Review Article

The Prevalence of Stevens–Johnson Syndrome Complications due to Antiepileptic Drug Use: A Systematic Review and Meta-Analysis

Abstract

Background: Stevens–Johnson syndrome (SJS) as a dermatological emergency, is a severe condition with a 5% mortality rate. Antiepileptic drugs (AEDs) are linked to an increased risk of SJS, but the magnitude of this risk varies between studies, so comprehensive investigations are needed to evaluate the prevalence of SJS complications associated with AEDs. **Methods:** Based on PRISMA guidelines, Online databases including PubMed/Medline, CINAHL (EBSCO), Web of Science (ISI), Scopus, and Embase were searched using related MeSH-term. Studies reporting SJS as a complication of AEDs or considering AEDs suspected of inducing SJS were included. The Studies which not published in English mentioned other complications instead of skin manifestations were excluded. The data was analyzed using the STATA 14 software. To investigate heterogeneity, the Q Cochrane test and I^2 test were used, and the random effects model was used for combining articles. **Results:** Of 1630 studies, 24 studies were included in meta-analysis. The overall pooled prevalence of SJS was 23.22% (95% CI: 17.32–29.11). The pooled prevalence of SJS was 22.56% (95% CI: 16.55–28.57) in the Retrospective Cohort; 30.90% (95% CI: 5.32–56.48) in perspective Cohort, 24.84% (95% CI: 18.02–31.67) in Asia, 11.20% (95% CI: 6.10–18.4) in America, and 11.70% (95% CI: 2.77–20.63) in Europe. The I^2 index for the overall pooled prevalence of SJS was 93.6%. The results of the meta-regression exhibited that the sample size, publication year, age, design study, and place showed no significant effect on heterogeneity ($P > 0.05$). This review found a significant prevalence of Stevens–Johnson syndrome (SJS) linked to antiepileptic drugs (AEDs) at 23.22%. **Conclusions:** Clinicians should be cautious when prescribing AEDs, especially to high-risk populations. More research is needed to understand SJS mechanisms and identify genetic markers for personalized treatment approaches.

Keywords: *Antiepileptics, prevalence, risk factors, Stevens–Johnson syndrome*

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Introduction

Stevens–Johnson syndrome (SJS) is a severe condition characterized by severe mucous membrane and skin reactions, including denuded skin, blisters, hemorrhagic erosions, erythematous macules, mucocutaneous tenderness, and erosion of the mucous membrane.[1,2] It can affect individuals of any age group, with the average age of patients being between 46 and 63 years old.[3] In 5%–15% of cases, SJS results in death.[4] While the exact cause remains elusive, several factors have been identified as potential contributors to the development of SJS. Below is an overview of these factors, along with an assessment of their relative contributions. Medications are the most common triggers for SJS, accounting for a significant majority of cases. The following drug classes have been particularly implicated: Anticonvulsants and Antiepileptic Drugs (AEDs), allopurinol, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs).[5-7] Antiepileptic Drugs (AEDs) such as carbamazepine, lamotrigine, and phenytoin have been frequently associated with SJS. The risk is often higher in individuals with specific genetic predispositions.[8-10] Antibiotics are known to trigger hypersensitivity reactions leading to SJS.[11,12] Some non-steroidal anti-inflammatory Drugs (NSAIDs) have been linked to SJS.[13,14] Allopurinol commonly used for gout, is another medication that has been associated with SJS.[15] Genetic predispositions can further amplify this risk.[14] Upper respiratory infections can also trigger SJS.[16] Certain malignancies have been associated with SJS.[17] This may be due

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to the underlying disease process or as a side effect of treatments such as chemotherapy. Genetic predispositions play a vital role in the development of SJS, especially concerning drug hypersensitivity reactions. Specific alleles, such as HLA-B*1502 in individuals of Asian descent and HLA-A*3101 in European populations, have been linked to increased risk when exposed to certain medications.[17,18] The contribution of genetic factors is significant in determining susceptibility but varies widely among populations. Their role is particularly crucial in personalized medicine approaches to prevent SJS. A notable number of causes of SJS remains unknown[11] despite thorough investigation. These idiopathic cases highlight the complexity of this condition. The identification of specific medications linked to an increased risk of SJS is critical for improving patient safety and minimizing adverse outcomes. Numerous studies have identified antiepileptic drugs as particularly concerning in increased risk of SJS.[19-21] However, the magnitude of this risk may vary between studies, necessitating comprehensive investigations to evaluate the relationship between AEDs and SJS. The current systematic review and meta-analysis study aimed to evaluate the Stevens–Johnson Syndrome (SJS) complications prevalence of Antiepileptic drugs (AEDs). Understanding the relationship between antiepileptic drug use and SJS is essential for clinicians to make informed decisions and implement preventive strategies effectively. Further research is necessary to enhance the diagnosis, treatment, and prevention of this life-threatening condition. Also, several knowledge gaps remain that warrant further investigation; for instance, there is a need to explore the biological and pharmacological mechanisms that lead to SJS in patients taking AEDs. Understanding these pathways could illuminate why certain individuals are more susceptible and could inform the development of preventative strategies. Future studies should focus on identifying genetic markers that may predispose individuals to SJS when using AEDs. Pharmacogenomics research could help tailor AED prescriptions based on a patient's genetic profile, potentially reducing the risk of severe adverse reactions. Investigating the effectiveness of educational interventions aimed at both healthcare providers and patients regarding SJS symptoms could enhance early detection and intervention rates. Understanding how to communicate risks associated with AEDs is crucial. The role of Co-medications in increasing the risk of SJS among AED users remains underexplored. Investigating potential drug interactions that may exacerbate this risk will be important for comprehensive patient management.

Methods

Study outline

All the steps of the present systematic review and meta-analysis were reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol of this study has been registered in the International Prospective Register of Systematic Review (PROSPERO) under the code CRD42023477879. The data of this research was collected and extracted separately by two researchers (S-T, F-H) and any discrepancies were referred to a third researcher (R-P). It should be noted that all steps were closely checked by the methodologist (R-P). If any deviations happened from the registered protocol, the methodologist addressed and notified other researchers.

