Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics

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Abstract—Background: Estimates of risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with some antiepileptic drugs (AEDs) have used denominators based on the number of prescriptions or daily doses. Because the risk of SJS is highest in new users of drugs, the use of denominators reflective of all users can lead to low estimates of risk associated with drugs. In this study, risk in new users is assessed. Methods: Data on all hospitalized patients with SJS and TEN with use of carbamazepine (CBZ), lamotrigine (LTG), phenobarbital (PHB), phenytoin (PHT), or valproic acid (VPA) were obtained from the German Registry for Serious Cutaneous Reactions. For 1998–2001, the numbers of new users were estimated from number of dispensed prescriptions in Germany, the average prescribed doses, and the duration of use in the Mediplus database (IMS Health) Germany, and assumptions that relate new use to growth in national dispensings. To minimize the probability of underestimating risk in new users, conservative estimates of new use that were somewhat lower than predicted from national prescription data were used. Results: More than 90% of SJS and TEN cases occurred in the first 63 days of AED use. Over the 4 years, increases in dispensing were 5% for CBZ, 65% for LTG, 6% for PHB, 16% for PHT, and 26% for VPA. Across a range of assumptions about frequency of incident use, the risk estimates vary between 1 and 10 per 10,000 new users for CBZ, LTG, PHT, and PHY and were consistently lower for VPA. Conclusion: Across a range of assumptions used, the risk of hospitalization for Stevens–Johnson syndrome or toxic epidermal necrolysis in new users is low for carbamazepine, lamotrigine, phenytoin, phenobarbital, and valproic acid. Because conservative incidence use fractions were used, it is likely that some risks were overestimated.

NEUROLOGY 2005;64:1134–1138

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can occur in association with more than 100 different medications, including some commonly used antiepileptic drugs (AEDs), particularly carbamazepine (CBZ), lamotrigine (LTG), phenobarbital (PHB), and phenytoin (PHT). Accurate estimates of the true incidence of these events are lacking due to inconsistent diagnosis of cases across all clinicians and difficulty in accurately estimating the population at risk and the number of new users of each medication.1,2

Both SJS and TEN are characterized by erythema, with a greater or lesser area of involvement of blisters and erosions of the skin, and are often associated with fever and malaise. In addition, hemorrhagic erosions of mucous membranes, such as stomatitis, balanitis, colitis, severe conjunctivitis, and blepharitis, occur. For decades, there was no clear definition of these severe skin reactions and often erythema exsudativum multiforme with mucosal involvement was considered as SJS. The challenges of identifying and classifying SJS and TEN and the importance of a consensus definition are demonstrated by the high frequency in which SJS and TEN are reported to authorities but not confirmed on review by expert dermatologists.3 For more details on SJS and TEN, see appendix E-1 and figures E-1 through E-3 on the Neurology Web site at www.neurology.org.

The analysis presented here combines data from a unique source of population-based cases of SJS and TEN classified with diagnostic accuracy and a novel approach to estimating new use of AEDs associated with SJS or TEN.

Methods. To estimate the total number of cases in a defined population, we used a unique source, the Registry of Serious Cutaneous Reactions (Dokumentationszentrum schwerer Hautreaktionen). This registry is an academically run data collection system for ascertainment of all hospitalized cases of SJS and TEN in Germany.

This population-based registry was established in 1990 and...
regularly contacts more than 1,700 departments likely to treat patients with severe skin reactions. These include departments of dermatology, pediatrics, internal medicine with intensive care facilities, and burn units. The registry is based on an intensive reporting approach resulting in a coverage rate of >90%. To identify cases of SJS or TEN that may have been overlooked, the registry periodically surveys hospital units by letter and phone call. Once a case is identified to the registry, a trained interviewer collects information on the clinical course, underlying diseases, infections, and previous drug exposures. Each case assessed is reviewed by a dermatologic expert committee that decides on the final diagnosis by using the consensus definition of severe skin reactions.

