

Research Article

Use of the Biopharmaceutics Drug Disposition Classification System (BDDCS) to Help Predict the Occurrence of Idiosyncratic Cutaneous Adverse Drug Reactions Associated with Antiepileptic Drug Usage

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Abstract. Cutaneous adverse reactions (CARs) from antiepileptic drugs (AEDs) are common, ranging from mild to life-threatening, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The identification of subjects carrying the HLA-B*15:02, an inherited allelic variant of the HLA-B gene, and the avoidance of carbamazepine (CBZ) therapy in these subjects are strongly associated with a decrease in the incidence of carbamazepine-induced SJS/TEN. In spite of the strong genetic associations, the initiation of hypersensitivity for AEDs is still not very well characterized. Predicting the potential for other AEDs to cause adverse reactions will be undoubtedly beneficial to avoid CARs, which is the focus of this report. Here, we explore the use of the Biopharmaceutics Drug Disposition Classification System (BDDCS) to distinguish AEDs associated with and without CARs by examining the binding relationship of AEDs to HLA-B*15:02 and data from extensive reviews of medical records. We also evaluate the lack of benefit from a Hong Kong population policy on the effects of screening for HLA-B*15:02 and previous incorrect structure–activity hypotheses. Our analysis concludes that BDDCS class 2 AEDs are more prone to cause adverse cutaneous reactions than certain BDDCS class 1 AEDs and that BDDCS Class 3 drugs have the lowest levels of cutaneous adverse reactions. We propose that BDDCS Class 3 AEDs should be preferentially used for patients with Asian backgrounds (i.e., Han Chinese, Thai, and Malaysian populations) if possible and in patients predisposed to skin rashes.

KEY WORDS: antiepileptic drugs; BDDCS; drug hypersensitivity; HLA-B alleles.

INTRODUCTION

Cutaneous adverse reactions (CARs) from antiepileptic drugs (AEDs) are common, ranging from mild to life-threatening, including maculopapular eruption, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (1,2). The mortality rates are approximately 10–15% in SJS, 30% in overlapping SJS/TEN, and up to 50% in TEN (3). For years, the pathological determinants of SJS/TEN remained elusive. The identification of subjects carrying the HLA-B*15:02, an inherited allelic variant of the HLA B gene, and the avoidance of carbamazepine (CBZ) therapy in

these subjects are strongly associated with a decrease in the incidence of carbamazepine-induced SJS/TEN (4–9). HLA-B*15:02 screening policies have been implemented in a number of countries with respect to CBZ dosing, including the USA when in 2007 the FDA published an alert (10) stating that “Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine.” In a research setting, screening in Taiwan was associated with a reduced incidence of CBZ-induced SJS/TEN (11). Recently, however, the results of a routine clinical service policy at a system-wide level in Hong Kong implemented in 2008 was reported to be associated with the prevention of CBZ-induced SJS/TEN without reducing the overall burden of AED-induced SJS/TEN in more than 110,000 epilepsy patients (12). Attempts to predict the potential for various AEDs to cause cutaneous hypersensitivity through structure–activity relationships, suggesting that CARs occur with aromatic AEDs, but not with non-aromatic AEDs (13,14), have ignored data for aromatic AEDs exhibiting low CARs incidence such as clobazam and clonazepam. Thus, in spite of the strong genetic associations and some structure–activity success, the initiation of hypersensitivity for AEDs is still not very well characterized. Predicting the potential for other AEDs to cause adverse reactions will be beneficial to avoid CARs, which is the focus of this report.

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In 2005, Wu and Benet proposed the Biopharmaceutics Drug Disposition Classification System (BDDCS) (15). BDDCS provides a useful tool in early drug discovery for predicting routes of elimination, oral drug disposition, food effects on drug absorption, transporter effects on drug absorption, and potentially clinically significant drug interactions that may arise in the intestine, liver, and brain (15,16). BDDCS recognizes that drugs exhibiting a high passive intestinal permeability rate (BDDCS class 1 and BDDCS class 2) are extensively metabolized in humans, while low passive permeability rate drugs (BDDCS class 3 and BDDCS class 4) are primarily eliminated as unchanged drug in the bile or the urine (Figure S1).

