# Antiepileptic Drug Switching and Epilepsy-related Events in Subjects with Epilepsy: A Case-Control Analysis of Health Insurance Claims Data

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## Abstract

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Background: Epilepsy is frequently debilitating and switching between bioequivalent antiepileptic drugs (AEDs) with narrow therapeutic index remains controversial. Methods: We investigated the association between A-rated switching and emergent treatment for an epilepsy-related event over a 1-year period using recent claims data from the Truven Health MarketScan® Commercial Database. Cases and matched controls with a diagnosis of epilepsy were identified using emergency services and inpatient visits or outpatient visit claims, respectively. Cases and controls were matched using a 1:1 ratio for age within 5 years of the case's age and seizure diagnosis category. The exposure was defined as an A-rated switch of an AED during the 90 days prior to index date. Adjusted analyses controlled for matching, sex, AED type (older vs. newer AEDs), Deyo-Charlson comorbidity index score, and total number of AED prescription

filled. Results: 1,873 of 7,843 (24%) cases and 1,566 matched controls (20%) experienced an A-rated switch. The unadjusted odds of an epilepsy-related event were 1.26 for switchers (95% CI: 1.17-1.36), and after controlling for all confounders, 1.15 (95% CI: 1.06–1.25). Compared with other AEDs, switching of carbamazepine and phenytoin is associated with increased risk of epilepsy-related events. Discussion: Individuals with epilepsy who switch between A-rated formulations of AEDs are more likely to experience an emergently treated epilepsy-related event compared with individuals who do not switch. Compared with newer AEDs, switching of some older AEDs such as carbamazepine and phenytoin is associated with increased risk of epilepsy-related events. Effective management of epilepsy requires clinicians, pharmacists, and patients to understand the factors associated with bioequivalent medication substitutions. Physicians and pharmacists should actively seek to prevent switching of anti-epileptic medications once patients are stabilized on a specific product – whether branded or generic version. Such switching increases the odds of an epileptic event.

## BACKGROUND

Epilepsy is a common and chronic disease that affects 10% of people in the United States (US) during the course of their lifetime.[1] Approximately 200,000 new cases are diagnosed each year and incidence is highest among children younger than age 2 and adults older than age 65 years.[2] Because of its prevalence, early age of onset, and effects on health and well being, epilepsy is associated with considerable direct and indirect costs. Epilepsy imposes an annual economic burden of $15.5 billion in the US in associated healthcare costs and losses in employment, wages, and productivity.[1]

The goal of epilepsy treatment is to achieve a seizure-free status without adverse effects from medications or surgical interventions.[3] Lifelong treatment with mono- or poly-therapy antiepileptic drugs (AEDs) is often required. The first-generation AEDs, such as phenytoin (Dilantin), valproic acid (Depakote/Depakene), ethosuximide (Zarontin), and carbamazepine (Tegretol/Carbatrol), continue to be commonly prescribed treatment options.[4] Since 1993, FDA-approval of newer, second-generation AEDs (e.g., gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), zonisamide (Zonegran)) considerably expanded the therapeutic options for the treatment of epilepsy.[5] Newer AEDs have less toxicity and fewer side effects compared with older AEDs.[6, 7] Despite a better drug profile, both newer and older AEDs are considered to be treatments with a narrow therapeutic index (NTI).[8-11] Drugs with a NTI have a narrow range between drug levels that are therapeutic and those that may cause an adverse event, thus requiring scrutiny in the dosing and monitoring during each treatment. A NTI implies that slight variations in drug absorption could result in significant negative health outcomes, seizures in the case of epilepsy.[11]

Despite the many treatment options, management of epilepsy remains controversial with regard to bioequivalent medication switching. The FDA supports bioequivalence of approved brand-name and generic AEDs, suggesting that generic drugs can be safely interchanged with brand-name or other generic products.[12] However, physicians and patients remain concerned about potentially increasing seizure events when switching between A-rated (bioequivalent) brand name and generic AED products, since AEDs possess a NTI.[13-18] The American Academy of Neurology also opposes antiepileptic generic substitution without physician approval.[3] However, the current evidence supporting the policy and clinical assertions has been conflicting.[19-21] Also, despite better tolerability profiles, there is limited effectiveness data showing that newer AEDs are associated with reduced risks of seizures compared with older agents.

