Acta Dermatovenerol Croat 2018;26(3):233-242 CLINICAL ARTICLE

An Epidemiological and Clinical Analysis of Cutaneous Adverse Drug Reactions Seen in a Tertiary Care Outpatient Clinic in Cairo, Egypt

***Eman A. El-Nabarawy*[1], Maha Fathy Elmasry[1], Mona Ibrahim El Lawindi[2], Yasmine Ahmed Tarek**

[1]Dermatology Department, Faculty of Medicine, Cairo University, Cairo, Egypt; [2]Public Health and Community Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Corresponding author:
Maha Fathy Elmasry, MD
Dermatology Department
Faculty of Medicine
Cairo University
Cairo
Egypt
mahafathy1214@gmail.com

Received: June 26, 2017
Accepted: July 11, 2018

ABSTRACT A cutaneous adverse drug reaction (CADR) is any undesirable change in the structure or function of the skin, its appendages, or mucous membranes caused by a drug. The frequency of CADRs is variable, with only few studies evaluating it. Our aim was to identify the clinical spectrum of CADRs and document the epidemiological data of different types of drug eruptions among Egyptian patients attending a tertiary care center. An observational hospital-based analytical study was planned for a period of six months (January-June 2015). All patients attending the outpatient Dermatology Clinic at Kasr El Aini hospital were examined to detect patients with CADRs, who were subjected to a detailed questionnaire with a detailed drug history. A skin biopsy was taken to confirm the diagnosis and to detect the type of CADRs. The primary incidence of CADRs reported in our study was 0.28% (78 patients) from a total number of 27,093 patients. The most common CADRs were SJS/TEN in 12 patients (15.3%) and lichenoid drug eruptions in 12 patients (15.3%), followed by exanthematous drug eruptions in 11 patients (14.1%) and vasculitic drug eruptions in 9 patients (11.5%). The most common drug incriminated was ibuprofen in 6 patients (7.6%), followed by penicillin in 4 patients (5.1%) and aspirin in 3 patients (3.8%). In conclusion, incidence of CADRs in our study was similar to incidence reported in different countries; however, the incidence of life-threatening reactions such as SJS/TEN was higher compared with studies conducted abroad.

KEY WORDS: cutaneous adverse drug reactions, epidemiology, incidence, outpatients

Abbreviations:
AGEP: Acute generalized exanthematous pustulosis
CADRs: Cutaneous adverse drug reactions
DIHS: Drug-induced hypersensitivity syndrome
DRESS: Drug rash with eosinophilia and systemic symptoms
FDEs: Fixed drug eruptions
GBFDE: Generalized bullous fixed drug eruption
NSAIDs: Nonsteroidal anti-inflammatory drugs
SCARs: Severe cutaneous adverse reactions
SD: Standard deviation
SJS: Steven-Johnson syndrome
TEN: Toxic epidermal necrolysis

INTRODUCTION

Constant advancements in the medical and pharmacological fields and development of new drugs contribute to the increasing number of cutaneous drug reactions reported every year. But the true incidence of drug eruptions is difficult to determine, mainly because many mild and transitory reactions are not recorded (1).

A cutaneous adverse drug reaction (CADR) is any undesirable change in the structure or function of the skin, its appendages, or mucous membranes caused

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by a drug (2). Almost any medication can induce skin reaction, and certain drug classes such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and antiepileptics have drug eruption rates approaching 1-5% (3).

CADRs are the most frequent of all manifestations of drug sensitivity and manifest with varied and diverse morphology (2). The majority of eruptions are mild and self-limiting (3), ranging from skin rashes, urticaria, fixed drug eruption, angioedema, and erythema multiforme (4). Severe cutaneous adverse reactions (SCARs) include Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DIHS), and drug rash with eosinophilia and systemic symptoms (DRESS). Acute generalized exanthematous pustulosis (AGEP) has been added to the list comprising SCARs (5).

