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Summary

Objective: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and potentially fatal adverse skin reactions that are most commonly triggered by certain medications. One class of medications that have been highly associated with SJS/TEN reactions are antiepileptic drugs (AEDs). We sought to quantify the risk of SJS/TEN associated with AEDs as a class, as well as individual AEDs, in the United States.

Methods: An analysis was performed of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) from July 2014 through December 2017. Rates of SJS/TEN were calculated for each AED compared with all other non-AEDs. Reporting odds ratios (ROR), proportional reporting ratios (PRR), and 95% confidence intervals (CI) were calculated using OpenEpi.

Results: AEDs had the most reports of SJS/TEN than any other medication class with 198 reports. AEDs as a class had a ROR of 8.7 (CI 7.5-10.2) and a PRR of 8.7 (CI 7.5-10.2) compared with all other non-AEDs. The AEDs with the highest risk estimates were zonisamide (ROR: 70.2, CI 33.1-148.7; PRR: 68.7, CI 32.9-143.5), rufinamide (ROR: 60.0, CI 8.3-433.5; PRR: 58.9, CI 8.4-411.5), clorazepate (ROR: 56.0, CI 7.8-404.1; PRR: 55.1, CI 7.8-385.0), lamotrigine (ROR: 53.0, CI 43.2-64.9; PRR: 52.2, CI 42.7-63.7), phenytoin (ROR: 26.3, CI 15.5-44.7; PRR: 26.1, CI 15.4-44.2), and carbamazepine (ROR: 24.5, CI 16.0-37.5; PRR: 24.3, CI 16.0-37.1).

Significance: While AEDs as a class were associated with 9 times the risk of SJS/TEN compared with non-AEDs, there were six AEDs with risk estimates greater than 20. Increased awareness of this risk among both prescribers and patients, particularly variations in risk among

different AEDs, along with education on early recognition of SJS/TEN signs/symptoms may help mitigate the number and severity of these adverse events.

Key Point Box:

- While several antiepileptic drugs (AEDs) have been associated with (SJS) and toxic epidermal necrolysis (TEN), the class effect and impact of other AEDs are not well-described.

- We sought to quantify the risk of SJS/TEN with AEDs using the Food and Drug Administration Adverse Event Reporting System (FAERS).

- For AEDs as a class, the reporting odds ratio for SJS/TEN was 8.7 (95% confidence interval 7.5-10.2), respectively, compared to non-AEDs.

- A third of AEDs assessed (11/34) were associated with a significantly increased risk of SJS/TEN (zonisamide, rufinamide, clorazepate, lamotrigine, phenytoin, carbamazepine, valproic acid, eslicarbazepine, oxcarbazepine, clonazepam, and levetiracetam).

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and life threatening adverse skin reactions often triggered by particular medications. Some medications that have been shown to trigger these reactions are antiepileptic drugs (AEDs), nonsteroidal anti-inflammatory drugs (NSAIDs), and certain antibiotics.[1-3] Although these reactions initially were thought to be separate conditions, they are now considered part of the same continuum. SJS is defined as detachment of less than 10% of total body surface area (BSA).[4] TEN is defined as detachment of greater than 30% of total BSA.[4] Estimated incidence of these reactions is 1.5-8.3 cases per 1,000,000 person-years.[5-7] Mortality from SJS is approximately 5% whereas mortality from TEN occurs in approximately 30% of patients.[8] Mortality risk continues after presentation of SJS/TEN with studies showing mortality even 1 year after hospitalization.[9, 10] Severity of disease appears to be the largest risk factor for mortality in the early phase of disease, and older age and comorbidities as the largest mortality risk factor at the 3-12 month timeframe.[11] Patients who survive SJS/TEN reactions are at a high risk of developing long-term complications involving the skin, eye, mucosal, respiratory, renal, and/or hepatic systems.[10, 11]