We sought to investigate the association between A-rated switching and the odds of emergent treatment for an epilepsy-related event over a 1-year period using the recent data from a large pooled commercial health plan database. Through this investigation we also assessed whether the risk of these events differed between older and newer AEDs.

## METHODS

### Data source

This case-control analysis utilized data from the Truven Health MarketScan® Commercial Claims and Encounters Database. MarketScan® data include the inpatient, outpatient, and prescription drug claims data for 45 million cumulative lives covered by a variety of US commercial health plans. Medicaid and Medicare recipients are not included in the commercial claims database and therefore were not included in this study. MarketScan® database is de-

identified in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations, thus making the study exempt from institutional review board review.

## Study design

Cases and controls with a diagnosis of epilepsy (International Classification of Disease, Version 9 (ICD-9) 345.xx), were identified in the database between January 1, 2010 and December 31, 2010. The index date was defined as the visit date for the first claim during the identification period that corresponds with the case and control definition. Cases were defined as subjects with a claim for an ambulance ride, emergency department (ED) visit, or inpatient hospitalization and a primary or secondary diagnosis of epilepsy during the identification period. Controls were non-cases with a claim for an outpatient office visit during the identification period and a primary or secondary epilepsy diagnosis. Cases and controls were matched using a 1:1 ratio for age within 5 years of the case's age and seizure diagnosis category. One control was randomly selected and matched to each case using a previously reported computer algorithm to assign the best matched control to each case.[22]

Subjects were included if they were continuously enrolled in their health plan for at least the most recent 6 months preceding the index date (pre-index period) and at least 12 months following the index date (post-index period), were between age 12 to 64 years, and had an AED medication filled for at least 145 days during the 6 months preceding the index date. Subjects were excluded if they had a primary diagnosis of infantile spasms (ICD-9 345.6x) or an ambulance ride, ED visit, or inpatient hospitalization with a diagnosis of epilepsy in the 6 months prior to the index date. Subjects younger than 12 years of age were not included in the

study due to unstable hormone levels increasing their risk for epilepsy exacerbations.[23] Subjects 65 years and older were not included because they are not uniformly represented in the MarketScan® Commercial Claims Database.

The exposure of interest was the occurrence of an A-rated switch of an AED (brand to generic, generic to brand, generic to generic) during the 90 days prior to the index date. A switch was defined as the first change in the first nine digits of the national drug code (NDC) within the same generic code number (GCN) in the 6 months prior to index. If multiple switches occurred, only the closest switch to the index date (the switch that was most likely associated with the outcome) was evaluated. Independent variables included the following demographic characteristics: patient age during the index year, sex, and US census region of the health plan. We controlled for comorbidity burden using the Deyo version of the Charlson Comorbidity Index (CCI) score, developed specifically for use with administrative claims databases[24, 25] The Deyo version is based on 17 diagnosis indicators and each is assigned a weight depending on its associated risk of mortality.[24] The scores are summed to a total comorbidity index score; the higher the score, the more severe the burden of comorbidity. We also controlled for the type of AED used during the study period, categorized as a binary indicator of older AEDs (with the most narrow therapeutic index) if the subject was treated with carbamazepine and phenytoin, and newer AEDs for all other agents. All diagnoses were grouped into six categories reflecting epilepsy diagnosis and history of seizure intractability. The six categories were ‘‘generalized” (345.0x-345.3x), ‘‘partial” (345.4x, 345.5x, 245.7x), and ‘‘other” (345.8x, 345.9x) with each subdivided into intractable (xxx.x1) and non-intractable (xxx.x0) designations. The study

outcome included utilization of ambulance, ED, or inpatient hospital routes of care with a primary diagnosis of epilepsy for the recorded event.

