■ Original article

Epileptic Disord 2021; 23 (3): 466-475

Epileptic Disorders

Cutaneous adverse reactions associated with antiseizure medication: clinical characteristics and implications in epilepsy treatment

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Received September 14, 2020;
Accepted January 2, 2021

ABSTRACT

Objective. To describe the clinical characteristics of cutaneous adverse reactions and cross-sensitivity induced by antiseizure medications and compare the pattern of use of antiseizure medications in patients with epilepsy according to skin rash history.

Methods. We analysed patients with a history of skin rash presenting for up to 12 weeks after initiating antiseizure medication. The history of skin rash was verified by medical charts, interviews, and identification of skin lesions by patients based on illustrative images. The minimum follow-up period was eight months. The control group comprised epilepsy patients with regular antiseizure medication use for at least 12 weeks without skin rash. We included 109 cases and 99 controls.

Results. The median (interquartile range) period from the index rash was six years (2-11). Carbamazepine was the trigger medication in 48% of cases and induced skin rashes in all patients with cross-sensitivity and carbamazepine exposure. Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reactions with eosinophilia and systemic symptoms affected 36% of cases. Carbamazepine- or oxcarbazepine-induced maculopapular exanthema occurred earlier (median: one week) than that induced by other antiseizure medications (median: three weeks) (p=0.006). Cross-sensitivity was more common in patients with at least one episode of Stevens-Johnson syndrome (29%) and Stevens-Johnson/toxic epidermal necrolysis overlap (50%) than in patients with maculopapular exanthema (8%) (p=0.01). Although most cases were mild, the pattern of antiseizure medication use differed from that of controls, with a lower proportion of antiseizure medication typically associated with severe cutaneous adverse reactions (carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, and lamotrigine) (p<0.001). Most cases exposed to high-risk medication, however, did not develop cross-sensitivity.

Significance. Cutaneous adverse reaction history may influence antiseizure medication use. Cross-sensitivity is more common in severe cases and most patients are affected by mild, self-limited skin rashes. Further research should consider the relevance of mild skin rashes in lifelong epilepsy treatment.

Key words: antiseizure medication, cutaneous adverse reaction, cross-sensitivity, epilepsy, antiepileptic.

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doi:10.1684/epd.2021.1288

Cutaneous adverse reactions (CARs) are among the main reasons for drug withdrawal [1]. Antiseizure medications (ASMs) are a remarkable CAR trigger, responsible for up to 23% of all CAR hospitalizations, and are associated with higher severe CAR (SCAR) incidence [2-4]. While prompt drug withdrawal is key in treating CAR, especially severe and life-threatening forms, [5] such withdrawal is worrisome with epilepsy, where it can lead to seizure recurrence and status epilepticus. Identifying a substitute ASM that is quickly titrated to an effective and safe blood level, affordable, and indicated for the patient's seizure type is challenging. After the acute CAR phase, these concerns will still haunt the attending physician, as patients with previous CAR presentation with an ASM are at higher risk of recurrence with a new one [6]. This is further hampered by the loss of clinical data on CARs over years of follow-up when former medical records may become difficult to retrieve, and the differentiation between mild and severe forms of CARs may rely mostly on the patient's self-report. We analysed the clinical characteristics of CAR cases due to ASMs and investigated whether these patients had a different pattern of ASM use compared to patients with epilepsy without CAR history.

Materials and methods

This case-control study was approved by the institutional review board of all four participating tertiary hospitals. Based on convenience sampling, we consecutively enrolled every patient with skin rash history due to ASMs:

- during CAR hospitalisation;
- during outpatient follow-up;
- or whose medical record included CAR safety warnings.

The following criteria were required to confirm a case:

- exanthematous eruptions presenting up to 12 weeks after ASM initiation;
- remission of the rash only after ASM withdrawal;
- and skin rash confirmed by one of the authors during its acute phase or documented in the medical chart and recognized by the patient when illustrative CAR pictures were shown. These pictures represented maculopapular exanthema, atypical target lesions, urticarial lesions, haemorrhagic erosions of mucous membranes, or areas of epidermal detachment. Patients unable to attend in-person meetings, who declined to participate or sign written consent, or those with unreliable information about ASM-related skin rashes were excluded.

