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Review

Distinguishing Benign Rashes From Severe Skin Reactions From Anti-Seizure Medications

Ram Mani, MD, MSCE[1,*]
Ahmad Almelegy, MD[1]
Thu Minh Truong, PharmD[1]
Gaurav N. Pathak, PharmD[1]
Mary L. Wagner, PharmD, MS[2]
Cindy Wassef, MD[3]

Address
[*,1]Department of Neurology, Rutgers Robert Wood Johnson Medical School, 125 Paterson St, CAB Suite 6200 Neurology, New Brunswick, NJ 08901, USA
Email: ram.mani2@rutgers.edu
[2]Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ, USA
[3]Center for Dermatology, Rutgers Robert Wood Johnson Medical School, 1 World's Fair Drive Suite 2400, Somerset, NJ, USA

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Abstract

Purpose of review This review describes risk factors for severe skin reactions to antiseizure medications (ASMs), the usage of updated tests to predict those with increased risk of a severe cutaneous reaction, and guides how to choose specific ASMs and dosing to lower the risk for these reactions. Information is given regarding specific mild versus severe reactions, initial diagnostic evaluation, and treatment. A table listing the risk of mild and severe cutaneous reaction risks as well as the management of potential seizures that may occur while stopping the culprit ASM are provided.
Recent findings Five new ASMs have joined the total of 26 FDA-approved ASMs since 2018. Cenobamate had three patients develop a drug reaction with eosinophilia and systemic symptoms. A lower starting dosing and slower titration have resulted in no further published cases. Based on limited data, rash risk is low for fenfluramine,

ganaxalone, and stiripentol. It is low-moderate for Epidiolex. Molecular tests can predict severe reactions.
Summary Skin reactions are a relatively common side effect of ASMs with aromatic ASMs having the greatest risk. Identifying and informing high-risk patients when to seek medical attention, stopping the culprit ASM when a severe reaction looks possible, and providing appropriate medical triage can reduce morbidity and mortality from severe skin and systemic reactions.

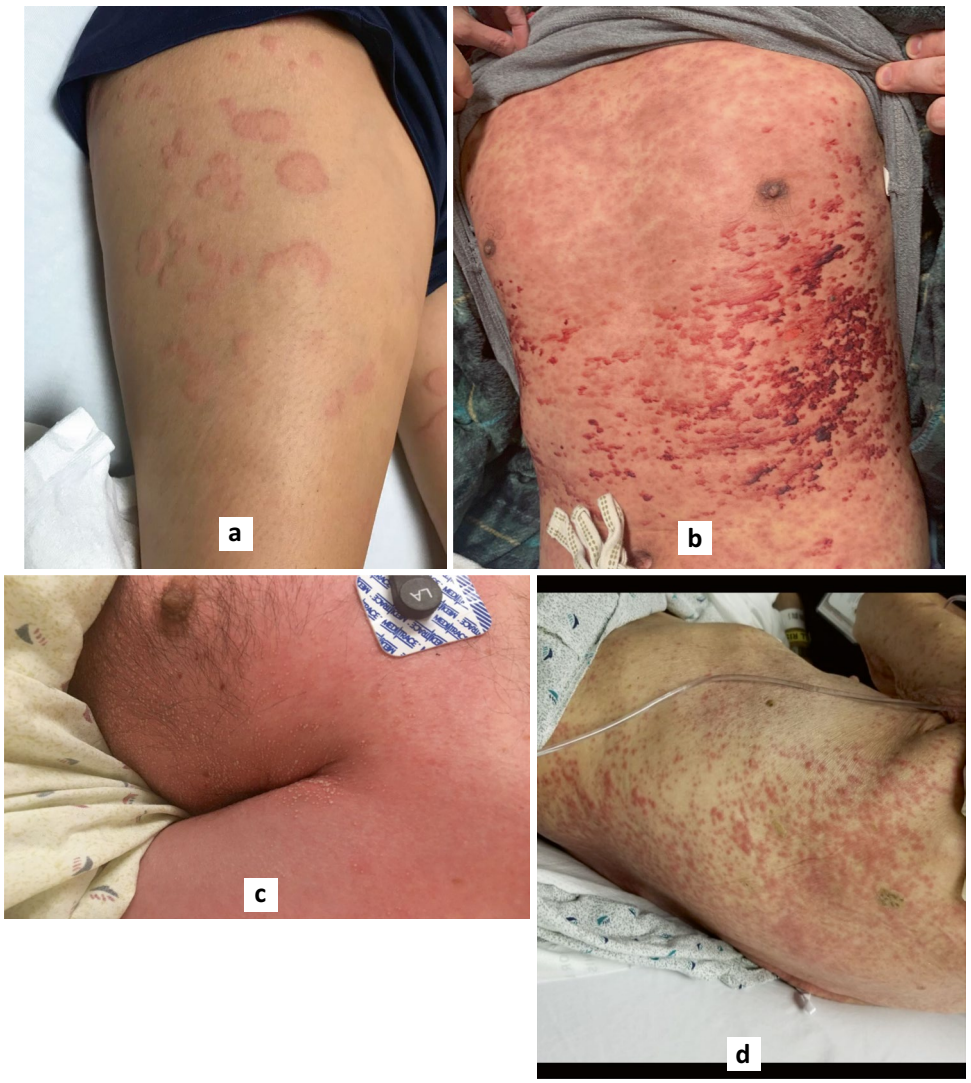

Fig. 1 Pictures of rashes. **a** Urticaria; **b** Stevens-Johnson syndrome (SJS); **c** acute generalized exanthematous pustulosis (AGEP); **d** morbilliform drug eruption.

