ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Dermatological adverse drug reactions with particular reference to Steven-Johnson syndrome and toxic epidermal necrolysis

Muddasir Sharief Banday[1], Sajad Ahmad Rather[2], Samina Mufti[3], Sabia Qureshi[4]

[1]Assistant Professor, Department of Clinical Pharmacology, [2]Assistant Professor, Department of Radiological Physics and Bioengineering, [3]Assistant Professor, Department of Hospital Administration, Sheri Kashmir Institute of Medical Sciences, Soura, Jammu and Kashmir, India, [4]Professor, Division of Veterinary Microbiology and Immunology, Faculty of Veterinary Sciences and Animal Husbandry, SKUAST Kashmir, Srinagar, Jammu and Kashmir, India

Submission: 19-09-2022 Revision: 26-11-2022 Publication: 01-01-2023

ABSTRACT

Background: Drug therapy is an inevitable cause of cutaneous adverse reactions. **Aims and Objectives:** The primary aim was to identify the incidence and magnitude of various dermatological adverse reactions including Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Moreover, secondary aim was to quantify the risks associated with the use of specific medications. **Materials and Methods:** A prospective and hospital-based study was conducted in the department of dermatology SMHS hospital on hospitalized cases of cutaneous adverse drug reactions (CADRs). Informed consent was sought and reactions were reported on validated questionnaire based on adverse drug reaction (ADR) monitoring form provided by Central Drug Standard Control organization Ministry of Health and Family Welfare, Government of India. These dermatological reactions were assessed for the clinical pattern, causative agents, and prognosis. The WHO-Uppsala Monitoring centre system for standardized case was used for causality assessment of all cases identified. **Results:** A total of 101 hospitalized patients with varied dermatological ADRs were reported during the study period. Cases were found more in females (n = 75, 74.25%) than in males (n = 26, 25.75%). CADRs that were reported in our study were exanthematous rash, fixed drug eruptions, urticarial rashes, SJS, TEN, urticarial vasculitis, anticonvulsant hypersensitivity syndrome, erythema multiforme, contact dermatitis, exfoliative dermatitis, mucosal hyperpigmentation, and nail pigmentation, respectively. After a meticulous drug history, the drugs implicated in causing the cutaneous reactions were anticonvalscents such as phenytoin, carbamazepine, lamotrigine, and phenobarbitone. Other drugs identified were non-steroidal anti-inflammatory drugs such as oxicam, antibiotics such as sulfasalazine, cefixime, cefpodoxime, amoxicillin, fluoroquinolones such as levofloxacin and ciprofloxacin, chemotherapeutic agents such as cyclophosphamide, 5FU, and hydroxurea. **Conclusion:** The present study concluded that skin is most common target for ADRs. Drug-induced cutaneous reactions can be as simple as a mild rash to rare life-threatening SJS and TEN. Moreover, certain group of patients is at increased risk for developing CADR's as women are more susceptible than men.

Key words: Steven-Johnson syndrome; Toxic epidermal necrolysis; Cutaneous adverse drug reactions

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v14i1.48506

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

The drugs which have ability of producing desired therapeutic effect have equally a potential to cause unwanted adverse effects. Dermatological manifestations are among the most frequent reactions to drugs.[1] Cutaneous adverse drug reactions (CADRs) comprise of approximately 3% of hospital admissions. These cases represent 2% of dermatological consultations.[2] CADRs range from being mild which usually disappear after

Address for Correspondence:
Dr. Muddasir Sharief Banday, Assistant Professor, Department of Clinical Pharmacology, Sheri Kashmir Institute of Medical Sciences, Srinagar - 190 011, Jammu and Kashmir, India. **Mobile:** +91-9149505159. **E-mail:** banday.muddasir@gmail.com