As a first step, clinical and epidemiological data were collected from chart reviews and interviews. We retrieved all medications in use during each CAR event, including doses and time since drug initiation, to identify any interaction potentially influencing that event. Patients who reported skin rash recurrence with another ASM were asked to identify either which ASM induced the most severe symptoms or which was the first to induce CARs; the identified ASM was considered as the case (index ASM) and the remainder were described as cross-sensitivity. Patients enrolled during acute CARs were followed by routine outpatient consultations or phone calls for at least eight months. Longitudinal data of patients enrolled, in addition to that of acute CAR, were retrieved by interview and data chart review from routine outpatient visits.

The used ASM was defined as an ASM that was regularly used for at least 12 weeks and did not trigger skin rash. ASMs were grouped according to the likelihood of provoking skin rashes as: (1) C3POL (drug notoriety with SCAR score 3 or 2 according to RegiSCAR-study: [7] carbamazepine [CBZ], phenobarbital [PB], phenytoin [PHT], primidone [PRM], oxcarbazepine [OXC], and lamotrigine [LTG]); and (2) other ASMs (valproic acid [VPA], topiramate [TPM], levetiracetam [LEV], lacosamide [LCM], gabapentin [GBP], pregabalin [PGB], acetazolamide [AZM], diazepam [DZP], clobazam [CLB], clonazepam [CZP] and sulthiame [STM]). Patients in the case group were further classified according to skin rash characteristics, including maculopapular exanthema (MPE), drug reaction with eosinophilia and systemic symptoms (DRESS) if they met the probable or definite RegiSCAR criteria [8], or Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) if they met the probable or very probable ALDEN criteria [9]. Epidermal necrolysis affecting <10%, 10-30%, and >30% of the total body surface area was defined as SJS, SJS/TEN overlap, and TEN, respectively. All data were reviewed by a single researcher between January 2018 and February 2020 to increase precision. SJS/TENS and DRESS were classified as severe CARs.

As a second step, we analysed the pattern of ASM use. First, we excluded cases using ASMs due to an indication other than epilepsy, those who stopped ASM treatment after a CAR, those who could not be followed for at least eight months, and fatal CAR cases. The use of a given ASM was defined by the above-mentioned criteria. ASMs not tolerated for at least 12 weeks for any other reasons, such as other adverse effects, treatment, or high cost, were not considered as used ASM.

The control group comprised consecutive patients from a tertiary epilepsy ambulatory clinic who denied ASM-related skin rash after regular use of one or more ASMs for at least 12 weeks. Each patient (cases and controls) was interviewed during an in-person meeting in which illustrative CAR pictures were shown.

Quantitative data were tested for normality using the Kolmogorov-Smirnov test. The Mann-Whitney U test and analysis of variance were used to compare non-parametric and parametric data, respectively. The Wilcoxon signed-rank test was used to compare non-parametric dependent data. The Pearson's chi-square test was used to compare qualitative data. For nominal variables with a sample size smaller than five, CAR types were grouped as mild CAR (MPE) and SCAR (DRESS, SJS, and TEN). If the sample size remained smaller than five, mild CAR and SCAR were compared by Fisher's exact test. A p value of <0.05 was considered statistically significant.

