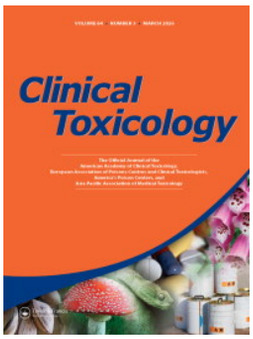

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REVIEW

Lamotrigine-induced Stevens–Johnson syndrome: a systematic review of case reports and case series

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ABSTRACT

Introduction: Lamotrigine is prescribed for neurological and psychiatric conditions, including epilepsy and bipolar disorder. Although generally safe, it may cause rare but severe cutaneous adverse reactions, such as Stevens-Johnson syndrome. This review synthesized case reports and case series on lamotrigine-induced Stevens–Johnson syndrome to improve clinical awareness and promote safer prescribing.

Methods: PubMed was searched from inception to December 2024 using terms related to lamotrigine and Stevens-Johnson syndrome. Eligible studies were case reports or case series demonstrating Stevens-Johnson syndrome after lamotrigine use. Studies not reporting Stevens–Johnson syndrome, lacking clinical details, or not implicating lamotrigine were excluded. A total of 264 records were identified, and 36 studies met the inclusion criteria. Screening, quality assessment, and data extraction were done independently by two reviewers. Data on demographics, indications for use, lamotrigine dosage, co-administered drugs, clinical features, management, and patient outcomes were extracted and synthesized.

Results: Thirty-six studies comprising 38 individual cases were included. Lamotrigine was used either alone or in combination, most frequently with valproic acid ($n=19$). Lamotrigine doses ranged from 12.5 to 750 mg/day, with most cases developing Stevens–Johnson syndrome within the first month of therapy. Clinical features included mucocutaneous lesions, epidermal detachment, and systemic symptoms such as fever and conjunctivitis. Management typically involved immediate lamotrigine discontinuation, corticosteroids, immunoglobulins, and supportive care. Most patients recovered within 2–3 weeks, although two deaths were reported.

Discussion: The findings show that the risk of lamotrigine-induced Stevens–Johnson syndrome is highest in the initial weeks of therapy, especially when lamotrigine is combined with valproic acid or titrated rapidly. Early warning signs such as fever and mucosal symptoms should be closely monitored to ensure timely intervention. Although corticosteroids and immunoglobulins are commonly used, their effectiveness remains uncertain, and supportive care continues to be the cornerstone of management.

Conclusion: Lamotrigine-induced Stevens–Johnson syndrome is a rare but serious reaction. Careful dose titration, early recognition of symptoms, and patient education are imperative. Standardized reporting and causality assessment are needed to strengthen the evidence base and support safer prescribing.

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Lamotrigine; Stevens–Johnson syndrome; adverse drug reactions; cutaneous reactions; systematic review

Introduction

Lamotrigine is a commonly prescribed medication used in the treatment of both neurological and psychiatric disorders. It is approved for managing different types of seizures, including focal onset seizures, generalized tonic-clonic seizures, and seizures associated with Lennox–Gastaut syndrome [1]. In psychiatric practice, it is frequently used in patients with bipolar disorder, mainly for the prevention of depressive episodes [2]. For adults, the recommended starting dose

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is 25 mg/day for the first 2 weeks, followed by 50 mg/day for the next 2 weeks. The dose can then be increased by up to 100 mg every one to two weeks until the desired maintenance dose is reached. Typical maintenance doses range from 100 to 200 mg/day, administered in one or two divided doses and may be increased to a maximum of 400 mg/day when required [3]. Lamotrigine belongs to the phenyltriazine class and works by blocking voltage-gated sodium channels in neurons. This action helps reduce the release of excitatory neurotransmitters such as glutamate and aspartate, leading to stabilization of neuronal activity, improved seizure control, and better mood regulation [4]. Due to its effectiveness, good tolerability, and relatively favorable safety profile, lamotrigine is often preferred for long-term use in clinical practice [5].

Despite its many benefits, lamotrigine is associated with the risk of some serious adverse effects, one of which is Stevens–Johnson Syndrome (SJS) [6–8]. The United States Food and Drug Administration (USFDA) has issued a black box warning emphasizing this risk [9,10]. Stevens–Johnson syndrome is a rare but life-threatening reaction that affects the skin and mucous membranes. It usually begins with flu-like symptoms such as fever, sore throat, cough, and eye discomfort, followed by the rapid appearance of painful red or purplish skin rashes, blisters, and skin peeling [11–14]. Mucosal involvement is common and may include the mouth, eyes, and genital area, causing pain, photophobia, difficulty in swallowing, and painful urination [7,11,15]. The severity of the condition is determined by the extent of skin involvement. Stevens–Johnson syndrome typically affects less than 10% of the body surface area. Toxic epidermal necrolysis (TEN), a more severe form, involves more than 30%, while SJS/TEN overlap affects between 10% and 30% [11]. These conditions can lead to serious complications such as dehydration, secondary infections, sepsis, acute respiratory distress, multiple organ failure, and even death. Mortality is especially high in patients with TEN, particularly in older adults and those with underlying medical conditions [16].

Among all antiepileptic drugs, lamotrigine is one of the most frequently associated with SJS and TEN [17,18]. A systematic review of rashes and SJS/TEN in patients taking lamotrigine reported that adverse skin reactions appear in approximately 8.3% of patients, with around 0.04% developing SJS/TEN [19]. Several risk factors contribute to the development of this condition. Genetic predisposition is one of the most important factors, with certain human leukocyte antigen (HLA) alleles such as HLA-B*15:02 and HLA-A*31:01 being strongly associated with increased risk, especially among individuals of Asian ancestry [9,20,21]. The underlying mechanism is primarily immune-mediated. The activation of cytotoxic T cells and natural killer cells leads to widespread death of skin cells, particularly keratinocytes. Important processes involved include the Fas ligand pathway and the release of granulysin, a cytotoxic molecule that damages skin tissue [14,22,23]. In addition to genetic and immunological mechanisms, pharmacokinetic interactions can also contribute to the risk. Concurrent use of drugs such as valproic acid, carbamazepine, and clobazam can increase lamotrigine levels and raise the likelihood of adverse reactions [24–26]. Other contributing factors include starting lamotrigine at a high dose and rapid dose escalation. Evidence indicates that the risk of lamotrigine-induced SJS is highest during the early phase of therapy, most commonly within the first month of initiation [6,9], although rare cases have also been reported following long-term use [18,21].

Although lamotrigine-induced SJS is rare, it is clinically significant and potentially life-threatening. Due to the low incidence of this condition, large observational studies are limited, and most of the available literature consists of case reports and case series. These individual reports, while informative, are scattered and lack systematic synthesis. This systematic review aims to collect and analyze all published case reports and case series on lamotrigine-induced SJS. By compiling and critically examining the evidence, the authors hope to raise awareness among clinicians, promote early recognition, support safer prescribing practices, and identify areas that need further research. The outcomes are intended to improve patient safety and contribute to more informed use of lamotrigine in both neurology and psychiatry.

Methodology

Literature sources and search methods

The literature search was run in the PubMed database to identify case reports and case series on lamotrigine-induced SJS published from inception until December 2024. The search was made using the terms "Lamotrigine" and "Stevens-Johnson Syndrome," and their synonyms. The complete search strategy is detailed in Supplementary Table 1. In addition, the reference lists of all articles selected for inclusion were manually appraised to identify any additional relevant studies not retrieved through the database search.

Inclusion and exclusion criteria

Inclusion criteria

- Case reports or case series describing SJS associated with lamotrigine use.
- Patients of any age, gender, or underlying clinical condition for which lamotrigine was prescribed.
- Reports in which lamotrigine was used alone or in combination with other medications.
- Articles published in any language with full text available.

Exclusion criteria

- Studies not reporting SJS or reporting adverse drug reactions that do not meet the clinical criteria for SJS.
- Reports in which lamotrigine was not implicated as a causative or contributing factor.
- Review articles, editorials, commentaries, or conference abstracts lacking sufficient clinical detail.
- Publications employing study designs other than case reports or case series.

Screening and selection of studies

All identified records were initially screened by examining their titles and abstracts. Articles that appeared potentially relevant were then retrieved for full-text assessment. Each full-text article was evaluated against the predefined inclusion and exclusion criteria. Two reviewers independently carried out the screening and selection process. Any disagreements were settled through discussion or, when necessary, by consulting a senior reviewer.

