



# Making Rash Decisions in Epilepsy: Evaluating Hypersensitivity Reactions to Anti-seizure Medications

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## The Frequency and Clinical Features of Hypersensitivity Reactions to Antiepileptic Drugs in Children: A Prospective Study

Güvenir H, Dibek Misirlioglu E, Civelek E. *J Allergy Clin Immunol Pract.* 2018;6(6):2043-2050. doi:10.1016/j.jaip.2018.02.018

**Background:** Antiepileptic drugs (AEDs) can cause hypersensitivity reactions during childhood. Studies report a wide clinical spectrum of reactions with AED use, ranging from a mild rash to severe cutaneous reactions. **Objective:** To determine the prevalence and clinical features of AED hypersensitivity reactions during childhood. **Methods:** Patients in our pediatric neurology clinic who were prescribed an AED for the first time between November 2015 and November 2016 were monitored and those who developed skin rash during this period were evaluated. **Results:** A total of 570 patients were evaluated. The median age of the patients was 8.86 (interquartile range, 4.2-13.7) years, and 55.8% (318) of patients were male. The most frequently used AEDs were valproic acid (42%, n = 285) and carbamazepine (20.4%, n = 116). Hypersensitivity reactions to AEDs developed in 5.4% of patients. Of these patients, 71% (29) had cutaneous drug reactions and 29% (9) had severe cutaneous drug reactions; 61.3% (19) were using aromatic AEDs, and the leading suspected AED was carbamazepine (45.2%). Comparison of patients who did and did not develop AED hypersensitivity showed that hypersensitivity was more frequent among patients who were younger than 12 years, who used aromatic AEDs, or who used multiple AEDs. In addition, according to regression analysis results, aromatic AED use significantly increased the risk of AED hypersensitivity ( $P < .001$ ). **Conclusions:** Although allergic reactions to AEDs are rare, they are of significance because they can cause life-threatening severe cutaneous drug reactions. Therefore, patients receiving AEDs, especially aromatic AEDs, must be monitored closely.

## Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis With Antiepileptic Drugs: An Analysis of the US Food and Drug Administration Adverse Event Reporting System

Borrelli EP, Lee EY, Descoteaux AM, Kogut SJ, Caffrey AR. *Epilepsia.* 2018;59(12):2318-2324. doi:10.1111/epi.14591

**Objective:** Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and potentially fatal adverse skin reactions that are most commonly triggered by certain medications. One class of medications that has been highly associated with SJS/TEN reactions is antiepileptic drugs (AEDs). We sought to quantify the risk of SJS/TEN associated with AEDs as a class, as well as individual AEDs, in the United States. **Methods:** An analysis was performed of the US Food and Drug Administration Adverse Event Reporting System from July 2014 through December 2017. Rates of SJS/TEN were calculated for each AED compared with all other non-AEDs. Reporting odds ratios (RORs), proportional reporting ratios (PRRs), and 95% confidence intervals (CIs) were calculated using OpenEpi. **Results:** With 198 reports, AEDs had more reports of SJS/TEN than any other medication class. The AEDs as a class had an ROR of 8.7 (95% CI, 7.5-10.2) and a PRR of 8.7 (95% CI, 7.5-10.2) compared with all other non-AEDs. The AEDs with the highest risk estimates were zonisamide (ROR, 70.2; 95% CI, 33.1-148.7; PRR, 68.7; 95% CI, 32.9-143.5), rufinamide (ROR, 60.0; 95% CI, 8.3-433.5; PRR, 58.9; 95% CI, 8.4-411.5), clonazepam (ROR, 56.0; 95% CI, 7.8-404.1; PRR, 55.1; 95% CI, 7.8-385.0), lamotrigine (ROR, 53.0; 95% CI, 43.2-64.9; PRR, 52.2; 95% CI, 42.7-63.7), phenytoin (ROR, 26.3; 95% CI, 15.5-44.7; PRR, 26.1; 95% CI, 15.4-44.2), and carbamazepine (ROR, 24.5; 95% CI, 16.0-37.5; PRR, 24.3; 95% CI, 16.0-37.1). **Significance:** Although AEDs as a class were associated with 9 times the risk of SJS/TEN compared with non-AEDs, there were 6 AEDs with risk estimates greater than 20. Increased awareness of this risk among both prescribers and patients, particularly variations in risk among different AEDs, along with education on early recognition of SJS/TEN signs/symptoms, may help mitigate the number and severity of these adverse events.