Search strategy

Online databases including PubMed/Medline, CINAHL (EBSCO), Web of Science (ISI), Scopus, and Embase were searched without the time and language restrictions to find the articles related to the prevalence of Stevens–Johnson syndrome complications due to antiepileptic drug use until 30th June 2023. Other related platforms in different publishers or sources like Springer, Willy, BMC, ProQuest, and Cochrane Library were used. Also, Google Scholar was used to find gray literature. The searches were done using text words and MESH terms like "Stevens–Johnson syndrome", "Antiepileptic drugs (AEDs)", "Toxic Epidermal Necrolysis Spectrum", "Lyell's Syndrome", "Prevalence", "Cross-Sectional Studies". The PICOT used in our study included: Population: Patients who used antiepileptic drugs

Intervention: None

Comparison: None

Outcome: Stevens–Johnson syndrome complications prevalence Time: from beginning to 30th June 2023

To find the related articles, the search strategy described below was developed for MEDLINE (MeSH, Medical Subject Headings) and then used in other databases (used keyword was showed in supplement 1):

1: Antiepileptic Agents [text word] OR Antiepileptic Agents [Mesh term]
2: Anticonvulsive Drug [text word] OR Anticonvulsive Drug [Mesh term]
3: Anticonvulsants [text word] OR Anticonvulsants [Mesh term]
4: 1 OR 2 OR 3
5: Prevalence [text word] OR Prevalence [Mesh term]
6: Frequency [text word] OR Frequency [Mesh term]
7: 5 OR 6
8: Cross-Sectional Studies [text word] OR Cross-Sectional Studies [Mesh term]
9: Observational Studies [text word] OR Observational Studies [Mesh term] 10: Retrospective Studies [text word] OR Retrospective Studies [Mesh term]
11: 8 OR 9 OR 10
12: Stevens–Johnson Syndrome [text word] OR Stevens–Johnson Syndrome [Mesh term]

13: Lyell Syndrome [text word] OR Lyell Syndrome [Mesh term]
14: 12 OR 13
15: 4 AND 7 AND 11 AND 14

Eligibility criteria for inclusion and exclusion

Studies that reported Stevens–Johnson syndrome as a complication of antiepileptic drugs, or considered antiepileptic drugs suspected of inducing Stevens–Johnson syndrome, were included in this systematic review. To ensure the quality and relevance of our study, we established exclusion criteria. These criteria included articles with insufficient data, mention of other complications instead of skin manifestations, and sources such as thesis, letters to editors, conference presentations, review articles, and case studies.

Data extraction

The items we extracted from the studies included the following: 1) author's name, 2) article title, 3) the year of publication, 4) the study period, 5) the design of the study, 6) the duration and location of the study, 7) the number of cases with Stevens–Johnson syndrome, 8) number of cases with exposure to antiepileptic drugs, 9) having antiepileptic drugs as suspected agent, 10) mean age and standard deviation (SD) 11) number of men, women and subjects with unknown gender identity, 12) information on the specific AEDs investigated in the included studies.

Quality assessment

Quality assessment was performed using the Newcastle-Ottawa Scale (NOS),[22] which evaluates studies based on three main criteria: 1. Selection: This includes the representativeness of the exposed cohort, selection of the non-exposed cohort, and the ascertainment of exposure. 2. Comparability: This assesses whether studies controlled for confounding factors, allowing for a clearer understanding of the relationship between antiepileptic drug use and Stevens–Johnson Syndrome. 3. Outcome: This examines the assessment of outcomes, including the method of outcome measurement and the duration of follow-up. Articles that scored more than five points on the NOS were included in the review, ensuring that only studies with moderate to high-quality evidence were considered for analysis.

Statistical analysis

To investigate the heterogeneity of the studies, the Q Cochrane test at the 95% confidence level and the I^2 test were used based on the Higgins classification.[23] Due to the heterogeneity of the articles, the random effects model was used to combine them. Meta-regression was also used for assessing changes in the prevalence of SJS according to the publication dates of studies and sample size.[24] The data was analyzed using the STATA software 14.0 (College Station, Texas, USA). Analysis of data were displayed as tables, flowcharts, and plots. Based on the Higgins classification approach, I^2 values of more than 0.7 were regarded as high heterogeneity. The "Meta prop" command and random-effect model were applied to calculate the pooled prevalence with a 95% confidence interval (CI) and to estimate the pooled prevalence, respectively. Factors (age, sample size, place, Design study, and year) affecting heterogeneity among studies were examined by the meta-regression analysis.

Results

Search results and characteristics

A total of 1630 records were initially identified through the search in various databases and sources. After removing 587 duplicate articles, 744 studies were excluded based on their abstracts for reasons such as not being relevant to the topic, lacking sufficient information, or not being in English. The full-text screening process resulted in the exclusion of 275 studies due to inadequate information, leaving a total of 24 studies for quality assessment and final analysis [Table 1, Figure 1].[16,25-47] The SJS prevalence in all eligible studies and the forest plot of SJS prevalence were illustrated in Table 1 and Figure 2, respectively. The minimum prevalence of SJS was reported by Acar *et al.*[46] (3.03 (95% CI: 0.54–15.32)). while the maximum prevalence was reported by Naveen *et al.*[44] (50.00 (95% CI: 30.72–69.28)). The number of studies in Asia, Europe, and America was 21, 1, and 2 studies, respectively.

Based on the results of the random-effect model approach, as shown in Figure 2, the pooled estimate for SJS prevalence was 23.22% (95% CI: 17.32–29.11) [heterogeneity Index: $I^2 = 93.6\%$; $P < 0.001$].

The pooled prevalence of SJS based on place and study design is demonstrated in Figure 3 and more details are provided in Supplementary Figures. The pooled prevalence of SJS was 24.84% (95% CI: 18.02–31.67; Number of studies: 21; heterogeneity I^2 index: 94.3%; $P < 0.001$) in Asia, 11.20% (95% CI: 6.10–18.4); heterogeneity I^2 index: 80.4%; $P < 0.024$) in America and 11.70% (95% CI: 2.77–20.63); heterogeneity I^2 index: ---%; P = ---) in Europe [Figure 3].

