Review Article
Journal of Epilepsy Research
pISSN 2233-6249 / eISSN 2233-6257

Cutaneous Adverse Drug Reactions to Antiseizure Medications

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Discontinuation of antiseizure medications (ASMs), primarily prompted by adverse effects, presents a formidable challenge in the management of epilepsy, and impacting up to 25% of patients. This article thoroughly explores the clinical spectrum of cutaneous adverse drug reactions (cADRs) associated with commonly prescribed ASMs. Ranging from mild maculopapular rashes to life-threatening conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the diverse manifestations are meticulously detailed. Diagnostic strategies, incorporating red flags and testing methodologies, are elucidated to ensure precise identification. The classification of adverse drug reactions (ADRs), with a specific focus on cADRs and their association with type A or type B reactions, is presented. Critical risk factors, encompassing patient demographics, drug-related skin reactions, and genetic predispositions, are thoroughly explored. The article underscores the role of human leucocyte antigen (HLA), including HLA*15:02, in predicting susceptibility to severe reactions like SJS/TEN, particularly with aromatic ASMs prevalent in specific populations. Management strategies for varying cADR severities are discussed, placing emphasis on drug discontinuation, symptomatic relief, and potential desensitization. The article concludes by consolidating current knowledge, providing clinicians with a roadmap for navigating the complexities of diagnosis and management. The integration of personalized medicine principles and evidence-based approaches emerges as a crucial paradigm for the future of epilepsy management, aiming to minimize the impact of ADRs on patient outcomes. **(2024;14:53-58)**

Key words: Anticonvulsants, Epilepsy/drug therapy, Skin diseases/drug therapy, Stevens-Johnson syndrome, Toxic epidermal necrolysis, HLA antigens/genetics

Received May 9, 2024
Revised May 31, 2024
Accepted June 2, 2024

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Introduction

Adverse effects present a significant challenge in the management of epilepsy, often leading to treatment discontinuation in up to 25% of patients and impeding the attainment of optimal therapeutic doses. Additionally, these effects substantially contribute to disability, morbidity, and mortality, imposing a considerable burden on healthcare utilization and costs.[1] Despite the efficacy of commonly prescribed antiseizure medications (ASMs), such as carbamazepine (CBZ), phenytoin (PHT), lamotrigine (LTG), oxcarbazepine (OXC), and phenobarbital (PB), in seizure control, and their usage is frequently curtailed due to the frequent occurrence of adverse drug reactions (ADRs).[2] Cutaneous adverse drug reactions (cADRs) to ASMs are among the most common, with an in-patient prevalence of approximately 3%. Notably, documented a rash in 15.9% of 1,649 patients taking ASMs over a 5-year period.[3] Some of these ADRs manifest as idiosyncratic reactions, unrelated to dosage (type B). Despite their low incidence, the most severe idiosyncratic reactions include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), posing a substantial risk of mortality or severe disability.[3,4]

Advancements in the epidemiological landscape and pharmacogenetics have deepened our understanding of the intricate aspects of ASM toxic effects, facilitating the identification of specific patient profiles at heightened risk for particular adverse reactions. These contributions empower us to test patients for certain mutations, potentially preventing the occurrence of serious ADRs.[1] This review not only provides insight into the clinical manifestations of each cADR but also discusses how to identify when a patient may be at risk for a severe reaction and outlines proper management for each clinical setting. Additionally, we explore the primary ASMs that cause these reactions and review mutations that put patients at risk of developing them.

Classification of cADRs

ADRs can be categorized in various ways. The World Health Organization classification establishes five types: 1) acute reactions related to the pharmacological properties of the drug (type A); 2) idiosyncratic reactions (type B); 3) chronic reactions (type C); 4) delayed reactions (type D); and 5) reactions secondary to drug interactions (type E). They can be further divided according to the type of hypersensitivity, into immediate (type 1) and delayed (type 4). Specifically, adverse effects of ASMs have been grouped into five classes:[1] cognition and coordination; mood and emotion; sleep; tegument and mucosa; and weight and cephalalgia. In this review, our primary focus is on cADRs, which tend to fall into either type A or type B categories, often associated with a type 4 hypersensitivity reaction.[2]

