

ORIGINAL RESEARCH ARTICLES

Effects of Antiepileptic Drug Substitutions on Epileptic Events Requiring Acute Care

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Study Objectives. To determine the odds of antiepileptic drug substitution among patients who had an epileptic event requiring acute care—ambulance service, emergency department visit, or hospitalization—relative to patients who did not have an event, and to compare these results with those from a recent study involving a similar method but different patients.

Design. Case-control analysis.

Data Source. United States health care claims from the PharMetrics database.

Patients. A cohort of patients aged 12–64 years with a primary diagnosis of epilepsy between October 1, 2005, and December 31, 2006; 991 cases (patients who experienced an epileptic event requiring acute care) and 2973 controls (patients who did not have an event) were matched in a 1:3 ratio for sex, age, and type of epilepsy.

Measurements and Main Results. Using discordant pairs analysis, we calculated the odds ratio of an epileptic event that required acute care occurring in patients whose antiepileptic drug underwent substitution to an A-rated (therapeutically equivalent) alternative (switch from branded product to generic, generic to branded, or generic to generic) versus those whose drugs were not substituted. For matched data, 109 (11.0%) of 991 cases had an A-rated antiepileptic drug substitution in the 6 months before the event, whereas only 186 (6.3%) of 2973 controls had a substitution (odds ratio 1.84, 95% confidence interval 1.44–2.36). Our results were similar to those of a previous study involving a different patient database, which showed substitution rates of 11.3% for cases versus 6.5% for controls (odds ratio 1.81, 95% confidence interval 1.25–2.63). Our sensitivity analyses were robust, and we found a temporal relationship in that numerous substitutions occurred in the month before the acute event.

Conclusion. Patients who had an epileptic event requiring acute care were about 80% more likely than matched controls without an acute event to have recently had an antiepileptic drug substitution. Our replication of a previously published case-control analysis revealed a similar association between substitution involving A-rated antiepileptic drugs and subsequent epileptic events requiring acute care, thereby lending credibility to the findings.

Key Words: antiepileptic drug, generic substitution, narrow therapeutic index, epilepsy, drug switching.

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Generic substitution is one of the most common methods for controlling the cost of prescription

drugs. For most drug classes, generic substitution results in substantial cost savings without

compromising patient health. However, for some drug classes such as antiepileptic drugs, safety issues have been raised.¹⁻³

The United States Food and Drug Administration (FDA) considers a generic drug and the original, branded drug to be equivalent if they have the same active ingredient, strength, dosage form, and route of administration. However, the agents are allowed to be different in other aspects, such as release mechanisms, excipients, pill characteristics (e.g., hardness), and expiration time. For generic drugs, the FDA requires the area under the concentration-time curve to be within the 90% confidence intervals (CIs) and their peak plasma concentrations to be within 80–125% of the branded drug.⁴

Some health care providers are apprehensive about substituting antiepileptic drugs because of the narrow therapeutic index of certain drugs in this class.^{5,6} Surveys of neurologists and other physicians from the United States and abroad have indicated concern that generic substitution of branded antiepileptic drugs may lead to adverse events in some patients, and reports have described patients who experienced breakthrough seizures after such a drug switch.⁶⁻⁸ For example, a recent study involved case reports of 50 patients who had seizures after generic antiepileptic drugs were substituted for their branded products.⁹ In a 2007 position paper about epilepsy treatment and generic antiepileptic drug substitution, the American Academy of Neurology stated that it opposes the practice without the attending physician's approval.¹⁰ In addition, the Epilepsy Foundation has advised that substitution should not occur without the expressed permission of the treating physician and the patient.¹¹

The hypothesized link between antiepileptic drug substitution and subsequent breakthrough seizures and other adverse events is based on a limited number of case reports; additional research in large populations is needed to test this relationship. The first known case-control

study of the association between substituting antiepileptic drugs and a need for emergency care for seizures was recently published.¹² The authors used a large U.S. claims database (Ingenix LabRx; Ingenix Health Intelligence, Salt Lake City, UT) to retrospectively assess the odds that drug substitution had occurred in patients who had an epileptic event needing hospitalization, ambulance service, or an emergency department visit versus those who did not. Antiepileptic drug substitutions were defined as "switches between any A-rated alternatives from different manufacturers, including brand-to-generic, generic-to-generic, and generic-to-brand" changes. The 416 cases were matched 1:3 with 1248 controls who were approximately the same age and who had the same seizure diagnosis. The odds that an antiepileptic drug was switched in the 6 months before the emergency event was 81% greater for cases (11.3%) than for controls (6.5%). The authors called for more research to test the association between antiepileptic drug substitution and adverse events.

