

**Anti-epileptic Medication Drug Formulation Changes and their Relationship to Outcomes
(Ambulance, Emergency Department, and Inpatient Events)**

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Anti-epileptic Medication Drug Formulation Changes and their Relationship to Outcomes (Ambulance, Emergency Department, and Inpatient Events)

Abstract:

Study Objective. Surveys and case reports suggest that some epilepsy patients may encounter health problems when switching between anti-epileptic product formulations. The main objective of the study was to determine the odds of a substitution of anti-epileptic medication for patients who had experienced an epileptic event requiring acute care (defined as an epilepsy-related ambulance service, ED visit, or inpatient visit) compared to those without an acute event. These results were then compared to a recent study using a similar methodology but a different patient database.

Design. Retrospective case-control analysis.

Setting. Data from a repository of US health plan claims (PharMetrics).

Patients. Age 12-64 with a primary diagnosis code for epilepsy (ICD-9 of 345.xx) between October 1, 2005 and December 31, 2006.

Measurements and Main Results. A 3:1 match was conducted based on gender, age, and type of epilepsy diagnosis. The odds ratio of an event between patients who had a medication change between A-rated alternatives for an anticonvulsant medication (defined as a switch) and those who did not was calculated using discordant pairs analysis. For the matched data, 109 of 991 patients (11.0%) who experienced an 'event' also had an A-rated AED substitution within 6 months before the event, while 186/2973 (6.3%) of patients who did not experience an 'event' had a switch (OR 1.84; 95% CI=1.44 to 2.36). This was similar to a previous study that used a different database (11.3% vs. 6.5%; OR 1.81; 95% CI=1.25 to 2.63). Sensitivity analyses were robust, and a temporal relationship was found in that a large number of switches occurred in the one month prior to the acute event.

Conclusions: Replication of a case-control analysis found a similar association between patients receiving epilepsy care in an emergency department, ambulance, or inpatient setting and the prior occurrence of formulation switching involving A-rated anti-epileptic medications.

Introduction

Generic substitution is one of the most common prescription drug cost control methods utilized today. For most drug classes, generic substitution results in significant cost savings without compromising patient health. However, for some drug classes, like anti-epileptic drugs (AEDs), safety issues have been raised.^{1,2,3} The FDA considers a generic and the original (branded) medication to be equivalent if they have the same active ingredient, strength, dosage form, and route of administration. However, they are allowed to be different in other aspects, such as release mechanisms, excipients, pill characteristics (such as hardness), and expiration time. The FDA requires generics to be within the 90% confidence intervals for area-under-the-curve (AUC) and within the intervals of 80% to 125% for peak plasma concentrations (C_{max}).⁴ Some health care providers are apprehensive about AED substitution due to the narrow therapeutic index of certain drugs in this class.^{5,6} Surveys of neurologists and other physicians from the U.S. and abroad have indicated concern that generic substitution of branded AEDs may lead to adverse events in some patients, and reports have surfaced of patients who experienced breakthrough seizures after such a medication switch.^{6,7,8} For example, a recent study by Berg et al. published case reports of 50 patients who experienced seizures after switching from branded AED therapy to generic products.⁹ In a 2007 position paper on the matter of epilepsy treatment and AED generic 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 prior expressed permission of the treating physician and the patient.”¹¹

The potential link of AED substitution to subsequent breakthrough seizures and other adverse events has been hypothesized based on a limited number of case reports, and more research with larger populations is needed to test this relationship. The first known case-control study examining the association between AED formulation switching and emergency care for seizures was recently published.¹² Authored by Zachry et al., this study used a large U.S. claims database (Ingenex LabRx) to retrospectively assess the odds of medication substitution for those who had an epileptic event (hospitalization, ambulance service, or emergency department [ED] visit) versus those that did not. AED formulation changes were defined as “switches between any A-rated alternatives from different manufacturers, including brand-to-generic, generic-to-generic, and generic-to-brand” substitutions.¹² Case patients (n=416) were matched 1:3 with control

patients (n=1248) of approximately the same age and with the same seizure diagnosis. The authors found that case patients had 81% greater odds of having an AED switch in the 6 months prior to the emergency event (11.3%) relative to patients in the control group (6.5%). They called for more research testing the association between AED substitution and adverse events.