In addition, Figure 3 shows the pooled prevalence of SJS based on the Design of the study. As mentioned earlier, Retrospective studies had the highest number of studies ($n = 22$) [Figure 3]. The pooled prevalence of SJS was 22.56% (95% CI: 16.55–28.57; Number of studies: 22; heterogeneity I^2 index: 93.7%; $P < 0.001$) in retrospective studies and 30.90% (95% CI: 5.32–56.48); heterogeneity I^2 index: 78.3%; $P = 0.032$) in prospective studies.

The I^2 index for the total prevalence of SJS was 93.6%. In other words, more than 93.6% of the variance in this study was due to real differences between the included studies [Figure 2]. The results of the meta-regression are shown in Table 2. According to meta-regression results, the Sample size (coefficient: −0.0003; $P = 0.952$),

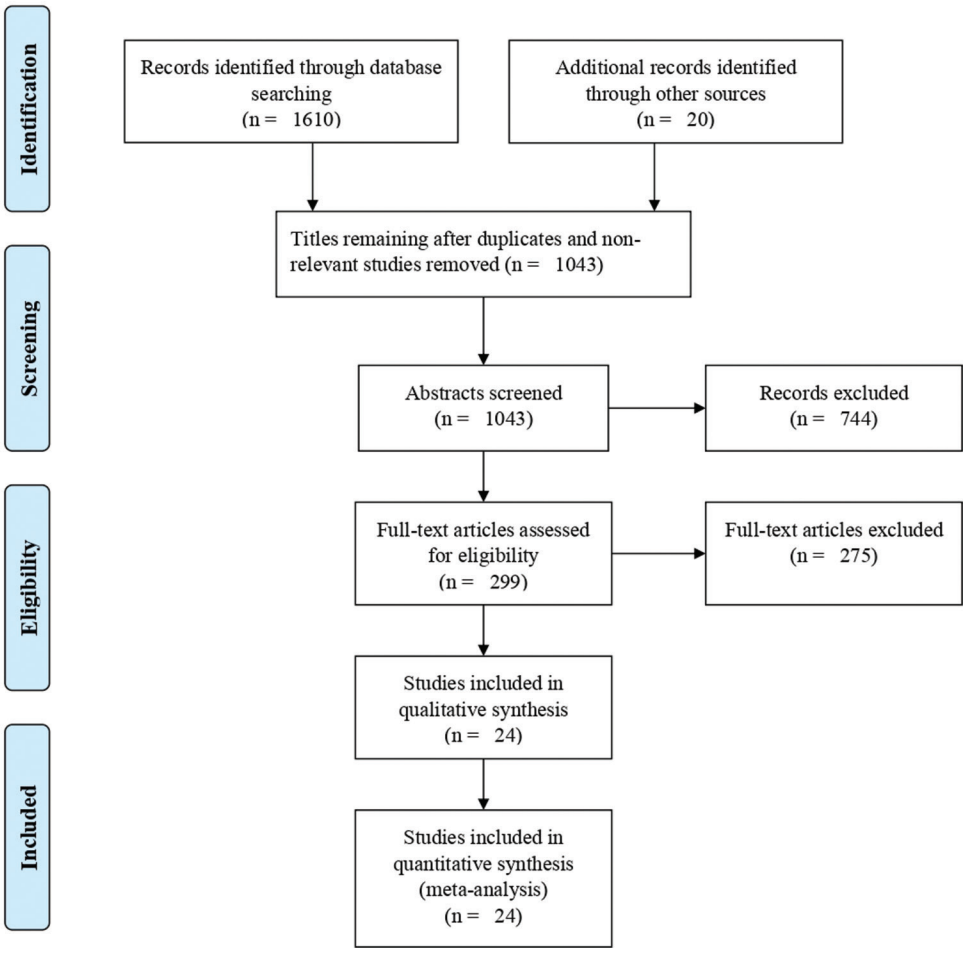

Figure 1: Flow diagram of study selection

publication year (coefficient: −0.372; $P = 0.941$, Figure 4a), Age (coefficient: −0.001; $P = 0.999$, Figure 4b), Design study (coefficient: 15.63; $P = 0.965$) and place (coefficient: 1.73; $P = 0.943$) showed no significant effect on heterogeneity.

Discussion

Around 6%–7% of hospital admissions are caused by negative reactions to drugs. which, particularly Stevens–Johnson syndrome (SJS), is a common cause of hospital admissions.[48] Many studies have mentioned specific medications, particularly antiepileptic drugs, as being associated with a higher risk of SJS.[19-21] In 5%–15% of cases, SJS results in death.[4] The prevalence of SJS as a life-threatening and serious complication of AEDs is a significant area of concern. Our research showed that the combined occurrence of SJS in AED users was 23.22% (95% CI: 17.32–29.11). However, it is important to highlight the high heterogeneity observed among the included studies, as indicated by an I^2 value of 93.6%. This substantial variability suggests that the prevalence rates reported in different studies may be influenced by a range of factors, including differences in study design, population characteristics, and geographical variations. The high heterogeneity could arise from several sources. For instance, variations in the definitions of SJS, differences in diagnostic criteria, and the methodologies employed in the studies could contribute to the discrepancies observed. Additionally, factors such as sample size, age distribution, and the specific AEDs being studied may also play a role. Although our meta-regression analysis did not find significant effects of sample size, publication year, age, study design, or geographic location on heterogeneity ($P > 0.05$), it is crucial to acknowledge that these factors may still influence the outcomes in more nuanced ways not captured by our analysis. There is also variability in the quality of reporting SJS in clinical studies. Standardizing definitions and diagnostic criteria for SJS across studies would enhance the comparability of data and improve future meta-analyses. The regional differences in prevalence rates further underscore the need for caution when interpreting these findings. For example, the pooled prevalence of SJS was notably higher in Asia (24.84%) compared to America (11.20%) and Europe (11.70%). These discrepancies may reflect varying prescribing practices, genetic susceptibility among populations, or differences in healthcare access and reporting standards.

