See COMMENTARY page 302

Refilling and Switching of Antiepileptic Drugs and Seizure-Related Events

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We sought to estimate the risk of seizure-related events associated with refilling prescriptions for antiepileptic drugs (AEDs) and to estimate the effect of switching between brand-name and generic drugs or between two generic versions of the same drug. We conducted a case–crossover study using health-care databases from British Columbia, Canada, among AED users who had an emergency room visit or hospitalization for seizure (index seizure-related event), defined using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) codes 345.xx (epilepsy and recurrent seizures) and 780.3x (convulsions), between 1997 and 2005. AED prescription refilling itself was associated with 2.3-fold elevated odds of seizure-related events when the refill occurred within 21 days before the index event (odds ratio (OR) 2.31; 95% confidence interval (CI) 1.56–3.44). The OR was 2.75 (95% CI 0.88–8.64) for refills that involved switching, yielding a refill-adjusted OR for switching of 1.19 (95% CI 0.35–3.99). Refilling the same AED prescription was associated with an elevated risk of seizure-related events whether or not the refill involved switching from a brand-name to a generic product.

Generic medications contain the same amount of the same active ingredient as their brand-name counterparts and must demonstrate bioequivalence to approved brand-name products according to pharmacokinetic parameters such as peak drug concentrations and area under the curve of drug concentration over time.[1–3] Some authors have hypothesized that small differences in between-product bioavailability, even those within the narrow bounds of allowable variation that determine bioequivalence, can lead to adverse clinical outcomes if a patient switches between brand-name and generic versions of narrow-therapeutic-index medications, such as antiepileptic drugs (AEDs).[4–6] Several surveys have documented widespread negative perceptions among patients, physicians, and pharmacists about antiepileptic generic drug substitution,[7–9] and the American Academy of Neurology opposes antiepileptic generic substitution without physician approval.[6] Others have argued that within-person variation in drug use patterns and nonadherence are at least as likely to explain variability in drug response as are pharmacokinetics.[10]

For more than two decades,[11] the hypothesis that switching between brand-name and generic AEDs (generic substitution) can lead to breakthrough seizures has been advanced on the basis of theoretical concerns, case reports, and data from small pharmacokinetics and bioequivalence studies.[12] Only recently have results emerged from observational studies that examined the clinical consequences of AED switching.[13–16] All but one of these studies suggested that switching between brand-name and generic AEDs, or between generic AEDs from different manufactures, increases the odds of seizure-related outcomes by ~80% as compared with not switching. However, clinical differences, if any, between brand-name and generic AEDs have not been consistently borne out by clinical trial data.[17]

Prescription switching can be viewed as a subset of prescription refilling, with additional variation potentially caused by between-manufacturer variability (in both bioavailability and peripheral drug features) that would not occur if the same drug from the same manufacturer had been refilled. However, no study has examined whether there is an elevated risk of seizure associated with prescription refilling of the same AED from the same manufacturer. We hypothesized that refilling a prescription for the same manufacturer's AED might itself be associated with risk of seizure-related events, possibly because of between-lot differences in bioavailability, delays in refilling, neurological symptoms that prompted the refill, or temporary nonadherence or minor changes in use patterns. We further hypothesized that these confounders may partly account for observed associations between AED switching and seizure outcomes. The purposes of this study were to define the risk of seizure-related events

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Received 23 December 2009; accepted 18 April 2010; advance online publication 14 July 2010. doi:10.1038/clpt.2010.90

associated with the refilling of a prescription for the same AED from the same manufacturer and to estimate the additional risk associated with switching between an AED manufactured by one company to the same AED manufactured by a different company.

RESULTS

From a database, we identified 1,762 patients who had had an index seizure-related event requiring emergency treatment between 1997 and 2005 and were eligible for this study (Table 1). The mean age of the patients was 35 (SD = 23.8) years, 53% were female, and most seizures were recorded as "other" (i.e., not generalized or partial) or "unspecified." On average, patients were dispensed 1.6 (SD = 0.9) different AEDs in the 43 days preceding the index event (Table 1), with day 1 preceding the event being the induction period, days 2–22 the case period, and days 23–43 the control period (Figure 1). Because only those with variation in exposure status between the case and control periods contribute to the analysis of case–crossover studies,[18] only a fraction of those eligible for the study were included in the primary analyses (Table 2).