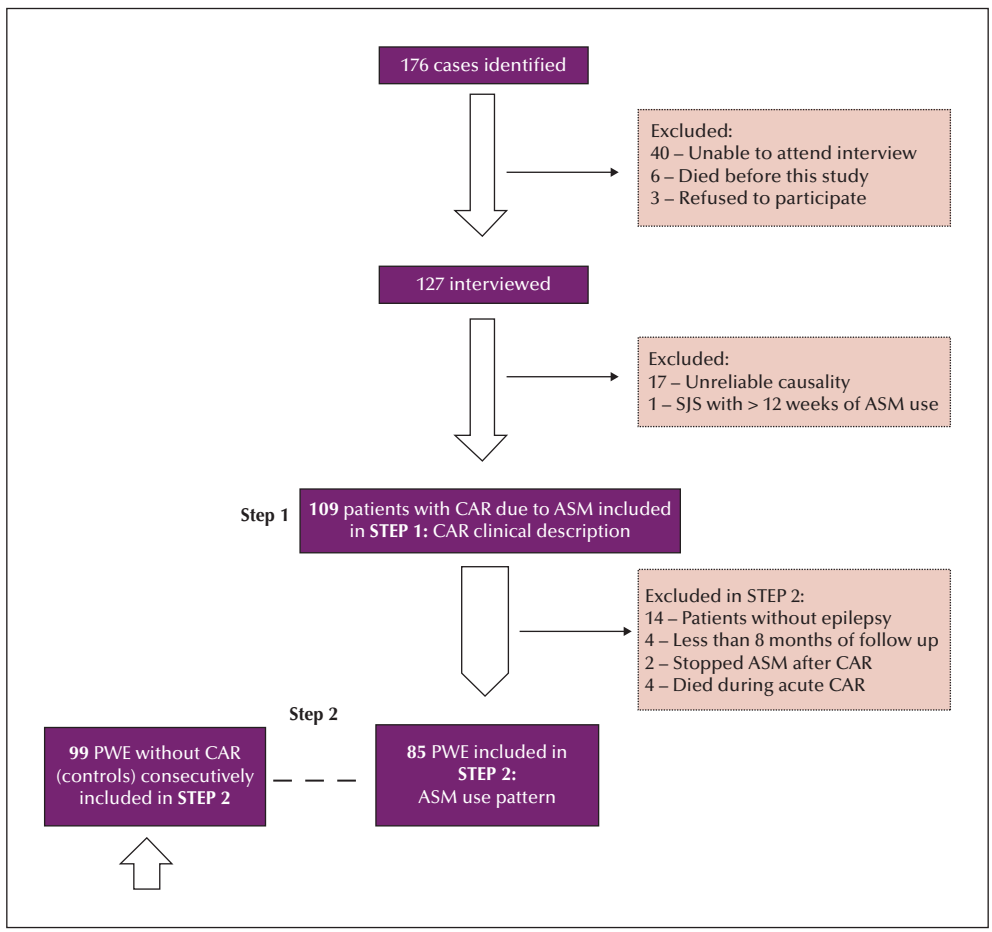
Results

A flow diagram of included and excluded patients at each step of data analysis is shown in *figure 1*.

Of 99 controls and 109 cases, 59 (59%) and 69 (63%) were female (p=0.68), with mean±SD ages of 39±13 and 32±23 years (p=0.28), respectively, at the date of the interview. The case demographics and main characteristics are described in *table 1*.

Seventeen (21%) patients complained of mucosal involvement associated with MPE and DRESS, characterized by erythema, oedema, and, rarely, blistering. These patients denied a resemblance to the haemorrhagic erosions typical of SJS/TEN shown in pictures and present in seven (100%) patients with TEN, six (100%) with overlapping SJS/TEN, and 11 (79%) with SJS. Two patients diagnosed with DRESS presented with skin erosions; one was characterized by bullous lesions without other hallmarks of SJS/TEN, and the other by ulceration, and biopsy showed extensive eosinophil and mononuclear dermal infiltrate. No patient identified the urticarial lesion picture as representative of their CAR lesions.

ASM mean±SD daily doses at the time of CARs were



■ **Figure 1.** Flow diagram of the study population selection including refusals and patient exclusion criteria for each step of data analysis.

370±210 mg for CBZ and 53±32 mg for LTG. The median (interquartile range [IQR]) dose of the ASM index was 100 mg (83–100) for phenobarbital, 300 mg (200–300) for phenytoin, and 750 mg (525–900) for OXC. The only CAR case with gabapentin was administered at 400 mg/day. There were no differences in specific ASM doses between CAR categories. Based on median values, MPE induced by CBZ and OXC started in the first week after ASM initiation; this contrasted with induction by PHT, PB, LTG and GBP which started at the third week of treatment (median [IQR] = 1 [1–2] and 3 [2–4], respectively) (p=0.006).

Thirty-eight (35%) patients with epilepsy were taking more than one ASM during CARs. The most frequently

▼ **Table 1.** Demographics and main characteristics of cutaneous adverse reactions according to type.