Epilepsy is one of the most common neurologic disorders worldwide and is classified as a chronic disorder of recurrent unprovoked seizures.[12] Approximately 3% of the population under the age of 75 is diagnosed with epilepsy.[13] Some antiepileptic drugs have additional FDA approved indications outside of epilepsy including: neuropathic pain, migraines, anxiety, insomnia, bipolar disorder, among others.[14] Therefore, their use extends beyond those with epilepsy, making them commonly prescribed. AEDs are associated with SJS/TEN reactions, in particular lamotrigine and carbamazepine as they have black boxed warnings regarding SJS/TEN

reactions.[15, 16] The black boxed warning for carbamazepine relates specifically to patients with the human leukocyte antigen (HLA)-B*1502 allele, as this has been found to increase the risk of developing SJS/TEN.[15] The HLA-B*1502 allele is mostly found in patients of Asian ancestry. As such, genetic screening for the HLA-B*1502 allele is recommended for patients of Asian ancestry prior to initiating carbamazepine.[15] Although not indicated with a black box warning, the package insert of oxcarbazepine also recommends genetic screening for the HLA-B*1502 allele due to the similar chemical structure of oxcarbazepine to carbamazepine along with clinical and non-clinical data suggesting an increased risk of SJS/TEN in these patients.[17]

In recent years, several case-control studies and analyses of adverse event reporting systems in Europe have explored the relationship between SJS/TEN and certain AEDs, specifically carbamazepine, lamotrigine, and phenytoin.[18, 19] However, the class effect and impact of other AEDs are not well-described. As such, we sought to quantify the risk of SJS/TEN associated with AEDs as a class, as well as individual AEDs, in the United States (US).

Methods

We reviewed adverse event reports from the US Food and Drug Administration Adverse Event Reporting System (FAERS) for a 42-month time frame of July 2014 through December 2017.[20] Follow-up reports were excluded, along with duplicate reports and reports missing event date, sex, and age. We conducted searches of the medical dictionary for regulatory activities (MedRA) terms "Stevens-Johnson syndrome" and "toxic epidermal necrolysis". Subsequent listings of adverse events were reviewed for inclusion. We included AEDs with a FDA indication for epilepsy or seizures (Table 1). Reports using brand names were categorized under their generic names. Since SJS and TEN are part of the same continuum, these reactions were

combined as SJS/TEN. The proportional reporting ratio (PRR), reporting odds ratio (ROR), and

corresponding 95% confidence intervals (CI) for SJS/TEN were calculated for each AED

medication compared to all other non-AEDs. The ROR, PRR, and corresponding 95% CI was

also calculated for the entire class of AEDs versus all other medications. All analyses were

conducted using OpenEpi (Version 3.01) which calculates Taylor series 95% CIs.[21]

Results

During the study period, there were 2,886,886 total adverse reactions of any type reported with

1,035 (0.04%) SJS/TEN reactions (690 SJS, 66.7%; 345 TEN, 33.3%). There were 76,251

(2.6%) adverse event reports, of any kind, which included AEDs. Of these reports with AEDs,

198 SJS/TEN reactions were reported (Table 2). Among the SJS/TEN reactions, AEDs were the

most common medications listed (19.1%) and which was more than 2 times higher than

NSAIDs, with the second most SJS/TEN reactions (n=80, 7.7%). Of the 34 different AEDS

evaluated, there were 17 AEDs (50.0%) that had at least one SJS/TEN reaction. The AEDs with

the most reported SJS/TEN reactions were lamotrigine with 106 reactions (53.5%),

carbamazepine with 22 reactions (11.1%), levetiracetam with 14 reactions (7.1%), phenytoin

with 14 reactions (7.1%), valproic acid with 9 reactions (4.5%), clonazepam with 8 reactions

(4.0%), and zonisamide with 7 reactions (3.5%). AEDs as a class had a ROR of 8.7 (95% CI

7.5-10.2) and a PRR of 8.7 (95% CI 7.5-10.2) compared with all other medications (Table 2,

