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Original Article

Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with anticonvulsants in a Japanese population: Matched case-control and cohort studies

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Abbreviations:

AUC, area under the plasma concentration

–time curve; ALDEN, algorithm of drug

causality for epidermal necrolysis;

CLR, conditional logistic regression;

CPRD, Clinical Practice Research Datalink;

CYP, cytochrome P-450; EMM, erythema

multiforme major; EMR, electronic medical

records; HIV, human immunodeficiency

virus; ICD-10, International Classification of

Diseases, 10th Edition; MHLW, Ministry of

Health, Labour and Welfare; PV, negative

predictive value; OTC, over-the-counter;

PPV, positive predictive value; SJS, Stevens-

Johnson syndrome; TEN, toxic epidermal

necrolysis; UGT, uridine diphosphate

glucuronosyltransferase

ABSTRACT

Background: Evidence for the risk and incidence of anticonvulsant-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Japan is scarce.

Methods: We conducted a matched case-control study using a large-scale Japanese claims database. SJS/TEN cases were identified using a claims-based algorithm developed in a previous study (sensitivity 76.9%, specificity 99.0%). Conditional logistic regression with Firth's bias correction to address an issue of rare events was used to estimate odds ratios (ORs) for SJS/TEN for each anticonvulsant use (90 days before the index date) versus non-use. 90-day cumulative incidence of SJS/TEN per 100,000 new users was calculated for 33 anticonvulsants. Causality between anticonvulsant use and SJS/TEN in each exposed case was assessed using the algorithm of drug causality for epidermal necrolysis (ALDEN) score.

Results: From 5,114,492 subjects, we selected 71 SJS/TEN cases and 284 controls. We observed significantly increased ORs for SJS/TEN among new users of carbamazepine (OR 68.00) and lamotrigine (OR 36.00) with ALDEN scores of "probable" or higher. Cumulative incidence of SJS/TEN was 93.83 for carbamazepine and 84.33 for lamotrigine. One case newly exposed to phenytoin which developed SJS/TEN was rated "unlikely" in ALDEN causality, resulting in cumulative incidence of 66.27. Cumulative incidence of SJS/TEN was 25.23 for levetiracetam, 7.52 for clonazepam, and 1.23 for diazepam, but their ALDEN scores were "very unlikely".

Conclusions: This study is the first to document the differential risk of SJS/TEN for anticonvulsants in a real-world setting in Japan. Exposure to carbamazepine and lamotrigine was associated with an increased risk of SJS/TEN.

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Introduction

The key feature of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is severe damage to the skin and mucous membranes, with detached epithelium, and commonly complicated with fever.¹ The main difference between the two conditions is in the affected surface area. In Japan, SJS is diagnosed when less than 10% of the body surface area is affected, and TEN

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when 10% or more is affected.² In Europe and the United States, SJS is diagnosed when less than 10% of the body surface area is affected, SJS/TEN overlap when 10–30% is affected, and TEN when 30% or more is affected.¹ The reported incidences of SJS/TEN are rare, at 1 to 7 cases per million per year for SJS and 0.4 to 1.5 for TEN in Japan, Europe, and the United States.^{1,3} More than 220 medications have been implicated in causing SJS/TEN, the majority of which are anticonvulsants, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs).⁴ Previous studies in European countries reported the risk of SJS/TEN induced by certain anticonvulsants, specifically carbamazepine,^{5–7} lamotrigine,^{6,7} phenytoin,^{5–7} and phenobarbital.^{5,6} A recent review showed that drug-induced SJS/TEN is often influenced by genetic and/or ethnic differences, and that the risk varies from country to country, even within Asia.^{8,9} The quantitative risk of SJS/TEN should therefore be assessed among individual ethnic groups.^{10,11} To date, however, few population-based studies on the risk of SJS/TEN have been conducted in Asian countries.^{12,13}

The Ministry of Health, Labour and Welfare (MHLW) in Japan designated SJS and TEN as intractable diseases and issued a series of manuals of care for serious diseases due to adverse drug reactions, including SJS and TEN.^{14,15} However, pharmacoepidemiological quantitative risk assessment of SJS/TEN for culprit drugs in Japan is lacking, primarily due to difficulties in tracking samples of sufficient size to provide the power required to detect and analyze such rare conditions. The limited sample size in conventional, prospective post-marketing surveillance studies in Japan has not allowed valid estimation of the factors and magnitude of risks of rare adverse drug reactions. Large-scale electronic health record databases, such as administrative claims databases and electronic medical records (EMR) databases, would therefore appear useful for these epidemiological studies, but data collected for purposes other than research, including claims reimbursement, have questionable validity for use in epidemiological studies of risk.^{16,17} To overcome this problem, we previously developed an EMR-based algorithm to identify SJS/TEN patients in database studies in Japan.¹⁸ Here, we used this algorithm to evaluate the relative and absolute risk of SJS/TEN in association with the new use of anticonvulsants.

Methods

Data source

The study population was derived from a large-scale employment-based claims database provided by JMDC Inc. (Tokyo, Japan). This database included data from 5.6 million employees and their dependents aged <75 years covered by the health insurance plans of primarily large private-sector corporations as of 2017.¹⁹ Elderly aged 75 years or older are covered by a separate national medical insurance system for the elderly, and were therefore not included in the database. The JMDC database contains claims for in-patient, out-patient, and pharmacy dispensing since 2005, and thereby provides longitudinal individual-level data on all medical encounters and healthcare resource consumption during the healthcare insurance coverage of employees. Given the traditionally life-long employment system in Japan, this enables long and complete follow-up. Claims data are anonymized when retrieved from the insurers and transferred to the JMDC claims database.²⁰ Individuals in the database can be tracked by a unique identifier unless they withdraw from their health insurance plan. The database has been used by pharmaceutical companies, academic facilities, and regulatory authorities for epidemiological research.^{21–23} The following information is available from the JMDC claims database: demographics (sex, year and month of birth), diagnoses coded according to the International

Classification of Diseases, 10th Edition (ICD-10) and standard disease name master compatible with ICD-10,²⁴ coded according to the National Health Insurance Drug List,²⁵ and procedures coded according to the Japanese national insurance reimbursement.²⁶ The present study analyzed data collected between January 1, 2005 and December 31, 2017. The study protocol and waiver of informed consent were approved by the Ethics Committee for Research Involving Humans of Keio University Faculty of Pharmacy (No. 180427-2), in accordance with local ethical guidelines for medical research involving human subjects.