Because the specific drug characteristics linking to adverse events remain controversial, here we expand the use of BDDCS in assisting the prediction of AED drug hypersensitivity reactions, conducted a systematic review to appraise the strength of BDDCS in the association of the incidence of CARs induced by AEDs, and performed *in vitro* studies to identify specific HLA/drug interaction patterns. In addition to exploring the use of BDDCS in the pathogenesis of CARs, the results of this work may help identify other AEDs or drugs in other therapeutic categories that can elicit SJS/TEN.

METHODS

HLA-B *In Vitro* Assay

We used the Biacore T200 SPR biosensor for analyzing the interaction between HLA-B proteins and drugs according to the manufacturer's protocol (GE). We immobilized the purified soluble HLA-B proteins (acting as ligands) on the chips by an amine coupling reaction, and the immobilized levels of sHLA-Bs were 9373-9812 response units (RU). PBS was used as running buffer and the flow rate was 10 mg/min. The compounds (ten AEDs, two active metabolites, and one non-active backbone structure) dissolved in PBS with 5% DMSO were evaluated and flowed through the solid phase with the running buffer PBS with 5% DMSO. Responses of the interaction were reference subtracted and corrected with a standard curve for the DMSO effects. We used BIA evaluation Version 3.1 for data analysis.

Compilation of AED-Related Adverse Cutaneous Reactions Studies

Data were extracted from four systematic published reviews of medical records of patients with epilepsy for documentation of CARs from AEDs. AED-related skin reactions studies were found in three main populations: American, Chinese, and Norwegian patients. We also used DailyMed (<http://dailymed.nlm.nih.gov/dailymed/>) to review rash and more serious dermatologic conditions reported in FDA package inserts, in addition to literature reports/reviews.

American Retrospective Study

The study in America was carried out at the Columbia Comprehensive Epilepsy Center between January 1, 2000,

and January 1, 2005. A total of 1875 patients were included with altogether 5050 exposures to 15 different AEDs (17). The attribution of rash was based on the patient's description of the rash or on the medical examination, if the physician concluded it was most likely due to the AED. Overall, 14.3% (269/1875) of patients experienced skin reactions to at least one AED.

Chinese Retrospective Studies

Although two Chinese studies were available in the literature and were carried out around the same time, we have analyzed them independently. The studies were carried out at the Epilepsy Center of the Chinese PLA General Hospital in Beijing, China. The first study period was from February 1999 to April 2010. A total of 3793 patients were included with altogether 7353 exposures to 11 different AEDs (18). Overall, 3.61% (137/3793) of patients experienced a skin reaction to at least one AED. The second study period was between February 1999 and September 2010. A total of 4037 patients were included with altogether 5355 exposures to 9 different AEDs (14). Overall, 4.06% (164/4037) of patients experienced a skin reaction to at least one AED. A CAR was defined as any type of rash (erythematous, maculopapular, papular, pustular, or unspecified) that had no other obvious cause apart from an AED that resulted in contacting a physician.

Norwegian Retrospective Study

The study in Norway was carried out in three specialist outpatient clinics in middle Norway served by neurologists from Trondheim University Hospital. A total of 663 patients were included with altogether 2567 exposures to 15 different AEDs (19). A skin reaction was defined as a diffuse rash (including MPE, DRESS, urticaria, erythema nodosum, and SJS) that was reported in the medical records and had no other obvious reason than a drug. As initial symptoms of hypersensitivity most frequently occur up to 8 weeks after starting a drug, treatments lasting less than 3 months and stopped for any other reason than a rash were not included as an exposure. Overall, 14% (93/663) of patients experienced skin reactions to at least one AED.

Determining the Changes in AED Prescribing Practice with HLA-B*15:02 and the Incidence of SJS/TEN

Data were extracted from the Hong Kong Hospital Authority Clinical Data Repository to determine changes in AED prescribing practice in all patients, in AED-naïve patients and in patients with newly treated epilepsy and the incidence of AED-induced SJS/TEN, following implementation of the HLA-B*15:02 screening policy (12). The study period covered 3 years before the implementation date (prepolicy: September 16, 2005, to September 15, 2008) and 3 years after (postpolicy: September 16, 2008, to September 15, 2011). Patients of interest were those who had at least one AED newly commenced and/or underwent testing for HLA-B*15:02 in the study period. An AED was defined as newly commenced if there was no record of its prescription in at least the previous 12 months. A total of 111,242 patients were

included and 4149 were tested for HLA-B*15:02. SJS/TEN was attributed to an AED if the patient was hospitalized for SJS/TEN within 90 days of commencing an AED, and the patient's allergy histories did not suggest other pharmaceutical products (12).