Type of CAR	Mild		Severe				p
	MPE		DRESS		SJS/NET		
Number of patients (%)	70 (64)		12 (11)		27 (24)		
Sex (female)	49 (70)		5 (42)		14 (52)		0.07
Age at CAR (years)[a]	29±24		27±23		26±21		0.14
Index ASM	CBZ	32 (46)	CBZ	4 (33)	CBZ	15 (55)	0.71
	LTG	14 (20)	LTG	3 (25)	LTG	6 (22)	0.70
	PHT	12 (17)	PHT	4 (33)	PHT	3 (11)	0.91
	PB	8 (11)	PB	1 (8)	PB	2 (7)	0.74
	OXC	3 (4)			OXC	1 (4)	1
	GBP	1 (1)					
Polytherapy at time of CAR	21 (30)		6 (50)		11 (41)		0.31
No. ASMs as polytherapy							
2	12 (57)		4 (66)		6 (55)		0.3
3	7 (33)		1 (17)		5 (45)		0.4
4	2 (9)		1 (17)		0		1
VPA as CAR polytherapy[b]	12 (57)		3 (50)		8 (72)		0.17
CLB as CAR polytherapy[b]	5 (24)		2 (34)		4 (36)		0.17
C3POL as CAR polytherapy[b]	12 (57)		2 (34)		2(18)		0.4
Days with CAR symptoms[a]	7 (3; 14)		28 (19; 41)		28 (7; 36)		<0.001
Dermatological lesions							
Desquamation	3 (4)		x		x		
Cutaneous oedema	7 (10)		x		x		
Mucosal lesions	12 (17)		5 (42)		x		0.05
Plaques	13 (19)		6 (50)		16 (59)		<0.001
Vesicles	4 (6)		2 (17)		14 (52)		<0.001
Pustules	0		1 (8)		4 (15)		1
Total hospitalisations	27 (39)		12 (100)		21 (78)		<0.001
CAR hospitalisations	14 (20)		11 (92)		21 (78)		<0.001
Ward	14 (100)		9 (75)		13 (62)		<0.001
ICU	0		2 (17)		8 (38)		0.39
CAR as intercurrence[c]	13 (19)		1 (8)		0		0.017

This table describes all patients with a history of CAR due to ASMs, regardless of their indication (patients without epilepsy included).
Data are described as n (%) unless otherwise noted.
[a]mean ± SD
[b]Proportion of patients with polytherapy at the time of CAR who were taking valproic acid, clobazam or any C3POL.
[c]CAR as intercurrence: patients who presented with CAR during hospitalisation due to illnesses other than CAR. Causes of hospitalization- MPE: status epilepticus (4); stroke (3); cranioencephalic trauma (2); encephalitis (1); sepsis (1); meningioma (1); bipolar disorder (1); DRESS: encephalitis (1)
x: Characteristic needed or expected for specific CAR diagnosis, not included in statistical analysis.
CBZ: carbamazepine; CLB: clobazam; GBP: gabapentin; LTG: lamotrigine; PHT: phenytoin; PB: phenobarbital; OXC: oxcarbazepine; VPA: valproic acid.

associated ASM was VPA, used by 23 patients (60% of those in polytherapy and 21% of all CARs). The other most frequently associated ASMs were CLB and any C3POL drug, used by 11 and 16 patients (10% and 15% of all CARs), respectively. No association between these ASMs or other drugs (non-ASM) and CAR severity was found. The combination of LTG and VPA was also not associated with CAR severity.

The median (IQR) time between CAR use and the last interview was 6 (2–11) years. Data were collected during the acute phase in 18 (17%) cases. In four (22%) acute cases, the patients died during the same hospital stay: one TEN and one DRESS case whose hospitalisation and deaths were caused by SCARs, and two cases of MPE, one hospitalized due to stroke and another due to status epilepticus, whose deaths were not directly caused by CARs.

