Use of antiepileptic drugs and risk of infection in Taiwan and Denmark: A collaborative cross-national sequence symmetry analysis

Edward Chia-Cheng Lai 1, MSc  Anton Pottegård 2, 3, PhD  Jesper Hallas 2, 3, MD, PhD  Yeu-Huei Kao Yang 1, 4, 5, GSPharm  

1. Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; Taiwan. 2. Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, DK-5230 Odense C, Denmark. 3. Department of Clinical Chemistry & Pharmacology, Odense University Hospital, DK-5000 Odense C, Denmark. 4. Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan.

Conflict of Interest
This study was funded by the Taiwanese Food and Drug Administration (TFDA), and by the University of Southern Denmark. The authors have no relationships to disclose.

Background and objectives
Antiepileptic drugs (AED) have been reported associated with infectious disorders; however, the association is potentially mediated by subjects using AED due to other chronic conditions that are related to frailty and thus risk of infection, such as stroke. We aimed to investigate the risk of infectious disorders associated with the use of AED, using nationwide registries from Taiwan and Denmark.

Methods
Data were extracted from the Taiwanese National Health Insurance Research Database (NHIRD) and the Danish Patient Registry and the Danish Prescription Register (DPR). New AED users from 2006-2010 without a history of cerebral palsy, stroke, dementia and disability after head trauma were included. We performed a sequence symmetry analysis (SSA). In brief, this entails testing whether there is a disproportionate amount of subjects initiating drug A following drug B, as opposed to the other way around (denoted as the sequence ratio, SR), thereby indicating that drug B causes a need for drug A. In this case, the index drug was AED while we used both prescriptions for antibiotics (ATC J01) or hospital diagnoses as markers for infection.

Results
A total of 1,376,220 and 198,925 AED users were identified in the NHIRD and DPR, respectively; 192,291 and 20,084 of which also redeemed an antibiotic. The baseline characteristics between Taiwanese and Danish samples were similar in terms of age and gender. Clonazepam was the most frequently used AED in Taiwan compared to gabapentin in Denmark. Overall, the use of AED was not associated with the use of antibiotics in Taiwan, showing adjusted SRs of 0.79 (95% CI, 0.78–0.79). In Denmark, some AED and some antibiotic classes showed an association, including cephalosporins and other beta-lactam (1.39; 1.14–1.68), sulphonamides/trimethoprim (1.10; 1.05–1.15) and miscellaneous antibiotics defined by ATC code J01X (1.07; 1.05–1.08). In addition, AED were associated with admission due to infectious respiratory (1.25; 1.15–1.37) and cardiovascular (1.23; 1.16–1.30) events in Denmark.

Only few individual AED were indicated to be associated with infection with relatively small effect sizes in Taiwan. In Denmark, several AED were associated with sulphonamides/trimethoprim use including carbamazepine, phenytoin, oxcarbazepine and gabapentin.

Interpretations/Conclusions
Overall, our study does not support the hypothesis that the use of AED is associated with infectious disorders. While no associations were observed in the Taiwanese setting, some AED were associated with infections in Denmark.

Table 1
Prescribing Order in Recipients of Both Antiepileptic Drugs and Marker Drug Diagnoses

<table>
<thead>
<tr>
<th>Marker drug / diagnosis</th>
<th>Taiwan</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casual Drug / Non-casual group</td>
<td>Adjusted SR (95%CI)</td>
<td>Casual Drug / Non-casual group</td>
</tr>
<tr>
<td>Antiepileptic compounds</td>
<td>71 (70-72)</td>
<td>70 (69-71)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>71 (70-72)</td>
<td>70 (69-71)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>71 (70-72)</td>
<td>70 (69-71)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>71 (70-72)</td>
<td>70 (69-71)</td>
</tr>
</tbody>
</table>

*Other beta-lactam include cephalosporins, monobactams, antistaphylococci

#Substitutes: benzodiazepins