Quality assessment

The methodological quality of the included studies was assessed using the tool developed by Murad et al. specifically designed for case reports and case series [27]. This tool includes eight questions grouped into four domains: selection, ascertainment, causality, and reporting. Each item was rated as "yes," "no," or "unclear" based on the information provided in the study. The total score ranged from 0 to 8. A score of 6 to 8 was considered good quality, 3 to 5 as moderate quality, and less than 3 as low quality [28]. Two reviewers independently assessed each study, and any disagreements were resolved through discussion or, if necessary, by involving a third reviewer to reach consensus.

Data extraction

Data were extracted using a predesigned Excel sheet developed after reviewing the relevant literature. Each study was identified by the name of first author and publication year. The extracted information included country, study design, patient age and gender, indication for lamotrigine use, dosage, duration of treatment, concomitant medications, results of causality assessment (if available), clinical manifestations (both dermatological and non-dermatological), medication withdrawal status, management strategies, and patient outcomes. Two reviewers independently performed the data extraction. Any discrepancies were resolved through discussion or with input from a senior reviewer.

Results

Search results

A total of 264 records were found through PubMed. After screening the titles and abstracts, 198 records were excluded based on the eligibility criteria. The remaining 66 records were retrieved for full-text review. Following a detailed evaluation of the full texts, 36 studies met the eligibility criteria and were included in the review, of which 31 were case reports, while 5 were case series. Two case series described two relevant cases each, while three reported a single relevant case. In total, these studies described 38 individual cases. Manual appraisal of the reference lists of all selected studies did not yield additional eligible reports. The study selection process is demonstrated in Figure 1.

Study characteristics

The included cases were reported from a wide range of geographic regions, including North America, South America, Europe, Asia, and Oceania. Lamotrigine was administered either as monotherapy or in combination with other medications. Commonly co-administered drugs included valproic acid, clobazam, clonazepam, carbamazepine, paroxetine, olanzapine, sertraline, fluoxetine, mirtazapine, escitalopram, fentanyl, quetiapine, buspirone, trifluoperazine, zuclopenthixol, among others. A few cases also involved nonpsychiatric medications such as antibiotics, corticosteroids, and COVID-19 vaccine. Of the 38 cases, 33 involved

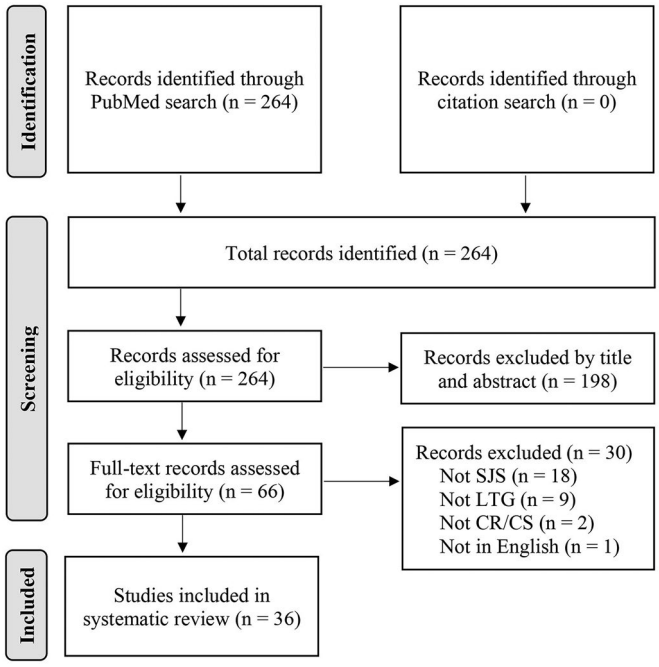

Figure 1. PRISMA diagram (SJS: Stevens-Johnson Syndrome; LTG: Lamotrigine; CR: Case Report; CS: Case Series).

isolated presentations of SJS, while the remaining 5 described cases with overlapping or mixed dermatological conditions. Specifically, three studies reported features consistent with both SJS and TEN (SJS/TEN overlap), and two studies involved cases of SJS co-occurring with drug reaction with eosinophilia and systemic symptoms (SJS/DRESS). Causality assessment was performed in four reports, with three classifying the association as "probable" using the Naranjo algorithm [26,29,30] and one determining it to be "definite" using the RegiSCAR criteria [13]. Skin biopsy was performed in some cases to support the diagnosis [8,13–15,30–34]; however, its use was not consistently documented across all reports. The general characteristics of all included studies, along with the results of methodological quality assessment, are presented in Table 1.

Indications for lamotrigine administration

Lamotrigine was prescribed for various neurological and psychiatric conditions, including epilepsy, seizures, bipolar disorder, depression, anxiety, schizophrenia, schizoaffective disorder, and attention deficit hyperactivity disorder. The age of patients ranged from four to 73 years, with 18 males and 20 females. The daily dose varied widely, from 12.5 mg to 750 mg. In most cases, lamotrigine was started at a low dose, such as 12.5 or 25 mg/day, and gradually increased over a period of one to three weeks. None of the cases reported SJS as a result of lamotrigine overdose or toxicity; however, several cases involved concomitant medications known to increase lamotrigine concentrations through pharmacokinetic interactions, thereby increasing the risk of SJS even within therapeutic dosing ranges. Eight cases documented the development of SJS following lamotrigine monotherapy, particularly at doses between 25 and 300 mg/day. The onset of SJS was commonly observed within two to four weeks of initiating lamotrigine, especially in patients who had recently started treatment. Valproic acid was the most frequently co-administered drug ($n = 19$), generally prescribed at 600 to 2,000 mg/day. The duration of lamotrigine therapy before the onset of symptoms ranged from 6 days to 10 years. In the majority of cases ($n = 25$), the duration was less than one month, while eight cases reported durations between 1 and 12 months, and five cases were associated with long-term use extending beyond one year. Detailed information on the medical conditions, lamotrigine dosage, treatment duration, and co-administered drugs is presented in Table 2.

Clinical symptoms of the adverse event

Clinical presentation included a combination of dermatological and nondermatological symptoms. Dermatological features typically included widespread erythematous or maculopapular rashes affecting the trunk, face, and extremities. In many cases, these rashes progressed to form vesicles, bullae, and eventually resulted in epidermal detachment. Hemorrhagic crusting and erosions of the lips and oral mucosa were

Table 1. General study characteristics.

Author, year	Country	Study design	Condition	Drugs administered	Quality
Chin et al. 2024 [22]	Canada	CS	SJS/DRESS	LTG	Moderate
Parker, 2015 [35]	Australia	CR	SJS	LTG	Moderate
Wang et al. 2012 [36]	China	CR	SJS	LTG	Good
Yasui-Furukori et al. 2014 [37]	Japan	CR	SJS	LTG	Good
Wolf et al. 2006 [31]	Israel	CR	SJS/DRESS	LTG	Moderate
Dooley et al. 1996 [38]	Canada	CS	SJS	LTG	Moderate
Frattini et al. 2024 [9]	Italy	CR	SJS/TEN	LTG	Moderate
De Luca et al. 2017 [32]	Italy	CS	SJS	LTG	Moderate
Vazquez et al. 2018 [39]	Uruguay	CR	SJS	LTG; VPA	Moderate
Maduemem et al. 2017 [40]	Ireland	CR	SJS	LTG; VPA	Moderate
Dumitra et al. 2017 [41]	Romania	CR	SJS	LTG; VPA	Moderate
Di Marco et al. 2015 [14]	Australia	CR	SJS	LTG; VPA	Moderate
Kavitha et al. 2015 [42]	India	CR	SJS	LTG; VPA	Moderate
Fein and Hamann, 2005 [43]	USA	CR	SJS	LTG; VPA	Moderate
Famularo et al. 2005 [29]	Italy	CR	SJS	LTG; VPA	Good
Sachs et al. 1997 [8]	Germany	CR	SJS	LTG; VPA	Good
Espinosa-Aguilar et al. 2023 [44]	Mexico	CR	SJS	LTG; VPA	Moderate
Reddy and Puri, 2020 [7]	USA	CR	SJS	LTG; SERT	Moderate
Aparcana-Choque et al. 2024 [12]	Peru	CR	SJS	LTG; VPA; PCM	Moderate
Yapici et al. 2014 [45]	Turkey	CR	SJS	LTG; VPA; CLBZ	Good
Im et al. 2015 [46]	Korea	CR	SJS	LTG; VPA; ARI	Moderate
Ertam et al. 2009 [25]	Turkey	CR	SJS	LTG; VPA; CLBZ	Moderate
Kocak et al. 2007 [26]	Turkey	CR	SJS	LTG; VPA; CBZ	Good
Duval et al. 1995 [33]	France	CR	SJS	LTG; VPA; CLON	Moderate
Srivastava et al. 2017 [21]	India	CS	SJS	LTG; VPA; FLU; OLZ; MTZ; CLBZ	Moderate
Jha et al. 2017 [34]	Nepal	CR	SJS	LTG; VPA; OLZ; CLON	Good
Yalcin and Karaduman, 2000 [24]	Turkey	CR	SJS	LTG; ZLPT; TFPZ; VPA	Moderate
Joshi et al. 2024 [47]	Nepal	CR	SJS/TEN	LTG; OLZ; SERT	Good
Parveen and Javed, 2013 [6]	UK	CR	SJS	LTG; SERT; BPR	Moderate
Shen et al. 2007 [48]	Taiwan	CS	SJS	LTG; QTP; ARI	Moderate
Hilas and Charneski, 2007 [30]	USA	CR	SJS	LTG; ARI; ECTP	Good
Guerry and Lemyze, 2012 [49]	France	CR	SJS/TEN	LTG; AMX; PDN; FYL; CLON; PAX	Moderate
Bertram et al. 2009 [13]	Germany	CR	SJS	LTG; MTZ; SERT	Good
Matthews et al. 2007 [50]	NS	CR	SJS	LTG; QTP; OLZ; interferon; ribavirin; filgrastim; albuterol; codeine; hydrocodone/PCM; MTZ; rabeprazole	Moderate
Silva Pereira et al. 2002 [51]	NS	CR	SJS	LTG; VPA; CLON; Metformin; Nifedipine	Moderate
Marcelino et al. 2022 [15]	Portugal	CR	SJS	LTG; VPA; PAX; BIS;mRNA COVID vaccine	Moderate