Compilation of BDDCS Properties, Correlation, and Statistical Analyses

Data are expressed as percentages of cutaneous incidence rate given the number of patients affected divided by the number of exposures associated with each AED together with the BDDCS class. The BDDCS class assignment and properties were obtained from the BDDCS applied to over 900 drugs paper (20). Missing data were complemented by literature searches. Data with absolute values of each AED exposure along with BDDCS were also included.

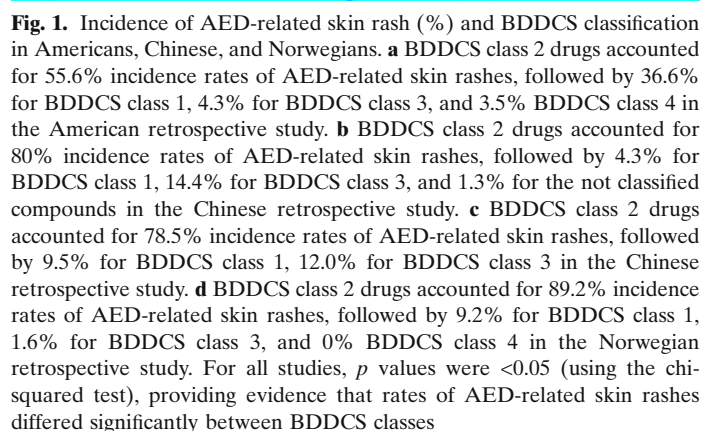
The BDDCS class prescription pattern across the three different groups: all patients, AED-naïve patients, and patients with newly treated epilepsy in the AED prescribing practice for HLA-B*15:02, was also analyzed. Data are expressed as the percent of each AED prescription in the prepolicy along with absolute values of each AED exposure and BDDCS class. Differences in the proportions of BDDCS classes associated with CARs and prescription patterns were determined using chi-squared tests. The differences of SJS/TEN incidence between the prepolicy and postpolicy were calculated using the Fisher's exact test.

The 12 AED-related compounds were evaluated using the *in vitro* assay relative response binding to HLA-B*15:02 versus the incidence of cutaneous adverse drug reactions reported with the Spearman rank correlation coefficient (ρ) and Spearman correlation test. For statistical tests, a *p* value less than 0.05 was considered significant. Analyses and plots were carried out using R (<http://cran.r-project.org>) and GraphPad Prism software version 6.0 (GraphPad Software, Inc., San Diego, CA).

RESULTS

Incidence of Cutaneous Adverse Reactions and BDDCS Class

Using the BDDCS classification, the drugs associated with the highest incidence of cutaneous adverse reactions fall



a high concordance between the available clinical data and the potential of the HLA-B *in vitro* assay to predict these cutaneous adverse reactions.

Figure 3, using BDDCS, depicts the change of AED prescription pattern from prior to post HLA-B*15:02 policy implementation in Hong Kong. Prior to policy implementation, phenytoin, valproic acid, and carbamazepine had the