Introduction

Antiseizure medications (ASMs) are commonly used to treat epilepsy, mood disorder, migraine, and other pain disorders. ASMs are well known to cause cutaneous adverse drug reactions (CADRs) of varying severity. The incidence of these reactions ranges from 2 to 16% and up to 25% for those with a prior history of CADR to an ASM [1, 2]. A subset of CADRs known as severe cutaneous adverse reactions (SCARs) include Stevens-Johnson syndrome (SJS) (Fig. 1b) and toxic epidermal necrolysis (TEN) and are associated with approximately 5–10% mortality [3••, 4].

Significant risk factors for the development of CADRs include the use of an aromatic ASM, higher early goal dose, and fast upward dose titration. Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, lamotrigine, rufinamide, and zonisamide are the most frequently reported aromatic ASMs to cause CADRs or SCARs [5, 6••]. Patients experiencing CADRs while receiving carbamazepine, oxcarbazepine, lamotrigine, or phenytoin also have a higher risk of cross-sensitivity when switching between these agents [7, 8]. Other reported risk factors include age less than 12 years, females younger than 50 years, genetic factors, and certain HLA subtypes associated with race for hypersensitivity to specific drugs. In addition, concomitant use of medications that decrease ASM clearance may increase the risk of CADRs [1, 6••, 9]. Immunosuppression and having certain autoimmune disease are also reported as possible risk factors [1]. SJS/TEN is reported at higher rates in patients with HIV (especially those receiving abacavir or nevirapine), systemic lupus erythematosus, use of anti-cancer immune checkpoint inhibitors, or active radiation therapy for cancer [10, 11, 12•, 13••].

Currently, the two main molecular markers for drug hypersensitivity prediction are specific HLA alleles and genetic polymorphisms in drug metabolism. HLA allele testing has utility and high specificity in identifying patients of specific racial subgroups at risk for SCARs to specific ASMs. This includes clear recommendations to test for HLA-B*15:02 (lamotrigine, phenytoin, carbamazepine, oxcarbazepine) and HLA-A*31:01 (carbamazepine, oxcarbazepine, phenytoin). The FDA labeling for carbamazepine and the prior two mentioned alleles discusses being aware of the status of those two alleles in patients with ancestry of sufficient allele prevalence. Additionally, different sources have also recommended testing HLA-B*15:11, HLA-B*15:21, HLA-A*33:03, HLA-B*40:01, and HLA-B*57:01 (carbamazepine), but the magnitude of the association SCAR and strength and reliability of the evidence to test these specific alleles has varied between publications [14•, 15•]. Additionally, genetic differences in drug metabolism of phenytoin and fosphenytoin impacting CADR risk can be predicted from mutations in CYP2C9 [15•]. Guidance for genetic testing is evolving and clinicians should refer to the Clinical Pharmacogenetics Implementation Consortium Online Genes-Drugs database (cpicpgx.org) for the most up-to-date information. Lastly, checking for clinically relevant drug-drug interactions and adjusting doses can also reduce CADRs. For example, the starting dose and titration are lower and slower for lamotrigine in patients who are also taking valproate or other inhibitors of lamotrigine metabolism [16].

Early on, it can be difficult to distinguish between relatively benign conditions versus potential life-threatening reactions as well as other potential causes of the rash. However, this is important because early cessation of the culprit drug can reduce morbidity and mortality for a SCAR. Removing an offending agent can increase the risk of withdrawal seizures, and practitioners need to be prepared to treat the CADR while managing potential seizures. To help neurologists correctly identify different CADRs, the following section will describe the presentation and treatment of a variety of common CADRs.

Skin eruption presentations

Benign cutaneous reactions

Morbilliform exanthematous eruptions

Morbilliform drug eruptions represent the single most common drug reaction, accounting for 50–95% of ASM CADRs [17] (Fig. 1d). Classically, this eruption can begin within 1 to 2 weeks of starting a medication. It can, however, present sooner on re-exposure to medication. It is characterized by erythematous macules and papules covering the trunk and extremities and may be associated with a low-grade fever [18]. The most frequent medications reported to cause the condition are carbamazepine, lamotrigine, oxcarbazepine, phenytoin, and zonisamide. The suspected agent should be discontinued if such an eruption occurs, with resolution expected within 1–3 weeks. It is important to note, however, that morbilliform eruptions can initially worsen within the first 3 days after discontinuation before abating [4]. Topical mid-to-high-potency corticosteroids can be used for symptomatic relief of pruritus. Because this is not a histamine-mediated reaction, antihistamines have limited utility beyond their use for sedation.

Fixed drug eruptions

Fixed drug eruptions typically present within hours after drug exposure but may present within the first 14 days. They are characterized by a single to a small number of round erythematous to violaceous plaques. The classic areas of presentation include the oral mucosa including lips, hands, feet, and genitalia. *The hallmark of this drug reaction is that upon re-exposure to the inciting agent, the lesions will appear in the same spot as prior eruptions*. The lesions can have associated bullae. Lesions will fade on their own within a few days after discontinuation of the medication but may leave behind a transient hyperpigmented patch [4]. Phenobarbital has been reported as a cause, however, the most common causative agents are antibiotics, NSAIDs, and acetaminophen/paracetamol [4]. No treatment is required; however, topical mid-potency steroids can be used for symptomatic relief [19].