Figure 2 presents the distributions of prescription refills and switches in the 56 days preceding the index event dates that were included in the analyses. A refill was associated with an increase in the risk of a seizure-related event: the odds of such an event were 2.3 times higher when a refill occurred in the 21-day case period rather than in the 21-day control period in the primary analysis (odds ratio (OR) 2.31; 95% confidence interval (CI) 1.56–3.44). Using 28-day case and control periods, we observed a 2.1-fold increase in this risk (OR 2.08; 95% CI 1.48–2.93). We then considered the instances of switching, involving the same AEDs but from different manufacturers (with dose and dosage form held constant). The ORs for 21- and 28-day case and control periods were 2.75 (0.88–8.64) and 2.17 (0.82–5.70), respectively (Table 2). After adjusting for the risk associated with prescription refilling *per se*, we found that the

Table 1 Characteristics of patients with seizure requiring emergency care or hospitalization, eligible for study inclusion (*n* = 1,762)

Characteristic	
Age at index date, mean (SD)	35.2 (23.8)
Female, *n* (%)	936 (53.1)
Primary seizure diagnosis type, n *(%)*	
Generalized	291 (16.5)
Partial	157 (8.9)
Other/unspecified	1,314 (74.6)
No. of different antiepileptic drugs dispensed during primary 43-day study period, mean (SD)	1.6 (0.9)
No. of patients to whom each antiepileptic drug was dispensed during primary 43-day study period, n *(% of all patients)*	
Carbamazepine	845 (48.0)
Phenytoin	698 (39.6)
Valproic acid	460 (26.1)
Clobazam	309 (17.5)
Clonazepam	180 (10.2)
Lamotrigine	129 (7.3)
Gabapentin	123 (7.0)
Topiramate	96 (5.4)

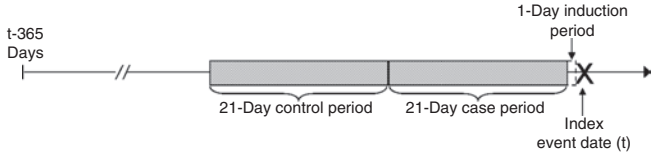

Figure 1 Case–crossover design to study the association between seizure-related outcomes and prescription refilling and switching of antiepileptic medications. Note: in primary analyses, the induction period was 1 day preceding the index event (i.e., day t–1), the case period was the 21 days prior to the induction period (i.e., days t–22 to t–2), and the control period was the 21 days prior to the case period (i.e., days t–43 to t–23).

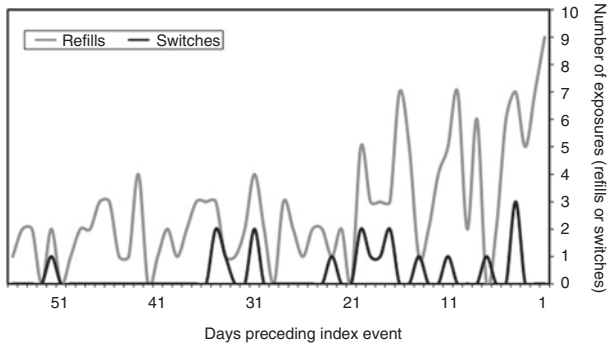

Figure 2 Distributions of exposures (refills and switches) in the 8 weeks preceding the index event dates.

Table 2 Odds ratios (95% CIs) for the association between antiepileptic prescription refilling and switching and incidence of seizure-related outcomes for primary analyses

No. of days in case/control periods	Refill of prescription for the same drug, strength, and dosage form from the same manufacturer[a]		Switch to a different manufacturer of the same drug, of the same strength and dosage form[b]		Refill-adjusted odds ratio for switching
	n[c]	Odds ratio (95% CI)	*n*[c]	Odds ratio (95% CI)	Odds ratio (95% CI)
21	116	2.31 (1.56–3.44)	15	2.75 (0.88–8.64)	1.19 (0.35–3.99)
28	151	2.08 (1.48–2.93)	19	2.17 (0.82–5.70)	1.04 (0.37–2.90)

In case–crossover studies, odds ratios are inherently adjusted for time-invariant patient factors.

CI, confidence interval.