From a dermatological perspective, adverse cutaneous drug reactions are a significant cause of morbidity, presenting in various forms ranging from mild urticaria and morbilliform eruptions to severe and potentially life-threatening conditions such as SJS and TEN.[5,6] Accurate classification of these reactions is crucial for proper diagnosis and treatment. Bastuji-Garin et al. (1993)[6] proposed a comprehensive classification system for TEN, SJS, and erythema multiforme (EM), based on the pattern of skin lesions and the extent of epidermal detachment. This system includes four categories. 1) Bullous EM: epidermal detachment involving less than 10% of the body surface area, characterized by the presence of typical target lesions. The etiology can be viral or bacterial. 2) SJS: epidermal detachment affecting less than 10% of the body surface area, with widespread erythematous or purpuric macules or flat atypical target lesions, and involving at least two mucous membranes. 3) SJS-TEN overlap: epidermal detachment affecting 10-30% of the body surface area, with purpuric macules or flat atypical target lesions. And 4) TEN: epidermal detachment involving more than 30% of the body surface area, with at least two mucosal surfaces affected, accompanied by purpuric macules or flat atypical target lesions.

Risk Factors

Critical risk factors for cADRs encompass various elements, including pediatric or geriatric patients, a history of previous drug-related skin reactions, high initial doses, and rapid escalation regimens. Additionally, immune system disorders like human immunodeficiency virus, liver disease, and specific concurrent medications contribute to heightened risk. In the context of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, infectious diseases may play a role in pathogenesis, with human herpes virus six and seven, as well as the Epstein Barr virus, identified as potential contributors.[2]

Genetic predisposition assumes a pivotal role in ASM hypersensitivity. The presence of certain human leukocyte antigens (HLAs) is strongly correlated with the risk of developing a cADR to ASMs. Among these, HLA*15:02 has undergone extensive study and is established as a significant risk factor for SJS and TEN following the use of CBZ. It is estimated to have a 98.3% sensitivity, 97% specificity, a 7.7% positive predictive value, and a 100% negative predictive value for developing SJS/TEN when using CBZ. The 2017 Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine also establish patients with HLA*

Table 1. HLA alleles associated with high risk of ADRs due to ASMs[3,7-9]

HLA	High-prevalence population	Cutaneous manifestations	Drugs associated with higher risk
HLA-B*15:02	Hong Kong, Malaysia, Thailand, Philippines, and Han Chinese	SJS/TEN	CBZ, PHT, LTG, and OXC
HLA-31*01	Japan, South India, Native Americans, Europe, South Korea, and Han Chinese	SJS/TEN, DRESS syndrome and maculopapular eruptions	CBZ
HLA-A*24:02	South China	SJS/TEN	Aromatic AEDs
HLA-B*1511	Japan, South Korea, and Central China	SJS/TEN	CBZ
HLA-A*02:01/Cw*15:02	Caucasians	SJS/TEN	PHT
HLA-B*1301, HLA-B*5602, and HLA-B*5604	Thailand	DRESS syndrome and drug hypersensitivity syndrome	PHT

HLA, human leukocyte antigens; ADR, adverse drug reaction; ASM, antiseizure medication; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; CBZ, carbamazepine; PHT, phenytoin; LTG, lamotrigine; OXC, oxcarbazepine; DRESS, drug reaction with eosinophilia and systemic symptoms; AEDs, associated with antiepileptic drugs.

15:02 at greater risk for OXC-induced SJS/TEN and don not recommend prescribing it. Even though the guidelines specify that other aromatic ASMs have weaker evidence linking them to SJS/TEN with the HLA*15:02 allele, they still advise caution when using them.[3] A Thai study found association of PHT-induced SJS in patients having HLA* 15:02, noting that not all patients were reactive to both drugs, which means this cross-reactivity is not always present.[4] In regions with a high prevalence of these alleles, such as Hong Kong, Malaysia, Thailand, and the Philippines, testing before prescribing these ASMs is recommended.[1,5] Other predisposing alleles are summarized in Table 1.