Lichenoid drug reactions

Lichenoid drug reactions are characterized by shiny purple polygonal papules. They often lack the Wickham striae seen in traditional lichen planus. The average age of a patient diagnosed with lichenoid drug reaction is 65 years old and the overall incidence is rare after ASM exposure. The most common agents are monoclonal antibodies, small molecule inhibitors (e.g., tyrosine kinase inhibitors), beta-blockers, and diuretics [20]. Papules are often found in a more generalized distribution on the trunk and extremities as opposed

to wrists and legs seen in classic lichen planus. The reaction can recur with offending medication rechallenge. However, in contrast to the other benign cutaneous reactions, the period between medication ingestion to rash presentation can be from months to years [21]. Time to resolution of this reaction upon discontinuation of medication can also be weeks to months [4]. No labs or biopsy are needed for diagnosis but can be confirmatory. Treatment options include mid-potency topical and oral steroids as well as phototherapy. Oral antihistamines can be used for symptomatic relief of pruritus if needed [22].

Erythema multiforme (EM)

Erythema multiforme (EM) is a benign self-limited skin condition characterized by abrupt onset of erythematous round "target-like" papules with well-defined pink to red patches or plaques in a concentric ring pattern. These lesions are fixed and symmetrically located on extremities and face and can recur. EM is mostly caused by infections, with herpes simplex virus (HSV) and *Mycoplasma pneumoniae* infections being most common and typically presenting within 24–48 h and self-resolving within 2 weeks [18]. Skin biopsy is not necessary for diagnosis when the clinical picture is clear. Approximately 10% of EM is induced by drugs, and ASMs have been reported as an uncommon etiology for EM [4]. It has also been seen with sulfonamides and other antibiotics, NSAIDs, allopurinol, and monoclonal antibodies use.

EM is divided into minor and major variants with the main difference being the presence of bullous lesions, extensive mucosal involvement, fever, and arthralgias. Clinical examination can distinguish between erythema multiforme and more severe drug reactions such as SJS/TEN. While previously thought to be on a spectrum, it is now accepted that erythema multiforme represents a separate disease process and cannot later progress to SJS/TEN [4]. Symptomatic relief can be achieved using oral antihistamines and mid-potency topical steroids. While oral acyclovir or prednisone may also be considered, their utility remains controversial [22].

Urticaria

Urticaria is characterized by erythematous juicy papules lasting less than 24 h. Onset is usually within minutes to hours of medication ingestion (Fig. 1a). They can appear anywhere on the trunk, face, and extremities and can vary in shape and size [4]. The most common medication causes are antibiotics, monoclonal antibodies, and NSAIDs. Phenytoin, carbamazepine, pregabalin, and lamotrigine have been reported as rare causes of urticaria. As this is a histamine-mediated reaction, antihistamines are the mainstay of treatment.

Serious cutaneous reactions

Acute generalize exanthematous pustulosis (AGEP)

AGEP is characterized by an acute onset of multiple sterile pustules on a background of erythema, starting in the intertriginous areas (Fig. 1c). It is usually associated with a high fever, burning sensation, and pruritus. The lesions quickly spread beyond the intertriginous areas within a few hours. Onset is usually within a few days up to 2 weeks of drug initiation and occurs in 5% of the cases. While not required, a biopsy can be performed to histologically confirm this diagnosis. Histopathological analysis of the biopsies consistently demonstrates spongiform subcorneal and/or intraepithelial pustules, an edematous papillary dermis, and perivascular infiltrates primarily composed of neutrophils, occasionally accompanied by eosinophils [23]. Antibiotics, antifungals, antimalarials, and hydroxychloroquine are the more commonly reported etiologies, and NSAIDS is a less common etiology. Carbamazepine, lamotrigine, levetiracetam, and phenytoin have been reported as rare etiologies. Upon discontinuation of the medication, AGEP usually resolves in 1 to 2 weeks with significant desquamation noted [4]. Topical steroids and antipyretics can be used for symptomatic relief while oral corticosteroids are indicated in severe cases. Notably, patients presenting with erythrodermic patterns will likely require inpatient management [24].

Drug reaction with eosinophilia and systemic symptoms (DRESS; also known as drug-induced hypersensitivity reaction, DIHS)

Drug reaction with eosinophilia and systemic symptoms (DRESS; also known as drug-induced hypersensitivity reaction, DIHS) is a life-threatening condition characterized by fever and morbilliform eruption starting within 2 to 6 weeks of medication initiation and typically resolves within 1 to 6 months, with subsequent exposure leading to sooner onset [17, 25]. In a French retrospective cohort series of 49 pediatric cases with DRESS, the median time from initiation of the culprit drug to onset of DRESS was 21 days for ASMs while it was 12 days for non-ASM culprit drug [26•]. Phenytoin, carbamazepine, lamotrigine, oxcarbazepine, and phenobarbital are the most common causes [27]. However, there is a case report of DRESS in a patient receiving levetiracetam (non-aromatic). Eslicarbamazepine acetate, zonisamide, perampanel, ethosuximide, valproate, fosphenytoin, clobazam, gabapentin, and cenobamate have also been reported [28]. Non-ASMs have been reported in a few case reports, but many of the cases reported in United States FDA Adverse Event Reporting System safety database and in databases from other countries were confounded by another possible culprit drug [29]. Other common etiologies include beta-lactams, allopurinol, sulfonamides, and vancomycin.

