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STEVENS-JOHNSON SYNDROME INDUCED BY LAMOTRIGINE: A CASE REPORT

GUILLAUME PEYRAC[1]*, REVATHI SINHA[2], LUKAS KESSELRING[3]

Affiliation

[1]Department of Pharmacovigilance, Jura Centre for Medicinal Chemistry, Lons-le-Saunier, France
[2]Department of Pharmacy Practice, Krishna Plateau College of Pharmacy, Khammam, India
[3]Department of Pharmacy Practice, Fichtelgebirge Centre for Drug Research, Hof, Germany

*Corresponding author: Guillaume Peyrac, g.peyrac@jcmc.fr
ORCID iD: Guillaume Peyrac 0000-0001-4345-8423; Revathi Sinha 0000-0001-1568-5290; Lukas Kesselring 0000-0001-1122-4833

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Abstract

Lamotrigine is widely prescribed for epilepsy and bipolar disorder, yet it remains one of the antiepileptic drugs most often linked to Stevens-Johnson syndrome (SJS). This narrative review draws on published case reports, case-control studies, pharmacogenetic work and treatment series to describe how lamotrigine-associated SJS arises, how it is recognised, and how it is managed. Dose, rate of titration and co-prescribed valproate emerge as the best-supported modifiable risks, while genetic markers are weaker than for carbamazepine. Early withdrawal and supportive care are the only measures with consistent support. Evidence for immunomodulators rests on small and conflicting studies. The review reports no new patient or experimental data.

1. INTRODUCTION

Few cutaneous reactions frighten prescribers as much as Stevens-Johnson syndrome (SJS). It begins unremarkably, often with fever and malaise that resemble an ordinary viral illness, and within days the skin and mucous membranes can begin to blister and detach. Along with toxic epidermal necrolysis (TEN), it sits at the severe end of the spectrum of drug-induced cutaneous adverse reactions, and the two conditions are now generally treated as variants of one disease distinguished by the extent of skin detachment [1, 2]. Mortality is real, and survivors frequently carry ocular, genital and psychological sequelae for years.

Medicines are the commonest identifiable trigger. Case-control studies and population-based registries in Europe and the United States have repeatedly pointed to a short list of offenders, among them allopurinol, sulfonamide antibacterials, nevirapine, oxicam-type anti-inflammatory

drugs and a group of aromatic antiepileptic drugs (AEDs) [3, 4]. Within that last group, lamotrigine holds an awkward position. It is generally well tolerated, it lacks the enzyme-inducing properties of older agents, and it is useful in several seizure types as well as in bipolar disorder. That popularity means a great many people start it every year, and a small fraction of them will react.

A case report of lamotrigine-induced SJS is easy to write but hard to learn from unless it is set against what is already known. For that reason this article does not describe an individual patient. It reviews the published case reports and the larger epidemiological, mechanistic and therapeutic literature that give such reports meaning. The sections that follow cover the pharmacology of lamotrigine that is relevant to rash, the evidence on incidence and risk, the immunology and genetics, clinical recognition, causality assessment, and management. Throughout, the aim is to separate what is firmly established from what is repeated in textbooks without much support.

A note on scope is useful. The discussion concentrates on severe cutaneous reactions in people taking lamotrigine for any indication, and it leans on evidence available up to 2022. Benign rashes, which are far more common than SJS, are mentioned only where they help to explain how clinicians try to anticipate the severe form. Anticonvulsant hypersensitivity syndrome, also called drug reaction with eosinophilia and systemic symptoms, overlaps clinically and is touched on in the section on differential diagnosis. Dose figures quoted come from labelling and the cited studies and should be checked against current national guidance.

Children deserve a separate comment, because the early paediatric experience shaped lamotrigine's labelling. Rash rates in trials were higher in children than in adults, and the first reports of serious reactions were disproportionately in young patients, many of whom had received valproate without dose reduction. Dosing in children is mostly weight-based and the dose steps are small, so practical errors in measuring or titrating the tablets are a recognised concern. Parents also tend to notice and report skin changes early, which in principle helps, but a mild illness with fever and rash in a child is very common, and it can be difficult to judge when a rash is more than a virus [5].