Statistical analysis

We performed univariate comparisons between cases and controls for all variables. Differences in mean values were tested with the Student's t-test. Differences in categorical variables were evaluated with Pearson chi-square tests. We also compared the mean time between a patient's last switch and the index date for cases versus controls using a Student's t-test assuming unequal variances. We estimated the odds of an emergently treated epilepsy-related event using a matched (discordant pairs) analysis. Conditional multiple logistic regression was used to estimate the relationship between switching and an emergently treated epilepsy-related event. A priori independent variables that most likely affect treatment and outcomes, such as age, diagnosis category, and total number of AED prescriptions filled, were selected based on earlier research.[26, 27] US census region is likely associated with the exposure; however, we did not include it in the final model after determining that it was not associated with the outcome and did not add to the predictive ability of the multivariate model. Our final model adjusted for matching, sex, CCI, AED type, and total number of AED prescriptions filled. All statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, NC).

**RESULTS**

Of more than 45 million subjects in the MarketScan® database, we identified 48,978 with an inpatient claim with at least one diagnosis of epilepsy and 125,327 with an outpatient claim with at least one diagnosis of epilepsy during the identification period (Table 1). After applying

exclusion criteria, among cases and controls, 7,368 and 19,125 were excluded because of age, 7,434 and 16,533 because of continuous eligibility 6 months prior to index date, 1,738 and 10,012 because of an ambulance ride, ED visit, or inpatient hospitalization with the primary diagnosis of epilepsy in the 6 months prior to the index date, and 24,595 and 54,753 because of having less than 145 days supply of AED, respectively. A total of 7,843 cases and 24,904 controls met the full inclusion criteria. Of the 24,904 controls, 7,843 were matched 1:1 to cases based on age and seizure diagnosis category.

Evaluation of the non-matched data revealed statistically significant differences in gender, census region, CCI, and seizure diagnosis between cases and controls (Table 2). The matching procedure removed differences in age and seizure diagnosis. In the matched sample, the mean age was 40.3 years and most seizures were recorded as other or unspecified nonintractable. Matched controls were comprised of a lower proportion of female (52.2% vs. 57.3%; $P<0.0001$) and scored lower on the CCI. Census region was 'Unknown' for <1% of the study population. During the 6 months prior to index 1,873 of 7,843 (23.9%) cases and 1,566 of 7,843 matched controls (20.0%) experienced an A-rated switch. A similar length of time from last switch to the index date was observed for cases and controls. Matched cases and controls differed in their distributions of AEDs involved in the switch (Table 3, P<0.0001). Levetiracetam, lamotrigine, valproic acid and topiramate were the most commonly switched medications.

The odds of an emergently treated epilepsy-related event when matched on age and seizure diagnosis were 1.26 (95% CI: 1.17-1.36), or 26% higher for those who experienced a switch (Table 4). After adjustment for potential confounders, the odds of an emergently treated

epilepsy-related event associated with an A-rated switch was 1.15 (95% CI: 1.06–1.25). Female subjects were 25% more likely than male subjects to experience an epilepsy-related event in the adjusted model (odds ratio [OR]=1.25; 95% CI: 1.159–1.352). As the number of comorbidities increased, the risk of an emergent epilepsy-related event increased. The odds of an epilepsy-related event were also 16% greater in subjects who were treated with carbamazepine and phenytoin than subjects treated with other AEDs (OR=1.16; 95% CI: 1.017–1.329). Also, a one-unit increase in the total number of AED prescriptions filled in the 6 months prior to index was associated with an 4% increased odds of an emergently treated epilepsy-related event (OR = 1.04; 95% CI: 1.032–1.049).