NS: not specified; CR: case report; CS: case series; SJS: Stevens-Johnson Syndrome; DRESS: drug reaction with eosinophilia and systemic symptoms; TEN: toxic epidermal necrolysis; LTG: lamotrigine; VPA: valproic acid; CLBZ: clobazam; ARI: aripiprazole; CBZ: carbamazepine; CLON: clonazepam; PAX: paroxetine; BIS: bisoprolol; FLU: fluoxetine; OLZ: olanzapine; MTZ: mirtazapine; SERT: sertraline; AMX: amoxicillin; PDN: prednisolone; FYL: fentanyl; ECTP: escitalopram; QTP: quetiapine; BPR: buspirone; TFPZ: trifluoperazine; ZLPT: zuclopenthixol; PCM: paracetamol.

common, along with ulceration of the genital and ocular mucous membranes. Other mucocutaneous manifestations included target-shaped lesions, purpuric rashes, and extensive skin necrosis. Nondermatological manifestations generally accompanied or preceded skin lesions, with fever being the most frequently reported systemic sign. Ocular involvement included conjunctivitis, periorbital swelling, conjunctival redness, chemosis, and eye pain or irritation. Oral symptoms such as painful ulcers, sore throat, difficulty swallowing, and mucosal congestion were also common. In more severe cases, respiratory manifestations such as dry cough, shortness of breath, and respiratory failure were reported. Two deaths were also documented [46,51]. A summary of the clinical manifestations observed in the included studies is presented in Table 3.

Management of condition and outcome

In most reported cases, management started with the immediate discontinuation of lamotrigine. Systemic corticosteroids (oral or intravenous) were the most commonly used treatment. Intravenous immunoglobulin was used in some severe cases, and few patients also received immunomodulators such as cyclosporine and etanercept. Supportive therapy included intravenous fluids, antiseptic mouthwashes, topical corticosteroids, antibiotics, analgesics, and eye preparations. Antibiotics like ceftriaxone, vancomycin, and cephalosporins were used to treat or prevent infections, while antihistamines such as cetirizine, fexofenadine, and hydroxyzine were given to relieve symptoms. Pain was managed using intravenous morphine, acetaminophen, and local anesthetics. For ocular involvement,

Table 2. Indications and dosage of lamotrigine.

Study	Age (years)	Gender	Medical condition	LTG dose and frequency	Duration of treatment with LTG	Dose and frequency of other drugs with LTG	Causality assessment
Chin et al. 2024 [22]	22	F	NR	NR	3 weeks	NR	NR
Parker, 2015 [35]	Mid 30s	F	Bipolar disorder	25 mg/day for 1 week, titrated to 200 mg/day	5 months	None	NR
Wang et al. 2012 [36]	9	F	Epilepsy	Double oral dose	3 years	NR	NR
Yasui-Furukori et al. 2014 [37]	19	F	Bipolar disorder; atopic dermatitis	25 mg/day, titrated to 50 mg/day by day 10	2 weeks	NR	NR
Wolf et al. 2006 [31]	43	M	Epilepsy	100 mg/day	NR	NR	NR
Dooley et al. 1996 [38]	12	F	Seizure	50 mg/day, titrated to 300 mg/day	~3 weeks	None	NR
Frattini et al. 2024 [9]	64	M	Epilepsy	20 mg/day, titrated to 120 mg/day	3 weeks	NR	NR
De Luca et al. 2017 [32]	73	M	Bipolar disorder	NR	4 weeks	NR	NR
Vazquez et al. 2018 [39]	8	M	Epilepsy; chronic encephalopathy; cerebral palsy	25 mg/day, titrated to 50 mg/day after 2 weeks	4 weeks	VPA 1125 mg/day	NR
Maduemem et al. 2017 [40]	9	M	Seizure; attention deficit hyperactivity disorder	25 mg alternate days (0.4 mg/kg/day)	6 weeks	VPA 800 mg/day	NR
Dumitra et al. 2017 [41]	5	F	Epilepsy	50 mg/day, titrated to 100 mg/day	3 weeks	VPA 600 mg/day	NR
Di Marco et al. 2015 [14]	14	M	Seizure	50 mg/day	6 days	VPA 1000 mg/day, reduced to 800 mg/day	NR
Kavitha et al. 2015 [42]	35	F	Seizure	25 mg/day	1 week	VPA 600 mg/day	NR
Fein and Hamann, 2005 [43]	22	F	Seizure	NR	5 weeks	VPA	NR
Famularo et al. 2005 [29]	24	M	Seizure	25 mg alternate days for 2 weeks, titrated to 25 mg/day, 200 mg taken mistakenly once	4 weeks	VPA 600 mg/day	"Probable" as per Naranjo scale
Sachs et al. 1997 [8]	30	M	Epilepsy	25 mg alternate days for 2 weeks, titrated to 50 mg/day	5 weeks	VPA 2500 mg/day	NR
Espinosa-Aguilar et al. 2023 [44]	9	F	Dyslexia; epilepsy	25 mg/day, titrated to 50 mg/day	3 weeks	VPA 300-200-300 mg/8 hr; CBZ (discontinued)	NR;
Reddy and Puri, 2020 [7]	33	F	Depression; anxiety	100 mg/day	2 weeks	SERT 50 mg/day	NR
Aparcana-Choque et al. 2024 [12]	40	M	Epilepsy; dengue	NR	10 years	VPA; PCM	NR
Yapici et al. 2014 [45]	7	M	Epilepsy; cerebral palsy	100 mg/day	~5 years	VPA 700 mg/day; CLBZ 20 mg/day	NR
Im et al. 2015 [46]	33	M	Epilepsy	100 mg/day	15 days	VPA 1200 mg/day; ARI 2.5 mg/day	NR
Ertam et al. 2009 [25]	4	M	Epilepsy	75 mg/day	4 weeks	VPA 900 mg/day; CLBZ 20 mg/day	NR
Kocak et al. 2007 [26]	23	F	Epilepsy	100 mg/day	3 weeks	VPA 1000 mg/day; CBZ 800 mg/day	"Probable" as per Naranjo scale
Duval et al. 1995 [33]	40	M	Epilepsy	25 mg alternate days for 2 weeks, titrated to 25 mg/day	25 days	VPA 2000 mg/day; CLON 2 mg/day	NR

(*Continued*)

Table 2. Continued.