2. PHARMACOLOGY AND RASH RISK

Lamotrigine is a phenyltriazine that stabilises neuronal membranes by blocking voltage-gated sodium channels, and it reduces the release of excitatory amino acids such as glutamate. It is absorbed almost completely after oral dosing and is cleared mainly by glucuronidation. In monotherapy the half-life is roughly a day or a little more, but this changes sharply with co-medication. Valproate inhibits glucuronidation and approximately doubles the half-life, whereas carbamazepine, phenytoin and phenobarbital induce it and shorten it considerably [6, 7]. Oestrogen-containing contraceptives also lower lamotrigine concentrations, which matters for dose adjustment in women.

The interaction with valproate is the pharmacological fact most relevant to rash. When the two drugs are combined without adjusting the lamotrigine dose, exposure rises well beyond what the nominal dose would suggest. Clinical trial and post-marketing analyses found that the rate of serious rash was higher in patients receiving valproate, and that it fell when the starting dose was reduced and escalation slowed [6, 8]. This is why current labelling recommends a halved starting dose and slower steps with valproate, and a higher schedule when enzyme inducers are present.

Why a drug that blocks sodium channels should provoke an immune reaction in the skin is not fully settled. One proposal is that reactive metabolites, possibly arene oxide intermediates, act as haptens, binding to proteins in keratinocytes or dendritic cells. Another is that the parent drug interacts directly with the T-cell receptor and an HLA molecule without needing processing. Both ideas have been explored mainly with carbamazepine and other aromatic compounds, and the evidence for lamotrigine specifically is thinner [9]. What can be said is that the reaction is delayed, dose-related in the sense of exposure rather than toxicity, and not predictable from the pharmacology alone.

Lamotrigine's place in therapy explains why this risk is tolerated at all. It is effective against focal and generalised seizures, it has a favourable cognitive and weight profile compared with several alternatives, and it is among the preferred options for women of childbearing potential. In bipolar disorder it is used mainly to prevent depressive relapse. Because of these advantages, the drug was widely adopted after licensing, and reports of severe cutaneous reactions accumulated in the years that followed. Early reviews of the post-marketing experience linked many of the serious cases to rapid titration and valproate, which led to revised dosing recommendations and a boxed warning on the product label in several jurisdictions [6, 10].

Rapid titration deserves special mention because it is the one risk factor prescribers fully control. Controlled and observational data suggest that exceeding the recommended starting dose or escalating faster than advised raises the chance of rash, and that some reported severe cases involved exactly that pattern [8, 11]. It would be too strong to claim that perfect titration eliminates SJS; reactions have followed careful schedules. But deviations from the schedule recur in case reports, and they are the easiest finding to prevent.

In practice the picture is further complicated by polytherapy. Many people prescribed lamotrigine have already had inadequate responses to other drugs, and so arrive on complex regimens with several interacting agents. The sequence in which drugs are introduced and withdrawn then affects both lamotrigine exposure and the interpretation of any later rash. Clinicians reviewing a suspected reaction should reconstruct that sequence in detail, because the culprit may not be the most recently added drug.

3. INCIDENCE AND RISK FACTORS

Rash of some kind affects around one in ten people starting lamotrigine in clinical trials, but most of these eruptions are mild maculopapular reactions that settle. Serious rash requiring admission was reported in about 0.3% of adults and close to 1% of children in the early development programme, with children clearly at higher risk [5, 6]. These figures come from trial populations treated under varying titration rules, and later practice with slower escalation has probably lowered them. SJS and TEN account for only a minority of the serious rashes, which is why incidence estimates of SJS itself are much lower and less precise.

Case-control studies give a different angle by estimating the relative risk against background. Registry data and earlier international studies placed lamotrigine among the AEDs with a clear excess of SJS and TEN, and a registry-based analysis of new users found that the excess was concentrated in the first two months of treatment [3, 12]. A study of the first weeks of AED therapy reached the same conclusion about timing, with the highest risk within roughly the first eight weeks [13]. Beyond that window new cases become uncommon, which is clinically useful: a rash arising after many months on a stable dose is less likely to be lamotrigine.

Absolute risk is best understood against the background incidence of the syndrome itself. SJS and TEN are rare in the general population, with estimates of a few cases per million people each year in Europe and North America, and higher rates in people with HIV infection or on certain drugs [14]. Among exposed groups the picture shifts. For lamotrigine, the excess is real but modest in absolute terms, and the absolute figures depend heavily on which dose schedule, comorbidity and co-medication are present. This perspective helps in counselling, since it avoids both false reassurance and unnecessary alarm about a drug that benefits many people [3, 14].