New ASMs are currently displacing aromatic ASMs, as there has been an increase in their prescription due to their improved safety profile and efficacy. Few cADRs have been reported with these medications. Among them, lacosamide seldomly causes mild cADRs, and the comparison of their incidence (2.9%) with placebo (3%) shows no statistical difference.[6-10] Regarding valproic acid (VPA), it does not appear to be a significant risk factor for severe cutaneous adverse reactions (SCAR) on its own, and mild rashes mainly occur with high-dose escalations. However, it has been linked to SJS/TEN cases when combined with aromatic ASMs, specifically LTG.[11,12] Gabapentin presented a 0.3% rate of rashes that prompted discontinuation in a 378-patient study. Topiramate has been associated only with pruritus and mild rashes.[12] Therefore, we can conclude that new ASMs appear to be at less risk of skin reactions compared to aromatic ASMs.

Clinical Presentation

cADRs constitute some of the most common type B effects associated with ASMs. In a Japanese cohort, these reactions comprised 75% of all ADRs to ASMs.[13] The clinical spectrum of cADRs exhibits variation in morphology and severity, ranging from mild maculopapular rashes to SCARs such as SJS/TEN and DRESS syndrome. Within this spectrum, diverse reactions, including urticaria, pruritus, alopecia, and erythema multiforme, can manifest.[2] Maculopapular eruptions are characterized by the presence of erythematous and pruritic cutaneous macules and papules, typically appearing 7 days to 14 days after the intake of the causative drug, and resolving spontaneously within 1 week to 2 weeks after discontinuation of the medication.[2] These eruptions are observed in 5-17% of patients taking CBZ, PB, PHT, and LTG.[1] Urticarial reactions are most common in children and young adults, especially those with a history of allergy or atopy. Characterized by itchy and confluent hives that fluctuate, urticarial reactions rarely last more than a few days.[14]

Fixed drug eruption presents as a single (or sometimes multiple) round erythematous or violaceous patch, plaque, or bullae with a darkened center that appears up to 1 week after drug intake. Recurrence after re-exposure typically involves the same site or sites. This entity can progress to generalized bullous fixed drug eruption (GBFDE), affecting most of the body surface area (BSA), and resembling SJS/TEN, making it more challenging to treat.[15] Acute generalized exanthematous pustulosis (AGEP) is an uncommon drug reaction (0.1-0.5/100,000 of the total population) characterized by pustules mainly on the chest and upper back, accompanied by fever, occasional mild mucous membrane involvement, and leukocytosis.[14]

SJS and TEN are severe and life-threatening cutaneous adverse reactions associated with medication intake. They are characterized by extensive necrosis and detachment of the epidermis, with mucous membranes almost always affected. SJS is diagnosed when <10% of the BSA is detached, compared to TEN, which affects >30% of BSA; anything in between is considered an overlap.[1,16] A Korean registry-based study found an overall mortality rate for severe cADRs of 3.8%, slightly varying from a study in pediatric patients estimating a mortality rate of 4%.[17,18]

DRESS syndrome is also life-threatening but exhibits a varied clinical presentation. Skin lesions are polymorphic and non-specific, while systemic involvement is prominent, including fever, leukocytosis with eosinophilia or atypical lymphocytosis, lymph node enlargement, and liver or renal dysfunctions developing 2 weeks to 6 weeks after drug exposure.[19] In a systematic review evaluating DRESS syndrome in the pediatric population, ASMs were the culprit drugs in 97% of cases (n=148), with CBZ accounting for 34%, PHT 30%, LTG 16%, PB 10%, OXC 3%, VPA, and levetiracetam 1% each.[18] SCARs such as DRESS and SJS/TEN affect 1-10 in 10,000 new users of ASMs. ASMs account for up to 53% of DRESS syndrome cases. CBZ is the most commonly implicated drug for DRESS syndrome and SJS/TEN, although this may be influenced by its frequency of use. However, milder reactions are not uncommon with CBZ, including erythematous rashes, urticaria, pruritus, or alopecia.[1,19,20]

Diagnosis

The initial approach to patients exhibiting a skin eruption after initiating treatment with ASMs should prioritize characterizing the dermatosis. Equally crucial is identifying red flags that may indicate a severe rash with a high risk of SJS/TEN, DRESS, or AGEP. These red flags may include fever, facial edema, lymphadenopathy, purpuric or

blistering rash, positive Nikolsky sign, hemorrhagic ulcers or erosions on mucous membranes, systemic symptoms (tachycardia, hypotension, malaise, and anorexia), erythroderma, skin tenderness, prominent neck and upper trunk involvement, and as well as abnormal blood and/or urine tests.