stopping the culprit drug others are life-threatening such as Steven-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) and last longer. Reactions usually take 4 weeks after initiation of therapy.[3] Both SJS and TEN are mucocutaneous diseases which show extensive keratinocyte cell death with a separation of significant areas of skin at the dermal - epidermal junction producing appearance of scalded skin. The cell death results in mucous membrane detachment and is associated with high fever, severe skin pain, anxiety, and asthenia. Globally, SJS and TEN show an annual incidence of 1.2–6 and 0.4–1.3 per million population, respectively. Females are effected more frequently than males with a ratio of 1.5–1 and incidence increases with age, previous history of adverse drug reactions (ADR's), immunocompromised, and those on radiotherapy.[4-7] Certain infectious diseases especially AIDS have a direct association with the incidence of SJS and TEN where the incidence is approximately 1000-fold higher than in general population.[8] The overall mortality associated is 5–12% for SJS to more than 25% for TEN. The high risk medication implicated is aromatic anticonvulsants, antibacterial sulfonamides, allopurinol, oxicam Non-steroidal anti-inflammatory drug (NSAIDs), quinolones, and aminopencillins[9-14] A prospective study was undertaken with an objective to assess and estimate the risk and burden of CADRs associated with use of various medications in our ethnic populations. The patients were also followed up to assess the complications and sequelae associated with these reactions.

Aims and objectives

The primary aim was to identify the incidence and magnitude of various dermatological adverse reactions including SJS and TEN.

MATERIALS AND METHODS

A prospective study was conducted by the department of pharmacology and in-patient department of dermatology in SMHS, tertiary care multispecialty hospital associated with Government Medical College, Srinagar, India. The study included a wide variety of CADRs ranging from urticarial rashes to a rare potentially fatal adverse cutaneous drug reactions of differing severity such as SJS and TEN. The study was conducted after an approval from the Institutional Ethical Committee vide No.GMC-IEC-2019–20/pharma. After seeking the informed consent from the participant's questionnaire was used to fulfill the requisite details of the patient including the definite antecedent drug history. Questionnaire was based on suspected ADR reporting form provided by the Central drug standard control organisation Ministry of Health and Family Welfare, Government of India. Information related to drugs, medical history, previous ADR's, if any, history of present illness, relevant laboratory parameters were all recorded in the questionnaire. Patients with pre-existing chronic liver disease, chronic renal failure, and HIV-positive patients were excluded from the study. Causality assessment was performed using Naranjo scored algorithm.[15] It comprises of 10 questions with a particular score based on presence or absence of criteria laid down in the scale. On the basis of scoring system, the causality was classified as definite (≥9), probable (5–8), possible (1–4), or doubtful (≤0). To enhance the reliability and precision of study, a more dependable (WHO-Uppsala Monitoring centre) system[16] was also applied. Combination of two tools has helped to overcome limitations ascribed with an individual method. Patients identified as SJS/TEN were evaluated for severity of illness by a prognostic scoring system SCORTEN in which seven parameters with equal weight have been integrated so as to make it possible to predict outcome[8,17] (Table 1).

RESULTS

In the present study, 101 patients were identified as CADR's with 74.25% of female and 25.75% of males. Patients were seen in all age groups and maximum patients were seen in age group 21–40 years. Table 2 depicts the age and gender distribution of participants in the study. Our prospective study evaluated various types of

Table 1: Scorten: A prognostic scoring system for patients with epidermal necrosis

Prognostic factors	Points
Age >40 years	1
Presence of malignancy/ hematological malignancy	1
Epidermal Detachment >30%	1
Heart rate >120/min	1
Bicarbonate <20 mmol/L	1
Urea >10 mmol/L	1
Glycaemia >14 mmol/L	1
Scorten	Probability of death (%)
0–1	3
2	12
3	35
4	58
≥5	90

Table 2: Age and gender distribution of the participants of the study

Age group	Males	Females	N=101
0–10	2	3	5
11–20	5	14	19
21–30	6	18	24
31–40	8	21	29
41–50	2	9	11
51–60	2	8	10
61 and above	1	2	3

CADR's and the commonly found were exanthematous drug eruptions, Fixed drug eruptions (FDE), urticariasis, SJS, TEN, urticarial vasculitis, erythema multiforme, anticonvulsant hypersensitivity syndrome, contact dermatitis, exfoliative dermatitis, hyperpigmentation of mucosa, and nails.