Case identification and assessment

We cautiously took two steps to identify true SJS/TEN cases as accurately as possible by using an algorithm developed by the authors in a previous study (Supplementary Table 1).¹⁸ In the first step, we reasonably assumed that any true SJS/TEN patients who were treated in a dermatology division would have at least one of the codes for SJS/TEN or other similar diagnoses which need to be differentiated from SJS/TEN (Supplementary Table 2). The ICD-10 codes shown in Supplementary Table 2 were selected by an expert dermatologist, HT, who is a committee member and an author of the SJS/TEN clinical practice guidelines.^{2,18} We decided to use the ICD-10 codes (Supplementary Table 2) only for the purpose of screening all SJS/TEN case candidates who had been recorded with these codes out of the total study subjects. In the second step, we applied the algorithm to all case candidates of SJS/TEN after the step 1 screening to determine the true SJS/TEN cases in the present study. The algorithm consisted of a combination of the following three domains and was developed in reference to the clinical guidelines for SJS/TEN (Supplementary Table 1): the first domain consisted of three items related to the clinical course for SJS/TEN, namely hospitalization, skin biopsy, and systemic treatments; the second domain included one item of medical encounters for mucocutaneous lesions from SJS/TEN (Supplementary Table 3); and the third domain included one test item to exclude paraneoplastic pemphigus.¹⁸ The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the algorithm were 76.9%, 99.0%, 40.5%, and 99.8%, respectively.¹⁸ The algorithm required weight data to calculate steroid therapy doses for prednisolone of ≥ 0.5 mg/kg/day, but these were not available in the JMDC claims database. We therefore assumed two different weights – 50.0 and 60.0 kg, regardless of age – to calculate the daily dose of steroids in verifying the robustness of the results. For pediatric patients also, steroid doses were calculated using the assumed body weight for those aged 0–15 years based on the mean weight per year of age.²⁷ A modified version of the algorithm incorporated an enzyme-linked immunosorbent assay (ELISA) to detect anti-BP180 antibody to exclude the possibility of bullous pemphigoid in cases when the assay was performed twice or more. The modified algorithm had the same diagnostic performance as the original (unpublished data) and was applied in a sensitivity analysis (Supplementary Table 1). When multiple events in a patient were detected, only the first event was eligible for the analysis of incident cases.

To assess causality between anticonvulsant use and SJS/TEN in each exposed case, we used the algorithm of drug causality for epidermal necrolysis (ALDEN).²⁸ The ALDEN grades causality with a drug for drug-induced SJS/TEN in the five levels of “very probable,” “probable,” “possible,” “unlikely,” or “very unlikely.” The first two grades “very probable” and “probable” are considered to indicate a causal relationship. The original ALDEN considers that a drug initiated 56 days or more prior to the onset of SJS/TEN as unlikely to be causal. We extended this period to 90 days in accordance with a previous study.⁷

Study design and population

This study used separate matched case–control and cohort designs. The matched case–control substudy aimed to estimate odds ratios (ORs) for SJS/TEN associated with anticonvulsant use versus anticonvulsant non-use. Case candidates were identified when they had the disease codes shown in [Supplementary Table 2](#),¹⁸ as diagnosed at departments of dermatology after April 1, 2012 ([Fig. 1](#)). To be eligible for analysis, cases had to meet the following criteria: 1) algorithm-positive, and 2) ≥ 180 days of active history in the JMDC claims database prior to the index date. The index date was set as the first recorded date of any of the diagnoses shown in [Supplementary Table 2](#). Because claims records under the national health insurance reimbursement scheme in Japan lacked information of dates before March 31, 2012, we searched for incident cases of SJS/TEN after April 1, 2012, and used the claims records before March 31, 2012 to examine active histories and past prescriptions. For each case, four controls meeting the following criteria were randomly selected and matched through risk set sampling with replacement by sex, age at the date of medical encounter with an allowance of three years, and date of medical encounter (within three days' difference), in descending order of priority.²⁹ The sampling date for each control was regarded as the index date. Control candidates were selected from patients without the disease codes shown in [Supplementary Table 2](#). Controls had to have medical encounters within 30 days before or after the index date and ≥ 180 days of active history prior to the index date, in accordance with a previous study.⁷ Drug exposure was defined as the first recorded prescription of an anticonvulsant ≤ 90 days before the index date. All anticonvulsants on the market between 2005 and 2017 in Japan were studied ([Supplementary Table 4](#)).

The cohort substudy estimated the cumulative incidence of SJS/TEN for new users of 33 anticonvulsants ([Supplementary Table 4](#)). We established 33 individual cohorts of new users of a single anticonvulsant between April 1, 2012 and October 3, 2017. New users of an anticonvulsant were defined as having a preceding lookback period of at least 180 days without any prescription of the

anticonvulsant of interest before the earliest record of anticonvulsant prescription in the study database, and were followed from the date of first prescription. To be eligible for analysis, new users were required to have a follow-up period of at least 90 days or to have developed SJS/TEN within 90 days after starting treatment with the anticonvulsant.

Statistical analysis

Patient characteristics were summarized with descriptive statistics for age, sex, history of epilepsy (ICD-10: G40 and G41) before the index date, anticonvulsant use within 90 days or any time before the index date, and the following SJS/TEN risk factors: concomitant high-risk drug administered within 90 days or more than 90 days before the index date, including allopurinol, carbamazepine, lamotrigine, nevirapine, oxycam analgesics, phenobarbital, phenytoin, and sulfonamides⁶; history of mycoplasma infection (A49.3, J15.7, J20.0, and P23.6 only for mycoplasma),³⁰ herpesvirus infection (A60 and B00),³¹ and cancer (C00 to C97) within 90 days before the index date³²; and history of lupus erythematosus (L93 and M32) before the index date.^{33,34}

In the matched case–control substudy, the expected absence or paucity of anticonvulsant users among the controls means complete or quasi-complete separation between SJS/TEN and use of several anticonvulsants, which could produce a potential issue in the calculation of ORs. Application of the conditional maximum likelihood method to a complete or a quasi-complete separation dataset is reported to result in inappropriately infinite ORs.³⁵ A number of analytical approaches have been proposed to address this issue, including exact conditional logistic regression (CLR),³⁶ CLR via penalized likelihood by data augmentation,^{37,38} and CLR with Firth's bias correction.³⁹ We chose Firth's method because the 95% CIs derived by this method do not extend to infinity. In contrast, exact CLR may yield implausible infinite 95% CIs.^{7,39} Further, while CLR via penalized likelihood by data augmentation obviates infinite 95% CIs, similarly to Firth's method, unless any preexisting evidence suggests a modest increase in ORs associated