Table 1: Characteristics of included studies to present systematic review and meta-analysis

	Year	Design	duration	Location	Sample Size	SJS (complication)	Anti-epileptic (suspected drug)	Antiepileptic (exposure)	SJS (outcome)	Prevalence (95%CI)	% (m:f)	(Mean age)	Specific AEDs investigate
Sanmarkan *et al.*[46]	2011	Ret	1998–2008	India	46	46	8			17.39 (9.09–30.72)	62:38	45	Phenytoin, Carbamazepine
Clark *et al.*[36]	2021	Ret	2005–2018	Singapore	123	123	27			21.95 (15.55–30.05)	38:62	56	-
Kanagarajan *et al.*[33]	2023	Pro	2016–2017	India	17			17	3	17.65 (6.19–41.03)	76.4:23.6	38.1±19.3	Phenytoin, Carbamazepine
Acar *et al.*[47]	2022	Ret	2008–2019	Turkey	33	33	1			3.03 (0.54–14.32)	39.4:60.6	60.9±21	-
Abtahi-Naeini *et al.*[28]	2022	Ret	2014–2018	Iran	101	101	47			46.53 (37.11–56.21)	47.5:52.5	24.98)	Carbamazepine, Phenytoin, Phenobarbital, Lamotrigine, Lamotrigine + Valproic acid, Topiramate, Levetiracetam
Lebrun-Vignes *et al.*[42]	2018	Ret	2002–2013	France	128	51	6			11.76 (5.51–23.38)	27:24	36.9±21	Carbamazepine, Phenytoin, Phenobarbital
Wetter *et al.*[16]	2010	Ret	2000–2007	USA	27	27	7			25.93 (13.17–44.68)	59:41	28.1±22.3	-
Ma *et al.*[29]	2021	Ret	2010–2020	Taiwan	119	87	15			17.24 (10.74–26.52)	38.7:61.3	45.6±22.7	Phenytoin, Carbamazepine, Oxcarbazepine, Lamotrigine, Zonisamide
Perwitasari *et al.*[43]	2021	CS	2006–2019	Indonesia	58	32	14			43.75 (28.17–60.67)	53:67	33.3±17.20	-
Cheng *et al.*[35]	2016	Ret	1999–2008	Taiwan	111	111	5			4.50 (1.94–10.11)	56.7:43.3	67.72	Phenytoin, Phenobarbital
Yoo *et al.*[30]	2022	Ret	2008–2019	Seoul	92	63	15			23.81 (14.99–35.64)	66.5:43.5	58.7±20.2	Carbamazepine, Lamotrigine, Gabapentin, Levetiracetam, Oxcarbazepine
Kim *et al.*[27]	2012	Ret	2001–2011	Korea	82	71	12			16.90 (9.94–27.26)	45.1:54.9	53.8	Carbamazepine, Phenytoin, Valporic acid, Phenobarbital
Su *et al.*[40]	2020	Ret	1999–2017	USA	466027	89	6			6.74 (3.13–13.94)	42:55.3	-	-
Naveen *et al.*[44]	2013	Ret	5 years	India	22	22	11			50.00 (30.72–69.28)	63:37	32.27	Lamotrigine, Phenytoin, Carbamezepine,

Contd...

Table 1: Contd...

	Year	Design	duration	Location	Sample Size	SJS (complication)	Anti-epileptic (suspected drug)	Antiepileptic (exposure)	SJS (outcome)	Prevalence (95%CI)	% (m:f)	(Mean age)	Specific AEDs investigate
													Phenobarbital, Oxcarbazepine, Gabapentin, Topiramate, Divalproex
Wang *et al.*[45]	2017	Ret	2006–2015	China	88	48	4			8.33 (3.29–19.55)	45.5:54.5	45±18	Carbamazepine, Lamotrigine, Valproate
Yang *et al.*[37]	2019	Ret	2005–2010	Korea	73	21	4			19.05 (7.67–40.00)	42:58	34.3±21.9	-
Talebi *et al.*[38]	2018	Ret	2010–2015	Iran	97	89	49			55.06 (44.73–64.97)	-	38.7±17.9	Carbamazepin, Depakine, Acetazolamide, Phenytoin, Phenobarbital, Lamotrigine
Sethuraman *et al.*[26]	2012	Ret	2007–2010	India	20	20	7			35.00 (18.12–56.17)	50:50	11.9±3.42	Phenytoin, Carbamazepine
Yang *et al.*[39]	2018	Ret	2006–2016	China	166	72	19			26.39 (17.59–37.58)	63:37	43.4±21.7	Carbamazepine, Lamotrigine
Manvi *et al.*[31]	2022	Ret	2010–2019	India	62			23	11	47.83 (29.24–67.04)	32.3:67.7	41.2±19.4	Phenytoin, phenobarbitone, Carbamazepine, sodium valproate, Lamotrigine, Phenobarbitone
Chatproedprai *et al.*[32]	2018	Ret	20 years	Thailand	36	20	5			25.00 (11.19–46.87)	40:60	8.6±4.2	-
Thakur *et al.*[41]	2021	Ret	2014–2018	India	51	7	2			28.57 (8.22–64.11)	-	38.2±17.6	henytoin, Carbamazepine, Lamotrigine, Valproate
Jeung *et al.*[34]	2010	Ret	2004–2008	Korea	298	20	7			35.00 (18.12–56.71)	60:40	58.5	Lithium, Carbamazepine, Oxcarbazepin
Kim *et al.*[25]	2020	Ret	2008–2017	Korea	2942	2942	106			3.6 (2.9–4.34)	49.3:49.5	42.22	Carbamazepine, Oxcarbazepine, Clobazam, Perampanel, Clonazepam, Phenobarbital, Diazepam, Phenytoin,

Contd...

Table 1: Contd...