Symptoms include malaise, fever, skin eruptions ranging from morbilliform to hemorrhagic, bullous lesions, and conjunctivitis. Facial edema is a classic finding. Lymphadenopathy, eosinophilia, and potentially life-threatening hepatic involvement are also seen [30, 31]. Other organ systems can also be affected including the heart and less commonly the thyroid, kidney,

and brain. Patients must be closely monitored for liver and thyroid functions. Moreover, careful follow-up is advised due to the prevalence of late-onset autoimmune thyroiditis, diabetes, and myocarditis after the resolution of symptoms. This reaction can continue for weeks despite drug discontinuation with mortality estimate at 2–6%. A scoring system from the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) can be used to help confirm the diagnosis [32] (Table 1). Oral or intravenous prednisone 1–2 mg/kg/day or oral or intravenous cyclosporine are the treatment of choice. The steroid tapering off should be done over 2 to 3 months [24].

Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN)

Stevens-Johnson syndrome and toxic epidermal necrolysis represent acute life-threatening dermatologic emergencies. They are distinguished by the percent body surface area of detached skin, with SJS representing < 10%, SJS/TEN representing 10–30%, and TEN representing > 30%. Frozen skin section biopsy can aid in the diagnosis. It is almost always secondary to medication use. It is characterized by fever, eye pain, and/or pain with swallowing 1 to 3 days prior to cutaneous manifestation. Cutaneous manifestations include erythematous to dusky macules and cutaneous and mucosal erosions. The macules can coalesce leading to blister formation. Slight pressure on the macules leads to epidermal detachment known as the Nikolsky sign. This process can take hours to days. The main morbidity is concomitant infection due to

Table 1. RegiSCAR for diagnosis of DRESS

Criteria	Weight		
	−1	**0**	**+1**
Fever ≥ 38.5 °C	N/U	Y	
Enlarged lymph nodes		N/U	Y
Atypical lymphocytes		N/U	Y
Skin rash extent > 50% BSA		N/U	Y
At least 2: edema, infiltration, purpura, scaling	N	U	Y
Biopsy suggesting DRESS	N	Y/U	
Disease duration > 15 days	N/U	Y	
Alternative diagnoses excluded (hepatitis A, B, C; blood cultures; ANA; mycoplasma; chlamydia)		N/U	Y
Internal organs involved (e.g., liver, kidney, lung, muscle, heart, pancreas, thyroid, brain)	+1 for one organ; +2 for two or more organs		
Eosinophilia	+1 if $0.7–1.49 \times 10^9$L (or 10–19.9% if WBC < 4.0×10^9L); +2 if > 1.5×10^9L (or > 20% if WBC < 4.0×10^9L)		

RegiSCAR score and DRESS probability: < 2 none; 2–3 possible; 4–5 probable; > 5 definite

Y yes, *N* no, *U* unknown, *BSA* body surface area, *ANA* antinuclear antibody

Table 2. SCORTEN for SJS/TEN mortality prognosis

Prognostic factor	Weight if present
Age > 40 years	1
Cancer or hematologic malignancy present	1
Heart rate > 120 beats/min	1
Serum BUN > 28 mg/dL (10 mmol/L)	1
Serum bicarbonate < 20 mmol/L	1
Serum glucose > 250 mg/dL (> 13.88 mmol/L)	1

SCORTEN Scoring Criteria for mortality rate is: 0–1 = 3.2%, 2 = 12.1%, 3 = 35.3%, 4 = 58.3%, ≥ 5 = 90% mortality rate

extensive denudation of the skin [30, 33]. The prognosis and mortality rate can be estimated using the SCORTEN scoring system [34] (Table 2).

SJS/TEN etiologies have significant overlap with those of DRESS. Lamotrigine, carbamazepine, phenytoin, phenobarbital, and oxcarbazepine are the most commonly reported ASM etiologies. Rarely, other ASMs have been reported as etiologies. Other etiologies include allopurinol, sulfonamides, nevirapine, and *Mycoplasma pneumoniae* [35•]. A somewhat different syndrome has been reported in thirteen patients having intense ultraviolet (UV) light exposure and starting various culprit drugs. They had an SJS/TEN-like presentation but did not have the typical flu-like symptoms before the cutaneous changes. The rash first occurred in the areas exposed to the UV light and preferentially affected those areas over the duration of the SJS/TEN. Four of those patients had recently started an ASM (i.e., carbamazepine, clobazam, lamotrigine) [36••].

Immediate discontinuation of the offending medication, supportive care, and admission to a burn unit for wound care are the first steps in treatment. A multidisciplinary approach to management is needed and consultation with nutrition, urology, gynecology, and ophthalmology should be obtained. Although no specific treatments have shown benefit in prospective control trials, small case reports support the use of pulse dose dexamethasone for 3 to 5 days and cyclosporine 3–5 mg/kg for 7 days as well as tumor necrosis factor-alpha inhibitors such as etanercept [4]. The North American Therapeutics in Epidermal Necrolysis Syndrome (NATIENS) is a recently started multi-center randomized controlled trial (RCT) examining the benefits of etanercept vs. cyclosporine vs standard of care in recently diagnosed adults with SJS or TEN.