Ten (9%) patients reported CARs with more than one ASM. Patients diagnosed with SJS and overlapping SJS/TEN presented new CAR episodes with another ASM more frequently (cross-sensitivity) than patients in the MPE group (29%, 50%, and 8%, respectively) (p=0.01). C3POL drugs accounted for 119 (96%) of all CAR events (index plus cross-sensitivity CAR=124). CBZ was the most common index ASM, related to 7 (70%) patients; it also induced CAR in all patients who showed cross-sensitivity and were exposed to it (9 patients). Five (50%) patients reported CAR cross-sensitivity

▼ Table 2. Rates of cutaneous adverse reactions, use, and exposure among pairs of C3POL drugs and among combinations of other ASMs with each C3POL drug.

	ASM	N	Event	Rate of CAR/use and exposure of ASM				
				CBZ	PHT	PB	OXC	LTG
Given CAR to this ASM:	CBZ	53	CAR		15% (2/13)	23% (5/22)	17% (1/6)	20% (2/10)
			Use		85% (11/13)	73% (17/22)	83% (5/6)	80% (8/10)
			Exposure		25% (13/53)	42% (22/53)	11% (6/53)	19% (10/53)
	PHT	20	CAR	29% (2/7)		14% (1/7)	25% (1/4)	0
			Use	71% (3/7)		86% (6/7)	75% (3/4)	0
			Exposure	35% (7/20)		35% (7/20)	20% (4/20)	0
	PB	15	CAR	63% (5/8)	50% (1/2)		33% (1/3)	33% (1/3)
			Use	37% (3/8)	50% (1/2)		67% (2/3)	67% (2/3)
			Exposure	53% (8/15)	13% (2/15)		20% (3/15)	20% (3/15)
	OXC	5	CAR	33% (1/3)	25%(1/4)	33% (1/3)		0
			Use	67% (2/3)	75% (3/4)	67% (2/3)		0
			Exposure	60% (3/5)	80% (4/5)	60% (3/5)		0
	LTG	25	CAR	20% (2/10)	0	11% (1/9)	0	
			Use	80% (8/10)	0	89% (8/9)	0	
			Exposure	40% (10/25)	0	36% (9/25)	0	
	Other	5	CAR	80% (4/5)	50% (1/2)	100% (1/1)	100% (1/1)	0 (0/2)
			Use	20% (1/5)	50% (1/2)	0% (0/1)	0% (0/1)	100% (2/2)
			Exposure	100% (5/5)	40% (2/5)	20% (1/5)	20% (1/5)	40% (2/5)

Data are described as % (numerator/denominator), as following:
CAR: rate (%) of patients with mild or severe CAR (a) among those exposed (a+b) - %(a/a+b)
Use: rate (%) of patients with regular use of ASMs for a minimum period of 12 weeks without occurrence of CAR (b) among those exposed (a+b) - %(b/a+b)
Exposure: rate (%) of patients with CAR (a) plus number of patients who used ASMs (b) among those with CAR induced by a given ASM (N). -% (a+b/N)
CBZ: carbamazepine; PHT: phenytoin; PB: phenobarbital; OXC: oxcarbazepine; LTG: lamotrigine; other: CAR induced by other drugs (valproic acid [1]; gabapentin [1]; levetiracetam [1]; clobazam [1]; topiramate [1]).
Note: Only one patient presented with a CAR due to primidone; this patient also presented with a CAR due to lamotrigine and was not exposed to the remaining C3POL drugs. Overall, four (2%) patients used primidone; two (2%) from the control group and two (2%) with a history of CAR (due to lamotrigine and gabapentin).

when switching from the index ASM to a new drug, for whom the new skin rash occurred after improvement of the first. Four (80%) of these patients were in the MPE group (p=0.2). The index ASM was the first to induce CARs in eight (80%) patients and the second in two (20%) patients (one with MPE and one with overlapping SJS/TEN). The rates of cross-sensitivity, use, and exposure among ASMs are reported in *table 2*.