Year	Design	duration	Location	Sample Size	SJS (complication)	Anti-epileptic (suspected drug)	Antiepileptic (exposure)	SJS (outcome)	Prevalence (95%CI)	% (m:f)	(Mean age)	Specific AEDs investigate
												Ethosuximide, Pregabalin, Fosphenytoin, Primidone, Gabapentin, Rufinamide, Lacosamidea, Topiramate, Lamotrigine, Valproic acid/ Divalproex sodium, Levetiracetam, Vigabatrin, Lorazepam, Zonisamide

Ref=retrospective, Pro=prospective, CS=cross-sectional, SJS=Stevens–Johnson Syndrome

Borrelli *et al.*[49] sought to assess the risk of SJS and toxic epidermal necrolysis (TEN) linked to AEDs as a group and for individual drugs in the United States. Their study analyzed data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) from July 2014 to December 2017, examining 198 reports of SJS/TEN with a focus on AEDs compared to other non-AED medications. The findings revealed that AEDs had a significantly higher incidence of SJS/TEN reports than any other class of medications. The reporting odds ratio (ROR) for AEDs as a group was 8.7 (95% CI 7.5–10.2), indicating nearly nine times the risk relative to non-AEDs. Certain AEDs exhibited even higher risk estimates: Zonisamide: ROR 70.2 (95% CI 33.1–148.7), Rufinamide: ROR 60.0 (95% CI 8.3–433.5), Clorazepate: ROR 56.0 (95% CI 7.8–404.1), Lamotrigine: ROR 53.0 (95% CI 43.2–64.9), Phenytoin: ROR 26.3 (95% CI 15.5–44.7), Carbamazepine: ROR 24.5 (95% CI 16.0–37.5). Anthony R. Mawson in a review article, declared that SJS may result from drug and biochemical interactions that cause problems in liver function and increased toxic concentrations of retinoid compounds leading to apoptosis via granulysin. a potential treatment involves lowering the concentration of circulating retinoids, such as through plasmapheresis, phlebotomy, or administering drugs that inhibit the expression of retinoids The pathophysiology of SJS involves complex immunological and biochemical mechanisms. Anthony R. Mawson in a review article, declared that SJS may result from drug and biochemical interactions that cause problems in liver function and increased toxic concentrations of retinoid compounds leading to apoptosis via granulysin, a cytotoxic protein released by activated T cells. a potential treatment involves lowering the concentration of circulating retinoids, such as through plasmapheresis, phlebotomy, or administering drugs that inhibit the expression of retinoids. Understanding this pathophysiology is crucial for both prevention and treatment strategies in clinical practice. Specifically, clinicians should consider genetic factors, such as HLA-B*1502 allele testing for patients starting carbamazepine, as this genetic marker has been linked to an increased risk of SJS. In terms of prevention, awareness of the potential for SJS should prompt healthcare providers to educate patients about the early signs and symptoms of the syndrome. This vigilance can facilitate prompt discontinuation of the offending drug, which is critical in mitigating the severity of the reaction. Regarding treatment, Mawson's insights into lowering circulating retinoid concentrations open avenues for therapeutic interventions. While traditional management of SJS primarily focuses on supportive care and symptom management, incorporating strategies such as plasmapheresis or phlebotomy could be explored in clinical settings. These approaches aim to reduce the toxic burden and potentially limit the progression of the syndrome. Additionally, understanding the immunological triggers of SJS can lead to targeted therapies that inhibit pathways involved in granulysin-mediated

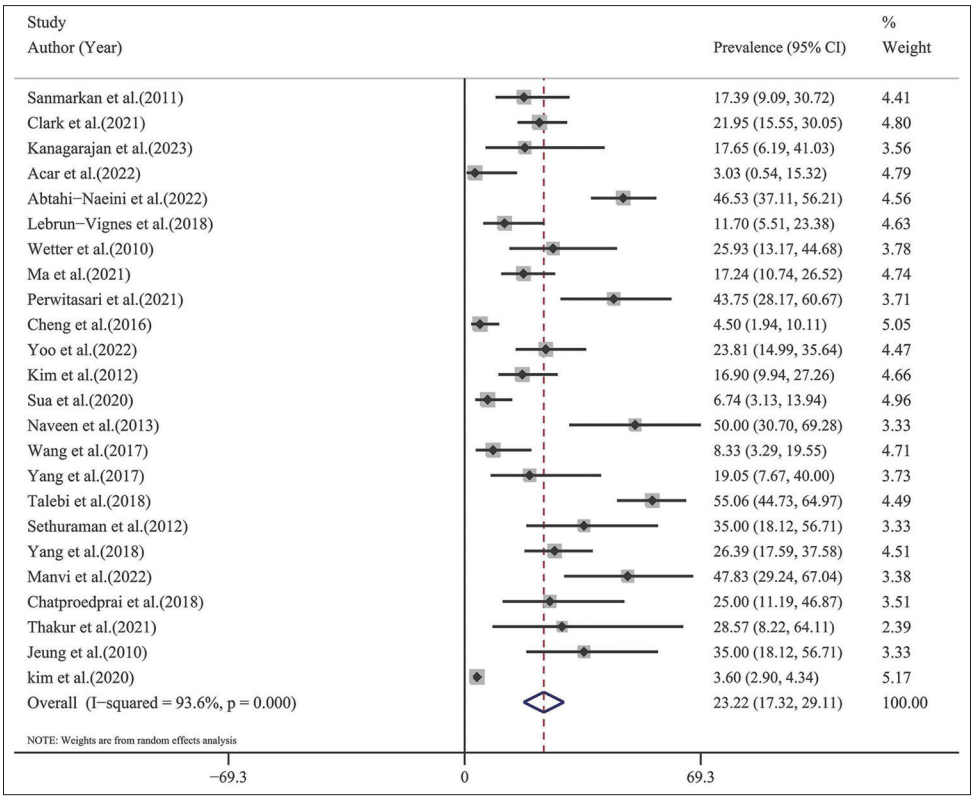

Figure 2: Forest plot of Stevens–Johnson Syndrome prevalence due to Antiepileptic drug use in all included studies according to the random effects approach. Every single study has been demonstrated by the first author (year). Each line segment's midpoint exhibits the prevalence estimation, the line segment length presents a 95% confidence interval (CI) in every study, and the diamond mark points out the pooled estimations