Several patient and treatment factors have been proposed. The strongest are co-prescription of valproate, a high initial dose, rapid dose escalation, and a history of rash with another AED [11, 15]. Younger age is associated with more severe rash in the early trials, although paediatric dosing was initially not adjusted for valproate in the way it is now [5]. Sex, ethnicity and indication have been examined with inconsistent results. Some work suggests that people with bipolar disorder have a lower rash rate, but this is hard to separate from differences in dosing

practice between psychiatric and neurological care.

Cross-reactivity between AEDs is a practical concern when a replacement must be chosen. A large single-centre analysis found that a history of rash with one AED raised the likelihood of rash with another, and that the aromatic agents carbamazepine, phenytoin, phenobarbital and lamotrigine showed the most overlap [15, 16]. Because SJS itself is a far more serious event than a benign rash, most guidance advises avoiding the whole aromatic group after SJS rather than relying on the modest cross-reactivity figures from milder reactions.

The main published findings on lamotrigine-associated SJS are brought together in table 1, which groups them by risk factor, genetic and mechanistic evidence, diagnostic tools and management. The distribution of entries by theme is shown in fig. 1. Two things stand out. Risk factors related to prescribing practice are better documented than those related to the patient, and the management entries rest more often on observational work than on trials. Readers should treat the table as a map of the literature rather than a ranking of effect sizes, because the studies involved differ in design, population and era.

4. IMMUNOPATHOGENESIS AND GENETICS

The histology of SJS is dominated by keratinocyte death, with scattered necrotic cells at first and then full-thickness epidermal necrosis and sub-epidermal blistering. The cells found in blister fluid are chiefly cytotoxic CD8+ T lymphocytes and natural killer cells. A landmark study identified granulysin, a cytolytic protein released by these cells, as a key mediator of the widespread keratinocyte death, with blister fluid concentrations far above those expected from the small number of infiltrating cells [17]. Levels of perforin and granzyme B also correlate with severity [18].

The Fas pathway has attracted attention for longer. Soluble Fas ligand is raised in the serum of patients with SJS and TEN before skin detachment, and it can induce keratinocyte apoptosis in culture [19]. An earlier report showed that pooled human intravenous immunoglobulin (IVIG) containing anti-Fas antibodies could block this process in vitro, which provided the rationale for clinical use [20]. Later clinical results did not repeat the early enthusiasm, and the discrepancy between a convincing bench rationale and unconvincing bedside outcomes is one of the unresolved puzzles of the condition.

Genetics has transformed prevention for some drugs. The association between HLA-B*1502 and carbamazepine-induced SJS, first described in people of Han Chinese ancestry and later reported in Thai patients, led to prospective screening in Taiwan, which markedly reduced the incidence in the screened population [21, 22]. For European patients a different allele, HLA-A*3101, carries risk for carbamazepine hypersensitivity of several types [23]. Pharmacogenetic dosing guidance now exists for carbamazepine, and its practical value is well established [24].

The reasons why only a few patients react also bear on how severe disease is described. A drug-specific T-cell response needs a susceptible HLA background, a suitable T-cell repertoire and probably a co-stimulating environment, and viral infection or other inflammation may provide the last of these. Reports describing SJS after a respiratory illness while taking lamotrigine are consistent with such a model, though they cannot prove it. If true, the same drug at the same dose would be harmless in most patients and dangerous in a few, which fits the observed epidemiology much better than a dose-dependent toxic effect would [9, 17].

Table 1: Published features of lamotrigine-associated SJS and the evidence behind them

Domain	Reported finding or recommendation	Ref.
Co-prescribed valproate raises exposure	Inhibits glucuronidation, prolongs half-life and is associated with higher rates of serious rash	[6, 7]
Dose escalation speed of titration	Higher starting dose and rapid increases linked to more rash; lower starting doses reduce it	[8, 11]

Domain	Reported finding or recommendation	Ref.
Timing of onset new users	Risk concentrated in the first eight weeks after starting treatment	[12, 13]
Previous AED rash cross-reactivity	Earlier rash with an aromatic AED raises the chance of a lamotrigine reaction	[15, 16]
HLA-B*1502 Han Chinese cohorts	Over-represented across aromatic AED cases, weak and inconsistent for lamotrigine	[25, 26]
HLA typing European patients	No marker with predictive value sufficient to justify routine screening	[23, 27]
Granulysin and Fas ligand mediators	Cytotoxic T-cell products implicated in widespread keratinocyte death	[17, 19]
ALDEN algorithm causality	Scores delay, drug presence, dechallenge, notoriety and alternative causes	[28, 29]
SCORTEN prognosis	Seven admission variables predict mortality and guide the level of care	[30, 31]
Early withdrawal culprit drug	Stopping the drug early is associated with lower mortality, especially for long half-life drugs	[32]
IVIG, steroids, ciclosporin immunotherapy	Evidence conflicting or observational; etanercept promising in one small trial	[33, 34, 35]