## DISCUSSION

This case-control study provides the most recent observational evidence containing pooled commercial health plan data from the US population. Our analysis suggests a moderate association exists between emergently treated epilepsy-related events and A-rated substitution even after adjusting for potential confounders. In particular, patients who experienced an A-rated switch for carbamazepine or phenytoin experienced higher odds of an emergently treated epilepsy-related event, compared with subjects taking any other AED.

Our findings are consistent with some studies from the available and conflicting literature. A recent systematic literature review and meta-analysis evaluated nine randomized controlled trials (RCTs), one prospective non-randomized trial, and six observational studies.[20] After pooling over 200 subjects from the nine RCTs, Kesselheim et. al. found no evidence of epilepsy-related events for generic substitutions of at least three types of AEDs. Conversely, the results from

observational studies in the review suggest less adequate seizure control in subjects with epilepsy who were switched from brand-name to generic formulations, based on the evaluation of changes in drug or health services utilization. Another literature review by Yamada and Welty[21] reported mixed results between retrospective and prospective studies. Contrary to evidence from prospective studies, the retrospective studies demonstrated an association between AED switching and adverse clinical outcomes. Interestingly, Yamada and Welty failed to evaluate all available published evidence at the time of their study.

Between the reviews by Kesselheim et. al. and Yamada and Welty, eight retrospective studies were evaluated and there was overlap in five of the studies. The studies in the two reviews generally demonstrated that generic substitution of AEDs resulted in higher use of medical services in patients with epilepsy. For example, case-control studies by Rascati et. al., Zachry et. al., and Hansen et. al. all reported an association between an A-rated switch and epilepsy-related events with odds ratios ranging from 1.57 to 1.81.[28-30] Labiner et. al. found a higher incidence rate of epilepsy-related medical services with generic AED substitution in unstable patients than in stable patients.[31] Gagne et. al. reported increased seizure-related events around the time of prescription refills, for brand-to-brand or generic-to-generic, compared to seizure-related events between prescription refills.[32] However, conflicting evidence were observed in three retrospective studies that were not reviewed by Kesselheim et. al. and Yamada and Welty. The three studies, a cohort-crossover study and two retrospective database studies, did not find an association between generic substitution and epilepsy-related events.[33-35] In the cohort-crossover study using Medicaid data, conversion to generic lamotrigine was not associated with a statistically significant increase in the odds of an ED visit, hospitalization, or condition-specific

encounter.[35] In a nested case-control study using commercial health plan data, Devine et. al. did not find a statistically significant increase in risk associated with generic conversion after adjusting for potential confounders and comorbidities (adjusted odds ratio = 1.08; 95% CI 0.91, 1.3).[33] Erickson et. al. also analyzed data from a large commercial health plan and failed to demonstrate that switching from branded lamotrigine or divalproex was associated with an increased risk of ED use or hospitalization.[34]

Despite the apparent inconsistency in the published evidence, the majority of the retrospective studies suggest A-rated substitution is associated with an elevated risk of epilepsy-related events. Among those studies, differences in databases, patient selection, and methodology may explain the mixed findings. Another potential reason is most studies pooled data of newer and older AEDs together in their analyses. Individual AEDs are not equal and differ by indication, mechanism of action and adverse event profile.[5, 11] For example, older, first-generation AEDs tend to have more impact on hepatic metabolism, more complex pharmacokinetic profiles, more frequent drug interactions, and more side effects than newer AEDs.[11] Owing to their less favorable pharmacokinetic profile, older AEDs may be more prone to problems with generic substitution than newer ones. After adjusting for potential confounders, our results correspond with the clinical evidence of older AEDs, suggesting that subjects treated with older AEDs have higher odds for an emergently epilepsy-related event than subjects treated with newer agents.