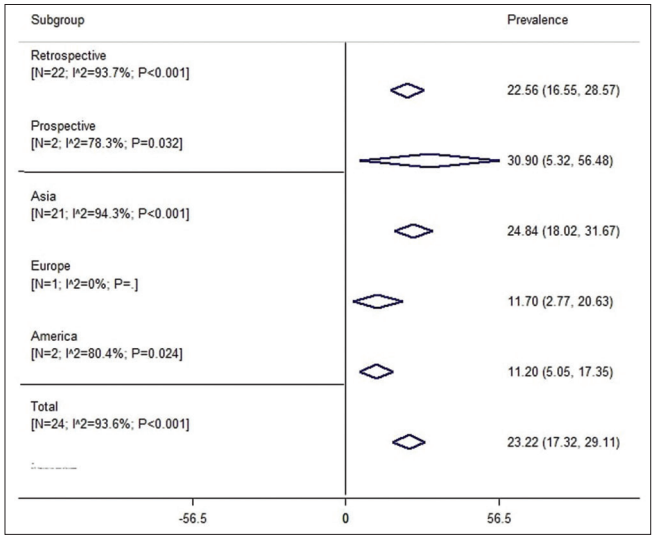

Figure 3: Pooled prevalence with 95% confidence interval (CI) and heterogeneity indices of Stevens–Johnson Syndrome prevalence due to Antiepileptic drugs use based on the different subgroups. The diamond mark exhibits the pooled prevalence and the diamond length shows 95% CI

apoptosis. For instance, exploring the use of immunosuppressive agents might be warranted in severe cases where conventional treatments fail. In summary, linking the pathophysiological insights into SJS with our study's findings emphasizes the importance of a proactive approach in both preventing and managing this

Table 2: The univariate meta-regression analysis on the heterogeneity of the determinants in included studies for the prevalence of SJS

Variable	Coefficient	95% CI	*P*
Sample size (Number)	−0.0003	−0.01 to 0.01	0.952
Publication year (year)	−0.372	−10.72 to 9.97	0.941
Age (yrs. Old)	−0.001	−1.65 to 1.65	0.999
Design study	15.637	−725.78 to 757.06	0.965
Place	1.73	−47.68 to 51.16	0.943

Code for Place=Asia=1, Europe=2, America=3, Code for Design study=Retrospective=1, and Prospective=2

life-threatening condition associated with AEDs. By integrating knowledge of drug interactions, genetic predispositions, and emerging treatment modalities, we can enhance patient safety and outcomes in those at risk for SJS.[50,51] A meta-analysis by Qin Xiang Ng *et al.*[52] found that the use of cyclosporine is associated with a decrease in mortality rates among patients with SJS. Treatment with systemic corticosteroids in SJS patients is controversial due to concerns about increased infection rates and delayed healing.[53] Screening for specific human leukocyte antigen (HLA) alleles is becoming more common to identify patients at risk for drug reactions, potentially reducing the incidence of reactions.[54,55] The study conducted by Bernardo Sousa-Pinto *et al.* analyzed an administrative database to examine the impact of Stevens–

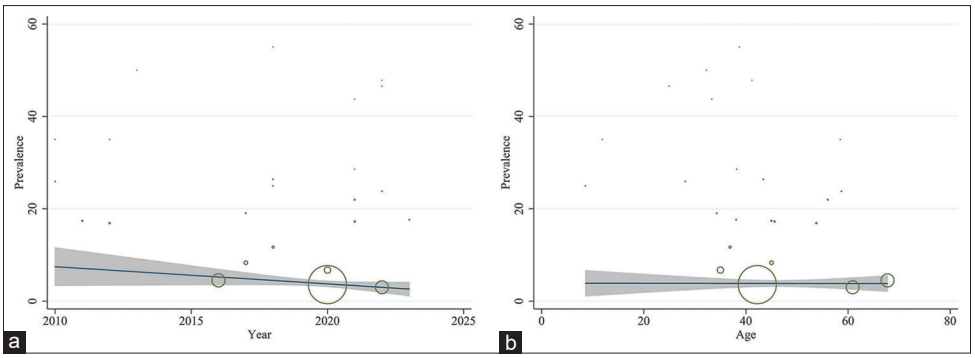

Figure 4: Association among (a) publication year and (b) mean age with the prevalence of Stevens–Johnson Syndrome by applying meta-regression. The circle size shows each study's precision

Johnson syndrome (SJS) compared to other drug-related mucocutaneous conditions. The results showed that SJS was associated with higher mortality rates and longer hospital stays. The study also found that older age increased the risk of in-hospital mortality for patients diagnosed with drug-related SJS. These findings provide important epidemiological information about SJS hospitalizations and identify factors that contribute to higher mortality rates. This knowledge can be valuable in diagnosing SJS earlier and initiating appropriate treatment sooner. Additionally, understanding the factors associated with higher fatality rates is crucial for implementing effective preventive measures. The study suggests that administrative databases are a useful tool for assessing nationwide SJS hospitalizations and conducting epidemiological studies in a cost-effective manner. The study conducted by Bernardo Sousa-Pinto *et al.*[56] analyzed an administrative database to examine the impact of Stevens–Johnson syndrome (SJS) compared to other drug-related mucocutaneous conditions. The results showed that SJS was associated with higher mortality rates and longer hospital stays. The study also found that older age increased the risk of in-hospital mortality for patients diagnosed with drug-related SJS. These findings provide important epidemiological information about SJS hospitalizations and identify factors that contribute to higher mortality rates. This knowledge can be valuable in diagnosing SJS earlier and initiating appropriate treatment sooner. Additionally, understanding the factors associated with higher fatality rates is crucial for implementing effective preventive measures. The study suggests that administrative databases are a useful tool for assessing nationwide SJS hospitalizations and conducting epidemiological studies in a cost-effective manner. The findings of the study by Bernardo Sousa-Pinto *et al.*[56] provide critical insights into the epidemiology of Stevens–Johnson syndrome (SJS) in the context of drug-related mucocutaneous conditions, particularly those associated with antiepileptic drugs (AEDs). Their analysis highlights that SJS is linked to higher mortality rates and longer hospital stays compared to other drug-related conditions which emphasizes the severe complications associated with SJS due to AED use. The use of administrative databases, as suggested by Sousa-Pinto *et al.*,[56] for assessing nationwide SJS hospitalizations adds another layer of utility to the findings of the meta-analysis. This approach can enhance our understanding of SJS trends over time and identify geographic or demographic patterns that could inform preventive measures. In summary, while both studies focus on different aspects of SJS related to AED use, they complement each other by reinforcing the critical need for awareness, early diagnosis, and tailored management strategies to mitigate the risks associated with this severe condition.[56] One limitation of our study is the high heterogeneity observed among the included studies, which may have affected the accuracy of the pooled estimates. However, the use of a random effects model and meta-regression analysis helped to account for this heterogeneity and strengthen the validity of the findings. Also, differentiation between SJS and TEN (Toxic Epidermal Necrolysis) was not adequately performed in articles. Despite these limitations, this systematic review and meta-analysis provide valuable insights into the association between AEDs and SJS. The findings suggest that AEDs may indeed increase the risk of developing SJS, although the magnitude of this risk may vary. This highlights the importance of considering the potential risks and benefits of AED use in patients, particularly those with a higher risk profile. The findings highlight the importance of clinicians being aware of this potential adverse effect when prescribing AEDs, especially in high-risk patients. Early recognition and management of SJS is crucial to prevent complications and reduce mortality rates. Clinicians should also consider alternative treatment options for patients who are at high risk of developing SJS. Further research is needed to better understand the underlying mechanisms and genetic factors that contribute to drug hypersensitivity reactions leading to SJS. Identifying specific alleles associated with increased risk could help personalize treatment plans and minimize the occurrence of SJS in susceptible individuals. The findings of this systematic review and meta-analysis underscore the significant prevalence of Stevens–Johnson syndrome (SJS) associated with antiepileptic drugs (AEDs). However, several knowledge gaps remain that warrant further