Angioedema

Angioedema represents edema of the dermal, subcutaneous, and submucosal tissues due to a loss of vascular integrity. It can be associated with urticaria, can be seen in Type I hypersensitivity reactions, and rarely progresses to anaphylaxis. Severe cases have been reported to start within a few minutes of medication intake. Angioedema is most associated with angiotensin-modulating agents, antibiotics, NSAIDs, and monoclonal antibodies. There have been very rare case reports from patients taking carbamazepine, oxcarbazepine, phenytoin, pregabalin, levetiracetam, Epidiolex, and brivaracetam [37]. The

most common clinical findings are sudden onset asymmetric swelling of the face with potential involvement of the oropharynx, larynx, and epiglottis. Its effects on the bowel wall can cause abdominal pain, nausea, vomiting, and diarrhea. Prompt discontinuation of the ASM and administration of an antihistamine and oral corticosteroids can be used for treatment with a taper often required after the condition is acutely managed [4]. Airway involvement or anaphylaxis is a medical emergency requiring more management.

Anaphylaxis

Anaphylaxis is a life-threatening reaction that often occurs within minutes of drug ingestion. It is associated with urticaria, hypotension, and tachycardia, although there can be some cases with no cutaneous manifestations. Other manifestations include hoarseness, dyspnea, wheezing, abdominal pain, and dizziness. Phenytoin, oxcarbazepine, felbamate, and levetiracetam have had very rare case reports associated with anaphylaxis, while it is most associated with antibiotics and NSAIDs [37]. Severe cases can lead to cardiogenic shock and death. Prompt discontinuation of the medication is necessary [4]. If angioedema and anaphylaxis conditions are severe, intramuscular epinephrine, securing the airway, vasopressors, and intravenous corticosteroids are indicated [19, 24].

Considerations for specific ASMs and when stopping a suspected ASM

Lacosamide, levetiracetam, brivaracetam, valproate, gabapentin, topiramate and clobazam have lower risk of rash and cross-reactivity [6••]

Of the newer ASMs receiving FDA approval since 2018, cenobamate has received the largest attention for CADR and SCAR risk. In early testing for epilepsy using a fast titration schedule (i.e., starting at 50 mg and increasing by 50 mg every 2 weeks to at least 200 mg/d), three cases of DRESS occurred and one of those resulted in fatality [38]. Since then, the manufacturer has recommended a lower starting dose and slower titration strategy (i.e., start at 12.5 mg/d, increase to 25 mg after 2 weeks, and further increases every 2 weeks following a schedule found on the Prescribing Information). The manufacturer has reported no further cases of DRESS or SJS/TEN despite several thousands of patients newly starting cenobamate over the past 4 years. For cannabidiol's brand formulation Epidiolex, the manufacturer issued an alert for patients to have caution if they are sensitive to sesame seed because part of the formulation is sesame seed oil; no SCARs have been reported with this formulation. There may be a small but increased risk of CADR with fenfluramine based of review of two pivotal RCT in of 122 patients with Dravet syndrome receiving it (Prescribing Information). The other four ASMs with FDA approval since 2018 have no likely SCARs published as of August 2023 (Table 3).

When stopping an ASM causing a SCAR, the risk of a severe seizure exacerbation in the next week is relatively low if the ASM is of low dosage, was

Table 3. Antiseizure medications and cutaneous adverse drug reactions

Antiseizure medications (USA FDA approval)	Relative cutaneous reaction risk, level of evidence for severe cutaneous reaction	Brief comments of reviewed literature	Reported cutaneous reaction patterns
	Aromatic ASMs		
Cannabidiol (2018)	Very low risk No SCAR	One case report of SJS with a commercial oil preparation for chronic pain (non-FDA approved form) [42] Epidiolex has sesame oil 2 RCT reported dose-dependent morbilliform dermatitis or angioedema [43, 44]. Systematic review of 12 RCTs found rash was reported in 1.1% (5/454) of participants [45].	Single SJS case; morbilliform dermatitis, angioedema [42–44]
Carbamazepine (1968)	Relatively high risk for rash and SCAR Very good evidence of SCAR	Outpatient retrospective review reports a 1.8% higher risk of a cutaneous reaction compared to other ASMs [1]. Prospective cohort study of children reported rash in up to 13% of children [46]. One of the most common ASMs causing SJS/TEN and DRESS	SJS/TEN; morbilliform dermatitis; DRESS; fixed drug eruption [1, 9, 25, 47–50]
Cenobamate (2019)	Low risk for rash (slow titration) Presently low risk for DRESS, and this has only been reported in faster titrations.	RCT reported a 3.3% rate of papular rash with no cases of DRESS occurring using a slow titration protocol in 1339 patients [38]. Successfully used in 5 patients with history of rash to other ASMs [51].	DRESS, "papular" rash; allergic dermatitis, urticaria [38, 52]

Table 3. (continued)