In an effort to contribute to the literature in the area of AED substitution and its possible effects on patients, we have conducted a study similar to that of Zachry et al.¹² using a different and U.S. claims database with a broader time period. In addition to conducting a replicative study, we employed a second methodology to test the association between AED substitution and emergency epilepsy care. The goal of this study was to determine the odds of a substitution of anti-epileptic medication for patients who had experienced an epileptic event requiring acute care (defined as an epilepsy-related ambulance service, ED visit, or inpatient visit) compared to those without an acute event.

Methods

A retrospective case-controlled design was utilized in this analysis of health claims data from the Pharmetrics™ database. The database contained information from 75 different managed care organizations, and its two billion claims (both medical and pharmacy) account for more than 55 million patients from various geographic areas of the U.S. Study approval was obtained from The University of Texas Institutional Review Board and all HIPPA requirements were met.

The patients in the study had a primary diagnosis of epilepsy as evidenced by an ICD-9 code of 345.xx, excluding infantile spasms. For inclusion, patients had to be between the ages of 12 and 64. The previous study by Zachry et al.¹² used an index time frame of July-December, 2006, but researchers for the current study were able to obtain data from a longer time period in order to increase the sample size of patients meeting all criteria. First, patients with acute epileptic events (index date) between October 1, 2005 and December 31, 2006 were identified if they had no acute events 6 months prior to their index date. Acute events were defined as an epilepsy-related ambulance service, ED visit, or inpatient visit. These patients served as the “case” patients. Controls had a primary epilepsy diagnosis in a physician’s office during the same time period. For the 6 months leading up to their index date, patients had to have as least 145 days (80%) of their anti-epileptic medication filled. Cases and controls were matched on seizure

diagnosis (generalized, partial or other, and intractable or non-intractable), gender, and on age within 5 years. A 3:1 (controls to cases) match was conducted.

Patient claims for cases and controls were then examined for 6 months prior to the index date to determine if a formulation substitution had taken place. A substitution was deemed to occur only if formulation changes between “A-rated” (as defined by the Food and Drug Administration’s Orange Book) anti-epileptic medications occurred. Similarly to the Zachry et al. study,¹² discordant pairs analyses were used to calculate odds ratios and level of significance to compare the rate of substitution between case and control patients. There were two post-hoc analyses conducted, first excluding patients who had a dosing change during the study period, and second excluding those patients receiving Medicaid benefits. Finally, logistic regression was employed as a second methodology to identify predictive factors of epilepsy-related emergency care. The independent variables included gender, age, region, diagnosis, use of multiple AEDs, and whether or not an A-rated AED switch had occurred.

Results

Demographics

The unmatched study population consisted of a total of 11,360 patients - 991 cases [those that had an ‘event’] and 10,369 controls [those that did not have an ‘event’] (Figure 1). Matching on age, gender, and diagnosis (3:1) provided a sample of 2,973 control patients and 991 case patients (Table 1). For unmatched data, although patients in the control group were older (39.2 ± 14.9 years) than those in the case group (35.6 ± 9.2 years), there was no significant difference in the groups with respect to gender. A statistical difference for region was found when data were matched. The proportions for each region are similar, however, and do not seem to indicate a practical difference between cases and controls. Type of insurance was also found to be statistically different after matching. Medicaid was the primary insurer for 6.5% of case patients versus 1.9% of controls. For non-matched data, a diagnosis of “non-intractable, other” epilepsy was most common (42.4%) for case patients while it was less common (22.1%) for control patients (Table 2).