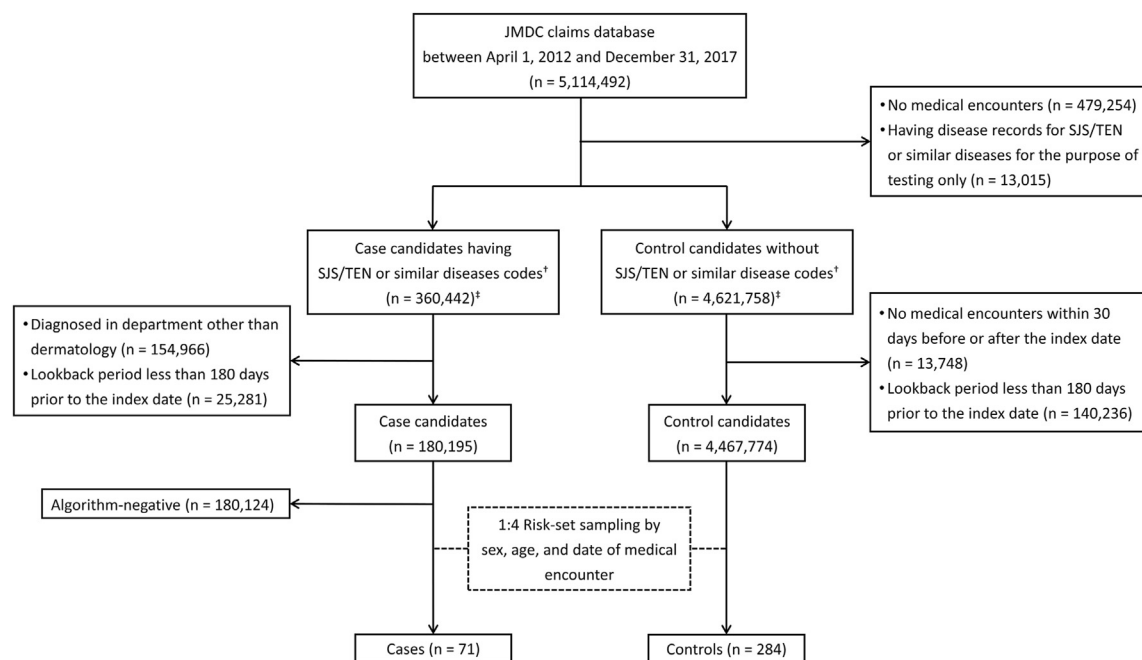


Fig. 1. Flow diagram for the case–control study. SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. † Codes of SJS/TEN or similar diseases are shown in [Supplementary Table 2](#). ‡ Multiple count-inclusive, due to risk-set sampling.

with anticonvulsant use, using a penalization may bias ORs toward the null, and is therefore unsuitable.⁴⁰ Adjustment was not performed due to sparse data bias arising from the small number of cases.^{36,41} For sensitivity analysis, we used conventional CLR for anticonvulsants where complete or quasi-complete separation did not exist.

In the cohort substudy, we calculated the 90-day cumulative incidences of SJS/TEN by dividing the number of incident cases by the total number of new users of the anticonvulsant. To assess the robustness of our results, we repeated the analysis while restricting the SJS/TEN cases to those with an ALDEN score of “probable” or higher.

All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). To implement the CLR with Firth's bias correction, we used the conditional Firth likelihood macro provided by Heinze.⁴²

Results

Patient characteristics

We identified 360,442 patients with at least one disease code shown in [Supplementary Table 2](#), recorded at a department of dermatology in the JMDC claims database between April 1, 2012 and December 31, 2017. A total of 71 SJS/TEN cases were identified, with 35 in males ([Fig. 1](#)), and these were matched to 284 controls for the case–control substudy. Mean age at the index date for cases and controls combined was 45.4 years (SD, 13.5). The number of SJS/TEN cases remained unchanged regardless of the assumed body weights used to calculate steroid doses. The modified version of the algorithm did not alter the results. Median follow-up period of the 71 SJS/TEN cases was 5.5 (interquartile range, 3.7–6.7) years. Compared with the controls, cases had more epilepsy (7.0% vs. 2.5%), anticonvulsant use (≤ 90 days before the index date, 18.3% vs. 1.4%; any time before the index date, 23.9% vs. 9.5%) ([Table 1](#)). The following anticonvulsants used in the study population also had other indications besides epilepsy: carbamazepine, lamotrigine, nitrazepam, phenobarbital, saiko-ka-ryukotsu-borei-to (a traditional Japanese herbal *Kampo* medicine, indicated for stress-related neuropsychiatric disorders), and valproate. The total number of anticonvulsant

users therefore exceeded the number of patients with the diagnosis of epilepsy. Cases carried more risk factors for SJS/TEN, notably high-risk drug use ≤ 90 days before the index date (33.8% vs. 9.5%), mycoplasma infection (4.2% vs. 0%), and herpesvirus infection (7.0% vs. 1.8%).

Matched case–control substudy

Among 71 identified SJS/TEN cases, eight and four were exposed to carbamazepine and lamotrigine within ≤ 90 days before the index date, respectively ([Table 2](#) and [Supplementary Table 5](#)). ORs were significantly increased for carbamazepine (OR 68.00, 95% CI 8.49–8792.29) and lamotrigine (OR 36.00, 95% CI 3.84–4770.48). All these incident cases had an ALDEN score of “probable” or higher, and 37.5% (3/8) of cases exposed to carbamazepine and 75.0% (3/4) cases exposed to lamotrigine had very probable causality. One SJS/TEN case exposed to phenytoin ≤ 90 days before the index date was identified, resulting in an insignificant OR of 4.00 (95% CI 0.32–49.25); this case received treatment with carbamazepine until SJS/TEN onset and concomitant 3-day treatment with phenytoin, which was discontinued 41 days before disease onset. The ALDEN scores for carbamazepine and phenytoin were therefore “probable” and “unlikely”, respectively. One SJS/TEN case concomitantly exposed to levetiracetam and diazepam ≤ 90 days before the index date was identified, resulting in the insignificant OR of 12.00 (95% CI 0.64–1751.04) for levetiracetam and 4.00 (95% CI 0.32–49.25) for diazepam; this case was also newly exposed to carbamazepine before SJS/TEN onset, and the ALDEN scores for each drug were rated as “very unlikely”. In one SJS/TEN case, exposure to clonazepam ≤ 90 days before the index date was found, resulting in the insignificant OR of 4.00 (95% CI 0.32–49.25); clonazepam was continued for more than a year after disease onset, and the ALDEN-based causality was therefore “very unlikely”.