Study	Age (years)	Gender	Medical condition	LTG dose and frequency	Duration of treatment with LTG	Dose and frequency of other drugs with LTG	Causality assessment
Srivastava et al. 2017 [21]	54	F	Bipolar disorder; anxiety	NR	15 days	VPA; FLU; OLZ; MTZ	NR
	16	M	Epilepsy	750 mg/day	1 year	CLBZ 10 mg/day; VPA 600 mg/day	NR
Jha et al. 2017 [34]	33	M	Bipolar disorder	Titrated to 100 mg/day over 3 weeks	6 months	VPA (discontinued); OLZ 10 mg; CLON 1 mg	NR
Yalcin and Karaduman, 2000 [24]	33	F	Schizoaffective disorder	25 mg/day, titrated to 150 mg/day	4 weeks	ZLPT; TFPZ; VPA	NR
Joshi et al. 2024 [47]	29	F	Recurrent depressive disorder	100 mg/day, titrated to 200 mg twice/day after 1 week	2 weeks	OLZ 5 mg/day; SERT 100 mg/day	NR
Parveen and Javed, 2013 [6]	56	F	Depression; anxiety	25 mg/day, titrated to 100 mg/day over 2 weeks	~4 weeks	SERT 150 mg/day; BPR 10 mg/day	NR
Shen et al. 2007 [48]	35	F	Schizophrenia	12.5 mg/day, titrated to 25 mg/day in week 2	<2 weeks	QTP 400 mg/day; ARI 10–30 mg/day	NR
	24	F	First psychotic episode (auditory hallucination and persecutory delusion)	12.5 mg/day, titrated to 25 mg/day in week 2	<2 weeks	ARI 10–30 mg/day	NR
Hilas and Charneski, 2007 [30]	29	F	Schizoaffective disorder	75 mg/day	4 weeks	ARI 30 mg/day; ECTP 10 mg/day	"Probable" as per Naranjo scale
Guerry and Lemyze, 2012 [49]	54	M	Depression; polyneuropathy	50 mg/day	5 months	AMX 2000 mg/day; PDN 20 mg/day; FYL patches 25 mcg/hr; CLON 3 mg/day; PAX 10 mg/day	NR
Bertram et al. 2009 [13]	62	F	Depression; migraine	25 mg/day	12 days	SERT 100 mg/day; MTZ 15 mg/day	Appraised as "definite" case of SJS using RegiSCAR
Matthews et al. 2007 [50]	41	M	Bipolar disorder	Titrated to 150 mg/day	18 weeks	QTP 25–50 mg/day; OLZ 20 mg/day; interferon; ribavirin; filgrastim; albuterol; codeine; hydrocodone/paracetamol; mirtazapine; rabeprazole	NR
Silva Pereira et al. 2002 [51]	57	M	Bipolar disorder	25 mg/day, titrated to 75 mg/day over 3 weeks	5 weeks	VPA 600–1200 mg/day; CLON 6 mg/day; nifedipine 15 mg/day	NR
Marcelino et al. 2022 [15]	44	F	Depression	NR	2 years	VPA; PAX; BIS; Comirnaty vaccine (2 doses)	NR

NR: not reported; M: male; F: female; LTG: lamotrigine; VPA: valproic acid; CLBZ: clobazam; ARI: aripiprazole; CBZ: carbamazepine; CLON: clonazepam; PAX: paroxetine; BIS: bisoprolol; FLU: fluoxetine; OLZ: olanzapine; MTZ: mirtazapine; SERT: sertraline; AMX: amoxicillin; PDN: prednisolone; FYL: fentanyl; ECTP: escitalopram; QTP: quetiapine; BPR: buspirone; TFPZ: trifluoperazine; ZLPT: zuclopenthixol; RegiSCAR: european register for severe cutaneous adverse reactions.

treatments included lubricants and steroid eye drops. Mucosal ulcers were treated with agents like chlorhexidine and diphenhydramine-based rinses. Skin lesions were managed with topical steroids. In more severe cases, patients required catheterization, intravenous nutrition, or intensive care, particularly those who developed septic shock or multiorgan involvement. Most patients recovered within 10 to 18 days, although a few had delayed recovery, hyperpigmentation, or scarring. Two deaths were reported. One patient, despite discontinuation of lamotrigine and treatment with corticosteroids and antihistamines, developed

Table 3. Dermatological and non-dermatological manifestations.

Study	Dermatological manifestations	Nondermatological manifestations
Chin et al. 2024 [22]	Periorbital and lip swelling; oral erosions (buccal mucosa, tongue); morbilliform eruption (face, hands); pseudo-vesicular papules (palms); widespread skin lesions (face, chest, back, hands, feet); erosive vulvar involvement	Fever; lymphadenopathy; epiglottic and eye pain; conjunctivitis
Parker, 2015 [35]	Itchy rash (right rib cage); blistering rash on trunk	Headache; swollen neck glands; photophobia; excessive thirst; metallic taste; nausea
Wang et al. 2012 [36]	Skin and mucosal eruption	Fever (39 °C); dyspnea; wheezing; cough; pneumothorax; right lung collapse; bronchial and lung abnormalities
Yasui-Furukori et al. 2014 [37]	Diffuse erythematous pruritic full-body rash; crusty oral/lip vesicles; epidermal apoptosis	Fever (39.3 °C); leukopenia (WBC: 840/μL; 0.840 x 10^9/L)
Wolf et al. 2006 [31]	Confluent erythematous macules (palms, soles, face); central blisters/bullae; epidermal necrosis	Fever (39.6 °C); sore mouth/lips; periorbital/lip swelling; bilateral conjunctivitis
Dooley et al. 1996 [38]	Disseminated raised rash (nailbeds, palms, soles); buccal mucosa desquamation; bullous lesions, including scalp	Dysuria; sore eyes; fever (38.7 °C); vaginal discharge; cervical lymphadenopathy; high CRP
Frattini et al. 2024 [9]	Symmetrical erythematous macules (face, trunk, limbs); purpuric spots with bullae; oral/nasal ulcers with hemorrhagic crusts; necrotic skin detachment (back, genitals); nail abnormalities	Fever; conjunctivitis; eye burning; dysphagia; dysuria; high CRP
De Luca et al. 2017 [32]	Maculopapular rash; oral ulcers; blistering; epidermal detachment	Fever; conjunctivitis; diffuse pain; HSV-2 IgM positive
Vazquez et al. 2018 [39]	Macular rash (thorax, back); lip, oral, pharyngeal ulcers; skin infection	Fever (39 °C); respiratory failure; eyelid edema; ocular ulcers; conjunctivitis; septic shock
Maduemem et al. 2017 [40]	Generalized vesicular rash with hemorrhagic crust (face); vesicular rash (torso, upper back, arms, scrotum); swollen, ulcerated tongue	High-grade fever; facial puffiness; chemosis; conjunctival membrane formation; high CRP
Dumitra et al. 2017 [41]	Polymorphous vesicular rash (trunk, limbs, face); oral vesicles; dry, cracked lips; genital mucosal lesions; perioral hemorrhagic crusts; oral ulcers	Fever; food refusal; vomiting; diarrhea; painful swallowing; face and periumbilical pain; conjunctivitis; pharyngeal congestion
Di Marco et al. 2015 [14]	Erythematous maculopapular rash (face, chest, neck, limbs, penis); itchy, dry skin; oral mucositis; swollen lips/palate	Fever; headache; myalgia; conjunctivitis
Kavitha et al. 2015 [42]	Bleeding, encrusted lips; diffuse erythematous plaques (face, neck, trunk); diffuse atypical target lesions (hands); painful oral ulcers	Fever; eye watering; restricted mouth opening
Fein and Hamann, 2005 [43]	Maculopapular rash (neck, chest) progressing to bullae; mucosal erosions (conjunctiva, mouth, vagina)	Fever (40.5 °C)
Famularo et al. 2005 [29]	Erythematous plaques (trunk, limbs, scrotum); oral aphthae, bullae; painful oral ulcers	Fever (40 °C); eyelid edema; conjunctival discharge
Sachs et al. 1997 [8]	Mucosal erosions (tongue, lips, buccal, and nasal mucosa, glans penis); atypical target lesions (trunk, extremities)	Flu-like symptoms; bilateral conjunctivitis
Espinosa-Aguilar et al. 2023 [44]	Non-painful and non-pruritic erythematous macules (thorax, upper limbs); edema (face and mouth); lip hyperemia; palpebral erythema, oral/genital ulcers, bloody crusts	Fever (38 °C); pain; conjunctival hyperemia; bilateral purulent discharge; general malaise
Reddy and Puri, 2020 [7]	Diffuse maculopapular rash (palms, forearms, trunk); lip bleeding; intraoral ulcers	Fever and chills; sore throat; cervical lymphadenopathy; lip swelling and tingling
Aparcana-Choque et al. 2024 [12]	Nonpruritic vesiculobullous lesions (face, chest, limbs); mucosal desquamation	Fever; respiratory distress; eye itching; general malaise
Yapici et al. 2014 [45]	Oral ulcers; maculo-papular and bullous rash [face, trunk, limbs]; crusted lips/nose; blisters; skin detachment (~10% BSA)	Fever (39.5 °C); conjunctival hyperemia; high CRP
Im et al. 2015 [46]	Diffuse erythema multiforme (~1 inch); mucosal edema (mouth)	Fever (40.6 °C); conjunctivitis; hepatic failure; coma; hepatic encephalopathy and coagulopathy; death
Ertam et al. 2009 [25]	Oral mucosal ulcerations; hemorrhagic lip/nose crusts; genital ulcers; trunk purpura	Fever; high CRP; conjunctival hyperemia
Kocak et al. 2007 [26]	Generalized erythematous bullous rash; crusted lips/eyelids; mucosal erosions (oral, vaginal)	Fever; weakness; sore throat; eyelid redness and swelling; eye synechiae; proteinuria; high CRP
Duval et al. 1995 [33]	Maculopapular trunk rash; ulcerative oral lesions; epithelial detachment	Fever; dry cough; conjunctivitis; pneumococcal infection
Srivastava et al. 2017 [21]	Case 1. Erythematous papules; mucosal necrosis (oral, nasal, genital) Case 2. Maculopapular rash; lip encrustation	Case 1. Fever; ear pain; mucosal congestion; conjunctivitis Case 2. Fever; facial puffiness; painful oral ulcers
Jha et al. 2017 [34]	Rash (neck, trunk, limbs); lip-crusting; ulcer (oral, genital)	Fever (100-102 °F); oral pain; dysuria
Yalcin and Karaduman, 2000 [24]	Targetoid papules, erythematous bullae; mucosal erosions (oral, genital, lips)	Fever (39.5 °C); severe conjunctivitis
Joshi et al. 2024 [47]	Maculopapular pruritic rash (trunk, extremities); oral/genital mucosal detachment; crusted lips	Malaise; sore throat; fever; facial edema; eye itching; conjunctivitis; high CRP; slightly elevated liver enzymes
Parveen and Javed, 2013 [6]	Oral mucosal erosions; erythematous popular and bullous skin lesions; epidermal detachment (palms, soles)	Fever; facial/lip swelling; conjunctivitis; high CRP
Shen et al. 2007 [48]	Case 1. Diffuse erythematous pruritic rash (face, neck, chest, arms) Case 2. Blistering/crusting; epidermal necrosis	Pain High fever; malaise
Hilas and Charneski, 2007 [30]	Full-body pruritic erythematous rash; vesicular/crusty lips and oral mucosa	Fever; mouth pain; irritation