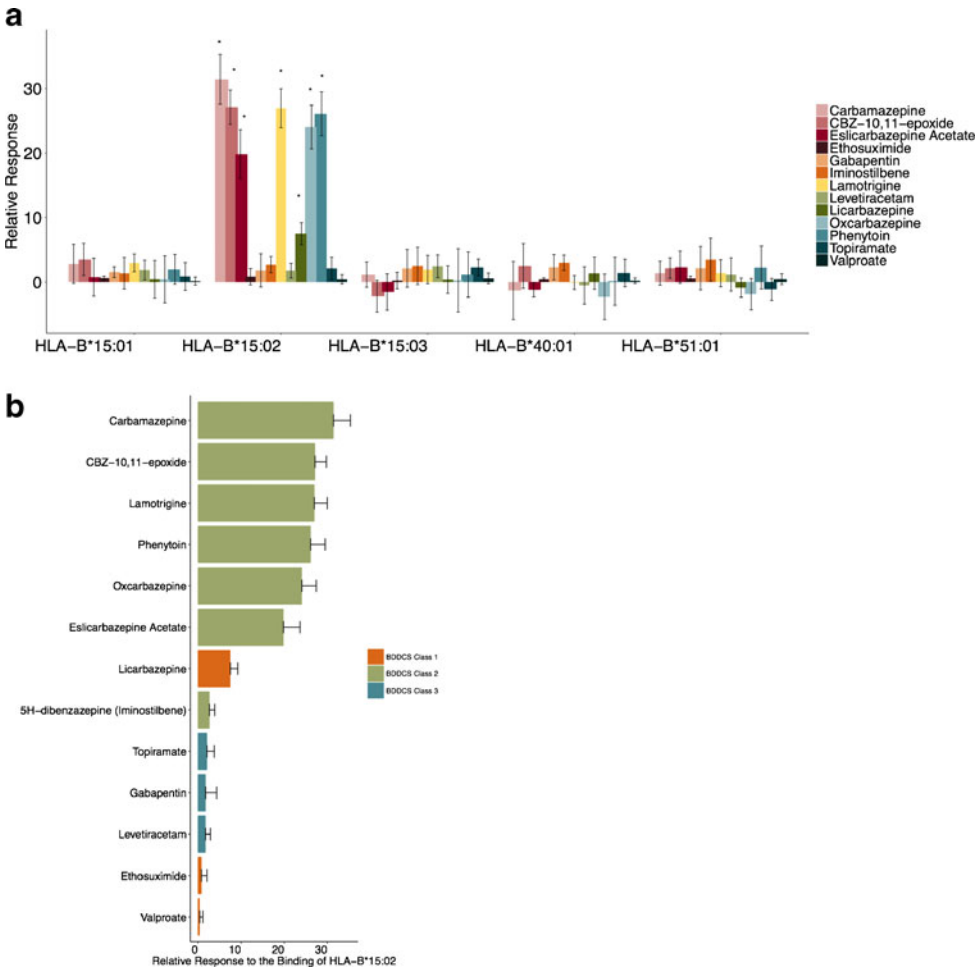


Fig. 2. **a** Surface plasmon resonance (SPR) data demonstrating the specific interactions of ten AEDs, two metabolites, and one non-active structural backbone (1 mM) to HLA-B*15:01, HLA-B*15:02, HLA-B*15:03, HLA-B*40:01, and HLA-B*51:01. * $p < 0.05$ shows compounds with a significant difference from the response of vehicle. All p values were calculated with a two-tailed Student's t test. Results are representative of six independent experiments (mean \pm SEM). **b** BDDCS classification of the SPR results with the AEDs

Table I. Relationship Between the Incidence of AED Rash from Fig. 1 for Drugs Investigated in at Least Two of the Four Retrospective Studies and Relative Response to the *In Vitro* Binding of HLA-B*15:02 from Fig. 2

Generic name	BDDCS class	Comments
Lamotrigine	2	High rash incidence and strong <i>in vitro</i> binding
Oxcarbazepine	2	High rash incidence and strong <i>in vitro</i> binding
Carbamazepine	2	High rash incidence and strong <i>in vitro</i> binding
Phenytoin	2	High rash incidence and strong <i>in vitro</i> binding
Phenobarbital	1	Intermediate rash incidence
Primidone	2	Low/no rash incidence
Gabapentin	3	Low/no rash incidence and weak <i>in vitro</i> binding
Felbamate	4	Low/no rash incidence
Clobazam	1	Low/no rash incidence
Clonazepam	1	Low rash incidence
Valproate	1	Low rash incidence and weak <i>in vitro</i> binding
Topiramate	3	Low/no rash incidence and weak <i>in vitro</i> binding
Levetiracetam	3	Low rash incidence and weak <i>in vitro</i> binding
Vigabatrin	3	No reported rash incidence

Two further BDDCS class 1 drugs (tiagabine, zonisamide) reported in only one study exhibited rash incidence, which would be classified as high
BDDCS Biopharmaceutics Drug Disposition Classification System