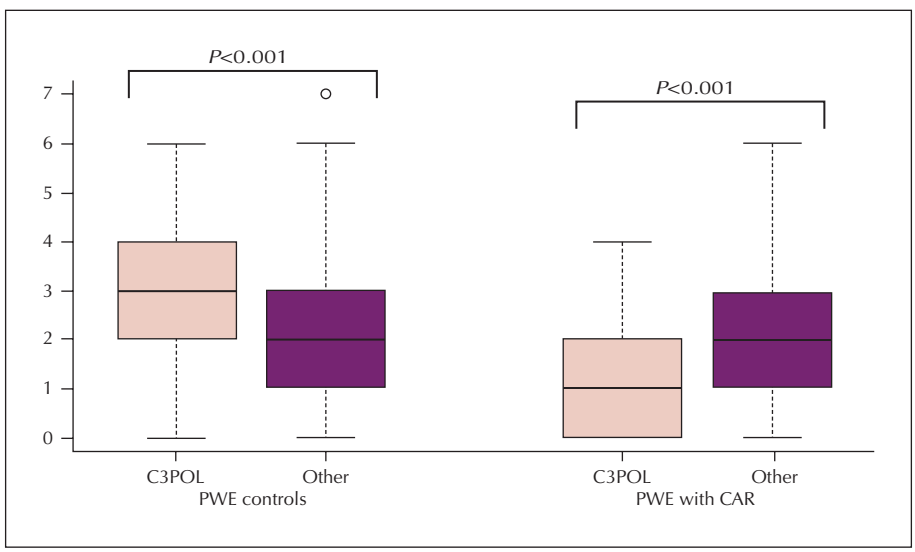
ASM was prescribed for indications other than epilepsy in 14 (13%) CAR patients (pain, mood, and movement disorders), four (4%) patients were followed for less than eight months after experiencing CARs, and two (2%) stopped seizure treatment after CARs. Since the four fatal cases were also excluded, the patterns of ASM use in 85 (78%) cases were available for analyses.

Drugs from the C3POL group represented a smaller proportion of all used ASMs among cases compared to controls (median [IQR] of 0.33 [0–0.5]) and 0.57 [0.5–0.67], respectively) (p<0.001) (*figure 2*). There was no difference between the number of other Used ASM between cases and controls (median [IQR] of 2 [1–2] and 2 [1–3], respectively) (p=0.06), but controls used a higher number of C3POL compared to cases (median [IQR] of 3 [2–4] and 1 [0–2], respectively) (p<0.001). Other drugs remained the most frequently used medications among CAR patients, even when the trigger ASM was included in the C3POL group (p<0.001).

Discussion

In our study, patients with a CAR history used C3POL drugs significantly less frequently than the control group (median [IQR] of 1 [0–2] and 3 [2–4], respectively). This pattern of use is consistent with the recommendation to avoid high-risk ASMs in patients with SCAR history, [10,11] for whom VPA, GBP, CLB, CZP, TPM, and LEV have been suggested as safe alternatives [10,12,13]. Most patients presented with mild CARs. It is unclear whether this caution contributed to the low incidence of cross-sensitivity (9%), considering previously reported rates of 8.8–36% [6,13,14].

Half of the patients with cross-sensitivity presented with a secondary CAR within days after complete recovery from the first one; these may represent "flare-up reactions" due to massive immune stimulation or true cross-sensitivity [15,16]. One would expect this phenomenon to occur more commonly in SCAR; although it was not statistically significant, most patients reporting consecutive CAR presented MPE (80% vs. 20% presenting SJS/TEN overlap). Remarkably, cross-sensitivity was more commonly seen in patients reporting at least one episode of SJS or SJS/TEN overlap (25%) than in those with recurrent MPE (7%) (p=0.03). Interestingly, the first CAR was reported as the worst at a high rate (80%), which cannot be explained by memory bias as this was reported equally among mild and severe CARs. Further work is needed



■ **Figure 2.** Number of lifelong antiseizure medications used by patients with epilepsy and a history of cutaneous adverse reactions and controls. C3POL ASMs included: carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), primidone (PRM), oxcarbazepine (OXC), and lamotrigine (LTG). Other ASMs included valproic acid (VPA), topiramate (TPM), levetiracetam (LEV), lacosamide (LCM), gabapentin (GBP), pregabalin (PGB), acetazolamide (AZM), diazepam (DZP), clobazam (CLB), clonazepam (CZP), and sulthiame (STM). PWE controls: patients with epilepsy controls. PWE with CAR: patients with epilepsy and a history of cutaneous adverse reactions.

to establish whether this may be explained by patient learning, leading to quicker recognition and management of CARs, or by true immunological adaptation.