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## Commentary

Adverse reactions to medications are a significant reason of concern in the setting of the outpatient epilepsy clinic where antiseizure medications (ASMs) are started, increased, changed, and combined frequently to achieve better seizure control. Every time we make these changes, we increase the risk of adverse cutaneous reactions. These reactions are reported in about 3% to 16% of patients using ASMs<sup>1,2</sup> and range from a mild and transient maculopapular rash to severe, life-threatening reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).<sup>2</sup>

The discussion of possible ASM-related hypersensitivity (ASM-H) reactions is never a trivial one when we consider adding or changing medications in the clinic. Proactive conversations on this topic will increase the likelihood of early reporting by patients and their caregivers, preventing or limiting the extent of these complications.

Guverni et al addressed the problem in a prospective manner by following all children who were started on a new ASM in the clinic over the extent of a year; 5.4% of these patients reported hypersensitivity reactions, of which 71% were cutaneous reactions and 29% noncutaneous. Twenty-nine percent of these reactions were severe; however, none of them fatal. The authors identified 3 risk factors associated with the development of ASM-H, including age younger than 12, aromatic structure of ASMs, and the concomitant use of multiple ASMs. Of these, only the aromatic chemical structure of the ASM reached statistical significance. The time between starting the new medication and the development of the rash ranged between 7 and 180 days with a median of 28.5 days. The rash was generalized in 64.5% of patients, and 16% of them had mucosal involvement.

Borrelli et al analyzed the US Food and Drug Administration Adverse Event Reporting System (FAERS) and compared the rates of reported SJS and TEN in relation to other non-ASM medications. In this comparison, ASMs were found to be the highest medication class associated with the outcomes of concern (in prospective studies, antibiotics and nonsteroidal anti-inflammatory medications have a stronger association with these adverse reactions) and different ASMs, which are not often described as the main suspected agents for ASM-H reactions were described as related to these severe events. Specifically, zonisamide, rufinamide, and clorazepate, in addition to the usual suspects such as lamotrigine, phenytoin, and carbamazepine,<sup>1</sup> were described. The main limitation of this study, as acknowledged by the authors, resides in the nature of the reporting system that is open to the public, including health-care professionals, consumers, and manufacturers to submit voluntary reports.

The FDA does not require that a causal relationship between a product and event be proven and that reports do not always contain enough detail to properly evaluate an event. As specifically noted by the FDA in their information site, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the US population. When addressing the

question of ASM-H reactions in the clinic, several considerations come to mind.

### Does the Presenting Symptom Correspond to a True ASM-H Reaction?

Skin reactions following the introduction of ASMs are common (8%-16%). Most of these reactions present in the form of a generalized rash, which is transient and clears completely within days after the offending agent is discontinued. Sometimes they resolve on their own after a desensitization process, even without making medication changes. Only about half of them are reported to the prescribing provider.<sup>2</sup>

Along with the severity of the symptoms, the time of presentation also varies; some present shortly after the exposure to the offending agent, in the form of urticaria (5%-22%), angioedema, or erythema. The most frequent presentation (50%-90%) is a delayed generalized maculopapular rash seen 3 to 20 days after the treatment was started.<sup>2</sup>

Adverse reactions to medications have been described in about 15% of hospitalized patients, of which 7% are considered serious events and fatal adverse reactions were estimated to happen in 0.32% of inpatients, making these a significant cause of mortality<sup>3</sup> for this specific population.