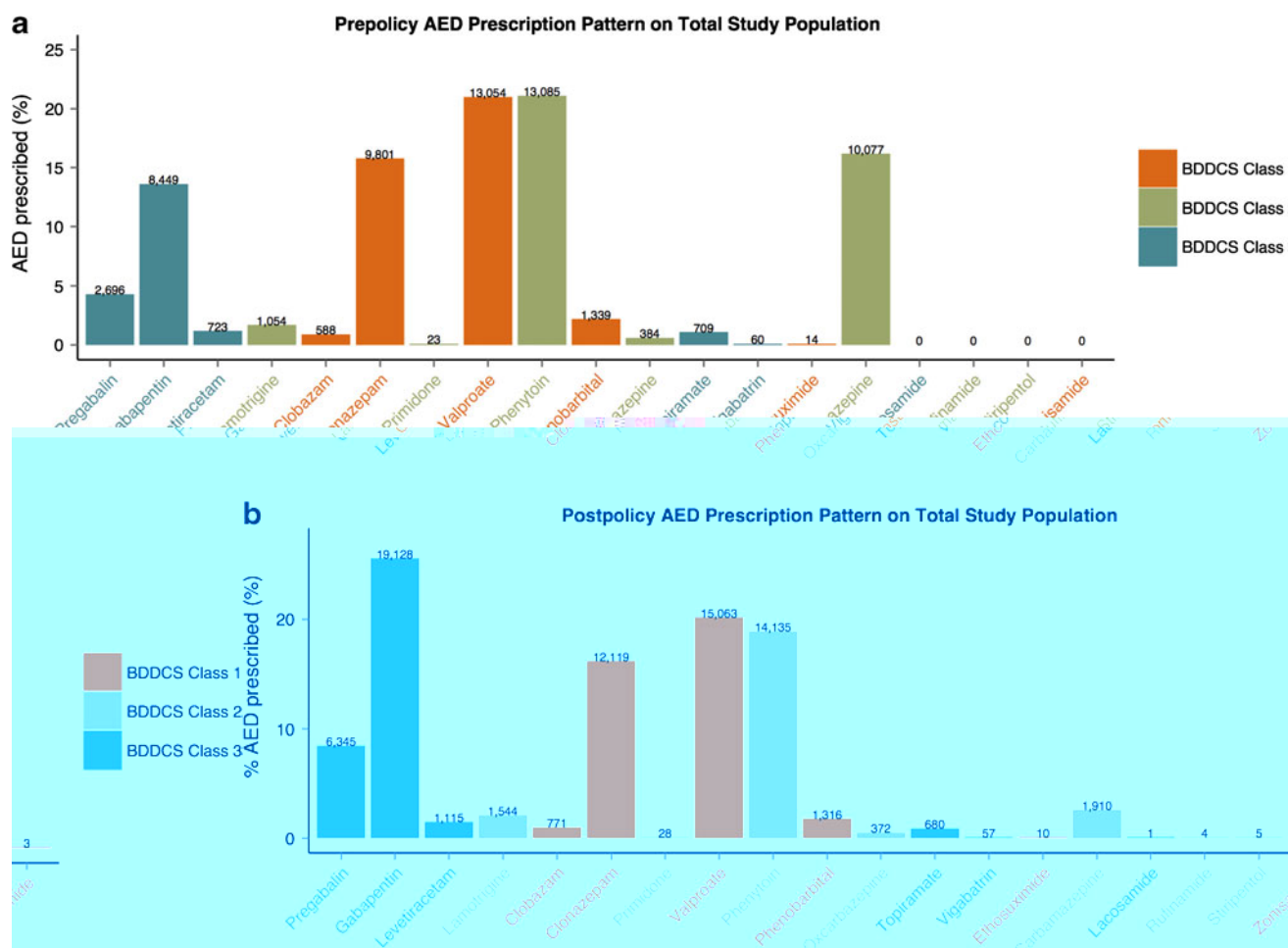


Fig. 3. AED prescription patterns prior and post HLA-B*15:02 screening implementation in the total Hong Kong population. **a** Prior to the policy implementation, BDDCS class 1 drugs accounted for 40.0% of all prescriptions, followed by 39.7% for BDDCS class 2 and 20.3% for BDDCS class 3. **b** In the postpolicy, BDDCS class 1 accounted for 39.2% of all prescriptions, followed by 36.5% for BDDCS class 3 and 24.3% for BDDCS class 2.

highest usage numbers in the total population. Following policy implementation, gabapentin, valproic acid, phenytoin, and clonazepam had the highest prescription numbers. Although there was a significant increase in the percent of BDDCS class 3 drugs (pregabalin, gabapentin, and levetiracetam) in the entire population, BDDCS class 2 drugs still represented 24.3% of prescribed AEDs. Similar trends were also observed in the subset of patients receiving their first ever AED where postpolicy 25.3% of prescribed AEDs were BDDCS class 2 drugs (Figure S4). In the newly treated epilepsy subset postpolicy, the decrease in carbamazepine prescriptions from prepolicy numbers was almost matched by the increase in class 2 phenytoin dosing (Figure S5). Thus, the high presence of BDDCS class 2 AEDs potentially hinders the lowering of CAR incidence in this population.