Table 3 shows drug reactions reported during the study period. Exanthematous or morbilliform eruptions were found in 24.75% of patients. This was followed by FDE (17.8%) and urticarial reactions (14.8%). SJS and TEN which are rare acute and life-threatening mucocutanoeus diseases were also reported. SJS was found in 11 (10.8%) and TEN in 8 (7.9%) patients. TEN was diagnosed in females only. It was noted that these events were due to exposure of some frequently implicated drugs such as aminopencillins, sulphonamides, fluoroquinolones (ciprofloxacin, levofloxacin, and ofloxacin) NSAID's (oxicam and ibuprofen), antiepileptics such as phenytoin (PHT), carbamazepine, lamotrigine (LTG), and valproic acid (VA). Hyperpigmentation has been observed in some patients on cyclophosphamide.

The study showed that the time interval to develop SJS/TEN was within 8–21 days after initiation of aromatic anticonvulsant drug or LTG. No mortality was seen in any of the CADRs including SJS/TEN. Figure 1 represents the average time between initiation of the drug and the onset of the severe CADR's. The offending drug should be withdrawn as soon as possible. The usual practice should be to discontinue all drugs that are non-essential.

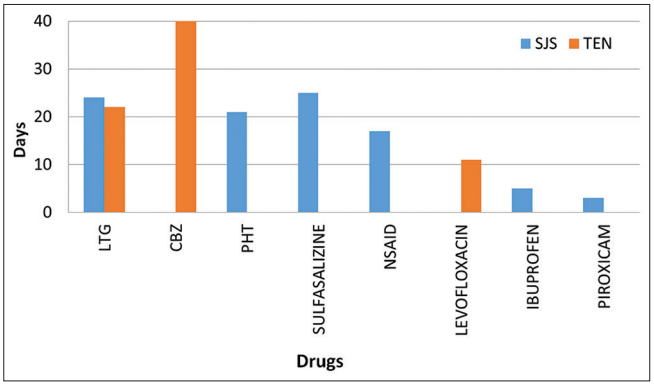

Figure 1: Drug-induced severe cutaneous adverse drug reactions (SJS and TEN) and days to onset (LTG: Lamotrigine, CBZ: Carbamazepine, PHT: Phenytoin, NSAID: Non-steroidal anti-inflammatory drug)

Ophthalmological sequel such as symblepharon and conjunctival syncytia entropion, cutaneous scarring was seen in two patients of TEN (Table 4).

DISCUSSION

The results of our study reveals that female was affected more than males. The age group with high frequency of CADRs was seen between 21 and 40 years. Exanthematous drug eruptions were seen as the most common ADR affecting the skin. The reactions usually occur at a time interval of 4–14 days after the initiation of the therapy. It presents a generalized maculopapular eruption with bilateral distribution symmetrically involving trunk and extremities. In our study, 18 cases of FDE's were reported. The lesions usually develop 1–2 weeks after a first exposure. With subsequent exposure, these appear with 29 h. These are extensively drug-induced reaction with round sharply demarcated erythematous and cutaneous plaques.[18] Relatively rare and potentially fatal adverse cutaneous drug reactions SJS and TEN were reported in 11 (10.8%) and 8 (7.9%) patients, respectively. These were characterized by mucocutaneous tenderness, erythema, and extensive exfoliation. In the present study, TEN was seen only in females and SJS in three males and eight females. This goes in conformity with other studies where females are at higher risk than males after initiation of medication and development of severe CADRs.[4-7] Some high risk medications frequently associated with SJS/TEN are aromatic anticonvulsansts, LTG, NSAID's, allopurinol, aminopencillins, sulfasalazine, and quinolones.[6,12,19,20] In the present study, the most common culprit drug which

Table 3: CADRs observed in the study subjects

S. No	Type of cases	Males	Females	n=101 (% age)
1	Maculopapular drug eruption	6	19	25 (24.7)
2	FDE	5	13	18 (17.8)
3	Urticarial reactions	6	9	15 (14.8)
4	SJS	3	8	11 (10.8)
5	TEN		8	8 (7.9)
6	Urticarial Vasculitis		2	2 (1.9)
7	Anticonvulsant hypersensitivity syndrome	2	4	6 (5.9)
8	Erythema multiforme		4	4 (3.9)
9	Contact dermatitis		4	4 (3.9)
10	Exfoliative dermatitis	1	4	5 (4.9)
11	Mucosal hyperpigmentation	1		1 (0.9)
12	Nail hyperpigmentation	2		2 (1.9)