We did not identify any SJS/TEN cases in association with the use of the other anticonvulsants ([Supplementary Table 6](#)). These results remained stable in sensitivity analysis with conventional CLR for anticonvulsants. Where a complete or quasi-complete separation was absent, ORs for phenytoin, clonazepam, and diazepam ≤ 90 days before the index date were 4.00 (95% CI 0.25–63.95) calculated by conventional CLR ([Supplementary Table 7](#)).

Cohort substudy

A total of 8526 new users of carbamazepine and 4743 new users of lamotrigine were identified in the cohort substudy, and eight carbamazepine and four lamotrigine new users were identified as cases, who were identical with the cases identified in the matched case–control substudy ([Table 3](#) and [Supplementary Table 5](#)). 90-day cumulative incidences per 100,000 new users were 93.83 (95% CI 46.92–187.63) for carbamazepine and 84.33 (95% CI 31.65–224.71) for lamotrigine. All carbamazepine and lamotrigine cases were rated “probable” or higher in the ALDEN grade and occurred within 70 days of first exposure. We identified 1509 new users of phenytoin, 3964 new users of levetiracetam, 13,294 new users of clonazepam, and 81,326 new users of diazepam, and one SJS/TEN case for each anticonvulsant cohort. These cases were identical with the cases identified in the matched case–control substudy. 90-day cumulative incidences of SJS/TEN per 100,000 new users were 66.27 (95% CI 9.33–470.47) for phenytoin, 25.23 (95% CI 3.55–179.10) for levetiracetam, 7.52 (95% CI 1.06–53.40) for clonazepam, and 1.23 (95% CI 0.17–8.73) for diazepam, albeit that these cases were rated “unlikely” or less in the ALDEN-based causality score. Numbers of new users were larger for acetazolamide, nitrazepam, saiko-ka-ryukotsu-borei-to

Table 1
Characteristics of case patients and controls.

Characteristic	Cases (n = 71)	Controls (n = 284)
Male, No. (%)	35 (49.3)	140 (49.3)
Age, mean (SD), years	45.5 (13.6)	45.4 (13.5)
Epilepsy, No. (%) [†]	5 (7.0)	7 (2.5)
Anticonvulsant use, No. (%)		
≤ 90 days before the index date	13 (18.3)	4 (1.4)
Any time before the index date	17 (23.9)	27 (9.5)
SJS/TEN risk factors, No. (%)		
Any known or suspected SJS/TEN risk factor	29 (40.8)	57 (20.1)
High-risk drug use [‡]		
≤ 90 days before the index date	24 (33.8)	27 (9.5)
> 90 days before the index date	30 (42.3)	104 (36.6)
Mycoplasma infection [§]	3 (4.2)	0
Herpesvirus infection [§]	5 (7.0)	5 (1.8)
Cancer [§]	1 (1.4)	11 (3.9)
Lupus erythematosus [†]	1 (1.4)	0

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[†] Recorded any time before the index date.

[‡] High-risk drugs include allopurinol, carbamazepine, lamotrigine, nevirapine, oxycam analgesics, phenobarbital, phenytoin, and sulfonamides.⁶

[§] Recorded within 90 days before the index date.

Table 2

Odds ratios for Stevens-Johnson syndrome and toxic epidermal necrolysis after exposure to anticonvulsants.

Anticonvulsant	No. of cases n = 71 (%)		No. of controls n = 284 (%)		OR [†]	(95% CI)	Cases (%) exposed to other concomitant HRDs [‡]	
Carbamazepine								
≤90 days before the index date	8	(11.3)	0		68.00	(8.49–8792.29)	1	(12.5)
>90 days before the index date	1	(1.4)	1	(0.4)	4.00	(0.32–49.25)		
Lamotrigine								
≤90 days before the index date	4	(5.6)	0		36.00	(3.84–4770.48)	1	(25.0)
>90 days before the index date	0		1	(0.4)	1.33	(0.01–24.99)		
Phenytoin								
≤90 days before the index date	1	(1.4)	1	(0.4)	4.00	(0.32–49.25)	1	(100)
>90 days before the index date	1	(1.4)	0		12.00	(0.64–1751.04)		
Levetiracetam								
≤90 days before the index date	1	(1.4)	0		12.00	(0.64–1751.04)	1	(100)
>90 days before the index date	2	(2.8)	1	(0.4)	6.67	(0.89–72.85)		
Clonazepam								
≤90 days before the index date	1	(1.4)	1	(0.4)	4.00	(0.32–49.25)	0	
>90 days before the index date	4	(5.6)	5	(1.8)	3.57	(0.90–14.01)		
Diazepam								
≤90 days before the index date	1	(1.4)	1	(0.4)	4.00	(0.32–49.25)	1	(100)
>90 days before the index date	1	(1.4)	10	(3.5)	0.57	(0.06–2.43)		
Fosphenytoin								
≤90 days before the index date	0		0		N/A		0	
>90 days before the index date	1	(1.4)	0		12.00	(0.64–1751.04)		
Phenobarbital								
≤90 days before the index date	0		0		N/A		0	
>90 days before the index date	1	(1.4)	1	(0.4)	4.00	(0.32–49.25)		
Saiko-ka-ryukotsu-borei-to								
≤90 days before the index date	0		0		N/A		0	
>90 days before the index date	1	(1.4)	1	(0.4)	4.00	(0.32–49.25)		
Valproate								
≤90 days before the index date	0		0		N/A		0	
>90 days before the index date	2	(2.8)	4	(1.4)	2.22	(0.39–10.02)		

OR, odds ratio; CI, confidence interval; HRDs, high-risk drugs; ALDEN, algorithm of drug causality for epidermal necrolysis.

When multiple anticonvulsants were prescribed to single patients, they were counted for each drug.

