifloxacin (1) Penicillin (16) = Amox-clav (10), Tazobactam ± Piperacillin (05), Penicillin G (1) Others (32) = Cotrimoxazole (11), Azithromyin (6), Vancomycin (6), Linezolid (2), Chloramphenicol (2), Doxycycline (2), Amikacin (1)	
2.	NSAIDS (63) (15.03%)	Nimesulide + Paracetamol (13), Aceclofenac + Paracetamol (12), Etoricoxib (10), Diclofenac (9), Ibuprofen (7), Paracetamol (7), Mefenamic acid (3), Piroxicam (2)	
3.	Antivirals (53) (12.64%)	Nevirapine (36), Zidovudine(10), Efavirentz (5), Acyclovir(2)	
4.	Drugs acting on central nervous system (50) (11.93%)	Phenytoin (18), Carbamazepine (13), Valproate (6), Lamotrigine (5), Risperidone (2), Amitryptiline + Chlordizepoxide (2), Oxcarbazepine (2), Levatirecetam (2)	
5.	Anti-tubercular agents (32) (7.63%)	Isoniazid (20), Rifampicin (8), levofloxacin(2), Ethionamide(2)	
6.	Anti leprosy drugs (26) (6.20%)	Dapsone (24), Clofazamine (2)	
7.	Antiprotozoals (24) (5.72%)	Ornidazole (12), Tinidazole (8), Metronidazole (4), Satronidazole (1)	
8.	Anticancer agents (20) (4.77%)	5FU (4), Doxorubicin (3), Paclitaxel (3), Cisplatin (2), Adriamycin (2), Carboplatin (2), Irinotectan (1), Etoposide (1), Docitaxel (1), Vinorelbin (1)	

9.	Antifungals (11) (2.62%)	Fluconazole (8), Grisiofulvin (1), Terbenafine (2)	
10	Immunosuppressants/ immunomodulators (12) (2.86%)	Methyl prednisolone (4), Sulfasalazine (3), Methotrexate (2), Allopurinol (2), Hydroxychloroquine (1),	
10.	Others (12) (2.86%)	Namcold (5), Sinarest (3), Losartan (1), Tretinoin cream (1), Epalrestat (1), Dicyclomine + paracetamol (1)	

*Total antimicrobial agents [263 (62.76%)] are Antibacterials including antitubercular and antileprotic agents=175, Antivirals=53, Antiprotozoals=24, Antifungals=11. (NAMCOLD= fixed dose combination of pseudoephedrine, cetirizine and nimesulide, SINAREST= fixed dose combination of chlorpheniramine maleate, phenylephrine and paracetamol

Table 4: Frequency of drugs implicated by Most Common Suspected CADRs

MPR ± Pruritus ± Erythema	FDE	SJS-TEN	DHS	AFE	UV	EM
Nevirapine (32)	Ofloxacin (9)	Phenytoin (9)	Dapsone (19)	Isoniazide (6)	Nimesulide + Paracetamol (2)	Cotrimoxazole (3)
Anti tubercular treatment category 1 (7) *	Ciprofloxaci (8)	Carbamazepin (5)	Nevirapine (2)	Methyl prednisolone (4)	Aceclofenac + Paracetamol (2)	Pseudoephedrine + Cetirizine + Nimesulide (2)
Cotrimoxazole (5)	Ornidazole (9)	Lamotrigine (5)	Allopurinol (1)	Phenytoin (4)	Diclofenac (2)	Ibuprofen (2)
Carbamazepine (4)	Norfloxacin (5)	Nimesulide + paracetamol (4)	Phenytoin (1)	Carbamazepine (3)	Ofloxacin (2)	Valproate (1)
Phenytoin (4)	Nimesulide (5)	Nevirapine and cotrimoxazole (4)	Carbamazepine (1)		Ceftriaxone+Sulbactam (2)	
Paracetamol (3)	Fluconazole (4)	Cefixime (4)	Sulphasalazine (1)		chlorpheniramine maleate, phenylephrine and paracetamol (2)	

Azithromycin (3)	Tinidazole (4)	Ceftriaxone (5)			Losartan (1)	
Etoricoxib (3)	Aceclofenac (3)	Amoxicillin + clavulanic acid and paracetamol (4)				