To contribute to the literature in the areas of antiepileptic drug substitution and its possible effects on patients, we conducted a similar study using a different U.S. claims database with a broader time period. In addition to conducting the replicative study, we applied a second method to test the association between antiepileptic drug substitution and emergency care for epilepsy. The objective of our study was to determine the odds of antiepileptic drug substitution among patients who had an epileptic event requiring acute care—defined as ambulance service, emergency department visit, or inpatient visit—compared with patients without an event.

Methods

We used a case-control design to analyze health care claims data from the PharMetrics database (IMS Health Inc., Watertown, MA). The database contained information from 75 managed care organizations, and its 2 billion medical and pharmacy claims represented more than 55 million patients from various geographic areas of the United States. The University of Texas institutional review board approved the study, and all requirements of the Health Insurance Portability and Accountability Act of 1996 were met.

Our cohort of patients had to have a primary diagnosis of epilepsy, as evidenced by an *International Classification of Diseases, Ninth Revision*, code 345.xx, excluding infantile spasms. They

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had to be aged 12–64 years, and for the 6 months leading up to their index date (defined below), they had to have some form of continuous

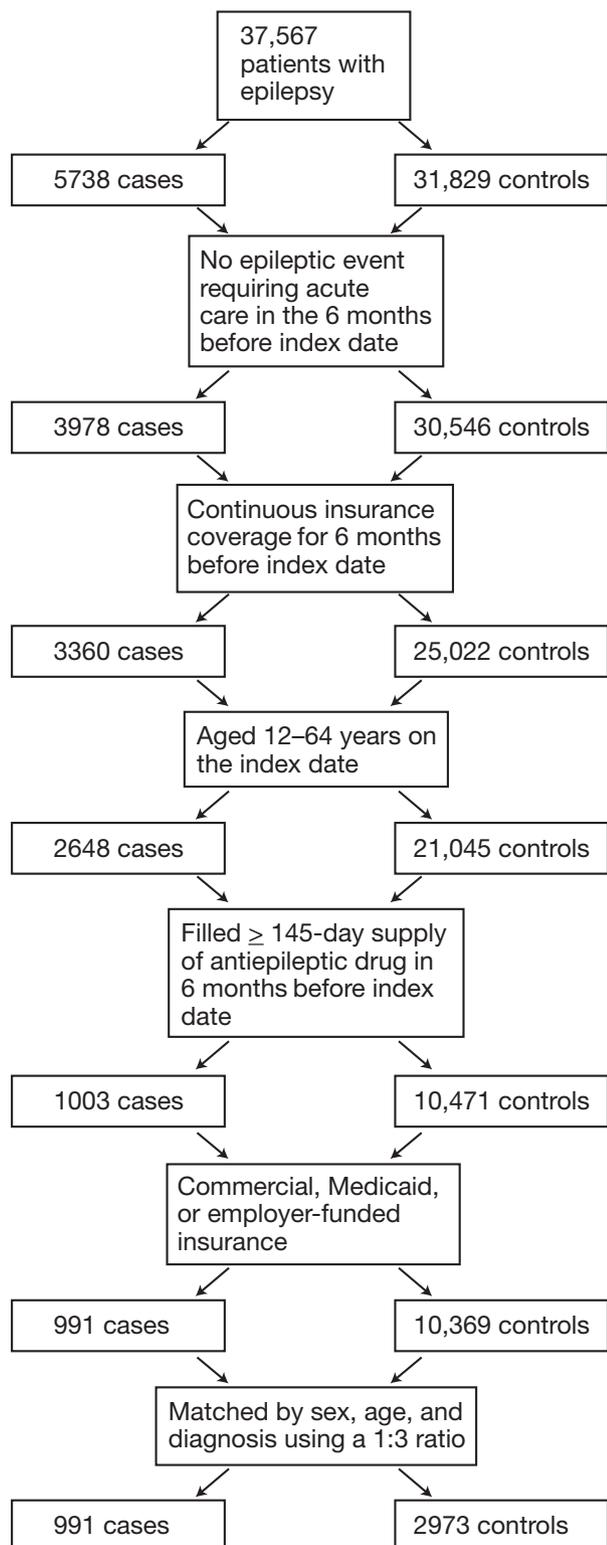


Figure 1. Flow diagram of patient selection criteria.

insurance coverage and have had filled prescriptions for their antiepileptic drugs for least 145 days (80% adherence). In the study discussed previously,¹² researchers used an index time frame of July–December 2006, but we were able to obtain data from a longer period to increase the sample size of patients meeting all criteria.