Figure 1, Figure 2). There were six AEDs with ROR/PRR risk estimates for SJS/TEN exceeding

20: zonisamide with a ROR of 70.2 (95% CI 33.1-148.7) and a PRR of 68.7 (95% CI 32.9-

143.5), rufinamide with a ROR of 60.0 (95% CI 8.3-433.5) and a PRR of 58.9 (95% CI 8.4-

411.5), clorazepate with a ROR of 56.0 (95% CI 7.8-404.1) and a PRR of 55.1 (95% CI 7.8-

385.0), lamotrigine with a ROR of 53.0 (95% CI 43.2-64.9) and a PRR of 52.2 (95% CI 42.7-

63.7), phenytoin with a ROR of 26.3 (95% CI 15.5-44.7) and a PRR of 26.1 (95% CI 15.4-44.2),

and carbamazepine with a ROR of 24.5 (95% CI 16.0-37.5) and a PRR of 24.3 (95% CI 16.0-

37.1). Significant associations were also observed for valproic acid, eslicarbazepine,

oxcarbazepine, clonazepam, and levetiracetam (see Table 2, Figure 1, Figure 2).

Discussion

The results of study show that SJS/TEN reporting rates were significantly higher with AEDs

compared to all other medications (non-AEDs). In our study, zonisamide, rufinamide,

clorazepate, lamotrigine, phenytoin, and carbamazepine demonstrated the highest increased risk

of SJS/TEN. We identified 17 AEDs with reported SJS/TEN reactions, and significant

associations were observed with 11 of these AEDs. While most listed SJS/TEN as possible

adverse reactions in the package inserts, four did not (clonazepam, clorazepate, diazepam, and

lorazepam).[15-17, 22-35]

Several European studies have explored the most common medications associated with

SJS/TEN. One matched case-control study conducted in the United Kingdom, evaluated the risk

of SJS/TEN specifically among new AED users.[18] This study was conducted using the Clinical

Practice Research Datalink (CPRD) and included validated SJS/TEN cases from 1995 to 2013.

Each case of SJS/TEN was matched to 4 patients with same birth year, sex, general practice, and

years of recorded history. Due to small numbers, the confidence intervals were wide, however,

even at the low end of the confidence interval, the odds of exposure among cases was 5-20 times

higher than control group, carbamazepine 92.57 (95% CI 19.89-∞), phenytoin 49.96 (95% CI 10.13-∞), and lamotrigine 26.90 (95% CI 4.88-∞).

The European case-control surveillance of severe cutaneous adverse reactions (EuroSCAR) study identified hospitalized cases of SJS/TEN and matched hospital controls from April 1997 to December 2001.[19] The study population consisted of patients from six countries (Austria, Italy, France, Germany, Netherlands, and Israel) among a network of 1,800 hospitals. For each case, patients were matched on age, sex, region, and date of interview to 3 hospital control patients. Odds ratios were adjusted for potential confounding factors, specifically concomitant medications that may affect the risk of SJS/TEN, as well as other medical conditions which may affect the risk of SJS/TEN, such as HIV/AIDS or recent cancer. They found that three of the top seven medications associated with SJS/TEN were AEDs: carbamazepine (adjusted OR [aOR] 72, 95% CI 23-225), phenobarbital (aOR 16, 95% CI 5-50), and phenytoin (aOR 17, 95% CI 4-68).