FDE: Fixed drug eruption, SJS: Steven-Johnson syndrome, TEN: Toxic epidermal necrolysis

Table 4: Characteristic of 19 cases of SJS and TEN with different drug therapies

S. No.	Age/ Sex	Drug therapy	Dose	Indications	Days to onset	Concomitant drug therapy	Cutaneous manifestation
1	36/F	Lamotrigine (LTG)	12.5 mg/day Initially F/b 25 mg/day, and 50 mg/day	Seizures with BPAD	21	Aripiprazole 10 mg/day Sodium valproate (600 mg/ day) Etizolam (0.5 mg/day) Propanolol (40 mg/day)	SJS
2	57/F	LTG	25 mg/day for week Then 50 mg/day second week Increased to 100 mg/day	BPAD	17	Metoprolol SR 50 mg/ day Olmesartan 20 mg/ day Rosuvastatin 5 mg/ day Quetiapine 25 mg/ day Clopidogril 75 mg/day Aspirin 150 mg/day	SJS
3	32/F	LTG	25 mg/day	BPAD with depression	15	Paroxetine 25 mg Clonezepam 0.5 mg/day	TEN
4	34/F	CBZ	400 mg/day,	Trigeminal Neuralgia	13	Aceclofenac -100 mg/day	TEN
5	62/M	PHT	300 mg/day	OLE Post-traumatic epilepsy	12	Gabapentin 400 mg/ day Nortriptyline 10 mg/ day Citicoline 500 mg/ day Piracetam 400 mg/day Vitamin B complex	SJS
6	27/M	NSAID	NA	Ankylosing spondylitis	17	Thiocholchicoside 8 mg/day	SJS
7	54/F	Levofloxacin	750 mg/day	UTI	13	Amikacin i.v	TEN
8	63/F	Piroxicam	40 mg, i/m stat	LBA	3	None	SJS
9	28/F	Ibuprofen	1200 mg/day for 2–3 days	Osteoarthritis	5	Paracetamol 1000 mg/day	SJS
10	25/F	Levofloxacin	500 mg/day i.v infusion F/b Levofloxacin 500 mg/day Cefpodoxime 400 mg/day for 5 days	RTI	8	None	TEN
11	52/F	Piroxicam	40 mg, i/m stat	LBA	3	None	SJS
12	36/F	Sulfasalazine (delayed release form)	1000 mg/day for month	Rheumatoid arthiritis	25	Aceclofenac 100 mg/day Thiocholchicoside 4 mg/ dayMtx 7.5 mg/day	SJS
13	55/F	LTG	Initially 50 mg/day F/b 100 mg/day after week	GTCS	30	Valproaic acid 1200 mg/day Levothroxine 75 mcg/day	TEN
14	22/F	CBZ	Initially CBZ CR 400 mg/day F/b CBZ CR 600 mg/day	GTCS	45	None	TEN
15	18/F	CBZ/PHT	Initially PHT 300 mg/day for 1 month Then CBZ-SR 200 mg/day for 3 day F/b CBZ SR 600 mg/day	GTCS	60	None	TEN
16	24/F	PHT	PHT 300 mg/day	Focal epilepsy	30	ATT	SJS
17	33/F	LTG	25 mg/day F/b 50 mg/day	BPAD	25	Aripiprazole 5 mg	SJS
18	45/M	LTG	25 mg/day	BPAD	17	Clonazepam 0.5 mg	SJS
19	36/F	LTG	50 mg/day F/b 100 mg/day	GTCS	21	Valproic acid 1200 mg/day Telmisartan 40 m/day	TEN