(*Continued*)

Table 3. Continued.

Study	Dermatological manifestations	Nondermatological manifestations
Guerry and Lemyze, 2012 [49]	Rash with epidermal detachment (face, trunk, palms, soles); blisters; mouth ulcers	Fever; conjunctivitis; tachycardia; stupor; respiratory failure; hypovolaemic shock; ventilator associated pneumonia; septic shock
Bertram et al. 2009 [13]	Generalized erythematous maculopapular and vesiculobullous lesions; skin detachment; stomatitis	Fever (38.3 °C); sore throat; shivering; low leukocyte count
Matthews et al. 2007 [50]	Dusky-red macular lesions	NR
Silva Pereira et al. 2002 [51]	Symmetrical erythematous papules, vesicles, bullae, erosions (palms, soles, genitalia); oral ulcers; hemorrhagic lip crusts	Fever (101 °F); dysphagia; hematuria; discharge from eyes; bilateral inguinal lymphadenopathy
Marcelino et al. 2022 [15]	Large, itchy, erythematous lesion at injection site; bullous/ macular lesions (neck, back); ulcers (lip, oral, nasal, genital)	Edema (hands/feet); conjunctival erythema; blurred vision; malaise

NR: not reported; BSA: body surface area; CRP: C-reactive protein.

hepatic encephalopathy and coagulopathy, and died within 5 days of admission due to hepatic failure [46]. Another patient, who was treated with ofloxacin and chlorpheniramine, died within two days of admission. This patient had multiple comorbidities, including diabetes mellitus, hypertension, septicemia, and a urinary tract infection, which likely contributed to the inability to recover [51]. Detailed treatment regimens and outcomes are provided in Table 4.

Discussion

In this review, 38 cases of lamotrigine-induced SJS were identified. Lamotrigine monotherapy was the suspected cause in eight cases, while the remaining cases involved concomitant medications. Valproic acid was the most frequently reported co-administered drug, present in 19 cases. This observation is consistent with the systematic review by Rashid et al. [52], which also identified lamotrigine and valproic acid as the most common drug combination in SJS cases. The increased risk associated with this combination may be explained by pharmacokinetic interaction. Valproic acid inhibits hepatic glucuronidation, the primary metabolic pathway for lamotrigine, thereby reducing its clearance by up to 60% [53]. This prolongs the half-life of lamotrigine from about 30-60 h, resulting in higher serum concentrations. Elevated lamotrigine levels can escalate immune-mediated skin reactions and may contribute to persistent or recurrent blistering [23]. Other frequently reported concomitant medications included clobazam, clonazepam, carbamazepine, and psychiatric medications such as olanzapine, paroxetine, sertraline, and fluoxetine. A case-control study from Japan also reported a significantly increased risk of SJS/TEN with lamotrigine and carbamazepine, with odds ratios of 36 and 68, respectively [54].

Most patients developed symptoms within the first month of starting lamotrigine therapy. In 33 cases, the mean duration before discontinuation was approximately 5.6 weeks. However, five patients developed symptoms more than one year after starting treatment. This indicates that the risk is not limited to the early phase. The clinical manifestation was almost consistent in most cases. Early symptoms often included fever, sore throat, malaise, and redness or discomfort in the eyes. These were usually the first warning signs. Skin changes followed, beginning with widespread red or raised rashes. These progressed to blisters, peeling of the skin, and painful ulcers. Mucosal involvement was common and often severe. The oral, ocular, and genital regions were most frequently affected. This included erosions, hemorrhagic crusting, and ulceration. Other skin manifestations were purpuric rashes, target lesions, and epidermal necrosis. Some patients developed respiratory symptoms such as cough and shortness of breath. Respiratory failure occurred in severe cases. Laboratory tests showed raised C-reactive protein levels and leukopenia in a few cases. These changes reflected systemic inflammation and organ injury. Complications included sepsis, multiple organ dysfunction, and hepatic failure. These observations emphasize the importance of clinical vigilance. Flu-like or eye symptoms soon after starting lamotrigine should raise suspicion. Early recognition and immediate discontinuation of the drug are essential for better outcomes.

In the included cases, the management of lamotrigine-induced SJS generally followed a consistent clinical approach, with the immediate discontinuation of lamotrigine being the first and most important step. This often resulted in improvement in skin lesions, showing the importance of early identification and prompt withdrawal of the culprit drug to prevent further progression. Systemic corticosteroids, including methylprednisolone and prednisolone, were commonly used either intravenously or orally. They suppress inflammation and modulate immune responses and have long been considered the first line of treatment for SJS/TEN [45]. Chin et al. proposed that corticosteroids may be particularly effective in cases presenting with characteristics of drug reaction with eosinophilia and

Table 4. Management of condition and outcome.