Antiseizure medications (USA FDA approval)	Relative cutaneous reaction risk, level of evidence for severe cutaneous reaction	Brief comments of reviewed literature	Reported cutaneous reaction patterns
Clobazam (2011)	Low risk for rash. Few reports of SCAR with good quality evidence and many with combination ASM.	Any rash risk of 1.5% in 171 patients [1] No rash was reported in 417 adults or FDA listing of 179 patients from pivotal trial [53]. Systematic review reported 6 cases of SJS/TEN [54•]. An RCT of 119 patients found 0 patients reported adverse cutaneous events compared to carbamazepine or phenytoin [55]. Cutaneous reactions reported in patients on multiple ASMs combined with clobazam, there are few reports of other cutaneous reactions to clobazam alone [56, 57].	SJS/TEN; DRESS [54•, 58]
Eslicarbazepine (2013)	Low-moderate risk for rash (depending on target dose). Very rare reports of SCAR with varying evidence quality.	A 13-year post-marketing study found that rash accounting for 17/402 of adverse events, with 14 reporting non-serious rashes, and 3 developing SJS, "erythematous" skin rash, and "allergic rash" [59]. RCT reported 1/193 patients treated with eslicarbazepine monotherapy having a "severe cutaneous reaction" [60]. A systematic review found rash in 1.9% (vs. 0.9% placebo) of 1021 treated adults; rate was 3.2% for 1200 mg/d target dose. In 202 treated children, rash risk was NOT increased vs. placebo; allergic dermatitis was 3% (vs. 0 placebo). Rash was rare and associated rarely with DRESS or urticaria [61].	SJS, DRESS; urticaria; EM [59, 61, 62]

Table 3. (continued)

Antiseizure medications (USA FDA approval)	Relative cutaneous reaction risk, level of evidence for severe cutaneous reaction	Brief comments of reviewed literature	Reported cutaneous reaction patterns
Ethosuximide (1960)	Moderate risk for rash. Few reports of SCAR of good quality.	Few reported cases of SJS/TEN. 3.9% of 154 treated children developed moderate or severe rash resulting in treatment failure [63].	SJS; TEN; DRESS; exfoliative dermatitis; urticaria [64–68]
Felbamate (1993)	Low risk, but possibly small risk increases with maximal target dose. No SCAR reports found.	Similar to placebo in dosages up to 3600/mg in treated adults (n=114) or children (n=31) [69]. 1% in 94 patients [1] 3.4% incidence (compared to 0 for low dose valproate) when used at 3600 mg/d as monotherapy in 58 adults.	None
Fenfluramine (2020)	Currently low-moderate risk with limited data. No SCAR reports.	FDA PI reports 5–8% rash (vs. 4% placebo) for 122 patients treated (dosages of 0.2–0.7 mg/d goal).	None
Ganaxalone (2023)	No skin rashes reported. No SCAR reports.		None
Lacosamide (2008)	Very low risk of rash. No SCAR reports.	4 pooled RCTs reported rash in 2.5% for 1307 treated patients, which was similar to 2.9% for placebo [70, 71]. One case report of a patient with mild popular rash in the first 10 days of the drug [72].	None

Table 3. (continued)

Antiseizure medications (USA FDA approval)	Relative cutaneous reaction risk, level of evidence for severe cutaneous reaction	Brief comments of reviewed literature	Reported cutaneous reaction patterns
Lamotrigine (1994)	At least moderate risk of rash (even higher risk with faster titrations or polytherapy). Numerous SCAR reports of good quality.	"Adverse dermatologic reaction" in 8.3% of 18,698 patients newly receiving lamotrigine monotherapy in systematic review of 122 RCTs [73]. 5% rash in one cohort study [1] Less but significant cross reactivity than carbamazepine, oxcarbazepine and phenytoin [7, 74] SJS is a serious but rare, incidence increases when combined with valproate	SJS/TEN, DRESS, AGEP, Urticaria, EM
Oxcarbazepine (2000)	Moderate to high risk of rash Numerous SCAR reports of good quality	2.5% in cohort study of 248 patients. [1] 8% rash risk in 210 patients receiving that drug in an RCT (compared to 1% receiving gabapentin) [75]	SJS/TEN; DRESS, AGEP
Perampanel (2012)	Low risk for rash 1 report of DRESS with moderate quality	2.3% rash risk in 771 treated patients (vs. 1.2% placebo) in 9 pooled RCTs [76]	DRESS [77]
Phenobarbital (introduced 1912)	Rash risk present but difficult to quantify. Numerous SCAR reports	2.3% rash [78] Case series for SCARs [79]	SJS/TEN; DRESS
Phenytoin (1953)	Moderate to high risk of rash Numerous SCAR reports of high quality	3.9% (19/486 patients) rash risk higher than average 30–58% hypersensitivity reaction incidence in patients with prior carbamazepine hypersensitivity reactions. SJS is common and serious side effect [1, 7, 74].	SJS/TEN; DRESS; AGEP; Urticaria

Table 3. (continued)

Antiseizure medications (USA FDA approval)	Relative cutaneous reaction risk, level of evidence for severe cutaneous reaction	Brief comments of reviewed literature	Reported cutaneous reaction patterns
Primidone (1954)	Rash risk present but difficult to quantify.	10% reported rash and other dysmorphic and idiosyncratic side effects of the 109 adults starting this drug in an RCT (reported as 14% for carbamazepine, 11% for phenobarbital, 22% phenytoin) [80]. 0% in cohort study of 60 patients receiving drug [1]	
Rufinamide (2008)	Low risk for rash Rare cases of DRESS and SJS in children reported	Rash occurred in 1–2% more patients compared to placebo for ages 3 yrs. to adulthood [81].	DRESS, SJS
Stiripentol (2018)	No skin rashes reported in limited data.		
Zonisamide (2000)	Low-moderate risk for rash. Numerous SCAR reports of high quality	3 and 3.7% had rash in RCTs of 593 treated children and adults (vs 2 and 2.4% in placebo) in Prescribing Info and other reports [82, 83]. 4.5% in cohort study of 219 patients taking drug [1]	Photosensitive lichenoid drug eruption, DRESS, SJS/TEN
	Non-aromatic ASMs		
Brivaracetam (2016)	Very low risk No SCAR	Rash in 1.3% 2542 treated patients (vs 1.1%) in pooled RCTs 1 case of EM [84]	EM
Gabapentin (2000)	Very low risk of rash, up to 1% No SCAR reports of individual patients.	1% reported allergic rash in 358 patients treated as part of a RCT of children and adults [75].	