Rate of Substitution

For the matched data, 109 of 991 patients (11.0%) who experienced an ‘event’ also had an A-rated AED substitution within 6 months before the event, while 186/2973 (6.3%) of patients who did not experience an ‘event’ had a substitution in medication formulation (OR 1.84; 95% CI=1.44 to 2.36) (Table 3). Of the 109 case patients that had an event, the most recent switch for about half of the patients was a generic-to-generic switch (N=53; 48.6%) and the remaining were for a brand-to-generic switch (N=35; 32.1%) or a generic-to-brand switch (N=21; 19.3%). Of the 186 control patients that had an event, the most recent switch for a little less than half of the patients was a generic-to-generic switch (N=83; 44.6%) and the remaining were for a brand-to-generic switch (N=77; 41.4%) or a generic-to-brand switch (N=26; 14.0%). The difference in type of switch was not statistically different between case and control patients ($\chi^2 = 3.0$; $p = 0.23$). Of the 109 case patients with a switch, 75.2% had prescriptions for more than one type of AED. Of the 186 control patients with a switch, 59.1% had prescriptions for more than one type of AED. This difference was significant ($\chi^2 = 7.8$; $p < 0.01$).

The exclusion of matched patients that experienced a dosing change during the study period resulted in a higher odds ratio of 2.86 (95% CI = 2.13 to 3.83). The exclusion of matched patients receiving Medicaid benefits yielded a minimal difference in risk (OR 1.83; 95% CI= 1.41 to 2.37). Of the cases that switched medications, 13.8% (15/109) had more than one switch, compared to 5.4% (10/186) for the matched controls (Table 3). The results in Table 3 were very similar to the findings of the previous study. Zachry et al.¹² found a 11.3% switch rate for case patients compared to 6.5% for control patients (OR =1.81; 95% CI=1.25 to 2.63).

Our logistic regression analysis also showed that an A-rated AED switch was predictive of epilepsy-related acute events, and yielded similar results to that of the discordant pairs analysis with an odds ratio of 1.51 (95% CI=1.17 to 1.96)

Out of 991 case patients, 26 (2.6%) had AED substitutions occur during the month prior to their epilepsy-related emergency event (the index date). Significantly fewer AED substitutions for the cases occurred during the remainder of the 6-month period (months 2 to 6) before the index date (1.5-1.8%). Control group substitutions were more consistent over the 6-month study period, ranging from 0.9 to 1.3% of all matched control patients (Table 4).

Discussion

Zachry et al.¹² conducted the first known study to provide evidence for a possible association between A-rated AED switches and emergency epilepsy care. Our objective was to test this association using a different database. The replication of a study calls for comparisons between the original and the replication. Compared to the previous study¹², the longer index period helped more than double the number of case patients, strengthening the replication. Both the Zachry et al. study and the current study found that patients with claims for epilepsy-related emergency care (defined as hospitalization, ED visit, or ambulance service) were over 80% more likely to have had an A-rated AED switch in the previous 6 months (84%, current study [discordant pairs analysis] versus 81%, Zachry et al. [discordant pairs analysis]). Similar results were also obtained from the post hoc analyses. Like the Zachry et al. study, the removal of patients with dose scheduling changes resulted in a higher odds ratio (2.86 current study; 2.01 Zachry study), while the exclusion of patients with Medicaid coverage made little difference (1.83 current study; 1.86 Zachry study).

Because the FDA requires the comparison of a new generic drug to the original branded version, and does not require generic-to-generic comparisons, one might hypothesize that the difference in drug levels for generic-to-generic switches may be higher than the brand-to-generic or generic-to-brand switches, since one generic product may result in a higher patient drug level than the brand product while another generic may result in a lower level than the brand product. For the matched cohorts in this study, we did not see a significant difference in the percent of generic-to-generic switches in the cohort with an event (49%) compared to the cohort without an event (45%).

In both studies more AED switches occurred a month prior to index than in the previous months. Zachry et al. found successive reductions in substitution rates during each month for case patients, while we found approximately the same substitution rate in cases from month 2 to month 6 before index. Results of both studies point to a possible temporal relationship between AED switches and emergency epilepsy events which should be further evaluated.