Severe ASM-H reactions are associated with mucosal involvement, skin eruptions, fever, lymphadenopathy, internal organ involvement, and varying degrees of epidermal detachment: <10% for SJS and >30% for TEN. The DRESS typically includes eosinophilia and multiple organ dysfunction (hepatitis, pneumonitis, and renal dysfunction).<sup>4</sup> These require in-hospital management and aggressive treatment with steroids, antihistamines, and immunoglobulin, often in intensive care environment.

### Is There a Need to Change Therapy to a Different ASM?

It is often challenging to change a patient from one ASM to a different one in a short period of time. The severity of the reaction has to be weighed against the risk of having breakthrough seizures and its complications. If the clinical situation allows us, we prefer to start a second ASM and perform a slow-up titration before the initial one is weaned, more so if seizures have been controlled. In addition, there is the possibility of cross-reactivity between medications that share a similar chemical structure and often mechanism of action. In the presence of a severe ASM-H, a slow titration/switch is not possible and the medication has to be stopped even if a short period of a bridging medication, often benzodiazepine, has to be used during the switch.

### Is There Increased Risk for ASM-H With Specific ASMs?

Up to 95% of ASM-H reactions have been reported in relation to ASM with an aromatic ring in their chemical structure, such



as carbamazepine, phenytoin, phenobarbital, oxcarbazepine, and lamotrigine.<sup>1,5</sup> Aromatic ASMs also more frequently associated with severe ASM-H reactions.<sup>6</sup>

Valproic acid is a nonaromatic ASM, but it has been involved in increased rates of ASM-H due to its metabolic properties as an inhibitor of CYP isoenzymes causing increased plasma concentration of aromatic ASMs and their metabolites, when used in combination therapy.<sup>7</sup>

### Are There Patient-Specific Risk Factors That Predispose Them to ASM-H Reactions?

Both ends of the age spectrum seem to make patients more vulnerable to severe ASM-H reactions. Guvenir and team described 1.5% severe cutaneous adverse reactions, which is comparatively higher than 1 to 6 cases per 5000 described in the general population.<sup>2</sup> The elderly patients are also reported to have more severe reactions and these tend to be fatal in a greater proportion of patients.<sup>8,9</sup> Severe ASM-H reactions have an elevated (10%) mortality rate.<sup>2</sup>

Cross-reactivity is described in up to 40% to 80% of patients with ASM-H reactions documented,<sup>2</sup> so having a prior reaction makes an individual more vulnerable to others. Interestingly, having common allergies does not seem to increase the risk for ASM-H reactions.<sup>10</sup>

Genetic factors are described to predispose population groups to ASM-H reactions. The best described is the increased risk for carbamazepine hypersensitivity and severe ASM-H reactions in patients carrying HLA-B15:02 (Han Chinese) and HLA-A31:01 (Europeans and Koreans) alleles.<sup>11</sup> Aromatic ASMs can directly interact with human leukocyte antigen (HLA) proteins.<sup>12</sup> Other specific HLA subtypes are described in other populations.<sup>13</sup>

### How to Report Hypersensitivity Reaction?

The manuscript by Borrelli et al rises awareness about the need of reporting medication adverse reactions in a more consistent and systematic way. Despite the limitations of the current reporting system including inconsistency of reporting, user bias, and no need for causality, it is still a valuable tool that should be used more often by prescribers, health-care providers, manufacturers, and consumers alike. General information about the FDA reporting system can be found at: <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/> and Medwatch reporting site at <https://www.fda.gov/Safety/MedWatch/default.htm>.

In conclusion, we owe it to our patients to be better educated about ASM-H reactions, both mild and severe. We should be proactive in discussing the possibility of cutaneous reactions when we make medication changes. The patient should be examined and closely followed when these reactions are reported. Severe reactions are rare but carry a high morbidity

and mortality, which can be limited if the offending agent is withdrawn and treatment is started early.

By Adriana Bermeo-Ovalle

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