[†] ORs were calculated by Firth conditional logistic regression.[‡] HRDs include allopurinol, carbamazepine, lamotrigine, nevirapine, oxicam analgesics, phenobarbital, phenytoin, and sulfonamides.⁶

and valproate than for lamotrigine, but no cases of SJS/TEN were observed among them (Supplementary Table 8). Further, no cases of SJS/TEN were identified for other anticonvulsants, including phenobarbital (4303 new users), having fewer new users than lamotrigine.

Discussion

This study is the first to investigate the risk of SJS/TEN in patients newly treated with anticonvulsants using a large-scale claims database in Japan. Significantly elevated ORs and larger incidences of SJS/TEN were found for carbamazepine and lamotrigine. One SJS/TEN case exposed to phenytoin was identified, resulting in a large incidence of SJS/TEN for phenytoin. One SJS/TEN case each was found among new users of levetiracetam, clonazepam, and diazepam, but ALDEN assessment did not support a causal relationship

for any. Although acetazolamide, nitrazepam, saiko-ka-ryukotsu-borei-to and valproate had more new users than lamotrigine, no cases of SJS/TEN were found among them. No SJS/TEN cases were found among new users of phenobarbital.

Previous case–control studies in several European countries reported that new exposure to carbamazepine^{5–7}, lamotrigine,^{6,7} phenytoin^{5–7}, or phenobarbital^{5,6} was strongly associated with the risk of SJS/TEN. A cohort study using the Clinical Practice Research Datalink (CPRD) reported the 84-day cumulative incidence of SJS/TEN per 100,000 new users was 20.38 (95% CI 12.07–34.41) for carbamazepine, 44.17 (95% CI 22.09–88.32) for lamotrigine, and 45.86 (95% CI 19.09–110.19) for phenytoin.⁷ These results cannot be directly compared with our present data because of the difference in algorithms used to identify SJS/TEN; nevertheless, our study also confirms the risks of SJS/TEN due to carbamazepine and lamotrigine.

Table 3

90-day cumulative incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with anticonvulsants.

Anticonvulsant	No. of new users	No. of SJS/TEN cases	Risk per 100,000 new users (95% CI)		No. of SJS/TEN cases with ALDEN score ≥ probable	Risk of ALDEN cases per 100,000 new users (95% CI)	
Carbamazepine	8526	8	93.83	(46.92–187.63)	8	93.83	(46.92–187.63)
Lamotrigine	4743	4	84.33	(31.65–224.71)	4	84.33	(31.65–224.71)
Phenytoin	1509	1	66.27	(9.33–470.47)	0	0	(N/A)
Levetiracetam	3964	1	25.23	(3.55–179.10)	0	0	(N/A)
Clonazepam	13,294	1	7.52	(1.06–53.40)	0	0	(N/A)
Diazepam	81,326	1	1.23	(0.17–8.73)	0	0	(N/A)

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; CI, confidence interval; ALDEN, algorithm of drug causality for epidermal necrolysis.

When multiple anticonvulsants were prescribed to single patients, they were counted for each drug.

It is reported that there is a greater risk of SJS/TEN when lamotrigine is co-administrated with valproate, one of uridine diphosphate glucuronosyltransferase (UGT) inhibitors. These inhibitors increase the area under the plasma concentration–time curve (AUC) of lamotrigine, thereby making it more likely to cause skin disorders.⁴³ Out of four SJS/TEN cases newly exposed to lamotrigine in this study, two were prescribed UGT inhibitors on the same day as the initial prescription of lamotrigine: one with valproate and UGT inhibitors including flunitrazepam and clonazepam; and the second with flunitrazepam.⁴⁴ In these cases, it appears highly likely that the concomitant UGT inhibitors raised the risk of SJS/TEN above that of lamotrigine alone. Nevertheless, the number of cases did not allow the assessment of interaction.

Phenytoin and phenobarbital are known to cause SJS/TEN. We identified one phenytoin case, and observed a high incidence of SJS/TEN. However, ALDEN assessment suggested that phenytoin causality was “unlikely”, given that the patient discontinued 3-day phenytoin treatment 41 days prior to SJS/TEN onset, and received concomitant carbamazepine until the day of the onset. It is known that cross-sensitivity between phenytoin and carbamazepine frequently occurs.⁴⁵ Therefore, the direct or indirect involvement of phenytoin in the etiology of SJS/TEN in this case administered carbamazepine cannot be denied. No SJS/TEN cases were identified among new users of phenobarbital in our study, which may be coincidental. One of the largest database studies of SJS/TEN using the CPRD also identified no SJS/TEN cases induced by phenobarbital, due to the small number of patients treated with this drug (N = 963), which is consistent with our finding.⁷ A descriptive study using severe cutaneous adverse reaction registries in Japan and Korea reported that phenytoin or phenobarbital accounted for only a few percent of the reported cases of SJS/TEN, smaller than carbamazepine or lamotrigine.^{9,10} These registries did not have information on the total population receiving anticonvulsants because they only collected information of cases. It is therefore not possible to calculate the absolute risk of SJS/TEN induced by each anticonvulsant, nor to discuss the magnitude of the risk for comparison. Closer scrutiny of this gap may require comparative studies powered by a sample size large enough to detect a sufficient number of cases.

We identified one SJS/TEN case following new exposure to clonazepam, but the ALDEN-based causality was “very unlikely” because clonazepam was continued for more than a year after disease onset. Clonazepam was reported not as a risk factor for SJS/TEN in a previous study with a large number of exposed patients.⁷ We also observed one SJS/TEN case in which diazepam and levetiracetam were used concomitantly within 90 days before the index date. However, owing to subsequent exposure to carbamazepine immediately before SJS/TEN onset, the ALDEN scores for each drug were rated as “very unlikely”. To our knowledge, no study has reported an increased risk of developing SJS/TEN due to drug–drug interaction between diazepam and carbamazepine. Levetiracetam was not identified as a risk factor for SJS/TEN in the previous case–control study using the CPRD,⁷ which is consistent with our results. On the other hand, case reports have suggested that levetiracetam can affect the pharmacodynamics of carbamazepine, in which affected patients develop disabling symptoms compatible with carbamazepine toxicity.⁴⁶ Accordingly, a causal relationship between levetiracetam and SJS/TEN cannot be ruled out.