DISCUSSION

We observed a high concordance between the HLA-B*15:02 *in vitro* assay and the incidence of cutaneous adverse reactions associated across all retrospective studies. Phenytoin, lamotrigine, carbamazepine, and oxcarbazepine showed

high levels of cutaneous adverse reactions. These drugs are also the major causative AEDs for CARs (2,21). Our BDDCS analysis shows that these AEDs share common properties of being highly metabolized and having low solubility, i.e., BDDCS class 2. In contrast, AEDs showing a high solubility and poor extent of metabolism (gabapentin, levetiracetam, and topiramate) showed a poor interaction for the HLA-B *in vitro* assay. In agreement with this, gabapentin, levetiracetam, and topiramate are also AEDs showing minimal levels of CARS (see Fig. 1, Table I). Iminostilbene, the carbamazepine structural backbone, had a lower binding affinity. We speculate that this low binding affinity is due to the lack of polar groups thereby not allowing the formation of H-bonds with the HLA-B pocket. However, iminostilbene also exhibits low, if any, antiepileptic potency. On the other hand, carbamazepine-10,11-epoxide presented a strong interaction. According to the results from the HLA-B *in vitro* test and the incidence of cutaneous adverse reactions, we observe that compounds that are extensively metabolized and have low solubility are more susceptible to interacting with HLA-B*15:02 *in vitro* and have higher incidences of cutaneous adverse reactions. Thus, we recommend that to minimize

CARs, epileptic patients be placed on BDDCS class 3 AEDs if possible and that for patients exhibiting the HLA-B*15:02 allele, all BDDCS class 2 AEDs may be expected to exhibit the same toxicity potential as carbamazepine. It is more difficult to extrapolate these findings to BDDCS class 1 AEDs, where some of these drugs (e.g., zonisamide and phenobarbital) cause significant CARs, while others (e.g., valproic acid, clobazam, clonazepam, and ethosuximide) exhibit similar adverse reaction profiles to the BDDCS class 3 drugs.

It has been previously hypothesized that “idiosyncratic” hypersensitive reactions occur with AEDs containing an aromatic ring in their chemical structure that can form an arene-oxide intermediate (13). This chemically reactive product may become immunogenic through interactions with proteins or cellular macromolecules in accordance with the hapten hypothesis (24). Apart from the hapten formation hypothesis, another immune mechanism might be involved. In this alternate hypothesis, there is a direct, non-covalent binding of the drug to the T cell receptor to specific T cell clones. Drug-specific T cells have been identified for lamotrigine and carbamazepine (25,26). Handoko and co-workers have also confirmed that the association for T cell-mediated reactions was strongest in cutaneous reactions (13).

Table III. Rash and More Serious Dermatologic Conditions from the FDA Package Insert and Literature Reports

Generic drug name	Rash incidence	BDDCS class
Clobazam	Package insert: • rash listed under Warnings and Precautions and Adverse Reactions (32) SJS/TEN: • listed under Warnings and Precautions and Adverse Reactions (32) Other sources: • approximately 2% (27)	1
Clonazepam	Package insert: • rash listed under Adverse Reactions (32) SJS/TEN: • not mentioned Other sources: • not available	1
Ethosuximide	Package insert: • rash listed under Warnings; Precautions and Adverse Reactions sections (32) SJS/TEN: • listed under Warnings (32) Other Sources: • not available	1
Phenobarbital	Package insert: • rash listed under Adverse Reactions (32) SJS/TEN: • not mentioned Other sources: • 1–2% (33) • 8.1/10,000 (34)	1
Tiagabine	Package insert: • rash rate: adults: 5% (32) • rash listed under Precautions and Adverse Reactions (32) Other sources: • 2.5% (27)	1
Valproate	Package insert: • rash: >1% but less than 5% in both epilepsy and migraine trials (32) • rash listed under Warning and Precautions and Adverse Reactions sections (32) SJS/TEN: • “Rare” (32) Other sources: • approximately 1% (27) • 0.5/10,000 (35)	1
Zonisamide	Package insert: • rash: adults = 1.4–2.2% (32) • rash listed under Warnings; Precautions and Adverse Reactions sections (32) SJS/TEN: • 46 per 1,000,000 (32) • listed under Warnings (32) Other sources: • 4% (27)	1
Carbamazepine	Package insert: • rash: 1/10,000–6/10,000 (32) • rash listed under Warnings and Precautions and Adverse Reactions (32) SJS/TEN: • listed under Boxed Warning; Warnings and Adverse Reactions (32) Other sources: • SJS/TEN: 1.4/10,000 (35) • rash: 4–11% (27)	2
Lamotrigine	Package insert: • rash: epilepsy trials = 4.5–10% in adults, 4.4–14% in pediatric cases; bipolar trials: adults = 7–11% (32))	