Estimation of total users of AEDs (prevalent users). Schwabe and Paffrath\(^5\) generated data annually on national use of medications based on prescriptions claimed through general health insurance and covering 85% of the German population (figure).\(^6\) These national dispensing data are in units of defined daily doses (DDDs), represent person-days of treatment based on the average maintenance dose expected to be taken per day for a drug used on its main indication and are defined by the World Health Organization\(^7\) for each drug (1,000 mg for CBZ, 300 mg for LTG, 100 mg for PHB, 300 mg for PHY, and 1,500 mg for valproic acid [VPA]). Prescribed doses are frequently different from the DDDs.\(^8\) Therefore, for each year, the national number of DDDs was adjusted for mean prescribed daily doses (PDDs) and then converted to total number of prevalent users by multiplying the national dispensing data by the ratio PDD/DDD (to convert to person-days based on PDDs) and dividing by the average duration of use per person in days. The mean PDD and average duration of use during the year 2000 were derived from the IMS HEALTH Mediplus database.\(^9\) The Mediplus database consists of anonymous electronic medical record data from 400 general practitioners, internal medicine specialists, and pediatricians and 18 neurologists nationwide.\(^10\)

Estimation of new users of AEDs (incident users). To estimate the number of new users, we developed an algorithm for assigning the new use fraction, the proportion of all users who start the medication during any year. The new use fraction assigned for each AED was similarly adjusted downward to 10%. For estimates of risk, we included all validated cases of possible, probable, and definite SJS or TEN occurring within 63 days of initiating therapy with each AED during 1998–2001. Risk estimates for this time period were derived by dividing the number of SJS, TEN, and/or SJS/TEN overlap cases by the total annual number of new users. Cls are not provided because, as a result of the calculations used to develop the estimates, the degree of precision is unknown. We compared the risk estimates with traditional indicators of risk in all users (e.g., number of cases/national number of DDDs). To assess the influence of our assumptions, we also calculated the risk by assuming 15% incident use for all AEDs regardless of annual prescription growth. We also derived incidence per million DDDs to incidence per 10,000 person-years by assuming 365 DDDs per person-year.

### Results

Table 1 describes the number of SJS, SJS/TEN overlap, and TEN cases occurring during the period 1998–2001 in people of all ages and the number occurring during the first 63 days of use of each AED. Of patients younger than 12 years of age, three were exposed to CBZ, two were exposed to LTG, three were exposed to PHB, and one was exposed to PHY. For the four drugs known to be associated with these serious reactions (CBZ, LTG, PHB, and PHY), most reactions (>90%) occurred within the first 63 days of use. Table 2 shows the annual national number of DDDs dispensed and the percentage of growth during the years 1998–2001. CBZ consistently showed small amounts of growth, and VPA showed somewhat greater growth for 2 years. PHT demonstrated a consistent decline in national number of DDDs, and PHB demonstrated an erratic percentage of change over the years but overall demonstrated no growth. LTG was growing most quickly and was assigned the highest incident use fraction.

Table 3 shows the average risk of SJS or TEN in new users (risk per 10,000 new users). With the exception of VPA, which had the lowest risk and is only very rarely associated with such reactions, all AEDs were associated with a similar order of magnitude of risk. In addition, the risk is relatively rare, a few cases per 10,000 new users. As expected, the relative rankings of the drugs change when the risk is based on total national DDDs because this estimate does not account for new use.

If we assume that a constant 15% of all users were incident users for each AED, the estimated risks in new users were 1.5 per 10,000 for CBZ, 3.8 per 10,000 for LTG, 8.2 per 10,000 for PHB, 6.9 per 10,000 for PHY, and 0.5 per 10,000 for VPA. Conversely, if frequency of new use is not accounted for at all and risk is estimated with total use (number of DDDs) in the denominator (see table 3), the annual growth, we assigned 20% new use, and for AEDs with >15% annual growth in national number of daily doses dispensed, we assigned 25% as new use; for those AEDs with >5% decline in national numbers of daily doses dispensed, the percentage of new use was similarly adjusted downward to 10%.