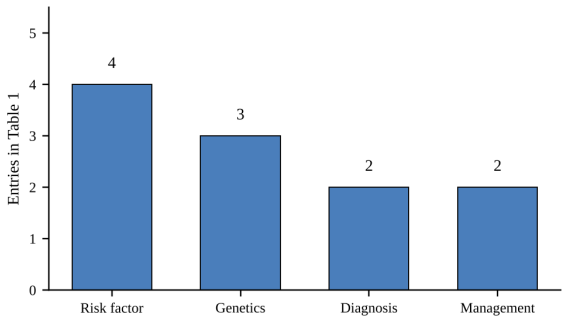


Fig. 1: Number of entries in table 1 by theme

Lamotrigine has not been so fortunate. A pooled analysis in Han Chinese patients found HLA-B*1502 over-represented across several aromatic AEDs, including some lamotrigine cases, while other cohorts gave weak or inconsistent signals [25, 26]. High-resolution HLA typing in lamotrigine-treated patients of European descent found no marker with enough predictive power to justify screening [27]. The numbers in these studies are small, because lamotrigine SJS is uncommon, and so the possibility of a modest or population-specific association is not excluded. At present no genotype test is recommended before lamotrigine is prescribed.

It is also worth remembering that most pharmacogenetic associations have low positive predictive value, even when strongly significant, simply because the reaction is rare. A marker carried by a sizeable share of the population will be present in many people who never react. This limitation explains why screening is advised only where the association is both strong and tied to a high-risk population, as in carbamazepine and HLA-B*1502.

5. RECOGNITION, CAUSALITY AND DIFFERENTIAL DIAGNOSIS

Recognising SJS early is the most important step, because the outcome depends on how quickly the culprit is withdrawn. A prodrome of fever, sore throat, conjunctival irritation and malaise typically precedes the rash by one to three days. The skin lesions begin as dusky, flat, atypical target-like macules, often on the trunk and face, which coalesce and blister. Painful erosions of the mouth, eyes and genitals are characteristic. Detachment of less than 10% of body surface area (BSA) defines SJS, 10–30% overlap, and more than 30% TEN, according to the widely used classification [2]. Positive Nikolsky sign and pain out of proportion to the visible rash should raise alarm.

Clinicians may find it helpful to think of the early illness in terms of warning features rather than a diagnostic checklist. Fever with a rash that is tender, spreads quickly, or involves the lips, mouth or eyes should prompt withdrawal of lamotrigine while the work-up proceeds. Most benign lamotrigine rashes are itchy, symmetrical and maculopapular, and they appear without mucosal erosions. Skin pain, dusky colour and blistering point the other way. Because a benign rash and the start of SJS can look alike for a day or two, many case reports describe delays in recognition, sometimes with continued dosing for several days after the

first skin changes [2, 6, 10].

The differential is wide. Erythema multiforme major, usually triggered by herpes simplex or *Mycoplasma pneumoniae* rather than by drugs, can look similar but spares the trunk and has typical raised targets [2, 36]. Staphylococcal scalded skin syndrome, generalised bullous fixed drug eruption, acute generalised exanthematous pustulosis and autoimmune blistering diseases all need to be considered. The anticonvulsant hypersensitivity syndrome, with facial oedema, lymphadenopathy, eosinophilia and organ involvement, may coexist with early SJS and has a later onset in many cases, though the two overlap [36].

Laboratory and histological work-up supports rather than makes the diagnosis. A skin biopsy showing full-thickness epidermal necrosis with a sparse dermal infiltrate helps to exclude mimics such as autoimmune blistering disease, although the changes are not specific to a drug cause. Blood tests typically show lymphopenia and sometimes raised liver enzymes. In vitro tests of drug-specific T-cell reactivity, such as the lymphocyte transformation test, have been studied, but their sensitivity is modest and varies with timing, so they are not used to confirm the culprit in routine practice. Patch testing is not performed in the acute phase, and for lamotrigine the value of any later testing is unproven, and re-exposure for diagnosis is not acceptable [36, 37].