Some limitations include assumptions made by the researchers. These include the assumption of patients with seizures seeking emergency care, the assumption of medication regimen compliance, and the lack of control for other factors that cause seizures (e.g., alcohol use, metabolic disturbances). Researchers used a surrogate marker of epilepsy-related ambulance, ED

visit, or hospitalization to determine if the patient may have had a breakthrough event (i.e., seizure or toxicity). The validity of this surrogate measure should be studied in more detail. All switches for any A-rated AEDs were collapsed for this analysis. As more data become available, product-specific analyses that test hypotheses about types of molecules (lipophilicity, therapeutic window, etc.) and population characteristics (type of epilepsy, history of intractable nature, etc.) can be conducted with appropriate power to validly describe their role.

Limitations of using reimbursement claims data for clinical analyses include possible miscoded or missing data. For example, this data source would not have information about AED medication switches 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). It should also be noted that these types of data sources do not include information on uninsured patients.

While the study design limits the results in that they indicate mere association, and not causation, it does provide clinicians with more information on this issue. At minimum, pharmacists should communicate with their epileptic patients, notifying them when a formulation change takes place and encouraging self-monitoring. Cost savings from formulation changes may shift costs to other areas of healthcare, such as those in an acute setting. In addition, patients' health-related quality of life may be reduced due to toxicity or break-through seizures.

Conclusion

This retrospective cohort study found that patients who had an epileptic-related acute event (ambulance, ED visit, and/or hospitalization) were about 80% more likely to have had a recent AED formulation switch compared to matched control patients without an acute event. The results of this replication study lend credibility to the findings of the original study by Zachry et al.¹² and supplement the limited literature in the area of AED switching. Serious questions have been raised over this issue for years, and this study supports the continued need for analysis on this topic. More research is warranted to further investigate potential health problems associated with A-rated AED substitution.

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Table 1 – Demographic Comparisons

	Non-Matched			Matched		
	Case (n=991)	Control (n=10,369)	p-value	Case (n=991)	Control (n=2973)	p-value
% Male	49.0%	46.8%	NS	49.0%	48.6%	NS
Mean Age (SD)	35.6 (15.1)	39.2 (14.9)	p<0.001	35.6 (15.1)	35.6 (15.1)	NS
Insurance						
Commercial	90.4%	93.5%	p<0.001	90.4%	93.6%	p<0.001
Medicaid	6.5%	1.8%		6.5%	1.9%	
Self-insured	3.1%	4.6%		3.1%	4.5%	
US Region						
West	9.3%	5.9%	p<0.001	9.3%	6.1%	p<0.001
Midwest	44.1%	44.1%		44.1%	42.8%	
South	22.9%	27.3%		22.9%	28.2%	
East	23.7%	22.8%		23.7%	22.9%	

Table 2 – Diagnoses/Seizure Type

Seizure Type	Non-Matched		Matched
	Case (n=991)	Control (n=10,369)	Case (n=991) and Control (n=2973)*
Generalized, nonintractable	28.7%	27.8%	28.7%
Generalized, intractable	3.0%	5.7%	3.0%
Partial, nonintractable	11.0%	27.9%	11.0%
Partial, intractable	10.7%	11.9%	10.7%
Other, nonintractable	42.4%	22.1%	42.4%
Other, intractable	4.2%	4.5%	4.2%

* Since controls were matched on this variable, the percentages after matching were identical for case and controls

Table 3 – Odds Ratios of A-rated Medication Substitution for Matched Cohorts

	All instances of a substitution to an A-rated alternative	
	Substitution Identified	No Substitution Identified
Case	109	882
Matched Control	186	2787
Odds Ratio	1.84 (95% CI = 1.44 to 2.36)	
	Excluding patients with a change in dosage schedule	
Case	86	660
Matched Control	112	2454
Odds Ratio	2.86 (95% CI = 2.13 to 3.83)	
	Excluding patients with Medicaid coverage	
Case	98	829
Matched Control	177	2740
Odds Ratio	1.83 (95% CI = 1.41 to 2.37)	

Table 4. Patient-level A-rated substitutions by Month Prior to Index - Most Recent Change Prior to Index

Month prior to index	Cases (n=991) Frequency (%)	Control (n=2973) Frequency (%)
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%)