The prevalence, clinical patterns, and causative drugs of CADRs vary among the different populations previously studied, comprising 10-30% of all reported adverse drug reactions (6). Since drug reactions are a major cause of patient morbidity and account for a significant number of patient deaths (7), it is therefore of utmost necessity for a dermatologist to possess a comprehensive understanding of the clinical spectra of CADRs as well as knowledge of the drugs which are frequently incriminated in such adverse reactions. This would help reduce or minimize the extent of iatrogenic morbidity and mortality (2) and is why special attention to monitoring and reporting of CADRs must be encouraged. Since the bulk of CADRs result from physician-prescribed drugs, awareness on part of the physician can help in their timely detection and management, thereby restricting the associated damage (8).

PATIENTS AND METHODS

The study was designed as an observational hospital-based analytical study. It was conducted at the outpatient clinic of the Dermatology Department, Faculty of Medicine, Cairo University Hospital (Kasr El Aini) over a period of six months (January-June 2015). After approval by the Dermatology Research Ethical Committee, written informed consent was obtained from each patient for the participation in the study and photography.

Patients

All patients with a clinical picture of CADRs attending the Dermatology Outpatient Clinic fulfilling the inclusion and exclusion criteria were included. The inclusion criteria included adults over 18 years of age with visible skin eruptions and with a history of drug intake. The exclusion criteria excluded patients whose skin lesions turned out to be disease-related (e.g. viral exanthems). Each patient was subjected to proper history taking, detailed drug history, and general and skin examinations.

METHODS

Clinical evaluation

After initial assessment by the investigator based on patient history and a general and cutaneous examination according to a predefined questionnaire for CADRs (Table 1) including detailed drug history, observers A and B both independently evaluated the cases clinically or by clinical photographs, and a provisional clinical diagnosis or a clinical differential diagnosis was suggested by the investigators. CADRs were classified according to their characteristic skin features into severe and non-severe types (9) (Table 2).

Skin biopsy and histopathological evaluation

If the patient had multiple similar lesions, only one representative biopsy was taken using a 4 mm punch biopsy. Biopsy was fixed in 10% neutral buffered formalin followed by embedding in paraffin. Routinely stained hematoxylin and eosin (H&E) slides were prepared. Light microscopic examination was carried out for the slides.

Histopathological diagnosis was based on the histopathological clues described in literature. A final diagnosis was established for each case based on the clinico-pathological correlation (10-12) (Table 3).

The data was coded, revised, and checked using the statistical package SPSS version 16.0. Data transformation, recoding, and grouping was performed regarding both severity and types of drug reaction. The severity classification into severe types of drug eruption and other types of drug eruptions was adhered to (9). Differences between the studied groups were assessed using the suitable inferential statistical tests. The student's t-test and one-way ANOVA test were used for quantitative independent variables regarding two or more levels and for dependent variables, respectively. The differences between qualitative variables were assessed using the chi-square test. All the above mentioned statistical tests were considered significant at a P-value <0.05.

RESULTS

A total of 78 patients with CADRs was reported, while the total number of patients attending the dermatology clinic during the study period was 27,093

Table 1. Cutaneous adverse drug reaction patient questionnaire:

Personal history	**Date:** **Name:** **Residence:** Governorate: **Area :** ○ Rural ○ Urban/slum ○ Urban/non slum **Age:** (in years) : **Occupation:** ○ House wife ○ Non working ○ Manual worker ○ Farmer ○ Trades/Business ○ Clerk ○ Semi-professional ○ Professional ○ Others **Gender:** ○ male ○ female **Tel. no :** **Marital status:** ○ married ○single ○ divorced ○ widow **Special habbits:** ○ NO special habbits ○Smoking ○Alcohol ○Drugs **Education:** ○Illiterate ○ Read & write ○ Primary ○ Preparatory ○ Secondary (general or technical) ○Intermediate (2 years) ○ University graduate ○ Postgraduate degree
Drug exposure history	**Name of the drug:** ● Category (antibiotics, antiepileptics…): ●Do not remember the drug **Nature of medication:** ○ Capsules ○Tablets ○Powder ○Eye drops ○Liquid ○Inhalants ●Skin preparations ○Ointment ○Cream ○Lotion ●Suppositories ○Vaginal ○Rectal **Dose:** **Cumulative dose:** **Route of administration:** ○Oral ○Topical ○Parenteral ○Rectal ○Inhaled ○Intradermal **Duration of drug intake** (in days): **Duration between initiation of the drug and the onset of the eruption** (in days): **Duration of the eruption** (in days): **Course of the eruption:** ○Progressive ○Regressive ○Stationary **Course of the eruption after withdrawal of the offending drug**: ○ Progressive ○ Regressive ○ Stationary **Improvement after decrease dosage or discontinuation of the drug (dechallenge):** ○Yes ○No **The re-exposure to a drug and the exacerbation of eruption (rechallenge):** ○Yes ○ No **Responsible drug (suspected drug probability):** ○ High ○ Medium ○ Low **Previous attacks**: ○Yes ○ No
Past history and general medical history	○ Viral disease ○ Autoimmune disease ○ CTD ○ Malignancy ○ Others ○ None
Family history	**Other diseases:** ○ CTD ○ Autoimmune ○ Drug reactions . clinical presentation: ○ None **Hypersensitivity syndromes (DRESS, DIHS) or anticonvulsant hypersensitivity syndrome:** ○Yes ○ No
Environmental/ Occupational exposure	**Sunlight, artificial tanning devices:** ○Yes ○No
Clinical picture	**a.Vital signs:** ○ Fever ○ Hypotension ○ Others **b.Systemic symptoms:** ○ Pruritis ○ Facial edema ○ HSM ○ Others **c. LNS:** ○Generalized ○Localized ○ None **d.Lesions:** **Primary lesion:** ○Macules ○Papules ○Patches ○Nodules ○Wheal ○Plaques ○Vesicles ○Tumor ○ Bullae ○ Comedones ○Pustules ○Palpable purpura ○Targetoid lesions ○ Edema of SC tissue **Secondary lesions:** ○ Scales ○Crusts○ Excoriations ○Abrasions ○Fissures ○ Ulcers ○Necrosis ○Erosion ○Others **Pigmentations:** ○ Yes ○ No e**. Distribution:** ○ Generalized ○ Acral ○ Photodistribution ○Grouping ○ Localized f**. Site:** ○ Scalp ○ Face ○ Arm ▫ B▫ F ○ Forearm ▫B ▫F ○ Hand ▫D ▫P ○T runk ▫ B ▫F ○ Thigh ▫B ▫F ○ Leg ▫ B ▫F ○ Foot ▫ D ▫P (B:back,F:front, D:dorsal, P:palmo plantar) g. **Mucous membrane:** ○ Ocular ○Nasal ○ Genital ● Oral ○ Labial ○ Buccal ●None h.**Type of eruption:** ○ Macular ○ Papular ○ Exanthematous DE ○ Pustular (AGEP) ○ Vesicular ○ Bullous ○ Fixed ○Generalized fixed DE ○ Urticarial ○ Vaculitic ○Lichenoid ○Acneiform ○ Psoriasiform ○Lymphomatoid ○ Erythrodermic ○ Angioedema ○ Others i. **Clinical diagnosis**:
Biopsy	●Site: ● No.: ● Date: ○ 24hrs ○48hrs ○72hrs ○Others ○Refused ● **Result:**

CADRs: cutaneous adverse drug reactions, TEN: toxic epidermal necrolysis

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Table 2. Classification of cutaneous adverse drug reactions (CADRs) into severe and non-severe types