Once the diagnosis is made, attribution matters because several drugs are usually in play. Generic causality scales, the Naranjo algorithm among them, are quick but were not designed for severe skin reactions, and they handle delayed hypersensitivity poorly [28]. The ALDEN algorithm was developed specifically for SJS and TEN, and it scores each drug on the delay from first intake, the presence of the drug in the body on the index day, prior exposure and reaction, the effect of withdrawal, the notoriety of the drug in earlier studies, and alternative aetiologies [29]. In validation against case-control data it separated high-risk from low-risk drugs reasonably well.

Applying ALDEN to lamotrigine has a subtlety that case reports do not always acknowledge. The algorithm gives its highest score for a delay of five to twenty-eight days, a window that fits lamotrigine well, but it also requires thought about how long the drug remains in the body. With valproate co-prescribed, lamotrigine persists longer than the nominal dose interval implies, and this affects the item on drug presence at onset. Notoriety is high for lamotrigine, which increases the score, so competing suspects such as a recently started antibiotic or allopurinol must be judged on the same terms.

Outcome expectations differ across the spectrum, and clinicians have to communicate them honestly. Mortality in SJS is lower than in TEN, with a risk that grows with age, comorbidity and the extent of detachment, and the SCORTEN estimate gives a more individual figure than the bare diagnostic label [30, 31]. Survivors are not necessarily well. Quality-of-life work and long-term follow-up studies report persistent symptoms in a substantial share, particularly of the eyes, skin and mood. Honest discussion of this at an early stage helps families prepare for a prolonged recovery that is rarely visible in the short case summaries found in journals [31, 37].

Pharmacovigilance reporting is the final element. Cases should be reported to national systems with the full medication timeline, doses, titration and interacting drugs, since aggregated reports are how rare signals are detected. Reports that omit the interacting drug or the dose history reduce the value of the entry considerably. Clinicians sometimes feel reporting duplicates the hospital record, but regulators rely on it, and the dose-timing details are exactly what makes a lamotrigine report informative.

6. MANAGEMENT AND OUTCOMES

The one intervention with consistent support is prompt withdrawal of the suspected drug. In a prospective study of patients with SJS and TEN, those who stopped the culprit on or before the day blisters first appeared had a lower risk of death than those who continued, with the effect most marked for drugs with long half-lives [32]. For lamotrigine, whose half-life is prolonged by valproate, this argument is especially forceful. Anyone

presenting with a rash plus fever or mucosal lesions during the first weeks of treatment should have the drug held until a dermatological opinion is available, even before the diagnosis is certain [6, 32].

Choosing replacement seizure control is a problem that case reports often leave unexplained. Stopping lamotrigine abruptly in someone with epilepsy exposes them to withdrawal seizures, yet the dermatological emergency leaves no room for tapering. Agents without an aromatic ring structure, such as levetiracetam, are commonly chosen as bridging treatment, because the cross-reactivity data indicate that other aromatic drugs carry extra risk [15, 16]. Valproate has been used in some reports but interacts with any remaining lamotrigine. Neurological input should be sought early, so that seizure control and skin management are planned together instead of in sequence [16, 37].

Supportive care determines the rest. Patients with extensive detachment are best managed in a burns or intensive care unit, where fluid replacement, nutrition, temperature control, wound care and analgesia can be coordinated. Ophthalmological review is needed early, since ocular involvement can lead to chronic scarring, and mucosal care of the mouth and genitals reduces adhesions. Sepsis is the main cause of death, so cultures are taken according to clinical need. Prophylactic antibiotics are not generally recommended. These measures lack randomised trial support, but they follow long clinical experience in burns care [37].

Skin care is aimed at protecting the exposed dermis rather than at removing it. Approaches differ between centres, with some leaving the detached epidermis in place as a biological dressing and others debriding it, and non-adherent dressings or silver-containing products are commonly used. No comparative trial exists, and conclusions rest on clinical series from burns units. Early transfer to a specialist centre appears to improve outcomes when it occurs within the first days, which is consistent with the pattern in survival analyses showing that delay in reaching expert care is associated with worse prognosis [31, 32, 37]. Fluid replacement is generally more modest than in thermal burns, since over-resuscitation causes oedema.

Ocular involvement receives special attention because the damage done in the first weeks is permanent in many survivors. Acute-phase measures include frequent lubricants, topical antibiotic or anti-inflammatory drops according to need, daily examination, and the lysis of early adhesions between the eyelid and the globe. Some centres use amniotic membrane grafts for severe corneal and conjunctival disease, and small series suggest benefit when applied early, though randomised data are lacking. Late complications include trichiasis, dry eye, corneal scarring and visual loss, and they remain among the most frequent reasons that survivors need long-term specialist care [37].