Table 3. (continued)

Antiseizure medications (USA FDA approval)	Relative cutaneous reaction risk, level of evidence for severe cutaneous reaction	Brief comments of reviewed literature	Reported cutaneous reaction patterns
Levetiracetam (1999)	Very low risk of rash, often reported in up to 2%. About 6 cases of DRESS reported A few cases of SJS/TEN are confounded by patient receiving multiple drugs [85].	2 and 4% reported skin and subcutaneous tissue in two recent RCTs where a total of 588 children and adults were treated with the drug [82, 83]. 1.1% of 835 adults reported rash treated with the drug (compared to 3.4% with valproate or carbamazepine) in an RCT [86]. 0.5% in cohort study of 627 patients receiving drug [1]	DRESS [87, 88••]
Pregabalin (2004)	Very low risk of rash, less than 1% No SCAR.	Rash was not reported in two RCTs of a total of 476 adults receiving the drug [89, 90].	
Topiramate (1994)	Low risk of rash, up to 4% No reliable SJS/TEN or DRESS reported monotherapy cases.	2–5% rash in SANAD studies for ages 5 to adulthood for 616 patients treated. [75, 91]	
Valproate (1983)	Low risk of rash Very low frequency of SCAR monotherapy reports	0.8% rash in RCT of 257 children and adults treated with monotherapy. [82] 1% rash in cohort study of 411 patients. [1] 1.7% mild cutaneous in 237 children receiving the drug; no SCAR on monotherapy. [9] Approximately 7 cases DRESS and SJS/TEN from valproate monotherapy have been reported. Many more reports are with valproate in polytherapy [92].	DRESS; SJS/TEN

Table 3. (continued)

Antiseizure medications (USA FDA approval)	Relative cutaneous reaction risk, level of evidence for severe cutaneous reaction	Brief comments of reviewed literature	Reported cutaneous reaction patterns
Vigabatrin (2009)	Low risk of rash No SCAR found.	1/43 patients reported eczema and no rash in 43 adults and older adolescents receiving the drug in RCT [93]. 3.8% of 130 patients receiving the drug reported rash (compared to 2.2% in placebo) in an RCT [94].	

started in the past 2 weeks, and when the patient remains on concurrent other long-term ASMS that have helped their epilepsy. One should plan for a replacement ASM, especially if the discontinued ASM had a clear benefit to a patient with a disabling and uncontrolled epilepsy. The replacement choice should favor an ASM that has a lower risk of cross-reactivity. Considerations of the mechanism of action, renal and hepatic dosing, route of administration, and other factors may also guide ASM selection. For patients needing to abruptly and emergently stop a moderate daily dosage of phenobarbital or benzodiazepine of more than 2 weeks usage, it is prudent and reasonable to utilize another benzodiazepine with regular dosing each day for approximately 5 days or longer for additional short-term seizure protection while the non-benzodiazepine ASM reaches steady state concentration.

Patients with uncontrolled seizures are more likely to have a significant worsening of their seizures when an ASM helpful for their seizure control is abruptly stopped. Patients most at risk have long-standing epilepsy with monthly or more frequent seizures, convulsive seizures and a history of status epilepticus or seizure clusters. If all ASMs for a patient are stopped in favor a new ASM, there is a significant risk of worse seizures. This can be estimated in a prior pooling of data from several conversions to monotherapy trials [6••]. In these trials, patients with uncontrolled epilepsy were tapered off their original one to two ASMs over a four-to-eight-week period and concurrently tapered up on a new ASM. A pooled analysis of the six conversion-to-monotherapy trials evaluating a total of 1258 patients demonstrated that 39% of patients had at least one seizure-related event concerning for insufficient efficacy of the newly introduced ASM when assessed over 16 weeks. Approximately two-thirds of patients had a doubling of seizure frequency over either multiple months or over a typical two-day period, while one-third had generalized convulsion, status epilepticus, or another more severe seizure manifestation not typical for their recent epilepsy history [6••].

A safer and much faster reduction of an ASM in the inpatient epilepsy monitoring unit (or similar to a well-monitored unit) can be useful for a patient with medically refractory epilepsy. Often in this setting, there is readily available nursing support, continuous video EEG monitoring, IV rescue medications, and treatment protocols and expertise for dealing with seizure urgencies. A recent study examined adult and pediatric patients on multiple ASMs with medically refractory focal epilepsy having inpatient continuous video EEG monitoring unit for epilepsy surgery planning. One of their long-standing ASMs was stopped over 24–48 h period in this prospective RCT of ASM taper speeds. The mean time to first seizure for these "fast taper" 65 patients was 3 days (1.7 days standard deviation), 21% had focal seizures spreading to bilateral tonic–clonic seizures, and 11% needed a rescue medication such as midazolam IV [39]. The closer expert monitoring and care, safety protocols, and the use of rescue medication helped avoid status epilepticus in this trial. Prior to discharge, counseling the patient should include seizure precautions (e.g., avoiding driving, swimming, cooking, or operating heavy machinery), whether to use rescue medicine (e.g., lorazepam tablet, intranasal diazepam or midazolam, or another fast-acting benzodiazepine), and an emergency response plan for worsening seizures or rash symptoms.