Study	Medication withdrawal decision	Treatment for SJS	Outcome
Chin et al. 2024 [22]	NR	Etanercept 50 mg subcutaneously on days 1 and 4; IVIg 2 g/kg on day 2; oral cyclosporine 5 mg/kg/day (increased to 6 mg/kg/day as liquid), stopped on day 5; IV methylprednisolone 2.5 mg/kg on days 5, 8, and 9; tapered oral prednisone; topical clobetasol; sitz baths; amniotic membrane transplant	Clinical improvement
Parker, 2015 [35]	LTG discontinued	None	Rash resolved after drug withdrawal; mild withdrawal symptoms persisted temporarily
Wang et al. 2012 [36]	NR	Cefaclor; dexamethasone; ambroxol hydrochloride; salbutamol sulphate aerosol; bronchoalveolar lavage; chest physiotherapy; reinflation of right upper lobe of lung; tube thoracotomy	Skin and respiratory symptoms resolved; discharged after 12 days
Yasui-Furukori et al. 2014 [37]	LTG discontinued	Ibuprofen 600 mg/day; fexofenadine 120 mg/day for 3 days; IV methylprednisolone 1000 mg/day for 3 days	Improvement observed; patient discharged after steroid tapering
Wolf et al. 2006 [31]	NR	Prednisolone 60 mg/day; cimetidine 300 mg/day; IV ceftriaxone 1 g/day; dexamethasone eye drops	Full recovery within one week
Dooley et al. 1996 [38]	NR	Bladder catheterization; total parenteral nutrition for 8 days	Recovered fully; discharged after 12 days
Frattini et al. 2024 [9]	LTG discontinued	IV methylprednisolone 1 mg/kg/day; IVIg 0.5 g/kg/day; antibiotics; antalgic therapy; fluid therapy; advanced dressings	Recovered without seizures
De Luca et al. 2017 [32]	LTG discontinued	IVIg 0.4 g/kg/day for 5 days; hydrocortisone 1 g bolus; oral prednisone 50 mg/day tapered; topical agents; echinocandin	Discharged after three weeks in good condition
Vazquez et al. 2018 [39]	LTG discontinued	IVIg for 48 h; oral sodium borate rinses; tobramycin eye drops; IV fluids; dopamine, milrinone, and norepinephrine for septic shock; antibacterial therapy	Recovered with stabilized seizures; discharged on valproic acid 375 mg/8 h and oral L-carnitine 2 g/day
Maduemem et al. 2017 [40]	LTG discontinued	IV acyclovir 250 mg/m^2 BSA; ceftriaxone 80 mg/kg/day; oral azithromycin; IV fluids; topical antibiotics and steroids for eyes; IV morphine; mouth wash; hydrocortisone and fusidic acid cream	Discharged after 12 days; fully recovered
Dumitra et al. 2017 [41]	LTG discontinued	Topical corticosteroids; herbal marigold extract; vitamin A; local anesthesia; eye drops	Discharged after 18 days with residual scars
Di Marco et al. 2015 [14]	LTG discontinued	IVIg 2 g/kg (single dose); prednisolone 50 mg/day; cetirizine; mometasone ointment; carboxymethylcellulose sodium eye drops	Initially discharged in five days, readmitted with recurrence, then discharged in another five days; fully recovered
Kavitha et al. 2015 [42]	LTG discontinued	Cyclosporine; methylprednisolone; IV fluids; lignocaine gel; chlorhexidine	Recovered in two weeks
Fein and Hamann, 2005 [43]	LTG along with valproic acid discontinued	Supportive care	Full recovery and discharge
Famularo et al. 2005 [29]	LTG discontinued	Prednisolone 2 mg/kg/day (tapered); valproic acid increased to 750 mg/day; cephalosporins; proton-pump inhibitors; fluids	Oral lesions resolved in one week; full recovery in one month
Sachs et al. 1997 [8]	LTG discontinued	Oral methylprednisolone 80 mg/day; topical glucocorticoids	Rapid improvement and recovery
Espinosa-Aguilar et al. 2023 [44]	LTG discontinued	Loratadine; neomycin eye drops; polymyxin B topical ointment; IV methylprednisolone 1 mg/kg/day for 5 days; IVIg 2 g/kg over 3 days; ceftriaxone 100 mg/kg/day; Philadelphia mouthwash; saline and soap washes; hypromellose and tobramycin eye drops	Discharged on day nine
Reddy and Puri, 2020 [7]	LTG along with sertraline discontinued	NR	Oral ulcerations healed in one month; lip scarring observed
Aparcana-Choque et al. 2024 [12]	NR	Dexamethasone; dermatologic and pain care; anticonvulsant modification	Shifted to the internal medicine department from the ICU in six days; discharged after 14 days

(*Continued*)

Table 4. Continued.

Study	Medication withdrawal decision	Treatment for SJS	Outcome
Yapici et al. 2014 [45]	LTG along with all other antiepileptic drugs discontinued	IV methylprednisolone 2 mg/kg/day; vancomycin 60 mg/kg/day; ceftriaxone 75 mg/kg/day; topical rifamycin; IV fluids; antipyretic; fluconazole 6 mg/kg/day	Lesions resolved by day seven; discharged on day 18
Im et al. 2015 [46]	LTG discontinued	Dexamethasone; antihistamines	Died on day five due to hepatic failure
Ertam et al. 2009 [25]	LTG discontinued	Oral prednisolone 1 mg/kg/day (tapered); antipyretics; topical treatment	Lesions resolved progressively
Kocak et al. 2007 [26]	LTG discontinued	IV fluids; valproic acid 1500 mg/day; carbamazepine 600 mg/day; methylprednisolone 60 mg IV increased to 40 mg/day on day 13; oral pheniramine 45.5 mg twice daily; nystatin oral suspension; chlorhexidine gluconate gargle; hydrocortisone acetate cream; carbomer-mannitol-thiomersal ophthalmic gel; hydroxypropyl methylcellulose eye drops; tobramycin sulfate eye drops	Recovered and discharged after 18 days; referred to ophthalmologist for eyelid synechiae
Duval et al. 1995 [33]	LTG discontinued	Intensive care; antibiotics	Fully recovered in 42 days
Srivastava et al. 2017 [21]	LTG discontinued	Antibiotics; steroids; antihistamines	Recovered and discharged
	LTG discontinued	Cyclosporine; methylprednisolone; IV fluids	Improved in two weeks and eventually recovered
Jha et al. 2017 [34]	LTG discontinued	Oral prednisolone tapered from 10 mg to 1 mg over 4 weeks, then stopped; ranitidine 300 mg; levocetirizine 10 mg; calamine lotion; chlorhexidine mouth rinse	Full symptom resolution in three weeks; pigmentation resolved in three months
Yalcin and Karaduman, 2000 [24]	LTG discontinued	Oral prednisolone 1 mg/kg/day; supportive topical care	Recovery in 10 days with tapering prednisolone
Joshi et al. 2024 [47]	LTG along with olanzapine and sertraline discontinued	IV methylprednisolone 125 mg (3 doses); cetirizine 10 mg; ranitidine 50 mg IV thrice daily; pheniramine 22.75 mg IV four times daily; clobetasol lotion and coconut oil; mupirocin ointment; normal saline irrigation; chlorhexidine gargle; triamcilone acetonide gel; multiple ophthalmic drops	ICU for four days; improved within seven days
Parveen and Javed, 2013 [6]	LTG along with other antidepressants (sertraline and buspirone) discontinued	ICU care	Recovered and discharged in two weeks
Shen et al. 2007 [48]	LTG discontinued	Oral antihistamines; IV fluids; methylprednisolone; antibiotics; analgesics	Condition stabilized with tapering steroids
	LTG along with the other anti-psychotic drugs discontinued	Oral antihistamines; IV fluids; methylprednisolone; supportive medical care	Condition improved and stabilized
Hilas and Charneski, 2007 [30]	LTG discontinued	Oral prednisone 40 mg; IV fluids; hydroxyzine; topical lidocaine; petroleum jelly; medicated mouthwash	Discharged on day three after substantial improvement
Guerry and Lemyze, 2012 [49]	NR	ICU care	Recovered from multiple organ failure; transferred from ICU to ENT ward after 26 days to continue treatment for vocal cord carcinoma
Bertram et al. 2009 [13]	LTG discontinued	IVIg 37.5 g/day for 3 days; topical corticosteroid ointment	Fully recovered
Matthews et al. 2007 [50]	All psychotropic medications discontinued	No treatment given	Rash subsided without recurrence
Silva Pereira et al. 2002 [51]	NR	Ofloxacin 400 mg IV/12 h; chlorpheniramine maleate 50 mg/12 h; symptomatic treatment for oral mucosal lesions and conjunctivitis	Died after two days of admission
Marcelino et al. 2022 [15]	LTG along with valproic acid discontinued	Cetirizine 10 mg twice daily; prednisolone 80 mg once daily; ocular dexamethasone; eye lubricants; skin emollients	Patient was discharged in 10 days; symptoms resolved completely within 1 month

NR: not reported; IVIg: intravenous immunoglobulin.

systemic symptoms (DRESS) [22]. In certain severe presentations, intravenous immunoglobulin was administered due to its ability to inhibit Fas-mediated apoptosis of keratinocytes and thereby limit epidermal damage [55]. Supportive care was also integral to recovery and included intravenous fluids to maintain hydration, antibiotics to prevent or treat secondary infections, analgesics for pain relief, and antihistamines to control allergic manifestations. Mucosal lesions were managed with antiseptic mouthwashes to reduce infection risk and promote healing, while ocular involvement was addressed with lubricants and steroid-based eye drops to prevent long-term complications such as vision loss. In the most severe cases, additional intensive interventions such as urinary catheterization, parenteral nutrition, or admission to an intensive care unit were required.