In line with the results of Hirsch *et al*., CBZ, LTG, PHT and PB were the most common ASMs related to CARs [14]. Taken together, C3POL drugs accounted for 96% of all CARs and 100% of SCARs. These ASMs are commonly reported to be most frequently associated with CARs [4,6,12-14,17,18]. CBZ is the second most used ASM in the last six years (after VPA, which is also widely prescribed for indications other than epilepsy) [19]. It is also the most commonly used ASM for epilepsy and is available free of charge in primary care as a first choice ASM for focal epilepsy [20,21].

C3POL drugs have the highest SCAR scores according to RegiSCAR [7], but the similar proportion of mild CARs and SCARs for each ASM observed herein suggests that these scores may be helpful for the management of not only SCARs, but also ASM-related CARs in general. We were surprised to notice that MPE occurred more quickly when the offending ASM was CBZ or OXC. Once these patients were not taking high mean doses of these ASMs and prior exposure could not be identified, no direct inference could me made from sensitisation or quick titration. However, CBZ is a known persistent organic pollutant [22] and is a highly frequently detected pharmaceutical residue in water bodies [23], including drinking water [24], rivers [25], and post-sewage treatment water [25,26], as well as fish [27]. This could be a source of unaware sensitisation. Future studies should address this issue to confirm sensitisation by environmental CBZ at low concentrations. Furthermore, most of our patients were using the immediate-release form of CBZ. Unlike many other countries where sustained release preparations are widely used, immediate-release is the most commonly used form in Brazil [19]. It is noteworthy that CBZ immediate-release has a higher bioavailability than its sustained-release preparations. In addition, the metabolism of CBZ undergoes self-induction with prolonged treatment. Therefore, what at first glance seems a low dose might imply a higher serum level of CBZ and that of its metabolite CBZ-epoxide in the first week of treatment. CBZ-epoxide has been shown to alter the peptide-binding motif of B*15:02-restricted peptides [28]. This human leukocyte antigen (HLA) molecule is classically implied in CBZ CAR among Asians, however, only one (1%) patient among our cases and controls was of Asian ancestry. To the best of our knowledge, no study has addressed the association between HLA and CAR in the Brazilian population or the relation between CBZ preparations and metabolism and time to CAR onset.

A smaller, yet significant, association between SJS/TEN and VPA, LEV and CZP was described in a study using the US web-based Adverse Event Reporting System [4]. Rashes due to LEV or VPA were rare in our study, but VPA is a drug commonly associated with CARs. Valproate is recognized to enhance the risk of SJS/TEN, while it inhibits the metabolism of other ASMs, particularly LTG [11], and increases the blood level of free fractions of PB, PHT and CBZ. However, it alone has a weaker causal relationship with SJS/TEN compared to C3POL drugs [7].

Patients with a history of one CAR are at increased risk of another reaction compared to those with no CAR history [6,14,29,30]. Our study was not designed for risk analysis, however, most of our CAR rates between two C3POL drugs are in good agreement with those reported in a retrospective study that analysed the charts of 1,875 patients with epilepsy [14]. The high cross-sensitivity rates between PB, CBZ and PHT (14–63%) also align with those results [14]. Cross-sensitivity between these three ASMs and between CBZ and PHT have also been reported previously [6,13,30]. Despite the high rate of new CARs among cases, our rate of use without rash was also high, indicating that most patients taking a second C3POL drug actually responded well. Striking exceptions were patients with rash induced by other drugs, most of whom presented with CARs when exposed to C3POL drugs; these values were higher than those previously reported [14] and may be due to our smaller sample size.