### Table 1 Comparison of cases of serious skin reactions after the use of antiepileptic drugs according to the start of drug intake (all cases of SJS, SJS/TEN overlap, and TEN, 1998–2001)

<table>
<thead>
<tr>
<th>Start of drug intake</th>
<th>CBZ</th>
<th>LTG</th>
<th>PHB</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;63 days</td>
<td>39</td>
<td>14</td>
<td>7</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>15</td>
<td>7</td>
<td>31</td>
<td>16</td>
</tr>
</tbody>
</table>

SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis; CBZ = carbamazepine; LTG = lamotrigine; PHB = phenobarbital; PHT = phenytoin; VPA = valproic acid.
Discussion. Although SJS and TEN are rare in patients using these AEDs, the case characteristics show that the highest risk period is during the first 2 months of use. Any one clinician is likely to see only one or two of these events in a lifetime, and the ability to identify a relatively narrow time window of high risk should facilitate the early detection of such events. Although nonserious drug eruption is relatively common with each of these AEDs (except VPA), the prescribing physician should warn patients about symptoms that differentiate SJS and TEN from mild exanthema, e.g., additional symptoms such as fever or blisters and erosions of the mucous membranes. When starting patients on CBZ, LTG, PHB, or PHT, signs for these events should be monitored carefully for at least 6 weeks.

In the past, estimates of population-based drug exposure have been based on the national number of DDDs and the national number of PDDs. Because such analyses do not identify new users of these agents, these analyses provide neither an estimate of the risk per patient initiating treatment nor an estimate of the relative risk across drugs. One published study reports a risk of hospitalization for SJS or TEN as 20 per 100,000 users of PHB. This estimate was based on managed care claims data and a single identified case of SJS or TEN among all users of PHB. Our results showed that the risk of SJS or TEN in patients initiating treatment with these AEDs is a few cases per 10,000 new users. The risks reported here for CBZ and PHT are comparable with those observed in a cohort study of new users of these AEDs.

LTG was first marketed for use in Germany in June 1993 with recommended doses that exceeded the current recommendations. There were five confirmed cases of SJS and TEN in the registry between June and December 1993, when the risk in all LTG exposures peaked. In subsequent years, coincidentally following modification of the dosing recommendations and despite increasing use of LTG, the number of cases per year and the risk of SJS and TEN decreased.

Table 2 AED sales data of DDDs (in millions) in Germany with relative changes between subsequent years and the assigned percent incident use*

<table>
<thead>
<tr>
<th>AED</th>
<th>DDD (mg)</th>
<th>1997</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>1,000</td>
<td>76.0</td>
<td>74.0 (-2.6/15)</td>
<td>78.0 (5.4/20)</td>
<td>76.0 (-2.6/15)</td>
<td>78.0 (2.6/15)</td>
</tr>
<tr>
<td>LTG</td>
<td>300</td>
<td>4.6</td>
<td>5.5 (+19.6/25)</td>
<td>7.1 (29.1/25)</td>
<td>6.8 (-4.2/15)</td>
<td>9.1 (33.8/25)</td>
</tr>
<tr>
<td>PHB†</td>
<td>100</td>
<td>4.9†</td>
<td>5.0† (2.0/15)</td>
<td>4.5† (-10.0/10)</td>
<td>4.6† (2.2/15)</td>
<td>5.3 (15.2/20)</td>
</tr>
<tr>
<td>PHT</td>
<td>300</td>
<td>29.0</td>
<td>25.0 (-13.8/10)</td>
<td>24.0 (-4.0/15)</td>
<td>22.2 (-7.5/10)</td>
<td>21.4 (-3.6/15)</td>
</tr>
<tr>
<td>VPA</td>
<td>1,500</td>
<td>31.0</td>
<td>31.0 (0/15)</td>
<td>35.0 (12.9/20)</td>
<td>38.0 (8.6/20)</td>
<td>39.0 (2.6/15)</td>
</tr>
</tbody>
</table>

* Based on annual change in DDD.
† No data for Luminal in the years 1998–1999. In 2001, there were an estimated 4.7 million DDDs for this brand name with an increase of 101.1%, which suggests 2.3 million DDDs in 2000. In our calculation, we assume 2.3 million DDDs for the years 1998–2000.
AED = antiepileptic drug; DDD = defined daily dose; CBZ = carbamazepine; LTG = lamotrigine; PHB = phenobarbital; PHT = phenytoin; VPA = valproic acid.