investigation: 1) Mechanisms of SJS Development: There is a need to explore the biological and pharmacological mechanisms that lead to SJS in patients taking AEDs. Understanding these pathways could illuminate why certain individuals are more susceptible and could inform the development of preventative strategies. 2) Genetic Susceptibility: Future studies should focus on identifying genetic markers that may predispose individuals to SJS when using AEDs. Research into pharmacogenomics could help tailor AED prescriptions based on a patient's genetic profile, potentially reducing the risk of severe adverse reactions. 3) Longitudinal Studies: Most existing studies are cross-sectional or retrospective, limiting the ability to establish causality. Longitudinal studies that track patients over time could provide deeper insights into the long-term risks associated with AEDs and the incidence of SJS. 4) Regional Variations: The observed differences in SJS prevalence across geographic regions suggest that environmental factors, healthcare practices, or genetic backgrounds may play a role. Future research should investigate these regional disparities in more detail to understand their implications for clinical practice. 5) Patient Education and Awareness: Investigating the effectiveness of educational interventions aimed at both healthcare providers and patients regarding SJS symptoms could enhance early detection and intervention rates. Understanding how best to communicate risks associated with AEDs is crucial. 6) Comparative Studies on AEDs: More research is needed comparing the risk of SJS across different AEDs to identify which medications pose the highest risk. This information could guide prescribing practices and improve patient safety. 7) Impact of Co-medications: The role of Co-medications in increasing the risk of SJS among AED users remains underexplored. Investigating potential drug interactions that may exacerbate this risk will be important for comprehensive patient management. 8) Quality of Reporting: There is variability in how SJS is reported in clinical studies. Standardizing definitions and diagnostic criteria for SJS across studies would enhance the comparability of data and improve future meta-analyses.

In summary, while this review highlights critical findings regarding the prevalence of SJS linked to AEDs, addressing these knowledge gaps through future research will be essential for improving patient safety, tailoring treatment approaches, and ultimately enhancing clinical outcomes for individuals at risk for SJS.

Conclusions

This systematic review and meta-analysis reveal a significant prevalence of Stevens–Johnson syndrome (SJS) linked to antiepileptic drugs (AEDs), with an overall prevalence of 23.22%, and provide evidence supporting an association between AED use and the development of SJS. Healthcare providers should be aware of this potential complication when prescribing AEDs, especially in patients with known risk factors. it is imperative for clinicians to exercise heightened vigilance when prescribing AEDs, particularly in populations identified as high-risk, such as those with a history of drug reactions or certain genetic predispositions, and should conduct thorough patient assessments and educate patients on SJS symptoms enabling timely recognition and intervention. The variability in prevalence across regions indicates the need for healthcare providers to consider local epidemiological data in their prescribing practices. The findings of this systematic review and meta-analysis underscore the significant prevalence of Stevens–Johnson syndrome (SJS) associated with antiepileptic drugs (AEDs). Additionally, further research is crucial to understand the underlying mechanisms SJS in AED users and to identify genetic markers that could inform personalized treatment approaches, enhancing patient safety and outcomes. Future studies should aim to further elucidate the underlying mechanisms and develop strategies for early detection, prevention, and management of SJS in patients taking AEDs.