Patients who had an acute epileptic event between October 1, 2005, and December 31, 2006, and no acute events 6 months before their index date (date on which acute event occurred) were defined as cases. Acute events were defined as an epilepsy-related ambulance service, emergency department visit, or hospitalization. Patients who had been diagnosed with epilepsy in a clinician's office during the same period but had not experienced an acute event were defined as controls. Cases and controls were matched using a 1:3 ratio for sex, age within 5 years, and seizure diagnosis (generalized, partial or other, and intractable or nonintractable).

We then examined any claims for the cases and controls for 6 months before the index date to determine if their antiepileptic drug had been substituted. A substitution was defined as a change in an A-rated antiepileptic drug (therapeutically equivalent, as defined in the FDA Orange Book).⁴

Statistical Analysis

We used χ^2 analyses to compare patient demographics and seizure types. Similar to the previous investigators,¹² we analyzed discordant pairs to calculate odds ratios (ORs) and the level of significance (with 95% CIs) to compare the rate of substitution between cases and controls. A *p* value of 0.05 or less was considered to indicate a statistically significant difference. We also conducted two post hoc analyses: one to exclude patients whose dosage was changed during the study period and one to exclude patients receiving Medicaid benefits.

Finally, we applied logistic regression as a second method to identify predictors of epilepsy-related emergency care. Independent variables were sex, age, region of residence, diagnosis, use of multiple antiepileptic drugs, and whether a switch involving an A-rated antiepileptic drug occurred.

Results

Patient Demographics

Of 37,567 patients with epilepsy who were screened for inclusion, the unmatched study

Table 1. Demographic Characteristics

| Characteristic | No. (%) of Nonmatched Patients | | p Value | No. (%) of Matched Patients | | p Value |
|--------------------------|--------------------------------|---------------------|---------|-----------------------------|-------------------|---------|
| | Cases (n=991) | Controls (n=10,369) | | Cases (n=991) | Controls (n=2973) | |
| Male | 486 (49.0) | 4848 (46.8) | p>0.05 | 486 (49.0) | 1446 (48.6) | p>0.05 |
| Insurance | | | p<0.001 | | | p<0.001 |
| Commercial | 896 (90.4) | 9697 (93.5) | | 896 (90.4) | 2783 (93.6) | |
| Medicaid | 64 (6.5) | 191 (1.8) | | 64 (6.5) | 56 (1.9) | |
| Self | 31 (3.1) | 481 (4.6) | | 31 (3.1) | 134 (4.5) | |
| Region | | | p<0.001 | | | p<0.001 |
| West | 92 (9.3) | 609 (5.9) | | 92 (9.3) | 180 (6.1) | |
| Midwest | 437 (44.1) | 4574 (44.1) | | 437 (44.1) | 1273 (42.8) | |
| South | 227 (22.9) | 2827 (27.3) | | 227 (22.9) | 838 (28.2) | |
| East | 235 (23.7) | 2359 (22.8) | | 235 (23.7) | 682 (22.9) | |
| Age, mean \pm SD (yrs) | 35.6 \pm 15.1 | 39.2 \pm 14.9 | p<0.001 | 35.6 \pm 15.1 | 35.6 \pm 15.1 | p>0.05 |

Table 2. Seizure Diagnoses

| Seizure Type | No. (%) of Patients | | | |
|----------------|-------------------------|---------------------|----------------------|-------------------|
| | Nonmatched ^a | | Matched ^b | |
| | Cases (n=991) | Controls (n=10,369) | Cases (n=991) | Controls (n=2973) |
| Generalized | | | | |
| Nonintractable | 284 (28.7) | 2884 (27.8) | 284 (28.7) | 852 (28.7) |
| Intractable | 30 (3.0) | 595 (5.7) | 30 (3.0) | 90 (3.0) |
| Partial | | | | |
| Nonintractable | 109 (11.0) | 2894 (27.9) | 109 (11.0) | 327 (11.0) |
| Intractable | 106 (10.7) | 1238 (11.9) | 106 (10.7) | 318 (10.7) |
| Other | | | | |
| Nonintractable | 420 (42.4) | 2290 (22.1) | 420 (42.4) | 1260 (42.4) |
| Intractable | 42 (4.2) | 468 (4.5) | 42 (4.2) | 126 (4.2) |

^ap<0.001, χ^2 test.^bp>0.05, χ^2 test.

population consisted of 11,360 subjects: 991 cases and 10,369 controls (Figure 1). By matching 1:3 for age, sex, and diagnosis, we obtained a sample of 991 cases and 2973 controls (Table 1).