Table 3 Risk estimates based on varying methodologies for AED users (1998–2001)

<table>
<thead>
<tr>
<th>AED</th>
<th>Total DDDs (millions)</th>
<th>Total PDDs (millions)</th>
<th>Total no. of new users</th>
<th>No. of SJS or TEN cases*</th>
<th>Incidence per million DDDs</th>
<th>Incidence per million PDDs</th>
<th>Risk per 10,000 new users †</th>
<th>Risk per 10,000 new users, if new use is 15% for all AEDs</th>
<th>Risk per 10,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>306</td>
<td>451</td>
<td>286,360</td>
<td>39</td>
<td>0.13</td>
<td>0.09</td>
<td>1.4</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>LTG</td>
<td>29</td>
<td>44</td>
<td>55,154</td>
<td>14</td>
<td>0.49</td>
<td>0.32</td>
<td>2.5</td>
<td>3.8</td>
<td>1.8</td>
</tr>
<tr>
<td>PHB</td>
<td>19</td>
<td>12</td>
<td>8,659</td>
<td>7</td>
<td>0.36</td>
<td>0.57</td>
<td>8.1</td>
<td>8.2</td>
<td>1.3</td>
</tr>
<tr>
<td>PHT</td>
<td>93</td>
<td>103</td>
<td>36,171</td>
<td>30</td>
<td>0.32</td>
<td>0.29</td>
<td>8.3</td>
<td>6.9</td>
<td>1.2</td>
</tr>
<tr>
<td>VPA</td>
<td>143</td>
<td>187</td>
<td>103,150</td>
<td>4</td>
<td>0.03</td>
<td>0.02</td>
<td>0.4</td>
<td>0.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Cases occurring within 63 days of AED start.
† Assuming incident use is related to growth in annual dispensings.
AED = antiepileptic drug; DDD = defined daily dose; PDD = prescribed daily dose; CBZ = carbamazepine; LTG = lamotrigine; PHB = phenobarbital; PHT = phenytoin; VPA = valproic acid.
TEN in new users decreased. While the registry data cannot be used to test hypotheses about causes of SJS and TEN, this temporal pattern is consistent with other observations that suggest that dosing is a risk factor for SJS and TEN in new users of LTG. Yet, a lesser risk in patients with correct dosing does not indicate the absence of risk. A relationship between dosing and the incidence of common cutaneous adverse reactions has been reported for LTG and for CBZ and PHT, and exantheamtous eruptions are seen after low doses of CBZ. Except for VPA, all the AEDs described here are also associated with similar rates of nonserious drug eruption, occurring at frequencies ranging between 2.5 and 6%. 

As the data sources used in this study provided no information regarding the patient population characteristics, the risks reported should not be taken as a direct comparison of attributable risks for each medication. Different age distributions, comedications, AED polypharmacy, and comorbidities between groups may reflect heterogeneous background risks and varying susceptibility. For example, in Germany, PHT is commonly used in patients with brain tumor, and this is reflected in the older age of the patients with SJS and TEN using PHT. These patients also receive medications that can alter immune function and may be using other medications that have relatively high attributable risks for SJS or TEN. Although frequency of pediatric use varies across these AEDs, as illustrated by a lower percentage of pediatric use for CBZ and PHT, we did not stratify the analysis by age because of the small numbers of patients with SJS or TEN within each age group. The adjustment of all daily doses dispensed for PDDs should account for the variability in pediatric use.