Severe CADRs	1. Steven-Johnson syndrome and Toxic epidermal necrolysis 2. Generalized bullous fixed drug eruption 3. Acute generalized exanthematous pustulosis 4. Drug reaction with eosinophilia and systemic symptoms 5. Anaphylaxis
Non-severe CADRs	1. Exanthematous or maculo-papular drug eruption 2. Fixed drug eruption 3. Angioedema and urticarial drug eruption 4. Erythema multiforme 5. Psoriasiform drug eruption 6. Lichenoid drug eruption 7. Vasculitic drug eruption 8. Acneiform drug eruption 9. Hyperpigmentation and ochronosis 10. Cutaneous lymphoid hyperplasia 11. Erythrodermic drug reaction

patients. The primary incidence of reported CADRs in our study was 0.28%. They included 78 patients, 29 men (37.1%) and 49 women (62.8%) with a male to female ratio of 1:1.69. Ages ranged from 18-80 years of age with a mean of 41.7±14.84 years (mean ± SD). A comparison of the demographic parameters in both severe CADRs and other non-severe types of CADRs regarding sex, age, education, occupation, and total number of patients showed no statistically significant difference (P-value >0.05).

Types of CADRs

The most common CADRs in our study were SJS/TEN (15.3%) and lichenoid drug eruptions (15.3%), followed by exanthematous drug eruptions (14.1%) and vasculitic drug eruptions (11.5%) as shown in Figure 1.

The most common drug category in each type of CADRs (Table 5)

There were 40 patients (51.0%) who could not recall the name of the drug, while 38 patients (48.7%) could recall the name of the drug. The most common drug incriminated in patients with CADRs was ibuprofen (7.7%), followed by penicillin (5.1%) and aspirin (3.9%). Antibiotics were the most common drug category causing SJS/TEN, exanthematous drug eruptions, and urticarial drug eruption. Analgesics were the most common incriminated drug category causing fixed drug reactions (FDEs), lichenoid drug eruptions, and vasculitic drug eruptions. Anticonvulsants were the most common incriminated drug category causing psoriasiform drug eruption.

Duration of drug intake, duration between initiation of the drug and onset of the reaction, and the duration of the eruption (Table 6)

A comparison of the duration of drug intake, duration between initiation of the drug and onset of the reaction, and the duration of the eruption in severe CADRs versus other non-severe types of CADRs showed a statistically significant longer duration in other non-severe types of CADRs (P-value = 0.008, 0.040, and 0.010 respectively).

Other related parameters

A comparison of the route of administration and the nature of medication taken in severe versus other non-severe types of drug reactions showed no statistically significant difference. A comparison of the disease course regarding previous attacks, responsible drug probability, re-challenge, de-challenge, course of the eruption, and course of the eruption after withdrawal of the offending drug in severe types of CADRs versus other non-severe types of CADRs, showed no statistically significant difference. A comparison of the associated risks regarding family history of hypersensitivity syndrome, past medical history, and associated diseases in severe CADRs versus other non-severe types of CADRs showed no statistically significant difference.

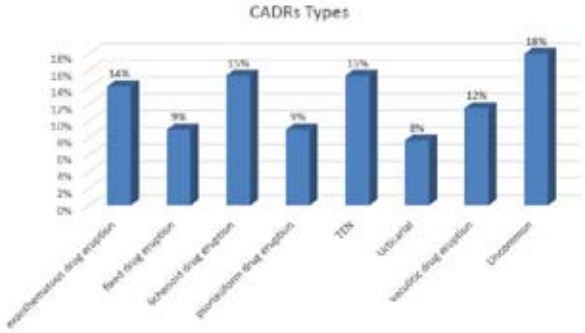

Figure 1. Different types of cutaneous adverse drug reactions (CADRs) in our study.
*TEN: toxic epidermal necrolysis

Table 3. Clinical and histopathological criteria of cutaneous adverse drug reaction (CADRs) (10-12)