LTG: Lamotrigine, BPAD: Bipolar affective disorder, CBZ: Carbamazepine, PHT: Phenytoin, OLE: Occipital lobe epilepsy NSAID: Non-steroidal anti-inflammatory drug, UTI: Urinary tract infection. RTI: Respiratory tract infection, LBA: Low back ache, FDE: Fixed drug eruption, ATT: Antitubercular treatment, CR: Continous release, NA: Not available, F/b: Followed by GTCS : Generalized tonic clonic seizures

was implicated with four cases of SJS and three cases of TEN was LTG. LTG is a broad spectrum anticonvulsant and specifically indicated for depressive phases of maniac depressive psychosis. The reaction occurred in a time interval of 7–21 days after initiation of therapy. The findings are in conformity with other studies where short-term use of LTG shows association with SJS/TEN.[21-26] The offending antiepileptic drug was stopped and patients switched over to alternative medication such as levetiracetam and clobazam to maintain a better remission period. Until recently, the marked immune reactions due to medications in some individuals remained obscure. Now, it is apparent that an individual's response to a particular drug depends on a complex influence and interplay of environmental and genetic factors. Therefore, the importance of pharmacogenetics to variability in drug response had surfaced. The genetic associations are drug specific as HLA-B 1502 has association with SJS/TEN with offending drugs such as carbamazepine, PHT, and LTG.[27] Likewise HLA-B 5701 and HLA-B 5801 show association with abacavir hypersensitivity and allopurinol-induced severe drug reactions, respectively.

In view of an increasing understanding of these genetic variations, it is highly recommended that pharmacogenetics be put in clinical practice to choose among right drugs, doses, dosing regimens, and treatment protocols. One acceptable approach is "point of care testing" where genotyping be undertaken at time of drug prescription as screening measure for these HLA-B alleles in an ethnic population. These approaches of genotyping different variants of HLA-B have proven to eliminate the risk for fatal skin reactions like SJS/TEN.

Limitations of the study

The study was unicentric and impact on patients in terms of disease prognosis due to incriminated drugs could not be carried out in many health care institutions.

CONCLUSION

Dermatological adverse reactions are inevitable consequences of some medications. Some reactions cure spontaneously or require minimum treatment while others can be life-threatening if diagnosis is delayed or not treated vigorously. Therefore, the cornerstone to reduce these adverse events is judicious and appropriate use of drugs vis-a-vis reporting an adverse effect of a drug to pharmacovigilance center at an earliest. Education and awareness to the concerned patients as well as healthcare workers have tremendous role to play in prevention of cutaneous drug reactions.

ACKNOWLEDGMENT

The authors acknowledge Department of Dermatology, Government Medical College Srinagar, for their assistance in carrying out the research programme.

REFERENCES

1. Arndtka KA and Jick H. Rates of cutaneous reaction to drugs. A report from the Boston collaborative drug surveillance program. JAMA. 1976;235(9):918-923.
2. Caranasos GJ, May FE, Stewart RB and Cluff LE. Drug associated deaths of medical inpatients. Arch Int Med. 1976;136(8):872-875.
3. Shinkai K, Stern RS and Wintroub BU. Cutaneous drug reactions. In: Longo DL, Favei AS, Kasper DL, Hauser SL, Jameson JL and Loscalzo J, editors. Harrison's Principles of Internal Medicine. New York: Mc Graw Hill; 2012. p. 432-440.
4. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Flechet ML and Girre JP. Toxic epidermal necrolysis (Lyell syndrome): Incidence and drug aetiology in France, 1981-85. Arch Dermatol. 1990;126(1):37-42.
   https://doi.org/10.1001/archderm.126.1.37
5. Schopf E, Stühmer A, Rzany B, Victor N, Zentgraf R and Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome: An epidemiologic study from West Germany. Arch Dermatol. 1991;127(6):839-842.
   https://doi.org/10.1001/archderm.1991.01680050083008
6. Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: A population based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol. 1990;126(1):43-47.
7. Naldi L, Locati F, Marchesi L and Cainelli T. Incidence of toxic epidermal necrolysis in Italy. Arch Dermatol. 1990;126(8): 1103-1104.
   https://doi.org/10.1001/archderm.1990.01670320127028
8. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J and Wolkenstein P. SCORTEN: A severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149-153.
   https://doi.org/10.1046/j.1523-1747.2000.00061.x
9. Roujeau JC and Stern RS. Severe cutaneous adverse reactions to drugs. N Engl J Med. 1994;331(19):1272-1285.
   https://doi.org/10.1056/NEJM199411103311906
10. Stern RS and Chan HL. Usefulness of case report literature in determining drugs responsible for toxic epidermal necrolysis. J Am Acad Dermatol. 1989;21(2 Pt 1):317-322.
    https://doi.org/10.1016/s0190-9622(89)70176-6
11. Ruiz-Maldonado R. Acute disseminated epidermal necrosis Types 1, 2, and 3: Study of sixty cases. J Am Acad Dermatol. 1985;13(4):623-635.
    https://doi.org/10.1016/s0190-9622(85)70207-1
12. Guillaume JC, Roujeau JC, Revuz J, Penso D and Touraine R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). Arch Dermatol. 1987;123(9):1166-1170.
13. Correia O, Chosidow O, Saiag P, Bastuji-Garin S, Revuz J and Roujeau JC. Evolving pattern of drug-induced toxic epidermal necrolysis. Dermatology. 1993;186(1):32-37.
    https://doi.org/10.1159/000247299
14. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Steven-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995;333(24): 1600-1607.
    https://doi.org/10.1056/NEJM199512143332404
15. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmucol Ther. 1981(2);30(2):239-245
    https://doi.org/10.1038/clpt.1981.154
16. The Use of the WHO-UMC System for Standardised Case Causality Assessment. Available from: https://who-umc.org/media [Last accessed on 2018 Apr 06].
17. Trent JT, Kirsner RS, Romanelli P and Kerdel FA. Use of SCORTEN to accurately predict mortality in patients with toxic epidermal necrolysis in the United States. Arch Dermatol. 2004;140(7):890-892.
    https://doi.org/10.1001/archderm.140.7.890
18. Valeyrie-Allanore L and Roujeau JC. Dermatological adverse drug reactions. In: Andrews EB and Moore N, editors. Mann's Pharmacovigilance. 3rd ed., Ch. 32. Chichester: Wiley Blackwell; 2014. p. 503-511.
19. Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology. 2007;68(20):1701-1709.
    https://doi.org/10.1212/01.wnl.0000261917.83337.db
20. Chang DK and Shear NH. Cutaneous reactions to anticonvulsants. Semin Neurol. 1992;12(4):329-337.
    https://doi.org/10.1055/s-2008-1041189