The strict description and classification of CARs is another challenging task and is sometimes hindered by the most pressing actions during treatment management, specifically, identifying and managing the cause of the rash. In our cases, mucosal involvement was found in 17% of MPE patients and nearly half of DRESS patients, and its presence may complicate differentiation from SJS/TEN. This delimitation may be especially difficult in the presence of fever, malaise, or a more severe rash, which commonly occur in DRESS and are possible in MPE. Plaques and vesicles were more common in SCARs ($p<0.001$), however, they were also found in MPE cases. Although maculopapular exanthema is common in the initial SCAR presentation, the progression from a true MPE to DRESS or SJS/TEN upon drug continuation is questionable [31]. Clearly, some overlap in the immune mechanisms underlying these CARs do exist, and probably multiple mechanisms are present in most drug eruptions [32,33]. From this perspective, some unorthodox CAR phenotypes are conceivable, especially among MPE, which has more lenient diagnostic criteria compared to SCAR[34-36]. Nonetheless, it is always wise to differentiate between mild and severe CARs. A study evaluating the progression of drug exanthemas to SCARs found that cutaneous pain, mucosal involvement, and antiseizure medication were significantly associated

with progression to SCARs [37]. In a retrospective study of 208 SJS/TEN cases evaluated by dermatology hospitalists, MPE and DRESS were the main mimickers [38]. That study suggested that the presence of atypical target lesions, lymphopenia, fever, and Nikolsky's sign are predictive of SJS/TEN [38]. Unfortunately, these signals are difficult to discern by interviewing patients and may not be described by the general hospitalist, thus hindering CAR classification by a physician absent in the acute phase. In this situation, previous CARs may be considered severe until the contrary is proved. The use of illustrative pictures during patient interviews helped to retrieve skin lesion data of our cases; this is a simple procedure and may be useful to differentiate between mild and severe CARs in real-life settings.

We are aware that our research has some limitations. First, most cases were retrospectively evaluated, leading to inevitable data loss. Furthermore, we were restricted to easily recognisable and widely used skin lesion descriptors, limiting case depicture. Additionally, our groups could not be paired by epilepsy type and duration which might have influenced ASM use. However, at the end of the study, CBZ, PB, PHT, LTG, VPA, TPM and CLB were available free of charge in our country, providing treatment for most epilepsies with first-choice ASMs [39]. Considering that four of these seven ASMs belong to the C3POL group, CLB is not available as monotherapy, and LEV and LCM had been commercially available in our country for less than four years, we believe that our control group represented ASM use by patients with epilepsy in our country.

Our study also has some strengths. Because our study was not based solely on chart review, we could exclude patients whose charts indicated ``allergy '' for whom other adverse drug effects or unreliable relationships between CARs and ASMs were identified on closer inspection. We were also able to review SCAR criteria through a combination of chart data, illustrative pictures, and data recovered from the patients' personal collection of pictures of the acute CAR and other medical documents in addition to original charts. The in-person interviews also ensured that patient exposure to each ASM reported as used was regular and sufficiently long to induce CARs in susceptible patients. To our knowledge, this is the first study of its kind in a cohort of patients with epilepsy.

Our work has outlined C3POL drugs as the most common ASMs associated with CARs. Additionally, in the cases reported here, these six ASMs were used less frequently than the remaining 11 ASMs available in our country, which differed from the pattern of use of our controls. We believe that this pattern indicates an avoidance of C3POL drugs among patients with CAR history, even though most cases were mild. However safe this may seem, avoiding C3POL raises costs and narrows therapeutic options for epilepsy treatment. Furthermore, it dangerously circumscribes medication alternatives, given the possibility of status epilepticus, once the most accessible parenteral drugs, PHT and PB, are removed from the equation. Further research is needed to establish a tool which is capable of accurately determining the personal risk of CAR for each ASM. This tool may not only increase treatment safety but also render treatment more affordable and expand the chances of a seizure-free life. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Acknowledgements and disclosures.
We thank Dr. Carlos A. Twardowschy (Cajuru University Hospital), Dr. Anna Flávia Ribeiro dos Santos (Marcelino Champagnat Hospital), and the Marist Group for supporting this research. We also thank Dr. Fabiane Mulinari Brenner (Dermatology Department, Universidade Federal do Paraná) for her kind review of this study. We would like to thank Editage (www.editage.com) for English language editing.

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TEST YOURSELF

(1) Why are cutaneous adverse reactions particularly relevant in epilepsy treatment?

(2) Which antiseizure medications are most associated with skin rashes?

(3) Is skin rash severity associated with a higher incidence of cross-sensitivity?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".