	Type of drug eruption	Clinical criteria	Histopathological criteria
Severe CADRs	Steven-Johnson syndrome and Toxic epidermal necrolysis	-Timing after drug intake: 7–21 days -Type of skin lesions: Dusky and/or dusky-red macules with epidermal detachment and erosions, macular atypical targets, bullous lesions, 10->30% BSA detachment -Distribution: trunk, face, neck, elsewhere -Mucosal involvement: severe -Systemic manifestations: fever, lymphadenopathy, hepatitis, cytopenias, nephritis	Variable epidermal apoptosis associated with basal cell hydropic degeneration or subpidermal vesiculation. A little superficial perivascular infiltrate predominantly lymphocytic with melanophages and few eosinophils.
	Generalized bullous fixed drug eruption	-Timing after drug intake: 1st exposure: 1-2 weeks, re-exposure: <48 hours -Type of skin lesions: generalized erythematous edematous plaques are seen, sometimes they have a dusky violaceous hue developing vesiculobullae and become erosive, and upon readministration of the causative drug, lesions recur in exactly the same sites. -Distribution: anywhere -Mucosal involvement: numerous mucocutaneous lesions	In acute lesions: Marked basal hydropic degeneration with lymphocyte tagging along the dermoepidermal junction and individual keratinocyte necrosis. Marked pigmentary incontinence is a typical feature. Subepidermal vesiculation in advanced cases. Lymphocytes, histiocytes and neutrophils are evident in the superficial dermis and may be some eosinophils.
	Acute generalized exanthematous pustulosis	-Timing: < 4 days -Type of skin lesions: numerous small, non-follicular sterile pustules; can coalesce leading to large areas of exfoliation -Distribution: beginning on the face or in the major intertriginous zones (i.e. axillae and groin), followed by dissemination over a few hours. -Systemic manifestations: high fever, peripheral neutrophilia -Mucosal involvement: in 50% of patients	Subcorneal and or intraepidermal pustule full of neutrophils and few acantholytic cells. Spongiosis, edematous dermal papillae and may be subepidermal vesiculation. A perivascular infiltrate of lymphocytes, histiocytes, many neutrophils and may be eosinophils. Leukocytoclastic vasculitis in advanced lesions.
	Drug reaction with eosinophilia and systemic symptoms	-Timing: 1-40 days -Type of skin lesions: widespread erythema, vesiculobullae and pustules, facial edema (hallmark of DRESS), maculopapular rash developing >3 weeks after starting therapy, prolonged clinical symptoms after discontinuation of the causative drug -Distribution: generalized -Systemic manifestations: peripheral eosinophilia (>1.5 × 109/L), fever (>38 °C), liver abnormalities, leukocyte abnormalities (leukocytosis, atypical eosinophilia), lymphadenopathy and HHV-6 reactivation, nephritis, myocarditis, interstitial pneumonitis, myositis, thyroiditis -Mucosal involvement: mild if present	Pathological features are non-specific according to the type of skin lesions.
Non- severe CADRs	Anaphylaxis	-Timing: within minutes -Type of skin lesions: combines skin signs of urticaria and/or angioedema, may be absent -Distribution: generalized -Systemic manifestations: hypotension and tachycardia, even cardiovascular shock -Mucosal involvement: severe edema	Urticaria: Variable dermal edema and sparse perivascular and interstitial mixed inflammatory infiltrate composed of lymphocytes, neutrophils, and eosinophils.