Our finding of no SJS/TEN cases among new users of valproate is consistent with the results of other studies on valproate conducted in European countries.^{6,7} For other anticonvulsants, including acetazolamide, nitrazepam, saiko-ka-ryukotsu-borei-to, for which our study also detected no cases, information on the risk of developing SJS/TEN was limited. Aromatic anticonvulsants such as carbamazepine, lamotrigine, phenytoin, and phenobarbital are

metabolized to arene oxides, which have been hypothesized to cause cell necrosis or a secondary immunological response.⁴⁷ Cross-reactivity between aromatic anticonvulsants is also frequent.⁴⁵ Further, we identified no SJS/TEN cases among patients treated with acetazolamide and valproate ≤ 90 days before the index date. This finding may support the pathophysiological involvement of the structure–activity relationship of aromatic anticonvulsants or arene oxides in the pathogenic mechanism of SJS/TEN.⁴⁸ These anticonvulsants are likely safe for the treatment of epilepsy in patients with a history of rash to an anticonvulsant,⁴⁹ albeit that further studies are required.

There were several limitations to our study. First, the diagnostic performance of the algorithm we applied is likely to differ from that in our original algorithm study because the study population from which cases and controls were sampled differed in several aspects.¹⁷ Before applying the algorithm in the present study population, we first limited case candidates to those carrying the ICD-10 codes shown in [Supplementary Table 2](#) as recorded at a department of dermatology to minimize the misclassification in the cases. Originally, the algorithm was developed using the EMR of the dermatology department of a single urban educational hospital and the components of the algorithm did not include the disease codes shown in [Supplementary Table 2](#). Limiting cases to those diagnosed in a dermatology department is consistent with Japanese practice, in which SJS/TEN patients are reviewed and diagnosed by qualified dermatologists at secondary or tertiary care hospitals.⁵⁰ Patients who did not have such codes or medical department data in the database were excluded from the cases. This may have led to the underestimation of incidence. Addressing this issue would require additional validation studies using extensive medical chart review. The controls were sampled from among patients not carrying the codes in [Supplementary Table 2](#) and thereby appear to well represent the general population in terms of exposure status in non-cases. Although this sampling minimized misclassification in controls, potential misclassification cannot be completely excluded. In addition, we did not select algorithm-negatives among the patients carrying the ICD-10 codes shown in [Supplementary Table 2](#) as controls because these are likely to include false negative cases due to potential misclassification. Moreover, a second source of potential misclassification due to the algorithm components employed should be considered. We calculated steroid therapy doses by considering patient age and age-standardized weight because of the unavailability of weight data in the study database, but this may have led to disease misclassification. Patients with erythema multiforme major (EMM) might have been detected as false positives because the differentiation of SJS/TEN and EMM requires pathological findings, but they are not available in the study database. Our algorithm to identify SJS/TEN cases requires medical encounters for mucocutaneous lesions, including ocular symptoms. A previous case series in Japan reported that SJS/TEN cases induced by anticonvulsants developed fewer ocular complications than those induced by antibiotics or NSAIDs.⁵¹ Accordingly, the possibility exists that, among cases without ocular complications, our algorithm missed true SJS/TEN cases as false negatives. The sensitivity of our algorithm may be lower in the anticonvulsant-exposed than unexposed group. Where this differential disease misclassification occurred, assuming that the true ORs were more than 1, the estimated ORs can be biased toward the null when the estimated ORs are ≥ 1 .⁵² Conversely, this bias may have manifested in the reverse direction when the estimated ORs are < 1 .⁵² When the true ORs are less than 1 under the presence of differential misclassification, the bias can proceed in either direction.⁵² Further, due to the suboptimal sensitivity of the algorithm used, the true cumulative incidence would be higher than the estimated incidence by a factor equal to the sensitivity of 76.9%.

Third, although NSAIDs and other over-the-counter (OTC) drugs are known to confer a non-negligible risk of SJS/TEN, the JMDC claims database did not include information on OTC use and this risk was not considered. Finally, we were unable to adjust for variables other than sex, age, and index date because of the small number of cases. Indeed, the only risk factors with a significant effect on incidence identified to date are cancer,³² lupus erythematosus,^{33,34} human immunodeficiency virus (HIV),⁵³ and gene polymorphism.⁸ It has been reported that patients with HIV infection have a 100-fold higher incidence of SJS/TEN than the general population,⁵³ but we were unable to account for this because HIV-related data were excluded from the database under the privacy protection policy of the data supplier. Data on gene polymorphism are also not available in the study database.

In conclusion, this study is the first to document the differential risk of SJS/TEN for anticonvulsants by pharmacological class in a real-world setting in Japan. Our analysis confirmed that incident exposure to carbamazepine and lamotrigine was associated with a significantly increased risk of SJS/TEN, consistent with previous reports. One SJS/TEN case each was found among new users of phenytoin, levetiracetam, clonazepam, and diazepam, none of which suggested causality in the ALDEN assessment. Despite a substantial number of patients exposed to acetazolamide, nitrzapam, saiko-ka-ryukotsu-borei-to, and valproate, no cases of SJS/TEN were observed among them. Practitioners and other health-care providers should use clinical insight to optimize the rational use and benefit/risk balance of anticonvulsant treatment based on evidence from pharmacoepidemiological research, including the present paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.01.004>.

Conflict of interest

HU has received research funds from Shionogi & Co., Ltd. and Senju Pharmaceutical Co., Ltd. The rest of the authors have no conflict of interest.

Authors' contributions

TF, HT, and HU were involved with the study concept and design. TF and KT performed the statistical analysis. TF and HU wrote the manuscript. All authors contributed to the discussion and reviewed, edited, and approved the final manuscript as submitted.

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Supplementary Table 1. Details of algorithms used to identify patients with Stevens-Johnson syndrome and toxic epidermal necrolysis

Algorithm domain and item (date required for each item)	Algorithm definition
Domain 1) Clinical course for SJS/TEN	
Item 1: Hospitalization (admission and discharge date required)	Patients with SJS/TEN should meet Items 1–3 within one week after the date of ICD-10 diagnosis shown in Supplementary Table 2.
Item 2: Skin biopsy (date of biopsy required)	
Item 3: Systemic treatments for SJS/TEN (order date required)	
Receiving any one of the following treatments: steroid therapy (≥ 0.5 mg/kg/day of prednisolone), intravenous immunoglobulin therapy, or plasma exchange therapy	
Domain 2) Medical encounters for mucocutaneous lesions from SJS/TEN	
Item 4: Medical encounters included any of the following (if any item is answered “yes”, Item 4 is considered as “yes”)	Item 4 should be met within two weeks before or after the diagnosis date
• Records of ICD-10 code for SJS/TEN at a department of ophthalmology or dentistry, or for mucocutaneous lesions shown in Supplementary Table 3 (no limitation on department) (date of diagnosis with ICD-10 code required)	
• Steroid eyedrops or ophthalmic ointment with order date	
• Slit-lamp microscopy (date of microscopy required)	
Domain 3) Exclusion of autoimmune bullous disease	
Item 5: Anti-desmoglein 1 or 3 antibody test $\geq 2^{\dagger}$ (date of testing required)	Item 5 should not be met.
Item 6, included only in the amended version: Enzyme-linked immunosorbent assay to detect anti-BP180 antibody $\geq 2^{\ddagger}$ (date of testing required)	Item 6 should not be met.