and valproate induced by the screening policy, such as the risk of teratogenicity (28), which is higher for valproate compared with carbamazepine may have exerted a negative effect on population health. Our analysis shows that there was no major shift in the BDDCS classes 2 and 1 prescription pattern, and this potentially explains the lack of reduction in SJS incidence.

The Food and Drug Administration (FDA) currently recommends that phenytoin, fosphenytoin, and lamotrigine should be avoided as an alternative for carbamazepine patients positive for HLA-B*15:02 (10,29). HLA-B*15:02 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans); nonetheless, we observe a strong correlation between the drugs associated with cutaneous adverse reactions across different populations. Other HLA-B alleles such as HLA-A*31:01 (30) and HLA-B*15:11 (31) have been associated with carbamazepine-associated SJS but no *in vitro* assay has been performed as yet with these other alleles. BDDCS class 2 AEDs appear to be more reactive than other BDDCS classes.

Through a review of FDA package labels, in contrast to the 2% or less incidence of SJS/TEN for the BDDCS class 3 drugs listed in Table II, the values for the BDDCS class 2 drugs phenytoin (5–10%), lamotrigine (10%), carbamazepine (4–11%), and oxcarbazepine (2.5%) are often much higher (see Table III). As seen in the data presented here, patient exposure to BDDCS classes 2 and 1 AEDs is much higher (see Figure S2). For clinicians to be able to reduce the number of patient suffering from drug hypersensitivity reactions, they should understand that continual high prescription exposure of BDDCS class 2 and certain class 1 drugs may contribute to the reported adverse cutaneous reactions in patients who are at risk.

Use of BDDCS in the FDA Guidance for Drug Hypersensitivity Reactions

The previous discussion of BDDCS and AEDs in the literature was related to generic equivalence and interchangeability of AEDs. In that work, Bialer and Midha (37) contrasted the aspects of the FDA guidance of waiver of bioequivalence studies based on the Biopharmaceutics Classification System (BCS) (38) and the clinician's interchangeability of brand *versus* generic AED prescriptions. It is important to understand the distinction between BCS, which is based on the *extent* of drug permeability/absorption, *versus* BDDCS, which is based on the *rate* of drug permeability/absorption. In the BCS system, levetiracetam, gabapentin, and vigabatrin are classified as BCS class 1 drugs (39). These compounds are completely absorbed, with the exception of gabapentin that is about 70% absorbed in humans (40), although quite slowly. These three drugs, in contrast, are classified as BDDCS class 3 (see Table S2). Thus, the predictability of hypersensitivity reactions for AEDs is based on BDDCS, not BCS, classification, since BCS does not predict whether drugs will be extensively metabolized or not.

CONCLUSIONS

Drug-induced CARs constitute the most frequent idiosyncratic reactions confronting clinicians treating patients with epilepsy. Unfortunately, there is no reliable way to determine

early in the clinical course of a rash if it is going to remain as a benign maculopapular rash or evolve into a severe skin reaction. Therefore, the drug should be discontinued as soon as possible in most cases. Our analysis concludes that BDDCS classes 2 and 1 AEDs are more prone to cutaneous toxicity and BDDCS class 3 AEDs have the lowest cutaneous rash incidence across the studied ethnic groups. We propose that, if possible, BDDCS class 3 AEDs should be preferentially dosed to patients of East Asian ancestry who most predominantly exhibit the HLA-B*15:02 allele (i.e., Han Chinese, Thai, and Malaysian populations), where an association between HLA-B*15:02 and carbamazepine-induced SJS and TEN has been demonstrated (4–9). We believe that categorizing drugs by BDDCS classification adds to the understanding of idiosyncratic reactions. We plan to further test other AEDs in the HLA-B *in vitro* assay. Other toxicity models using BDDCS such as the Torsade de Pointes (41) and drug-induced liver injury (DILI) (42) are starting to emerge. BDDCS may help characterize and predict drugs having the potential for greater toxicity.

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COMPLIANCE WITH ETHICAL STANDARDS

Disclosure None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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