Non-severe CADRs	Exanthematous drug eruption	-Timing: 4-14 days -Type of skin lesions: symmetrically distributed pruritic erythematous macules, papules, and/or urticarial lesions -Distribution: initially on the trunk and upper extremities; over time they can become confluent -Systemic manifestations: low grade fever -Mucosal involvement: spared	Normal epidermis or commonly focal parakeratosis is seen. The characteristic changes include mild spongiosis with lymphocyte exocytosis associated with basal cell liquefactive degeneration and few dyskeratotic cells. Perivascular infiltrate of lymphocytes, histiocytes and variable eosinophils.
	Fixed drug eruption	-Timing after drug intake: first exposure: 1-2 weeks, re-exposure: <48 hours -Type of skin lesions: one or a few, round to oval, sharply demarcated, erythematous edematous plaques are seen, sometimes they have a dusky violaceous hue or develop vesiculobullae and become erosive, often leave residual postinflammatory brown pigmentation; lesions recur in exactly the same sites upon readministration of the causative drug -Distribution: anywhere -Mucosal involvement: usually affected	In acute lesions: Marked basal hydropic degeneration with lymphocyte tagging along the dermoepidermal junction and individual keratinocyte necrosis. Marked pigmentary incontinence is a typical feature. Subepidermal vesiculation in advanced cases. Lymphocytes, histiocytes, and neutrophils are evident in the superficial dermis and may be some eosinophils.
	Angioedema and urticarial drug eruption	-Timing: minutes to hours -Type of skin lesions: transient, often pruritic, erythematous and edematous papules and plaques angioedema is acute, asymmetric, pale or pink, subcutaneous swelling involving the face -Distribution: anywhere on the body, including the palms, soles, and scalp -Systemic manifestations: stridor if severe, abdominal pain, nausea, vomiting, and diarrhea -Mucosal involvement: in angioedema	Urticaria: Variable dermal edema and sparse perivascular and interstitial mixed inflammatory infiltrate composed of lymphocytes, neutrophils, and eosinophils.
	Erythema multiforme	-Type of skin lesions: typical targets, papular atypical targets, occasionally bullous lesions -Systemic manifestations: fever, arthralgias -Mucosal involvement: present	Combination of basal cell hydropic degeneration and keratinocyte apoptosis. The dermis shows heavy superficial lymphohistiocytic infiltrate associated with lymphocytic exocytosis and satellite cell necrosis.
	Psoriasiform drug eruption	-Type of skin lesions: from limited or generalized psoriatic plaques to erythroderma and pustulosis -Distribution: anywhere, the palms and soles, nail changes and scalp involvement may also be observed.	The histological features overlap lichen simplex chronicus and psoriasis or may just be indistinguishable from psoriasis vulgaris.
	Lichenoid drug eruption	-Timing: latent period of several months -Type of skin lesions: lichen planus-like but more eczematous, or pityriasis rosea-like -Distribution: generalized and symmetric; often spares the "classic" sites of lichen planus, frequent photodistribution -Mucosal involvement: usually spared	Histological features are indistinguishable from typical lichen planus plus focal parakeratosis and spongiosis. The epidermis is often thinner and hypergranulosis is less evident. Cytoid bodies are seen high up in the epidermis.

Non-severe CADRs	Vasculitic drug eruption	-Timing: 7 to 21 days -Type of skin lesions: purpuric papules, urticaria-like lesions, hemorrhagic blisters, pustules, digital necrosis, and ulcers -Distribution: primarily on the lower extremities -Systemic involvement: is very unusual but may be fever, myalgias, arthralgias, and/or headache, arthritis, nephritis, peripheral neuropathy, and gastrointestinal bleeding.	Histological features of leukocytoclastic vasculitis.
	Acneiform drug eruptions	-Type of skin lesions: papules and/or pustules -Distribution: primarily on the face and upper trunk, the same sites favored by acne	Histological features of acne vulgaris.
	Hyperpigmentation and ochronosis	-Timing: over months or years -Type of skin lesions: purple, yellow or blue-gray cutaneous hyperpigmentation, blue-black dermal discoloration 2ry to prolonged use of skin bleaching creams containing hydroquinone in ochronosis -Distribution: sun-exposed areas -Mucosal involvement: possible	Histological features depend on detection of the incriminated pigment (according to its type) either within the epidermis (melanin pigment) or within the macrophages in the dermis.
	Cutaneous lymphoid hyperplasia	-Timing: over a period of months or even years -Type of skin lesions: erythematous to violet papules, plaques, or nodules -Distribution: localized or generalized -Systemic involvement: often associated lymphadenopathy	Dense superficial perivascular or band-like infiltrate composed of lymphocytes, histiocytes, eosinophils, and atypical lymphoid cells with irregular enlarged and hyperchromatic nuclei. Epidermal spongiosis is also seen.
	Erythrodermic drug reaction	-Timing: variable -Type of skin lesions: erythema and peeling scaling -Distribution: >80-90% of the skin surface -Systemic involvement: peripheral lymphadenopathy hypoalbuminemia, facial edema, thermoregulatory disturbances, and hepatomegaly	Non-specific features. Parakeratosis, psoriasiform hyperplasia and variable mild spongiosis. Dermal chronic inflammatory cell infiltrate with variable eosinophils.