Adapted from Fukasawa et al.¹⁸

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; ICD-10, International Classification of Diseases, 10th Edition.

[†] Differential diagnosis for paraneoplastic pemphigus generally requires multiple testing of two times or more.

‡ Differential diagnosis for bullous pemphigoid generally requires multiple testing of two times or more. Item 6 was only used in sensitivity analysis.

Supplementary Table 2. ICD-10 codes for Stevens-Johnson syndrome or toxic epidermal necrolysis and diseases requiring differentiation from them

ICD-10 code	Diagnosis name	Standard disease code
A48.3	Toxic shock syndrome	8838282
L00	Staphylococcal scalded skin syndrome	8839830
L01	Impetigo, excluding eosinophilic pustular folliculitis	6840005
		6840016
		6840021
		6840022
		8831223
		8831425
		8831701
		8831792
		8832120
		8832793
		8832794
		8835436
		8835440
		8836534
		8836535
		8837977
		8837991
		8838140
		8838684
		8840200
		8841386
		8841198
L08.0	Acute generalized exanthematous pustulosis	8845530
L10.8	Paraneoplastic pemphigus	8846140
L27.0	Generalized skin eruption due to drugs and medicaments, excluding lupus erythematosus and steroid-induced dermatitis	6923006
		8834475
		8839576
		8845614
		8847016
		9952025

L27.1	Localized skin eruption due to drugs and medicaments	8833851
L27.9	Toxicoderma	6929235
L51.0	Nonbullous erythema multiforme	8839286
L51.1	Bullous erythema multiforme and Stevens-Johnson syndrome	6951003
		8835719
L51.2	Toxic epidermal necrolysis [Lyell]	8840866
		8840867
		8845586
L51.8	Other erythema multiforme	6951008
		8845563
L51.9	Erythema multiforme, unspecified	6951007

Adapted from Fukasawa et al.¹⁸

ICD-10, International Classification of Diseases, 10th Edition.

Supplementary Table 3. ICD-10 codes of mucocutaneous lesions from Stevens-Johnson syndrome and toxic epidermal necrolysis

ICD-10 code		Diagnosis name	Standard disease code
H10.2	Pseudomembranous conjunctivitis and Conjunctivitis medicamentosa		3720006
			3720013
H10.3	Acute conjunctivitis		3720008
H10.8	Conjunctival erosion and Conjunctival ulcer		3720011
			3725002
H10.9	Conjunctivitis		3723001
H11.2	Symblepharon		3744008
H11.4	Conjunctival injection		3727016
H16.0	Corneal erosion		3714004
H16.1	Corneal epithelial erosion, Diffuse punctate keratitis, Superficial punctate keratitis, Superficial keratitis, and Superficial punctate keratopathy		3702006
			3702012
			3702014
			8831181
			8849040
H16.2	Keratoconjunctival erosion, Keratoconjunctivitis, Acute keratoconjunctivitis, and Medicamentosa keratoconjunctivitis		8831156
			8831164
			8832295
			8840714
H16.8	Medicamentosa keratitis		3702018
H16.9	Keratitis and Acute keratitis		3709002
			8832296
H18.8	Corneal epithelial abrasion, Corneal abrasion, Multiple corneal erosion, and Corneal epithelial defect		3714020
			3718002
			8831191
			8847163
H18.9	Pericorneal injection		8831175
K12.1	Stomatitis, Hemorrhagic stomatitis, Vesicular stomatitis, Multiple stomatitis, Ulcerative stomatitis, and Intractable stomatitis		5280017
			5280035
			5280051
			8835717
			8837020

		8846197
K12.3	Oral mucositis (ulcerative)	8849511
		8845775
K13.0	Perleche, Angular stomatitis, Angular cheilitis, Lip erosion, Cheilitis, and Canker sore	5285042
		6868003
		8833344
		8833346
		8833461
		8833463
K14.0	Tongue erosion, Glossitis, and Tongue ulcer	5290011
		5290016
		5290019
K62.8	Anal erosion	8844718
N48.5	Ulcer of penis	6078012
		6078025
		8830636
		8832236
N76.2	Vulvitis	6161027
N86	Cervicovaginal erosion and Cervicovaginal pseudoerosion	8834245
		8834247
S05.0	Corneal epithelial wound and Superficial conjunctivitis wound	8831180
		9182002

Adapted from Fukasawa et al.¹⁸

ICD-10, International Classification of Diseases, 10th Edition.

Supplementary Table 4. Anticonvulsants that were on the market between 2005 and 2017 in Japan

Anticonvulsant of interest	First 7 digits of drug code
Acetazolamide	2134400
	2134001
	2134002
Acetylpheneturide	1131001
Carbamazepine	1139002
Clobazam	1139006
Clonazepam	1139003
Diazepam	1124402
	1124701
Ethosuximide	1139001
Ethotoin	1132001
Fosphenytoin	1132401
Gabapentin	1139007
Lacosamide	1139015
Lamotrigine	1139009
Levetiracetam	1139010
	1139402
Midazolam	1139401
Nitrazepam	1124003
Perampanel	1139014
Phenobarbital	1125003
	1125004
	1125402
	1139400
Phenytoin	1132002
	1132400
Phenytoin and phenobarbital	1139100
	1139103
	1139104
	1139105
Piracetam	1190013
Potassium bromide	1126001
Primidone	1135002

Rufinamide	1139012
Saiko-ka-ryukotsu-borei-to	5200050
Sodium bromide	1126002
Stiripentol	1139011
Sulthiame	1137001
Tetracosactide	2411401
Topiramate	1139008
Trimethadione	1133002
Valproate	1139004
Vigabatrin	1139013
Zonisamide	1139005