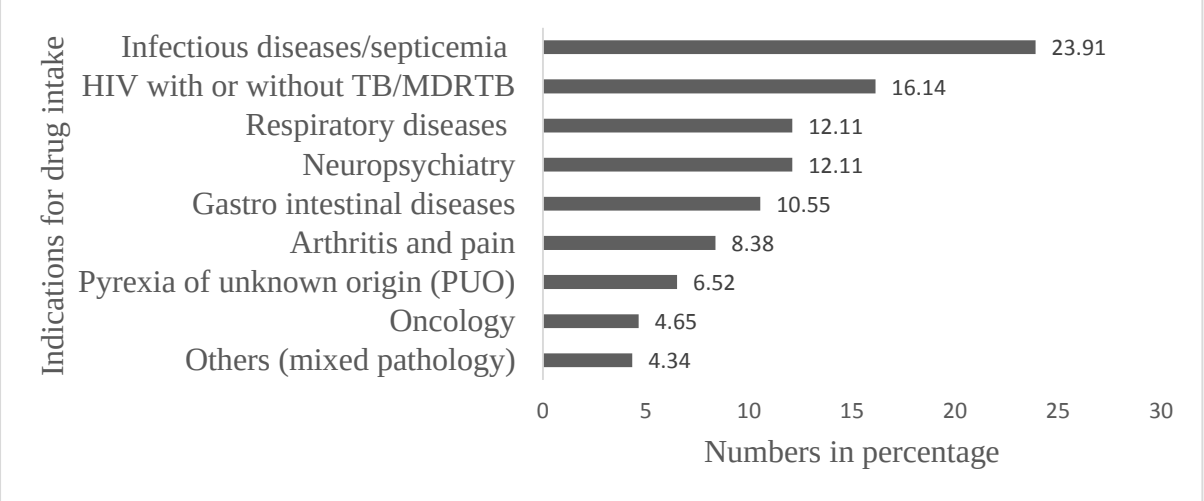
* As per RNTCP, Govt of India (Rifampicine + Isoniazid + Pyrazinamide + Ethambutol), + means Fixed dose combinations

Table 5: Important Cutaneous Reactions and Time Period Between Intake and Onset of Symptoms