DISCUSSION

The primary incidence of CADRs calculated in this study was 0.28% (78 patients with CADRs) from a total number of 27,093 outpatients attending the Dermatology clinic in Kasr El Aini, Cairo University, in a period of 6 months.

Similar studies performed among outpatient dermatology clinics were limited in number and reported variable incidence rates with variable duration (13). Indian studies, such as those by Chatterjee *et al.* (14) and Saha *et al.* (2), reported an incidence of

Table 4. Number of patients and their percentages of different types of CADRs detected in our study:

CADRs	Percentage	Number of Patients
SJS/TEN‡	15.39%	12
Lichenoid Drug Eruption	15.39%	12
Exanthematous Drug Eruption	14.10%	11
Vasculitic Drug Eruption	11.54%	9
Fixed Drug Eruption	8.97%	7
Psoriasiform Drug Eruption	8.97%	7
Urticarial Drug Eruption	7.69%	6
Uncommon Types	17.95%	14

‡TEN: toxic epidermal necrolysis

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Table 5. The most common drug category in each type of cutaneous adverse drug reaction (CADR)

CADRs	Category	Number of patients	Percentage
Exanthematous drug eruption	Antibiotics	6	54.50%
Fixed drug eruption	Analgesics	6	85.70%
Lichenoid drug eruption	Analgesics	11	91.70%
Psoriasiform drug eruption	Anticonvulsants	3	42.90%
TEN‡	Antibiotics	6	50.00%
Urticarial drug eruption	Antibiotics	4	66.70%
Vasculitic drug eruption	Analgesics	4	44.40%
Uncommon	Antibiotics	5	35.70%

‡TEN: toxic epidermal necrolysis

2.6% (739 patients among a total number of 27,726 patients) and 0.28% (72 patients among a total number of 25,773 patients) of CADRs, respectively, over one year. In 2015, Qayoom *et al.* (15) reported a low incidence of 0.16% (92 patients), also over year, among a total of 48,238 patients attending the dermatology outpatient clinic in Kashmir Valley, India, whereas Talib *et al.* (16) reported an incidence of 0.2% (134 patients) in a retrospective one-year study in Malaysia among a total of 69,849 patients attending the dermatology outpatient clinic. The low incidence rate of CADRs in our study can be explained by the fact that Kasr El Aini is a tertiary care unit and receives the most complicated cases, while minor drug reactions and self-limiting cases often go unreported as they can be easily managed in the primary care unit. Comparable or even higher incidence of CADRs was reported among inpatients. Charli-Joseph *et al.* (17) reported an incidence of 2%-3% among inpatients. These rates among inpatients could be explained by the multiple drugs used and the underlying illness and co-morbidities among hospitalized patients.

The mean age of patients with CADRs in our study was 41.7±14.84 years, which is relatively high compared with other studies (2,6,14,16). Two similar Indian studies (15,18) reported similar results, with a mean age of 37±30.12 and 39.6±16.77, respectively. In our study, there was a female predominance with a male:female ratio of 1:1.69. In contrast, Chatterjee *et al.* (14) reported a male predominance with a male: female ratio of 1:0.87. This difference in the demographic profile can be explained by the difference in the demography of the patients, as there was a female predominance among the total patients attending the clinic.

The most common drug reaction patterns reported in our study were SJS/TEN (15%) and lichenoid drug eruptions (15%). Two studies conducted in Malaysia (6,16) reported that SJS/TEN was the second most common type of drug reaction (9.7%). In contrast, most studies reported that exanthematous drug eruption was the most common drug reaction (2,16,19).

A high incidence of SJS/TEN has been reported in Indian studies (18,20,21), while Western studies (22) reported the occurrence of SJS/TEN as a rarity. This might reflect the close surveillance, monitoring, and reporting of any drug reaction in the Western health systems, with the tendency to withdraw any suspected drugs even in cases of minor skin reactions.