For the unmatched data, although patients in the control group were older (39.2 \pm 14.9 yrs) than those in the case group (35.6 \pm 15.1 yrs), we observed no significant difference with respect to sex. When data were matched, we found a significant difference for region of residence between cases and controls. Still, proportions for each region were similar and did not seem to indicate a practical difference between cases and controls. Type of insurance was also significantly different after matching. Medicaid was the primary insurer for 6.5% of cases versus 1.9% of controls. For nonmatched data, with regard to seizure diagnosis, a diagnosis of nonintractable, other epilepsy was more common (42.4%) for cases than for controls (22.1%; Table 2).

Rate of Substitution

For the matched data, 109 (11.0%) of 991 cases had an A-rated antiepileptic drug substitution within 6 months before the event. In contrast, 186 (6.3%) of 2973 controls had a drug substitution (OR 1.84, 95% CI 1.44–2.36; Table 3).

Of the 109 cases, the most recent switch for 53 (48.6%) was generic to generic. Among the remaining cases, 35 (32.1%) were given a brand-to-generic switch, and 21 (19.3%), a generic-to-brand switch. Of 186 controls whose antiepileptic drug was substituted, the most recent switch for 83 (44.6%) was generic to generic. For the remaining controls, 77 (41.4%) underwent a brand-to-generic switch, and 26 (14.0%), a generic-to-brand switch. The type of switch did not statistically differ between cases and controls ($\chi^2 = 3.0$, p=0.23).

Of 109 cases who had a substitution, 82

Table 3. Documentation of Substitutions of A-Rated Antiepileptic Drugs

| Variable | Substitution Identified | | Odds Ratio (95% CI) |
|--|-------------------------|------|------------------------|
| | Yes | No | |
| No. of patients who received an A-rated substitution | | | |
| Cases | 109 | 882 | 1.84 |
| Matched controls | 186 | 2787 | (1.44–2.36) |
| Excluding patients with a dosage change | | | |
| Cases | 86 | 660 | 2.86 |
| Matched controls | 112 | 2454 | (2.13–3.83) |
| Excluding patients with Medicaid coverage | | | |
| Cases | 98 | 829 | 1.83 |
| Matched controls | 177 | 2740 | (1.41–2.37) |

CI = confidence interval.

(75.2%) had prescriptions for more than one type of antiepileptic drug. Of 186 controls whose antiepileptic drug was substituted, 110 (59.1%) had prescriptions for more than one type of antiepileptic drug; this difference was significant ($\chi^2 = 7.8$, $p < 0.01$).

The exclusion of matched patients whose dosage was changed during the study period raised the OR to 2.86 (95% CI 2.13–3.83; Table 3). The exclusion of matched patients receiving Medicaid benefits yielded a minimal difference in risk (OR 1.83, 95% CI 1.41–2.37).

Of the 109 cases whose antiepileptic drug was substituted, 15 (13.8%) had more than one switch compared with 10 (5.4%) of 186 matched controls.

Our logistic regression analysis showed that an A-rated antiepileptic drug substitution was predictive of epilepsy-related acute events. The analysis yielded results similar to those of the discordant pairs analysis, with an OR of 1.51 (95% CI 1.17–1.96).

Of 991 cases, 26 (2.6%) had antiepileptic drug substitutions during the month before their epilepsy-related emergency event (the index date). Significantly fewer antiepileptic drug substitutions occurred among cases (1.5–1.8%) than among controls during months 2–6 before the index date. Substitutions were more consistent in the control group than in the case group over the 6-month study period, with rates of 0.9–1.3% of all matched controls (Table 4).