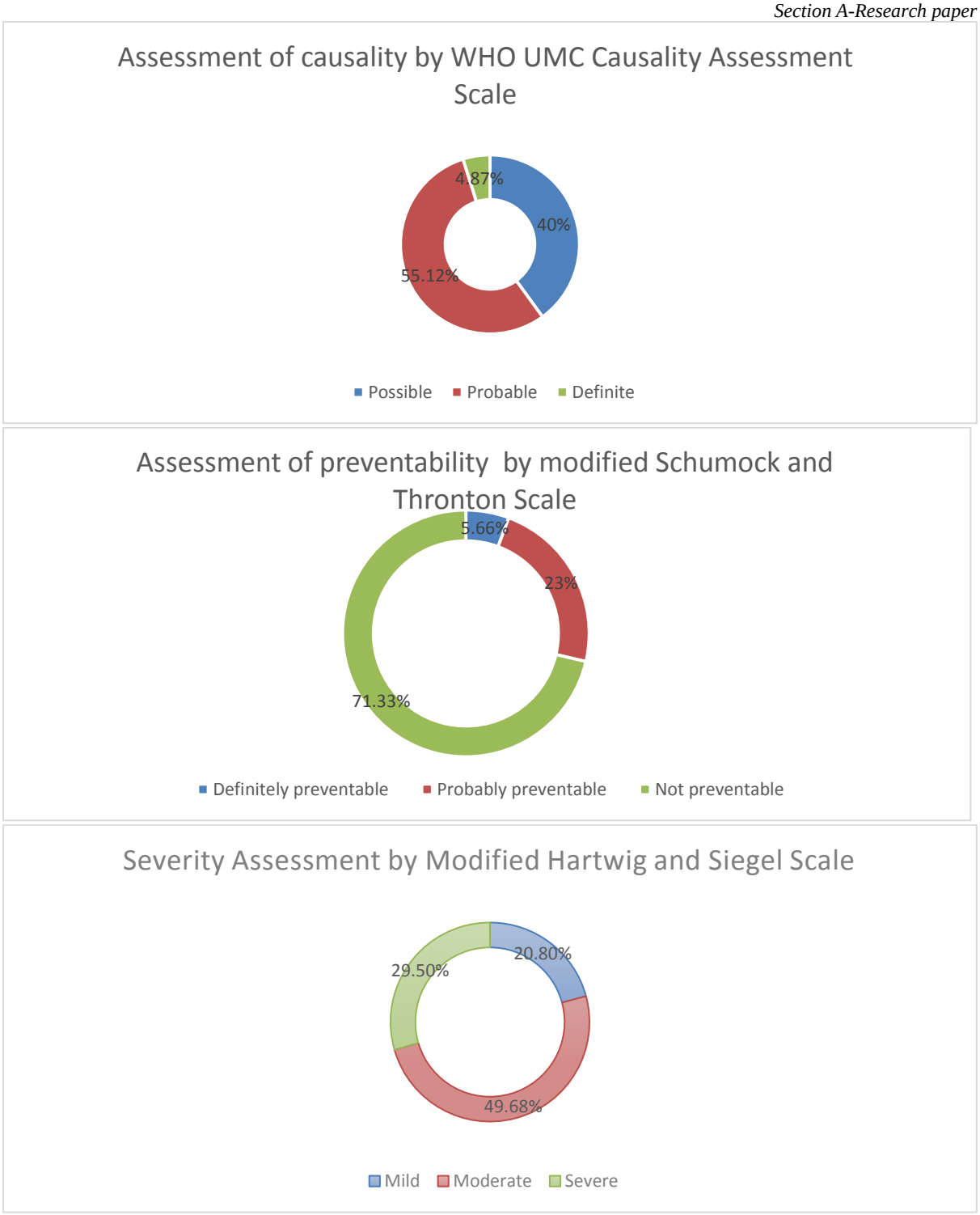
Serial no	Type of reaction	Mean±SD (time period in days between onset of symptoms)	Median time period (in days) between onset of symptoms	Duration of occurance from minimum to maximum (Range)
1.	Maculo papular rash	5.30±4.88	4 (2-7)	1 day - 28 days
2.	Fixed drug eruption	1.52±1.32	1 (.25-2.5)	1.5 hours - 4 days
3.	SJS-TEN overlap syndrome	4.33±4.00	3.5 (.87-7)	6 hours - 14 days
4.	Drug hypersensitivity syndrome	19.96±8.67	15 (14-21)	14 days – 42 days
5.	Acneform skin eruption	13.88±7.06	10 (8-20)	7 days – 28 days
6.	Urticarial Vasculitis	6.97±12.34	1 (0.28 - 10.5)	7.5 hours – 42 days
7.	Erythema multiforme	3.37±1.84	2.5 (2-4.75)	2 days – 7 days
8.	Lichenification	9.71±2.62	10 (7-12)	7 days – 14 days
9.	Red man syndrome	----------	----------	5-10 Minutes
10.	Phototoxicity	6.40±4.56	5 (3-10.5)	3 days – 14 days
11.	DRESS	15.60±3.04	14 (14-18)	14 days - 21 days
12.	Erythroderma	14.00±5.71	14 (8.75-19.25)	7 days – 21 days

Table 6: Association between severity and variables

Variables	Groups in variables	mild	moderate	severe	p-value
Median age group	≤31	41	74	50	0.952
	>31	37	76	44	
Gender	Men	39	79	55	0.504
	Women	39	71	39	
BMI	Underweight	11	11	05	0.413
	Normal	17	30	22	
	Over weight	06	20	12	
	Obese	08	14	07	
Residency	Rural	60	113	79	0.261
	Urban/semi urban	18	37	15	
SES	≤Lower middle class	62	126	75	0.602
	>Middle class	16	24	19	
Comorbidities	Yes	34	55	36	0.591
	No	44	95	58	
Prescribed drugs	Yes	55	110	69	0.886
	No	23	40	25	
No of drugs/prescription	<=three	46	90	56	0.989
	>=four	32	60	38	



Figuare 1: Indications for medication intake in the different CADRs categories (N=322)



Figuare 2: Causality, Preventability and Severity Assessment For Suspected CADRs

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