Very few studies highlighted the time lag between the initiation of the drug intake and the onset of the reaction as in our study. In our study, the mean time of onset was 10 days, with a minimum duration of one day and maximum duration of 365 days. In 2015, Talib *et al.* (16) reported a mean of duration of 2 weeks, with a minimum duration of 5 minutes and a maximum duration of 120 days. This wide range of variation may be due to total dependence patient self-reports (which may lack accuracy depending on the educational level of the patient), as the patient history was our main reference in the outpatient dermatology clinic, unlike hospitalized patients where a medical record is available, which includes the exact time of administered drugs, dosages, and drug forms.

In our study, we compared the duration of drug intake, the duration between initiation of drug and onset of the reaction, and the duration of the eruption in severe CADRs versus other non-severe types of CADRs, all of which had a statistically significantly longer duration in other non-severe types of CADRs. On reviewing the literature, no similar studies comparing these data in severe CADRs versus other non-severe types were found; this may be due to the natural course of the severe CADRs which require prompt intervention to lower mortality in addition to causing severe morbidity.

Severe CADRs comprised 19.2% of total CADRs in our study, which was similar to other studies performed in Malaysia that showed a slightly higher rate

Table 6. Comparison between severe cutaneous adverse drug reactions (CADRs) and other non-severe types of drug eruptions regarding the interval (duration) of drug intake, duration between initiation of drug, and onset of the reaction and duration of the eruption

Duration Parameters											P-value*
	Severe CADRs					Other non-severe types of CADRs					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Duration of drug intake (days)	7.20	6.39	5.00	1.00	20.00	8.76	9.79	7.00	1.00	545.00	0.008
Duration between initiation of drug and onset of eruptions (days)	9.07	6.11	7.00	2.00	21.00	3.95	3.46	10.00	1.00	365.00	0.040
Duration of the eruption (days)	8.60	5.04	7.00	3.00	21.00	3.62	7.63	10.00	1.00	365.00	0.010

**P-value (significant if <0.05); SD: standard deviation*

of 24.5% (16). This high percentage may be attributed to referral of most of the severe CADRs to our dermatology clinic as they could not be managed in a primary care unit, while minor rashes could be treated by other health care facilities.

The most common implicated groups of drugs causing CADRs in our study were NSAIDs (19.22%), antimicrobials (16.6%), and anticonvulsant drugs (6.4%). These percentages were lower than other studies, which reported that antimicrobials (57.33%), NSAIDs (21.3%), and anticonvulsant drugs (17.33%) represented the majority of the offending drugs (15). These low percentages in our study in comparison with other studies may be attributed to the high percentage of patients (51.28%) who could not recall the name of the incriminated drug.

Among NSAIDs, ibuprofen was the most common implicated drug causing CADRs in our study, which was similar to the study by Chattopadhyay and Chakrbart (23) that reported ibuprofen as the second most common implicated NSAID causing CADRs, following diclofenac. However, this is in contrast to Qayoom *et al.* (15), who reported piroxicam followed by diclofenac as the most common NSAIDs causing CADRs.

Among antimicrobials in our study, beta-lactam antibiotics were the most common category of drugs causing CADRs (10.26%), followed by sulfonamides (2.56%) and quinolones (2.56%). This is in contrast to Qayoom *et al.* (15), who reported quinolones as the most common antimicrobial causing CADRs. In addition, a 6-year study from Chandigraph, India and a multicenter analysis from Italy reported sulfonamides as the most common implicated drugs causing CADRs (24,25).

Phenytoin (2.56%) and carbamazepine (1.28%) were the most common drugs among the anticonvulsant group of drugs causing CADRs in our study. This was found to be similar to several previous studies (14,15,18,25). Other implicated anticonvulsants in our study were lamotrigine (1.28%) and carbamazepine (1.28%).

CONCLUSION

It is notable that the incidence of CADRs in our study was similar to incidences reported in different countries but the incidence of life-threatening reactions like SJS/TEN was higher compared with studies conducted abroad.

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