Most patients recovered within two to three weeks, although some required longer treatment and experienced complications such as skin pigmentation changes, scarring, or ocular damage. Two fatalities indicate the potential severity of lamotrigine-induced SJS. While early drug withdrawal and supportive therapy generally result in recovery, mortality can occur, particularly in patients with significant comorbidities or severe systemic involvement. Caution is therefore necessary when prescribing lamotrigine, especially in combination with valproic acid, for patients with mood disorders who also have significant comorbidities.

Causality assessment tools were not consistently used across the reported cases. Only four studies applied standardized methods, such as the Naranjo algorithm [26,29,30] or the RegiSCAR criteria [13], to evaluate the link between lamotrigine and SJS. The use of skin biopsy, an important diagnostic tool for confirming SJS and differentiating it from other skin conditions, was also inconsistently reported. These gaps in both causality assessment and diagnostic confirmation weaken the strength of the conclusions and highlight the need for more standardized reporting practices. Improved pharmacovigilance, consistent use of causality assessment tools, and routine documentation of confirmatory diagnostics, such as skin biopsy, are essential for improving our understanding of lamotrigine-induced SJS.

The results of this review advocate the importance of cautious use of lamotrigine, especially during the first two months of therapy and when used alongside valproic acid. The benefits of such a combination are to be weighed against potentially disastrous side effects before starting the therapy. Clinicians should follow recommended dosing and titration schedules to minimize the risk of adverse events. Educating patients about early warning signs such as fever, sore throat, or rash is necessary for early detection and intervention. Healthcare providers should also take time to counsel patients and their caregivers about possible adverse effects and emphasize the importance of reporting any unusual symptoms without delay. Genetic screening for HLA-B*15:02 and HLA-A*31:01 alleles in high-risk populations may also help prevent adverse reactions. Long-term follow-up is important for detecting delayed complications such as pigmentary changes or ocular sequelae. Well-designed studies with standardized protocols are needed to identify risk factors, assess outcomes, and optimize management strategies for patients at risk of developing lamotrigine-induced SJS.

Limitations

This review has some limitations. The search was restricted to descriptive studies available on PubMed. Furthermore, the review relied on case reports and case series, which are inherently subject to publication and reporting biases, thereby affecting the generalizability of the findings. Furthermore, the absence of standardized causality assessment tools in most reports limits the ability to draw strong conclusions about the relationship between lamotrigine use and the occurrence of SJS. There was also variability in the diagnostic approach across cases, with inconsistent use of confirmatory evaluations such as skin biopsy and limited documentation of investigations to rule out infectious causes.

Conclusion

Although SJS is a rare adverse effect of lamotrigine, its potential severity makes early recognition and prevention critical. Clinicians should exercise caution when initiating lamotrigine, especially during the initial weeks of treatment. Starting with a low dose, increasing it gradually, and closely monitoring the patient can help minimize risk. It is also important to educate patients about early warning signs of serious skin reactions and encourage them to report any unusual symptoms promptly. Timely identification and immediate discontinuation of lamotrigine are essential to prevent severe complications and improve patient outcomes.

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Author's contributions

MRB, KP, KKS, and BP contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AS, VC, SK, NAS, RK, and AKJ. AS, VC, SK, NAS, RK, and AKJ wrote the first draft of the manuscript. All authors reviewed and commented on previous versions of the manuscript and approved the final version.

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Data availability statement

All data relevant to this review are included in the manuscript or its supplementary file.

References

[1] Motte J, Trevathan E, Arvidsson JFV, et al. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. N Engl J Med. 1997;337(25):1807–1812. doi: 10.1056/NEJM199712183372504.

[2] Ng F, Hallam K, Lucas N, et al. The role of lamotrigine in the management of bipolar disorder. Neuropsychiatr Dis Treat. 2007;3(4):463–474. doi: 10.1111/j.1399-5618.2007.00484.x.

[3] NICE. British national formulary, lamotrigine. https://www.nice.org.uk/bnf-uk-only. Accessed 7 March ; 2025.

[4] Costa B, Vale N. Understanding lamotrigine's role in the CNS and possible future evolution. Int J Mol Sci. 2023;24(7):6050. doi: 10.3390/ijms24076050.

[5] Watanabe Y, Hongo S. Long-term efficacy and safety of lamotrigine for all types of bipolar disorder. Neuropsychiatr Dis Treat. 2017;13:843–854. doi: 10.2147/NDT.S128653.

[6] Parveen S, Javed MA. Stevens Johnson syndrome associated with lamotrigine. Pak J Med Sci. 2013;29(6):1450–1452. doi: 10.12669/pjms.296.4385.

[7] Reddy S, Puri S. Lamotrigine-induced Stevens-Johnson syndrome: a clinical report. Int J Case Rep Images. 2020;11:101175–Z101101. SR102020.

[8] Sachs B, Rönnau AC, von Schmiedeberg S, et al. Lamotrigine-induced Stevens-Johnson syndrome: demonstration of specific lymphocyte reactivity in vitro. Dermatology. 1997;195(1):60–64. doi: 10.1159/000245690.

[9] Frattini C, Corrà A, Mariotti EB, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis induced by lamotrigine in a patient with a cerebral cavernous malformation: a case report. Dermatol Reports. 2025;17(2):10007. doi: 10.4081/dr.2024.10007.

[10] USFDA. FDA drug safety communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal). Silver Spring: FDA. ; 2018. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-serious-immune-system-reaction-seizure-and-mental-health. Accessed 17 June 2025.

[11] Zimmerman D, Dang NH. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN): immunologic reactions. Oncologic Critical Care. 2019;9:267–280.

[12] Aparcana-Choque WD, Pisconti-Palacios YM, Cordova-Tello I, et al. Steven-Johnson syndrome in a patient with dengue infection in Peru: a case report. J Investig Med High Impact Case Rep. 2024;12:23247096241242574. doi: 10.1177/23247096241242574.

[13] Bertram L, Liss Y, Grözinger M. Neopterin and C-reactive protein in the course of Stevens-Johnson syndrome: report of a case. Acta Derm Venereol. 2009;89(3):285–287. doi: 10.2340/00015555-0631.

[14] Di Marco N, Schaink JM, Cranswick NE, et al. Stevens-Johnson syndrome: old and new opportunities for prevention. J Paediatr Child Health. 2015;51(9):924–926; quiz 926. doi: 10.1111/jpc.12883.

[15] Marcelino J, Vieira J, Ferreira F, et al. Stevens-Johnson syndrome related with Comirnaty® coronavirus disease 2019 vaccine. Asia Pac Allergy. 2022;12(3):e30. doi: 10.5415/apallergy.2022.12.e30.

[16] Palmieri TL, Greenhalgh DG, Saffle JR, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. J Burn Care Rehabil. 2002;23(2):87–96. doi: 10.1097/00004630-200203000-00004.

[17] Borrelli EP, Lee EY, Descoteaux AM, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs: an analysis of the US food and drug administration adverse event reporting system. Epilepsia. 2018;59(12):2318–2324. doi: 10.1111/epi.14591.

[18] Edinoff AN, Nguyen LH, Fitz-Gerald MJ, et al. Lamotrigine and Stevens-Johnson syndrome prevention. Psychopharmacol Bull. 2021;51(2):96–114. doi: 10.64719/pb.4398.

[19] Bloom R, Amber KT. Identifying the incidence of rash, Stevens-Johnson syndrome and toxic epidermal necrolysis in patients taking lamotrigine: a systematic review of 122 randomized controlled trials. An Bras Dermatol. 2017;92(1):139–141. doi: 10.1590/abd1806-4841.20175070.

[20] Thong BY-H. Stevens-Johnson syndrome/toxic epidermal necrolysis: an Asia-Pacific perspective. Asia Pac Allergy. 2013;3(4):215–223. doi: 10.5415/apallergy.2013.3.4.215.