When attempting to identify the causative drug, the gold standard is provocation testing. However, this approach can be extremely dangerous, especially in the presence of a SCAR. A safer alternative is the atopy patch test (APT), where a minimal dose of the suspected drug is applied to the forearm skin and evaluated 48 hours to 72 hours later for any reaction. Delayed intradermal testing is similar to APT but needs to be performed several weeks after the rash disappears.[14]

Management

The treatment for ADRs varies depending on clinical presentation and severity. In general, most cases (if not all) require discontinuation of the drug. For mild reactions, such as fixed drug eruption or maculopapular eruption, and symptomatic management is recommended. Pruritus relief may be achieved with medium or high-dose topical corticosteroids or oral H1 antihistamines. If mild oral lesions are present, they can be managed with topical corticosteroids or calcium carbonate. In cases without red flags, reducing the ASM dose and closely monitoring the patient until improvement occurs is recommended, after which the dose can be slowly escalated. If a high risk of hypersensitivity to a drug is confirmed, the ASM must be replaced; however, switching to another aromatic ASM can be risky (a patient allergic to OXC or PB has an estimated 70% risk of a similar reaction to CBZ).

In such cases with only a mild reaction, desensitization is an option if the risk of leaving the patient without an ASM is greater. Patients must consent to desensitization, and during the process, they should be monitored daily for the appearance of any red flags. Three regimens can be used: 1) introducing the ASM at a 0.1% dose and doubling the amount every 2 hours until the desired dose is reached; 2) similar to the first regimen, but the doubling interval is every 24 hours; and 3) the initial 0.1% dose is taken throughout a week, and then every next week the dose is doubled. The latter is considered the safest option; however, it is not ideal for patients with epilepsy who require continuous ASM treatment. Examples of individuals who would benefit from desensitization are women of childbearing age in remission on LTG or CBZ, patients with trigeminal neuralgia, and patients with kinesogenic dyskinesia.[14,15]

When any SCAR is suspected, clinicians must create a comprehensive drug chart, including every drug the patient has consumed in the past 6 weeks, to evaluate which one coincides with the onset of symptoms. The removal of all unnecessary drugs, including the suspected culprit, is a cornerstone of treatment that can improve prognosis. Rechallenge is never advised in these cases. In the context of a patient with AGEP, along with removing the drug, only symptomatic treatment with topical corticosteroids (2 days for 1 week), emollients, and infection prevention is advised. AGEP typically resolves spontaneously and mostly leaves no sequelae.[21] For GBFDE, treatment is similar to AGEP, but systemic corticosteroids may be added, even though no strong evidence supports their use.[15]

In the case of SJS/TEN, patients require in-hospital management. The algorithm of drug causality for epidermal necrolysis may be useful to determine the drug that conditioned the reaction.[22] Calculating the affected BSA can help differentiate SJS from TEN and evaluate severity. Prognosis can be assessed through the Severity of Illness Score of Toxic Epidermal Necrolysis. Management is multidisciplinary and includes supportive care, wound care, fluid and temperature management, nutritional supplementation, pain control, prevention and treatment of infections, and addressing complications. At times, surgical intervention may be necessary. Although there is no established pharmacological treatment due to limited evidence, clinicians may consider the use of systemic corticosteroids, intravenous immune globulin, cyclosporine, plasmapheresis, or anti-tumor necrosis factor agents.[23]

When patients meet the diagnostic criteria for DRESS syndrome, discontinuation of the culprit ASM is the first step in their management. The latency period to rash onset ranges from 2 weeks to 6 weeks. First-line pharmacological treatment is with systemic corticosteroids (1-2 mg/kg/day of prednisone), although evidence for steroid-sparing therapies, mainly cyclosporine, has been growing lately. Due to the potential involvement of viral reactivation, antivirals such as ganciclovir can be administered. Mortality associated with DRESS syndrome is around 5-10%.[24]

Conclusion

The management of epilepsy is fraught with significant challenges, primarily due to the high prevalence of adverse effects associated with antiepileptic drugs (AEDs). While some cutaneous reactions are mild and self-limiting, others can severely impair quality of life, lead to disability, and in extreme cases, and result in mortality. A thorough

understanding of the wide spectrum of these reactions is crucial for accurate diagnosis and individualized management.