Our findings were similar to CPRD and EuroSCAR studies, although the magnitude of risk for carbamazepine was lower in our study (ROR 25 versus OR 93 in CPRD and aOR 72 in EuroSCAR). This may be explained by the difference in study time periods and implementation of genetic screening prior to initiating carbamazepine among those of Asian ancestry. While the CPRD and EuroSCAR studies demonstrated lower risk with lamotrigine compared to the other AED comparators, in our study, the ROR for lamotrigine was 53.0 (95% CI 43.2-64.9), more than 2-fold that of phenytoin (26.3, 95% CI 15.5-44.7) and carbamazepine (24.5, 95% CI 16.0-37.5). In our study, there were no reports of SJS/TEN reaction with phenobarbital. One possible reason for this is the declining utilization of phenobarbital which has become a nonpreferred

therapy option in treatment guidelines due to (1) its less favorable side effect profile, (2) inclusion in the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, (3) unfavorable pharmacokinetic properties, and (4) multiple drug-drug interactions.[36-38]

In two studies which utilized data from adverse event reporting systems, AEDs were among the top medications associated with SJS/TEN.[39, 40] Lamotrigine and carbamazepine were among the top five most common medications listed in reports for SJS/TEN in the Japanese Adverse Drug Event Report database over a 12-year period from April 2004 through April 2015.[39] Adjusted RORs were calculated for reporting year, gender, and age. The RORs were 5.7 (95% CI 5.2-6.3) and 11.5 (95% CI 10.3-12.8) for carbamazepine and lamotrigine, respectively. In a letter to the editor by the same authors, they describe a similar analysis of US FAERS data. From January 2004 to March 2013, two AEDs were among the top medications listed in reports of SJS/TEN (lamotrigine and phenytoin).[40] The RORs were 20.4 (95% CI 19.2-21.8) and 12.0 (95% CI 11.3-12.7) for phenytoin and lamotrigine, respectively. As compared with our study, the risk associated with these AEDs were substantially lower than what we observed during a shorter and more recent time period (RORs, lamotrigine 53.0 versus 11.5 and 12.0, carbamazepine 24.5 versus 5.7, phenytoin 26.3 versus 20.4; time period, 2014-2017 versus 2004-2013/2015).

Greater than 90 percent of SJS/TEN reactions associated with AEDs occur within the first 2 months of treatment initiation,[41] although some AEDs have been associated with such reactions during long term use (phenobarbital and valproic acid).[1] Previous studies have indicated that SJS/TEN reactions may be associated with the starting dose and rate of titration for some AEDs.[42, 43] An approach to preventing cutaneous reactions such as SJS/TEN in AEDs, is to use a

low starting dose and slow titration schedule, as has been used with lamotrigine.[44] Further

research is needed to see which AEDs pose the highest risk for SJS/TEN, based on dose and

titration schedule to determine whether lower starting doses and slow titration schedules would

decrease occurrences of SJS/TEN.

There were several limitations to our study. Incidence and prevalence cannot be calculated as

the total number of patients using these medications is undetermined.[45] Due to the voluntary

nature of reporting to FAERS, underreporting is expected.[46] A reporting bias that may have

influenced the number of reactions reported is the Weber effect,[47] in which adverse event

reporting starts to decline in the 2 years after market introduction.[48] All of the AEDs included in

our study with reports of SJS/TEN have been on the market for greater than two years with the

exception of eslicarbazepine, and therefore decreases in reporting likely occurred over time.

Another known limitation of the FAERS database is that causality between the adverse event and

medication does not have to be established in order for a report to be submitted, which may be

further complicated by concomitant medications and patient comorbidities.[46] Additionally, drugs

with frequent side effects can increase the number of overall adverse effects and therefore

decrease ROR and PRR.[49] This may have occurred in our study since the two medications with

the most adverse reaction reports (pregabalin and gabapentin) were tied for the eighth most

SJS/TEN reactions but had two of the three lowest RORs and PRRs. Whereas, two of the three

highest RORs and PRRs were among medications with only one SJS/TEN reaction (rufinamide

and clorazepate) and they had the two lowest total adverse reaction reports. As there was only

one report of SJS/TEN with clorazepate and rufinamide, the confidence intervals of the ROR and

PRR were large and though statistically significant, the magnitude of the lower end of the

confidence interval was closer to that of the overall class. The magnitude and statistical significance of these associations may change as more adverse event reports are submitted for clorazepate and rufinamide.