Supplementary Table 5. Characteristics of cases newly exposed to anticonvulsants within 90 days before the index date

Characteristic	Carbamazepine (n = 8)	Lamotrigine (n = 4)	Clonazepam (n = 1)	Diazepam (n = 1)	Levetiracetam (n = 1)	Phenytoin (n = 1)
Male, No. (%)	5 (62.5)	2 (50.0)	1 (100)	0	0	1 (100)
Age, mean (SD), years	47.9 (12.7)	45.0 (12.2)	51.0	24.0	24.0	57.0
Epilepsy, No. (%) [†]	3 (37.5)	2 (50.0)	0	1 (100)	1 (100)	1 (100)
SJS/TEN risk factors, No. (%)						
Any known or suspected SJS/TEN risk factor	1 (12.5)	1 (25.0)	0	1 (100)	1 (100)	1 (100)
Other concomitant high-risk drug use [‡]						
≤90 days before the index date	1 (12.5)	1 (25.0)	0	1 (100)	1 (100)	1 (100)
>90 days before the index date	5 (62.5)	3 (75.0)	1 (100)	1 (100)	1 (100)	1 (100)
Mycoplasma infection [§]	0	0	0	0	0	0
Herpesvirus infection [§]	0	0	0	0	0	0
Cancer [§]	0	0	0	0	0	0
Lupus erythematosus [†]	0	0	0	0	0	0

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

When multiple anticonvulsants were prescribed to single patients, they were counted for each drug.

[†] Recorded any time before the index date.

[‡] High-risk drugs include allopurinol, carbamazepine, lamotrigine, nevirapine, oxycam analgesics, phenobarbital, phenytoin, and sulfonamides.⁶

[§] Recorded within 90 days before the index date.

Supplementary Table 6. Odds ratios for Stevens-Johnson syndrome and toxic epidermal necrolysis after exposure to anticonvulsants with no cases

Anticonvulsant	No. of cases n = 71 (%)	No. of controls n = 284 (%)	OR [†] (95% CI)	Cases (%) exposed to other concomitant HRDs [‡]
Acetazolamide				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Acetylpheneturide				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Clobazam				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Ethosuximide				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Ethotoin				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Gabapentin				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	

Lacosamide

≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	

Midazolam

≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	

Nitrazepam

≤90 days before the index date	0	2 (0.7)	0.80 (0.01–9.83)	0
>90 days before the index date	0	1 (0.4)	1.33 (0.01–24.99)	

Perampanel

≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	

Phenytoin and phenobarbital

≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	

Piracetam

≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	

Potassium bromide

≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	

Primidone

≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Rufinamide				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Sodium bromide				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Stiripentol				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Sulthiame				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Tetracosactide				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Topiramate				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Trimethadione				
≤90 days before the index date	0	0	N/A	0

>90 days before the index date	0	0	N/A	
Vigabatrin				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	0	N/A	
Zonisamide				
≤90 days before the index date	0	0	N/A	0
>90 days before the index date	0	1 (0.4)	1.33 (0.01–24.99)	

OR, odds ratio; CI, confidence interval; HRDs, high-risk drugs; ALDEN, algorithm of drug causality for epidermal necrolysis.

When multiple anticonvulsants were prescribed to single patients, they were counted for each drug.

† ORs were calculated by Firth conditional logistic regression.

‡ HRDs include allopurinol, carbamazepine, lamotrigine, nevirapine, oxicam analgesics, phenobarbital, phenytoin, and sulfonamides.⁶

Supplementary Table 7. Odds ratios calculated by conventional conditional logistic regression for anticonvulsants where complete or quasi-complete separation did not exist

Anticonvulsant	No. of cases n = 71 (%)	No. of controls n = 284 (%)	OR (95% CI)	Cases (%) exposed to other concomitant HRDs [†]
Carbamazepine				
>90 days before the index date	1 (1.4)	1 (0.4)	4.00 (0.25–63.95)	
Phenytoin				
≤90 days before the index date	1 (1.4)	1 (0.4)	4.00 (0.25–63.95)	1 (100)
Levetiracetam				
>90 days before the index date	2 (2.8)	1 (0.4)	8.00 (0.73–88.23)	
Clonazepam				
≤90 days before the index date	1 (1.4)	1 (0.4)	4.00 (0.25–63.95)	0
>90 days before the index date	4 (5.6)	5 (1.8)	3.56 (0.88–14.48)	
Diazepam				
≤90 days before the index date	1 (1.4)	1 (0.4)	4.00 (0.25–63.95)	1 (100)
>90 days before the index date	1 (1.4)	10 (3.5)	0.40 (0.05–3.13)	
Phenobarbital				
>90 days before the index date	1 (1.4)	1 (0.4)	4.00 (0.25–63.95)	
Saiko-ka-ryukotsu-borei-to				
>90 days before the index date	1 (1.4)	1 (0.4)	4.00 (0.25–63.95)	
Valproate				
>90 days before the index date	2 (2.8)	4 (1.4)	2.00 (0.37–10.92)	

OR, odds ratio; CI, confidence interval; HRDs, high-risk drugs; ALDEN, algorithm of drug causality for epidermal necrolysis.

When multiple anticonvulsants were prescribed to single patients, they were counted for each drug.

† HRDs include allopurinol, carbamazepine, lamotrigine, nevirapine, oxicam analgesics, phenobarbital, phenytoin, and sulfonamides.⁶

Supplementary Table 8. Number of users of anticonvulsants with no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis

Anticonvulsant	No. of new users
Acetazolamide	7,221
Acetylpheneturide	0
Clobazam	478
Ethosuximide	81
Ethotoin	0
Fosphenytoin	1,965
Gabapentin	519
Lacosamide	130
Midazolam	200
Nitrazepam	8,524
Perampanel	311
Phenobarbital	4,303
Phenytoin and phenobarbital	20
Piracetam	15
Potassium bromide	18
Primidone	55
Rufinamide	58
Saiko-ka-ryukotsu-borei-to	9,038
Sodium bromide	1
Stiripentol	10
Sulthiame	26
Tetracosactide	93
Topiramate	996
Trimethadione	0
Valproate	16,757
Vigabatrin	4
Zonisamide	828

When multiple anticonvulsants were prescribed to single patients, they were counted for each drug.