[21] Srivastava S, Ramanujam B, Ihtisham K, et al. Cutaneous adverse drug reactions to lamotrigine and human leukocyte antigen typing in North Indian patients: a case series. Ann Indian Acad Neurol. 2017;20(4):408–410. doi: 10.4103/aian.AIAN_234_17.

[22] Chin LD, MacGillivary ML, Purdy KS, et al. Stevens-Johnson syndrome with overlapping features of DRESS syndrome: a report of two cases. SAGE Open Med Case Rep. 2024;12:2050313X241307097. doi: 10.1177/2050313X241307097.

[23] Iannetti P, Raucci U, Zuccaro P, et al. Lamotrigine hypersensitivity in childhood epilepsy. Epilepsia. 1998;39(5):502–507. doi: 10.1111/j.1528-1157.1998.tb01412.x.

[24] Yalçin B, Karaduman A. Stevens-Johnson syndrome associated with concomitant use of lamotrigine and valproic acid. J Am Acad Dermatol. 2000;43(5 Pt 2):898–899. doi: 10.1016/S0190-9622(00)70216-7.
[25] Ertam I, Sezgin AO, Unal I. A case with Stevens Johnson syndrome triggered by combination of clobazam, lamotrigine, and valproic acid treatment. Int J Dermatol. 2009;48(1):98–99. doi: 10.1111/j.1365-4632.2009.03865.x.
[26] Kocak S, Girisgin SA, Gul M, et al. Stevens-Johnson syndrome due to concomitant use of lamotrigine and valproic acid. Am J Clin Dermatol. 2007;8(2):107–111. doi: 10.2165/00128071-200708020-00007.
[27] Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23(2):60–63. doi: 10.1136/bmjebm-2017-110853.
[28] Kumari S, Chaudhary V, Makota VF, et al. Mephentermine use and adverse effects among athletes: a systematic review. J Subst Use. 2024;29(6):1167–1172. doi: 10.1080/14659891.2023.2275016.
[29] Famularo G, Simone CD, Minisola G. Stevens-Johnson syndrome associated with single high dose of lamotrigine in a patient taking valproate. Dermatol Online J. 2005;11(1):25. doi: 10.5070/D321T5616D.
[30] Hilas O, Charneski L. Lamotrigine-induced Stevens-Johnson syndrome. Am J Health Syst Pharm. 2007;64(3):273–275. doi: 10.2146/ajhp060071.
[31] Wolf R, Davidovici B, Matz H, et al. Drug Rash with eosinophilia and systemic symptoms versus Stevens-Johnson Syndrome - a case that indicates a stumbling block in the current classification. Int Arch Allergy Immunol. 2006;141(3):308–310. doi: 10.1159/000095437.
[32] De Luca F, Losappio LM, Mirone C, et al. Tolerated drugs in subjects with severe cutaneous adverse reactions (SCARs) induced by anticonvulsants and review of the literature. Clin Mol Allergy. 2017;15(1):16. doi: 10.1186/s12948-017-0072-5.
[33] Duval X, Chosidow O, Semah F, et al. Lamotrigine versus carbamazepine in epilepsy. Lancet. 1995;345(8960):1301–1302. doi: 10.1016/s0140-6736(95)90945-1.
[34] Jha KK, Chaudhary DP, Rijal T, et al. Delayed Stevens-Johnson syndrome secondary to the use of lamotrigine in bipolar mood disorder. Indian J Psychol Med. 2017;39(2):209–212. doi: 10.4103/0253-7176.203130.
[35] Parker G. Development of an incipient Stevens-Johnson reaction while on a stable dose of lamotrigine. Australas Psychiatry. 2016;24(2):193–194. doi: 10.1177/1039856215612993.
[36] Wang WP, Ni YF, Wei YN, et al. Bronchiolitis obliterans complicating a pneumothorax after Stevens-Johnson syndrome induced by lamotrigine. J Formos Med Assoc. 2015;114(3):285–289. doi: 10.1016/j.jfma.2012.02.026.
[37] Yasui-Furukori N, Hashimoto K, Tsuruga K, et al. Comorbidity of Stevens-Johnson syndrome and neutropenia associated with lamotrigine: a case report. Gen Hosp Psychiatry. 2014;36(6):761.e9-761–e11. doi: 10.1016/j.genhosppsych.2014.07.010.
[38] Dooley J, Camfield P, Gordon K, et al. Lamotrigine-induced rash in children. Neurology. 1996;46(1):240–242. doi: 10.1212/wnl.46.1.240.
[39] Vázquez M, Maldonado C, Guevara N, et al. Lamotrigine-valproic acid interaction leading to Stevens-Johnson syndrome. Case Rep Med. 2018;2018:5371854–5371855. doi: 10.1155/2018/5371854.
[40] Maduemem K, Vatca A, O'Neill T, et al. Stevens - Johnson syndrome induced by combination of lamotrigine and valproic acid in a 9-year-old boy. Ir Med J. 2017;110(6):586.
[41] Dumitra S, Pilat L, Iftode A, et al. Post-medication Stevens-Johnson syndrome in a girl hospitalized for a norovirus and rotavirus infection. Rom J Morphol Embryol. 2017;58:681–683.
[42] Kavitha S, Anbuchelvan T, Mahalakshmi V, et al. Stevens-Johnson syndrome induced by a combination of lamotrigine and valproic acid. J Pharm Bioallied Sci. 2015;7(Suppl 2):S756–S758. doi: 10.4103/0975-7406.163545.
[43] Fein JD, Hamann KL. Images in clinical medicine. Stevens-Johnson syndrome. N Engl J Med. 2005;352(16):1696–1696. doi: 10.1056/NEJMicm031127.
[44] Espinosa-Aguilar E-J, Piña-Ballantyne S-A, Espinosa-Aguilar K-L, et al. Steven-Johnson syndrome induced by lamotrigine and valproic acid in a pediatric patient: a case report. Cureus. 2023;15(7):e41267. doi: 10.7759/cureus.41267.
[45] Yapici AK, Fidanci MK, Kilic S, et al. Stevens-Johnson syndrome triggered by a combination of clobazam, lamotrigine and valproic acid in a 7-year-old child. Ann Burns Fire Disasters. 2014;27(3):121–125.
[46] Im SG, Yoo SH, Park YM, et al. Liver dysfunction induced by systemic hypersensitivity reaction to lamotrigine: case report. Clin Mol Hepatol. 2015;21(2):180–182. doi: 10.3350/cmh.2015.21.2.180.
[47] Joshi A, Palikhe A, Acharya S, et al. A singular case analysis: lamotrigine-associated Stevens-Johnson syndrome. Case Rep Crit Care. 2024;2024:4835223. doi: 10.1155/crcc/4835223.
[48] Shen YC, Chen SJ, Lin CC, et al. Concomitant use of lamotrigine and aripiprazole increases risk of Stevens-Johnson syndrome? Int Clin Psychopharmacol. 2007;22(4):247–248. doi: 10.1097/01.yic.0000224789.21406.81.
[49] Guerry MJ, Lemyze M. Acute skin failure. BMJ. 2012;345(aug06 1):e5028–e5028. doi: 10.1136/bmj.e5028.
[50] Matthews AM, Fireman M, Hauser P. Lamotrigine-associated Stevens-Johnson syndrome after discontinuation of interferon, ribavirin, and filgrastim: a case report. J Clin Psychiatry. 2007;68(4):637–638. doi: 10.4088/jcp.v68n0423e.
[51] Silva Pereira YD, Lal H, Miranda MF, et al. Stevens Johnson syndrome in a bipolar patient treated with lamotrigine. Indian J Psychiatry. 2002;44(2):170–172.
[52] Rashid M, Kashyap A, Undela K. Valproic acid and Stevens-Johnson syndrome: a systematic review of descriptive studies. Int J Dermatol. 2019;58(9):1014–1022. doi: 10.1111/ijd.14411.
[53] Weintraub D, Buchsbaum R, Resor SR, Jr, et al. Effect of antiepileptic drug comedication on lamotrigine clearance. Arch Neurol. 2005;62(9):1432–1436. doi: 10.1001/archneur.62.9.1432.
[54] Fukasawa T, Takahashi H, Takahashi K, et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with anticonvulsants in a Japanese population: matched case-control and cohort studies. Allergol Int. 2021;70(3):335–342. doi: 10.1016/j.alit.2021.01.004.
[55] Barron SJ, Del Vecchio MT, Aronoff SC. Intravenous immunoglobulin in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with meta-regression of observational studies. Int J Dermatol. 2015;54(1):108–115. doi: 10.1111/ijd.12423.