Limitations

The results of this study must be interpreted with appropriate consideration of certain limitations inherent in retrospective database studies. First, while the data represent final, adjudicated claims

in a health plan setting, it is possible that the data elements used are subject to coding or misclassification error. Also, given the chronic nature of epilepsy, not all individuals with epilepsy seek emergency treatment for seizures. It is possible that our study population represent a select sample of patients who experienced a seizure that was severe enough to require visits to health care providers. This can potentially result in attenuation of the effect of switching towards the null. A second limitation is that we relied solely on pharmacy dispensing records to measure the switch event because we did not have direct measures of adherence or compliance. Pharmacy claims for filled prescriptions do not necessarily indicate that the medications were used as prescribed.[36] This limitation was minimized by excluding both cases and controls that were dispensed less than 145 days supply of AED medication for the 6 months prior to the index date. Third, confounding by indication remains a possibility since we were unable to directly assess the indication for the switched medications that we have evaluated or the use of combination therapies. Fourth, we used a prevalent user design, including all subjects with epilepsy. Despite using a rigorous matching procedure, the use of prevalent cases and controls may potentially bias our estimates since the study population may contain a higher proportion of stable patients who had previously switched with or without an adverse outcome. Fifth, using the greedy matching algorithm, we were only able to randomly match one control to every case based on age and seizure type. Although 1:1 matching may yield sufficiently precise estimates in large studies,[37] the potential for distortion of the association between exposure and disease is greater compared to previous case-control studies that employed 1:3 matching of cases and controls. Sixth, our study cohort was comprised of a commercially insured population under age 65 years, therefore our study findings may not be generalizable to elderly subjects age 65 years and older. Seventh, there are likely unobserved and unmeasured factors that likely affect switching in individuals

with epilepsy, such as disease severity. Claims data does not provide access to important clinical measures to guide insight into the progression and severity of each patient's epilepsy. We used a proxy of epilepsy severity (i.e., total number of AED prescriptions filled in the 6 months prior to index) to control for some portion of confounding by disease severity. Lastly, as a nonrandomized retrospective study of observational data, it is possible that despite the use of rigorous statistical methods, unobserved treatment selection bias may have contributed to the outcomes.

## CONCLUSIONS

Using recent data from a large commercial health plan, this case-control study found a modest association between the switching of A-rated products and risks for emergently treated epilepsy-related events. Our analysis suggests that switching of carbamazepine and phenytoin is associated with an increased risk of epilepsy-related events as measured by medical resource utilization. With the emergence of newer AEDs in recent years, further studies comparing differences in risks for epilepsy-related events in older and newer AEDs are needed. In the absence of conclusive evidence, it is important that physicians, pharmacists, and patients understand the factors associated with generic substitution of AEDs. Physicians and pharmacists should actively seek to prevent switching of anti-epileptic medications once patients are stabilized on a specific product – whether branded or generic version. Such switching increases the odds of an epileptic event.

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Table 1. Patient selection (index event occurring between 1 January 2010 and 31 December 2010)

| | Number of patients with an epilepsy event | Patients P12 and <65 years of age | Patients with continuous eligibility 6 months prior to index event | Patients without an epilepsy event requiring hospitalization, ER visit, or ambulance during 6 months prior to index event | Patients with ≥145 days' supply of AED | Patients matched 1:1 by age and seizure type |
|---|---|---|---|---|---|---|
| *Requiring hospitalization, ER visit, or ambulance* | | | | | | |
| Cases | 48,978 | 41,610 | 34,176 | 32,438 | 7,843 | 7,843 |
| *Requiring an office visit* | | | | | | |
| Controls | 125,327 | 106,202 | 89,669 | 79,657 | 24,904 | 7,843 |

Table 2. Demographic and clinical characteristics: Non-matched and matched case and control groups