Comparison with Previous Study

One of our objectives was to test the possible association between A-rated antiepileptic drug

Table 4. Most Recent Substitutions of A-Rated Antiepileptic Drugs Before the Index Date

| Month Before Index Date | No. (%) of Patients | |
|----------------------------|---------------------|----------------------|
| | Cases (n=991) | Controls (n=2973) |
| 1 | 26 (2.6) | 40 (1.3) |
| 2 | 15 (1.5) | 28 (0.9) |
| 3 | 17 (1.7) | 30 (1.0) |
| 4 | 17 (1.7) | 36 (1.2) |
| 5 | 16 (1.6) | 26 (0.9) |
| 6 | 18 (1.8) | 26 (0.9) |

substitution and emergency epilepsy care, as recently reported in another study¹² using a different database. Replication of a study calls for comparisons between the original work and the replication. Our longer index period helped us more than double the number of cases and strengthened our replication. Our results indicating an 11.0% switch rate for cases compared with 6.3% for controls (OR 1.84, 95% CI 1.44–2.36) were similar to findings from the previous study showing an 11.3% switch rate for cases compared with 6.5% for controls (OR 1.81, 95% CI 1.25–2.63).¹² Discordant pairs analysis from both the previous study and ours revealed that patients with claims for epilepsy-related acute care were, respectively, 81% and 84% more likely than controls to have had A-rated antiepileptic drug substitutions in the previous 6 months. Post hoc analyses also yielded similar results. In the previous study¹² and in ours, removal of patients with dosage changes raised the OR (2.01 and 2.86, respectively), whereas exclusion of patients with Medicaid coverage made little difference (1.86 and 1.83, respectively).

Discussion

The FDA requires new generic drugs to be compared with the original branded versions, but it does not require generic-to-generic comparisons. Therefore, one might hypothesize that generic-to-generic switches can cause more variance in patient drug levels than brand-to-generic or generic-to-brand switches do. One generic product may result in drug levels higher than those measured with a brand product, whereas another generic may lower levels. For the matched cohorts in this study, we did not observe a significant difference in the percentages of generic-to-generic switches in the cohort with an event (49%) compared with the cohort without an event (45%).

In the comparison study¹² and in our study,

more antiepileptic drug switches occurred the month before the index date than in previous months. The other investigators found successive reductions in substitution rates during each month for cases, whereas we found approximately the same substitution rates in cases from month 2–6 before the index dates. Results of both studies indicated a possible temporal relationship between antiepileptic drug substitution and epilepsy events requiring acute care that should be further evaluated.

Limitations include assumptions made by the researchers. These included the assumption that patients with seizures seek emergency care and that patients comply with their drug regimens. Another limitation was a lack of control for other factors that cause seizures (e.g., alcohol use, metabolic disturbances). Also, we used the surrogate marker of epilepsy-related ambulance service, emergency department visits, or hospitalization to determine if the patient had a breakthrough event (i.e., seizure or toxicity). The validity of this surrogate measure should be studied in detail.

All substitutions for A-rated antiepileptic drugs were collapsed for this analysis. As more data become available, product-specific analyses to test molecular features (e.g., lipophilicity, therapeutic window) and population characteristics (e.g., type of epilepsy, history of intractability) can be conducted with appropriate power to validly describe their roles.

Limitations of using reimbursement claims data for clinical analyses include the possibility of miscoded or missing data. For example, the data source could not have provided information about antiepileptic drug substitutions during an inpatient stay unrelated to epilepsy. (If patients had an epilepsy-related inpatient stay within 6 months before the index date, they would have been excluded from the analysis.) Also of note, this type of data source does not include information about uninsured patients.

Our study design limited the results, which indicated merely association and not causation. Still, the findings provide clinicians with additional information on this issue. At a minimum, pharmacists should communicate with their patients with epilepsy, notifying them when a drug change takes place and encouraging self-monitoring. Cost savings from drug changes may shift costs to other areas of health care, such

as those incurred in an acute care setting. In addition, patients' health-related quality of life may be reduced due to toxicity or breakthrough seizures.

Conclusion

In this case-control analysis, patients who had an epileptic event requiring ambulance service, emergency care, and/or hospitalization were about 80% more likely than matched control subjects without an acute event to have recently had an antiepileptic drug substituted. Results of our replication study lend credibility to findings of the original study and supplement the limited literature in the area of antiepileptic drug substitution. Serious questions have been raised about this issue for years, and our work supports the continued need for analysis on this topic. Additional research is warranted to further investigate potential health problems associated with substitution of A-rated antiepileptic drugs.

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