Conclusion

Our study supports previous evidence that certain AEDs are associated with a higher risk of SJS/TEN, in particular, lamotrigine, phenytoin, and carbamazepine. Further, we identified 8 other AEDs significantly associated with SJS/TEN: zonisamide, rufinamide, clorazepate, valproic acid, eslicarbazepine, oxcarbazepine, clonazepam, and levetiracetam. While AEDs as a class were associated with 9 times the risk of SJS/TEN compared with non-AEDs, there were six AEDs with risk estimates greater than 20. Increased awareness of this risk among both prescribers and patients, particularly variations in risk among different AEDs, along with education on early recognition of SJS/TEN signs/symptoms may help mitigate the number and severity of these adverse events.

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Declarations of interest

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Table 1: Table of antiepileptic medications evaluated

Antiepileptic Drugs	
Acetazolamide	Lamotrigine
Amobarbital	Levetiracetam
Brivaracetam	Lorazepam
Carbamazepine	Methsuximide
Clobazam	Oxcarbazepine
Clonazepam	Pentobarbital
Clorazepate	Perampanel
Diazepam	Phenobarbital
Divalproex sodium	Phenytoin
Eslicarbazepine	Pregabalin
Ethosuximide	Primidone
Ethotoin	Rufinamide
Ezogabine	Tiagabine
Felbamate	Topiramate
Fosphenytoin	Valproic acid/ valproate sodium
Gabapentin	Vigabatrin
Lacosamide	Zonisamide

Table 2: Adverse event report counts and risk estimates of Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN) for antiepileptic medications

Generic	Total reports	SJS	TEN	Total SJS/ TEN	ROR	95% CI	PRR	95% CI
All antiepileptic medications*	76,251	140	58	198	8.7	7.5-10.2	8.7	7.5-10.2
Carbamazepine*	3,038	13	9	22	24.5	16.0-37.5	24.3	16.0-37.1
Clonazepam*	3,896	7	1	8	6.9	3.4-13.9	6.9	3.4-13.8
Clorazepate*	61	0	1	1	56.0	7.8-404.1	55.1	7.9-385.0
Diazepam	2,895	1	0	1	1.2	0.2-8.3	1.2	0.2-8.2
Divalproex	2,585	1	0	1	1.3	0.2-9.2	1.3	0.2-9.2
Eslicarbazepine*	338	0	1	1	10.0	1.4-71.0	9.9	1.4-70.4
Gabapentin	10,949	2	2	4	1.2	0.5-3.3	1.2	0.5-3.3
Lacosamide	1,497	0	1	1	2.2	0.3-16.0	2.2	0.3-15.9
Lamotrigine*	6,826	81	25	106	53.0	43.2-64.9	52.2	42.7-63.7
Levetiracetam*	7,102	8	6	14	6.6	3.9-11.3	6.6	3.9-11.2
Lorazepam	2,282	1	0	1	1.5	0.2-10.5	1.5	0.2-10.5
Oxcarbazepine*	1,116	3	0	3	9.1	2.9-28.2	9.0	2.9-28.0
Phenytoin*	1,801	11	3	14	26.3	15.5-44.7	26.1	15.4-44.2
Pregabalin	19,029	3	1	4	0.7	0.3-1.9	0.7	0.3-1.9
Rufinamide*	57	1	0	1	60.0	8.3-433.5	58.9	8.4-411.5
Valproic Acid*	2,891	4	5	9	10.5	5.4-20.2	10.5	5.4-20.1
Zonisamide*	342	4	3	7	70.2	33.1-148.7	68.7	32.9-143.5

*Estimates that are statistically significant
Reporting odds ratios (ROR) and proportional reporting ratios (PRR) were calculated for each drug compared with all other non-antiepileptic medications.

Figure 1: Antiepileptic medications and Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN), reporting odds ratios

Figure 2: Antiepileptic medications and Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN), proportional reporting ratios