Declarations

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Contributors

R-P, A-S, S-T, M-O, F-H, and A-A participated in the conception, design, and data analysis, and wrote the manuscript. R-P and S-T contributed to the conception and design of the study and its review. R-P, S-T the senior authors were active in the conception, design, and writing and edition of the manuscript. All authors approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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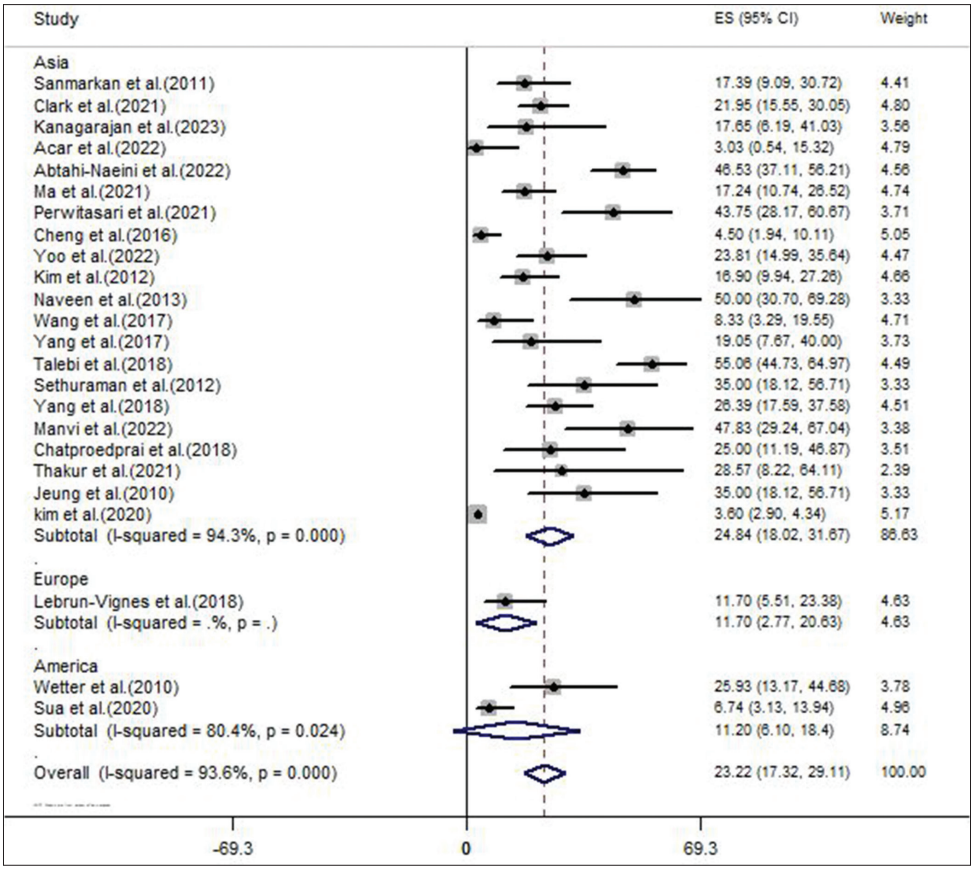
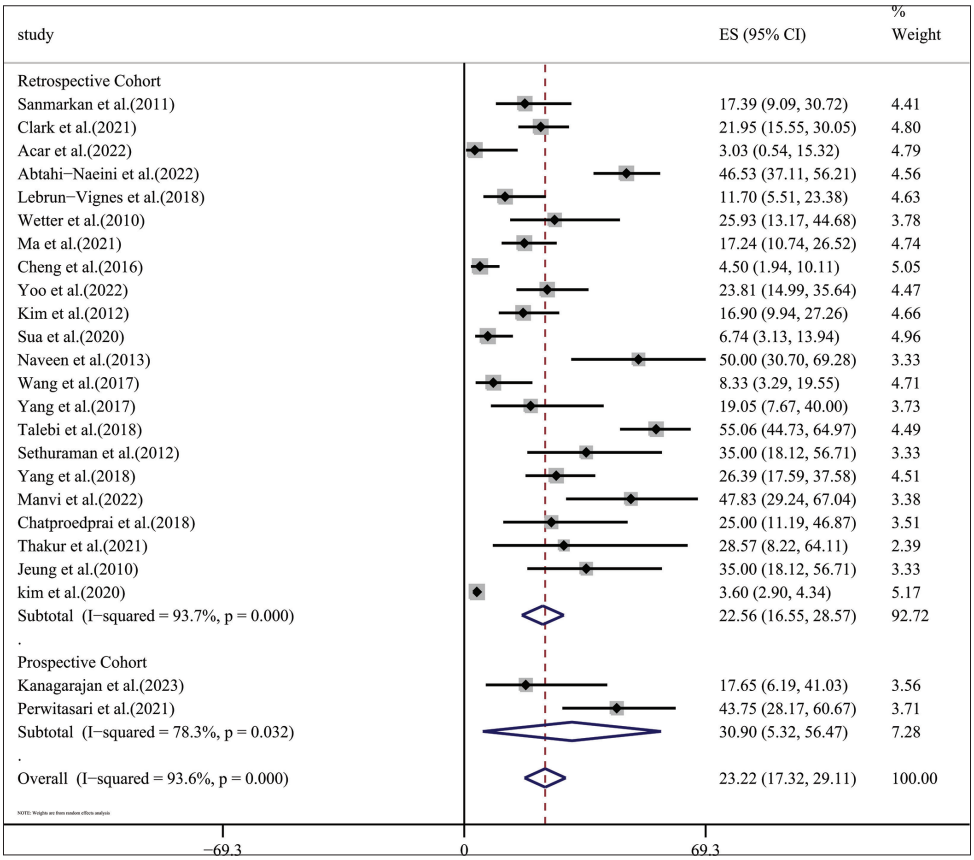
Supplementary Figures




study
ES (95% CI)
% Weight
Retrospective Cohort
Sanmarkan et al.(2011) 17.39 (9.09, 30.72) 4.41
Clark et al.(2021) 21.95 (15.55, 30.05) 4.80
Acar et al.(2022) 3.03 (0.54, 15.32) 4.79
Abtahi−Naeini et al.(2022) 46.53 (37.11, 56.21) 4.56
Lebrun−Vignes et al.(2018) 11.70 (5.51, 23.38) 4.63
Wetter et al.(2010) 25.93 (13.17, 44.68) 3.78
Ma et al.(2021) 17.24 (10.74, 26.52) 4.74
Cheng et al.(2016) 4.50 (1.94, 10.11) 5.05
Yoo et al.(2022) 23.81 (14.99, 35.64) 4.47
Kim et al.(2012) 16.90 (9.94, 27.26) 4.66
Sua et al.(2020) 6.74 (3.13, 13.94) 4.96
Naveen et al.(2013) 50.00 (30.70, 69.28) 3.33
Wang et al.(2017) 8.33 (3.29, 19.55) 4.71
Yang et al.(2017) 19.05 (7.67, 40.00) 3.73
Talebi et al.(2018) 55.06 (44.73, 64.97) 4.49
Sethuraman et al.(2012) 35.00 (18.12, 56.71) 3.33
Yang et al.(2018) 26.39 (17.59, 37.58) 4.51
Manvi et al.(2022) 47.83 (29.24, 67.04) 3.38
Chatproedprai et al.(2018) 25.00 (11.19, 46.87) 3.51
Thakur et al.(2021) 28.57 (8.22, 64.11) 2.39
Jeung et al.(2010) 35.00 (18.12, 56.71) 3.33
kim et al.(2020) 3.60 (2.90, 4.34) 5.17
Subtotal (I−squared = 93.7%, p = 0.000) 22.56 (16.55, 28.57) 92.72
.
Prospective Cohort
Kanagarajan et al.(2023) 17.65 (6.19, 41.03) 3.56
Perwitasari et al.(2021) 43.75 (28.17, 60.67) 3.71
Subtotal (I−squared = 78.3%, p = 0.032) 30.90 (5.32, 56.47) 7.28
.
Overall (I−squared = 93.6%, p = 0.000) 23.22 (17.32, 29.11) 100.00
NOTE: Weights are from random effects analysis
−69.3
0
69.3