In our study, the data-derived mean prescribed daily dose for each AED (678 mg for CBZ, 198 mg for LTG, 155 mg for PHB, 269 mg for PHY, and 1,146 mg for VPA) was less than the defined daily dose for each AED, confirming a similar relationship observed in other studies. In addition, the average durations of use for these AEDs (257 days for CBZ, 178 days for LTG, 221 days for PHB, 356 days for PHY, and 319 days for VPA) were consistent with the observed national percentage of growth in dispensing and with the incident use fractions assigned. For example, LTG, with the highest growth for most years, had the lowest average duration of use per patient per year, an observation consistent with high incident use.

The assignment of incident use fraction inserts the greatest uncertainty into these estimates. However, the incidence use must be at least as large as the annual increase in use for medications showing annual growth, and for the AEDs with large annual increases, to avoid underestimating risks, we conservatively assigned the incidence use fractions to be less than the annual growth. For medications showing declining annual use (PHT), it is unknown whether the incident use fraction should be higher or lower. To avoid unfairly weighting analyses against the medications with declining use (e.g., PHB and PHY), we assigned the incident use fraction disproportionately high relative to the observed annual change in national dispensing. Some less common generic brands of PHB and in-hospital use of IV PHT are not included in the prescription data. This will result in an underestimate of use and a corresponding small overestimate of risk. However, patients newly exposed to these preparations will represent a small proportion of new users. To confirm that the estimated numbers of new users are consistent with other data, we applied the incidence of epilepsy (28.9 to 53.1 per 100,000) to the population of Germany (82.2 million) and estimated that there are 95,000 to 175,000 new patients with epilepsy over 4 years (1998–2001). In the above analysis, we estimated the total number of new users, including people treated for conditions other than epilepsy and switches to new AEDs, to be 489,494. Thus, our estimates of new users are consistent with the magnitude of the population under treatment.

By ignoring the evidence that the period of risk for SJS and TEN is during the first weeks of use and ignoring real-world data on the average daily dose and duration of use for each AED, the incidence, in cases per 10,000 person-years, remained between 1 and 10, despite the fact that the relative rankings across the medications changed. Although it is a challenge to quantify the incidence use fraction for the various AEDs, a range of assumptions point to a risk between 1 and 10 per 10,000 new users or between 1 and 10,000 person-years for these AEDs.

Fortunately, these serious reactions are rare and relatively predictable in occurring within the first 2 months of therapy. Clinicians prescribing these AEDs should communicate to their patients the signs and symptoms to watch for during this time period of highest risk.

References


MRI of segmental zoster paresis
Miharu Samuraki, MD; Mitsuhito Yoshita, MD, PhD; and Masahito Yamada, MD, PhD, Kanazawa, Japan

Herpes zoster (HZ) rash with burning pain occurred in a 76-year-old man, involving the right C4–6 dermatomes. Four days after onset of the rash, he developed weakness of the right arm with the clinical diagnosis of segmental zoster paresis. Results of the CSF study were normal. Although the patient had no myelopathic symptoms, MRI revealed hyperintensity in the right spinal posterior horn at the C4 vertebral level in a T2-weighted image (figure). This MRI finding indicates direct viral spread from the dorsal root ganglia to the posterior horn, which sometimes evolves into myelitis.1 This finding is consistent with the neuropathologic findings showing more extensive lesions than clinically expected in HZ.2 The posterior horn lesion in our patient may be related to neuralgia to some degree, but not to zoster paresis, which may be caused by polyradiculoneuritis without involvement of the anterior horn.

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Figure Axial T2-weighted MRI image showing hyperintensity in the right posterior horn of the spinal cord at the level of the C4 vertebral body. This lesion shows isointensity on a T1-weighted image with no gadolinium enhancement.
MRI of segmental zoster paresis
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Neurology 2005;64;1138
DOI 10.1212/01.WNL.0000149909.64485.4F

This information is current as of April 11, 2005