| | Non-matched | | | Matched[b] | | |
|---|---|---|---|---|---|---|
| **Variable** | **Case (N=7,843)** | **Control (N=24,904)** | **P-value** | **Case (N=7,843)** | **Control (N=7,843)** | **P-value** |
| Female (%) | 57.3 | 54.1 | <0.0001 | 57.3% | 52.2% | <0.0001 |
| Age, mean (SD) | 40.3 (15.4) | 40.2 (15.3) | NS[a] | 40.3 (15.4) | 40.3 (15.4) | NS |
| US region (%) | | | 0.0159 | | | 0.0015 |
| West | 15.1 | 14.6 | | 15.1 | 15.7 | |
| North Central | 29.4 | 29.9 | | 29.4 | 31.0 | |
| South | 40.1 | 39.9 | | 40.2 | 38.1 | |
| Northeast | 15.1 | 15.0 | | 15.0 | 14.6 | |
| Unknown | 0.3 | 0.6 | | 0.3 | 0.6 | |
| Seizure type (%) | | | <0.0001 | | | NS |
| Generalized, non-intractable | 10.5 | 25.8 | | 10.5 | 10.5 | |
| Generalized, intractable | 0.8 | 4.8 | | 0.8 | 0.8 | |
| Partial, non-intractable | 4.9 | 27.4 | | 4.9 | 4.9 | |
| Partial, intractable | 3.8 | 11.0 | | 3.7 | 3.7 | |
| Other, non-intractable | 75.0 | 28.4 | | 75.0 | 75.0 | |
| Other, intractable | 5.0 | 2.6 | | 5.0 | 5.0 | |
| Deyo-Charlson index score (%) | | | <0.0001 | | | <0.0001 |
| 0 | 81.0 | 97.1 | | 81.0 | 96.3 | |
| 1 | 11.4 | 2.1 | | 11.4 | 2.8 | |
| 2+ | 4.7 | 0.7 | | 7.5 | 0.9 | |

[a]NS, not significant, P > 0.05.

[b]Cases and controls were matched 1:1 by age and seizure type.

Table 3. Characteristics of A-rated switches: Cases and Controls[a]

| Drug, N(%) | Cases with switch N=1,873 | Controls with switch N=1,564 | Total with switch N=3,437 |
|---|---|---|---|
| Levetiracetam | 456 (13.3) | 343 (10.0) | 799 (23.3) |
| Lamotrigine | 296 (8.6) | 320 (9.3) | 616 (17.9) |
| Divalproex Sodium | 256 (7.5) | 248 (7.2) | 504 (14.7) |
| Topiramate | 230 (6.7) | 175 (5.1) | 405 (11.8) |
| Phenytoin | 139 (4.0) | 142 (4.1) | 281 (8.2) |
| Clonazepam | 177 (5.2) | 72 (2.1) | 249 (7.2) |
| Zonisamide | 130 (3.8) | 73 (2.1) | 203 (5.9) |
| Carbamazepine | 77 (2.2) | 122 (3.6) | 199 (5.8) |
| Gabapentin | 102 (3.0) | 55 (1.6) | 157 (4.6) |
| Primidone | 10 (0.3) | 14 (0.4) | 24 (0.7) |

[a]For patients who had more than one switch, only the last switch is characterized here.

Table 4. Odds of a seizure related event comparing switchers and non-switchers

| | **All instances of a switch to an A-rated alternative** | |
|---|---|---|
| | **Switch identified** | **No switch identified** |
| Case | 1,873 | 5.970 |
| Control | 1,564 | 6,279 |
| Odds ratio (Mantel–Haenszel) | 1.26 (95% CI=1.16-1.36), P<0.0001 | |
| Effect | Point estimate (OR) | 95% Wald confidence limits |
| *Conditional logistic regression model*[a] | | |
| Switch | 1.15 | 1.05 - 1.24 |
| Carbamazepine/Phenytoin vs. other AED | 1.16 | 1.02 - 1.33 |
| Female | 1.24 | 1.16 - 1.33 |
| Total fills[b] | 1.04 | 1.03 - 1.05 |
| Deyo-Charlson index score | | |
| 0 | Ref. | |
| 1 | 5.06 | 4.30 - 5.97 |
| 2+ | 11.53 | 8.79 - 15.13 |

[a]Including adjustment for case–control strata, sex, CCI, older AED vs. newer AED, and total number of AED prescriptions filled.
[b]Total number of AED prescriptions in the 6 months prior to the index date.