Prognostic scoring helps decide the level of care. SCORTEN incorporates seven variables at admission: age over 40 years, malignancy, heart rate above 120 per minute, initial BSA detachment over 10%, serum urea above 10 mmol/L, serum glucose above 14 mmol/L and bicarbonate below 20 mmol/L [30]. Each present item adds a point, and predicted mortality rises steeply with the total. Later survival analyses confirmed the score's usefulness while noting that it works best when applied in the first days [31]. It is a triage tool, not a measure of treatment effect.

Specific immunomodulatory treatment is where the evidence is weakest. Systemic corticosteroids, IVIG, ciclosporin, and TNF antagonists have each been used. A retrospective analysis from the EuroSCAR cohort found no clear survival benefit from IVIG or corticosteroids compared with supportive care alone [33]. A later systematic review and meta-analysis concluded that IVIG did not show a benefit, while corticosteroids and ciclosporin showed signs of reduced mortality, though the data were observational and heavily confounded [34]. A randomised trial of etanercept, set against corticosteroids, reported faster skin healing and lower than predicted mortality, but it was small and from a single population [35].

Long-term follow-up is not an afterthought. Survivors may have dry eye, symblepharon, visual loss, cutaneous pigment changes, nail dystrophy and genital synechiae, and some

develop psychological distress that is rarely captured in the hospital literature [37]. Documenting the culprit drug in the record and giving the patient a clear card or letter listing lamotrigine, and cautioning against related aromatic AEDs, is a practical step with real protective value, particularly when the patient later sees clinicians unfamiliar with the history.

7. GAPS AND FUTURE DIRECTIONS

The literature has recurring weaknesses. Most lamotrigine-specific reports are single cases or small series, which are prone to selection and reporting bias, and the denominators needed to estimate true incidence are usually missing. Severe rash definitions vary between studies, titration schedules changed over time, and valproate use is reported inconsistently. As a result, statements about relative risk often combine eras and populations that are not strictly comparable [3, 12, 13].

Several questions are open. Whether a clinically useful genetic marker exists for lamotrigine in any population remains unclear, and larger multi-ethnic cohorts with high-resolution typing would be needed to answer it. The value of therapeutic drug monitoring for patients on valproate has been proposed but not tested against rash outcomes. Standardised reporting of titration and co-medication in case reports would make pooling possible. Finally, adequately powered randomised comparisons of immunomodulators are needed, since current practice relies on small trials and observational contrasts [34, 35].

Regulatory and pharmacovigilance systems also shape what is known. Spontaneous reporting provides signals but cannot give incidence, and different countries apply different label warnings and titration schedules, which makes cross-national comparison difficult. Prescriber awareness has probably improved with time, so older estimates of risk may not apply to current practice. Linked health-record databases that record dose, interacting drugs and outcomes together would give a better picture, provided the severe cutaneous reactions are validated by clinical review rather than coded from diagnosis labels alone [3, 6, 14].

8. CONCLUSION

Lamotrigine-induced SJS is uncommon but not rare enough to ignore, and the literature points to a fairly consistent picture. Risk is highest in the first two months, rises with valproate co-prescription, high starting doses and fast titration, and is somewhat higher in people who have reacted to another aromatic AED. Genetic tests that work well for carbamazepine have not been shown to help with lamotrigine, so careful prescribing remains the main preventive tool (table 1) [6, 8, 11, 27].

Once a reaction is suspected, the evidence favours speed: stop the drug, refer, and provide supportive care in a unit able to deal with extensive skin loss. Causality tools such as ALDEN and prognostic scores such as SCORTEN structure decisions but do not replace judgement [29, 30, 32]. Immunomodulators remain unproven. Better reporting of dose histories, larger pharmacogenetic studies and well-designed trials would do more for patients than further isolated case descriptions, and until they exist, vigilance and patient counselling are the most reliable safeguards [9, 18, 24, 34, 35, 37].

9. ABBREVIATIONS

SJS-Stevens-Johnson syndrome, TEN-Toxic epidermal necrolysis, AED-Antiepileptic drug, HLA-Human leukocyte antigen, IVIG-Intravenous immunoglobulin, BSA-Body surface area, ALDEN-Algorithm of drug causality for epidermal necrolysis, SCORTEN-Severity-of-illness score for toxic epidermal necrolysis, EuroSCAR-European Study of Severe Cutaneous Adverse Reactions, TNF-Tumour necrosis factor

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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