If the CADR is mild and not progressing, many practitioners first attempt to reduce the dose after assessing the patient to see if the rash resolves. If this is not successful, the medication should be stopped. However, all hope is not lost for future use of the ASM of concern. Some patients stopping the ASM in this instance have been able to successfully restart the same ASM 4 weeks or later at a lower dose and titrate much more slowly without issues. This was summarized in a case series and literature review of lamotrigine causing mild CADR. After stopping lamotrigine, it was restarted 4 weeks or later beginning at 5 mg/d, increasing by 5 mg every 2 weeks to eventually 25 mg/d, and then following a typical dose increase at that point. Twenty of the twenty-seven patients in that study and 85% of the 75 patients in the literature review combined analysis were able to successfully restart lamotrigine and titrate it up. The reinitiation of lamotrigine was less likely to be successful when restarting earlier than 4 weeks before first discontinuation (36 vs. 7% failure) or when the first rash presentation had more potentially serious features (23 vs. 0% failure). The potential serious features in the first rash presentation include the following: exfoliation or erythroderma (and this was given three times the importance compared to the other criteria); purpura, tenderness, or blistering; facial or mucous membrane involvement; lymphadenopathy; hematological abnormalities (e.g., eosinophilia) or elevated transaminase enzymes; and constitutional symptoms (fever, malaise, arthralgia, pharyngitis, cough). The authors did not attempt to rechallenge patients with 3 or more points on this scale [40]. A similar study was done in 20 patients in Korea with prior CADR to oxcarbazepine. There were no risky findings on HLA-A*3101 or HLA-B*1502 testing for these patients. They were rechallenged by starting at up to 3 mg/d of oxcarbazepine and increasing gradually every 1–2 weeks to an eventual dose of 612 mg/d between weeks 10 and 12 (10 mg/kg/d). All patients completed the twelve-week protocol without a persistent rash or related reactions. However, 5/20 had a transient rash of the face and extremities develop during the rechallenge titration (mostly at weeks 4–6). This rash was resolved by lowering the drug dose, and antihistamines were used for symptoms. There were no SCARs from this rechallenge, and follow-up ranged from 1 to 7 years [41]. More information for published protocols for desensitization to phenytoin, phenobarbital, lamotrigine, carbamazepine, oxcarbazepine, and valproate can be found in a prior review article [6••]. *In summary from these lessons, many patients with a mild CADR may be able to safely restart a culprit ASM that was essential to their management by: testing for HLA and/or CYP specific for ASM metabolism when appropriate; and using a very low dose and slow, medically-monitored, titration strategy after at least 4 weeks from culprit drug discontinuation.*

Conclusion

CADRs from ASMs are a relatively common side effect. Certain aromatic ASMs are the most common culprits, and most presentations are limited morbilliform drug eruptions that start in the first few months and will resolve in 1 to 3 weeks with drug stoppage. However, SCARs may occur

with other non-cutaneous signs or symptoms and lead to significant morbidity and mortality, and thus a multidisciplinary approach is important. Counseling the patient to be aware of these mild versus severe scenarios and the next steps in order to quickly triage and begin early cessation of the ASM with inpatient management can reduce morbidity and mortality. Patients may need adjunctive ASM treatment to prevent withdrawal seizures and a new ASM (preferably a non-aromatic ASM). Recognizing risk factors, specific dosing strategies, and implementing genetic testing in certain subgroups can decrease CADR occurrence. A multidisciplinary team approach for patients with AGEP, DRESS/DIHS, or SJS/TEN to include dermatology, neurology, and other specialties on a case-by-case basis can allow more accurate diagnosis and better patient-specific management. Topical or systemic steroids and/or antihistamines are a common treatment for some patients with the CADRs. Currently, there is active research into identifying better treatments for SJS/TEN. For patients with a mild CADR, reducing the ASM dosage and slowing the taper upwards can be done in some cases if the CADR improves, in the absence of systemic signs/symptoms, and if the ASM is very valuable in management. When benefits outweigh risks, some ASMS can be safely and successfully reintroduced in patients who previously had a mild ASM CADR by following dose titration protocols that are available in the literature [6••].

Author Contribution

RM, CW, and MW provided design and outline leadership. RM, TT, GP, and AA wrote the manuscript. RM, AA, CW, and MW revised the manuscript. RM, AA, TT, GP, and MW provided information for the tables. RM and AA revised tables and figures. CW provided information for the figures. All authors reviewed the manuscript.

Compliance with Ethical Standards

Conflict of Interest

Ram Mani declares that he has no conflict of interest. Ahmad Almelegy declares that he has no conflict of interest. Thu Minh Truong declares that he has no conflict of interest. Gaurav N. Pathak declares that he has no conflict of interest. Mary L. Wagner declares that he has no conflict of interest. Cindy Wassef declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

The authors did not disclose patient identifying data in the manuscript. For the pictures in the manuscript, there is no way for a patient to be identified based on the review of the picture. No patient rights were infringed upon during the writing and publishing of this manuscript.

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- • Of importance
- •• Of major importance

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