21. Chaffin JJ and Davis SM. Suspected lamotrigine-induced toxic epidermal necrolysis. Ann Pharmacother. 1997;31(6):720-723. https://doi.org/10.1177/106002809703100609
22. Duval X, Chosidow O, Semah F, Lipsker D, Frances C and Herson S. Comment on: Lamotrigine versus carbamazepine in epilepsy. Lancet. 1995;345(8960):1301-1302.
23. Sterker M, Berrouschot J and Schneider D. Fatal course of toxic epidermal necrolysis under treatment with lamotrigine. Int J Clin Pharmacol Ther. 1995;33(11):595-597.
24. Fogh K and Mai J. Toxic epidermal necrolysis after treatment with lamotrigine (Lamictal). Seizure. 1997;6(1):63-65. https://doi.org/10.1016/s1059-1311(97)80055-6
25. Vukelic D, Bozinovic D, Tesovic G, Dobric I, Loncaric D, Knezović I, et al. Lamotrigine and toxic epidermal necrolysis. Dermatology. 1997;195(3):307. https://doi.org/10.1159/000245974
26. Page RL, O'Neil MG, Yarbrough DR 3rd and Conradi S. Fatal toxic epidermal necrolysis related to lamotrigine administration. Pharmacotherapy. 1998;18(2):392-398.
27. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia. 2008;49(12):2087-2091. https://doi.org/10.1111/j.1528-1167.2008.01719.

Authors Contribution:
MSB- Concept of the study and data collection; **SAR-** Data analysis and methodology; **SM-** Manuscript writing and editing; and **SQ-** Interpreted the results and reviewed the manuscript preparation.

Work attributed to:
Sheri Kashmir Institute of Medical Sciences, Soura - 190 011, Jammu and Kashmir, India and Government Medical College Srinagar, Jammu and Kashmir, India.

Orcid ID:
Dr. Sajad Ahmad Rather - https://orcid.org/0000-0002-8676-6132
Dr. Samina Mufti - https://orcid.org/0000-0003-0683-7808
Dr. Sabia Qureshi - https://orcid.org/0000-0002-7731-3334

Source of Funding: Nil, **Conflicts of Interest:** None declared.