Identifying risk factors, including patient demographics and genetic predispositions, and provides critical insights for predicting and preventing adverse reactions. Notably, aromatic AEDs are frequently implicated in severe cutaneous adverse reactions such as SJS, TEN, and drug reaction with eosinophilia and systemic symptoms syndrome.

Treatment strategies emphasize the need for personalized approaches based on the severity of ADRs. The cornerstone of management involves the immediate discontinuation of the offending drug. Subsequent interventions may include symptomatic management, dosage adjustments, and desensitization techniques, all tailored to the clinical presentation and the patient's unique profile.

This review synthesizes current knowledge on cutaneous adverse effects associated with AEDs, providing clinicians with a comprehensive guide to navigate the complexities of diagnosis and management. The integration of personalized medicine principles and the application of emerging evidence-based strategies are poised to transform epilepsy management, significantly mitigating the impact of ADRs on patient outcomes.

By leveraging the latest advancements in epidemiology and pharmacogenomics, healthcare providers can enhance their ability to foresee and manage these adverse effects, ultimately improving the therapeutic landscape for individuals with epilepsy.

Conflicts of Interest

None.

References

1. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol* 2012;11:792-802.
2. Chung WH, Hung SI, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. *Expert Opin Drug Saf* 2010;9:15-21.
3. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. *Clin Pharmacol Ther* 2018;103:574-81.
4. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008;49:2087-91.
5. Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. *Drug Saf* 2007;30:1011-30.
6. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993;129:92-6.
7. Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007;68:1701-9.
8. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006;16:297-306.
9. Shi YW, Min FL, Zhou D, et al. HLA-A*24:02 as a common risk factor for antiepileptic drug-induced cutaneous adverse reactions. *Neurology* 2017;88:2183-91.
10. Ramírez E, Bellón T, Tong HY, et al. Significant HLA class I type associations with aromatic antiepileptic drug (AED)-induced SJS/TEN are different from those found for the same AED-induced DRESS in the Spanish population. *Pharmacol Res* 2017;115:168-78.
11. Li J, Sun M, Wang X. The adverse-effect profile of lacosamide. *Expert Opin Drug Saf* 2020;19:131-8.
12. Kavitha S, Anbuchelvan T, Mahalakshmi V, et al. Stevens-Johnson syndrome induced by a combination of lamotrigine and valproic acid. *J Pharm Bioallied Sci* 2015;7(Suppl 2):S756-8.
13. Gaeta F, Alonzi C, Valluzzi RL, Viola M, Elia M, Romano A. Hypersensitivity to lamotrigine and nonaromatic anticonvulsant drugs: a review. *Curr Pharm Des* 2008;14:2874-82.
14. Hikino K, Abe Y, Sakashita K, Ozeki T, Mushiroda T. Characteristics of adverse drug reactions associated with antiepileptics at a tertiary children's hospital in Japan: a retrospective observational cohort study. *Epilepsy Res* 2021;173:106614.
15. Fowler T, Bansal AS, Lozsádi D. Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting. *Seizure* 2019;72:61-70.
16. Patel S, John AM, Handler MZ, Schwartz RA. Fixed drug eruptions: an update, emphasizing the potentially lethal generalized bullous fixed drug eruption. *Am J Clin Dermatol* 2020;21:393-9.
17. Park CS, Kang DY, Kang MG, et al. Severe cutaneous adverse reactions to antiepileptic drugs: a nationwide registry-based study in Korea. *Allergy Asthma Immunol Res* 2019;11:709-22.
18. Kim GY, Anderson KR, Davis DMR, Hand JL, Tollefson MM. Drug reaction with eosinophilia and systemic symptoms (DRESS) in the pediatric population: a systematic review of the literature. *J Am Acad Dermatol* 2020;83:1323-30.
19. Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. *Immunol Allergy Clin North Am* 2009;29:481-501.
20. Wang YH, Chen CB, Tassaneeyakul W, et al. The medication risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in asians: the major drug causality and comparison with the US FDA label. *Clin Pharmacol Ther* 2019;105:112-20.
21. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. *J Am Acad Dermatol* 2015;73:843-8.
22. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for

assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther* 2010;88:60-8.
23. Creamer D, Walsh SA, Dziewulski P, et al. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. *Br J Dermatol* 2016;174:1194-227.
24. Wei BM, Fox LP, Kaffenberger BH, et al. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. Part II diagnosis and management. *J Am Acad Dermatol* 2024;90:911-26.