[a]Includes refilling of prescriptions for brand-name products and for generic products. [b]Includes switching between brand-name and generic products, generic and brand-name products, and two generic products from different manufacturers. [c]Represents the number of index events that contributed to the estimation of the odds ratio.

Table 3 Odds ratios (95% CIs) for the association between antiepileptic prescription refilling and switching and incidence of seizure-related outcomes, stratified by type of refill or switch

Exposure type	*n*[a]	Odds ratio (95% CI)
21-Day case and control periods		
Refill		
Brand-name	79	2.29 (1.42–3.70)
Generic	37	2.36 (1.17–4.78)
Switch		
Generic–generic	10	2.33 (0.60–9.02)
Brand-name–generic or generic–brand-name	5	4.00 (0.45–35.79)
28-Day case and control periods		
Refill		
Brand-name	105	1.92 (1.28–2.87)
Generic	46	2.54 (1.34–4.82)
Switch		
Generic–generic	13	2.25 (0.69–7.31)
Brand-name–generic or generic–brand-name	6	2.00 (0.37–10.92)

CI, confidence interval.

[a]Number of index events that contributed to the estimation of the odds ratio.

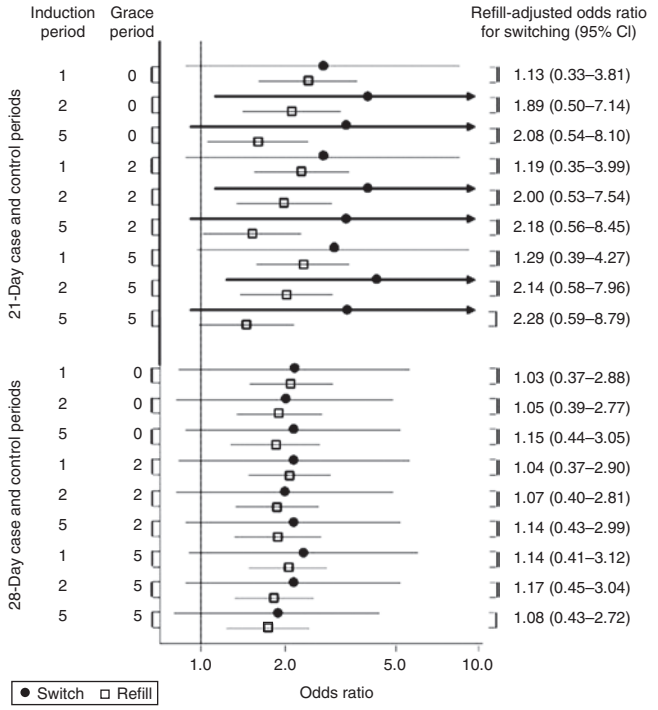

Figure 3 Results of sensitivity analyses (odds ratios and 95% confidence intervals (CIs)) for the association between prescription refilling or switching antiepileptic medications and incidence of seizure-related outcomes, along with difference-in-difference results, varying the case and control periods, the induction period, and the grace period.

refill-adjusted analyses yielded ORs of 1.19 (95% CI 0.35–3.99) and 1.04 (95% CI 0.37–2.90) for the primary 21- and 28-day analyses, respectively (Table 2).

The ORs were similar regardless of whether patients refilled their prescriptions with a brand-name medication or a generic medication (Table 3). In the 21-day analysis, switching between brand-name and generic versions was associated with a higher event risk than switching between generic products from different manufacturers, but this was based on only a few cases, and the 95% CIs for ORs were widely overlapping (Table 3).

Adjusted analyses and sensitivity analyses yielded results similar to primary analyses (Figure 3 and Table 4).

DISCUSSION

To our knowledge, this is the first study to document that AED prescription refilling itself may be associated with an elevated risk of seizure-related outcomes. We observed that, with dose and dosage form held constant, refilling the same AED prescription from the same manufacturer was associated with an approximately 2.1- to 2.3-fold increase in the odds of emergency treatment for seizure; point estimates for switching between AEDs from different manufacturers were similar, but with wide CIs. The refill-adjusted effect of switching between products from different manufacturers was small, with a 4–19% increase in odds of seizure-related outcomes.

Although the exact mechanisms underlying these phenomena have not been determined, we propose two important possible explanations. First, prescription refilling may follow a lapse in pharmacotherapy continuity, which itself may lead to breakthrough seizures. Or, it may be prompted by the recurrence of subtle neurological symptoms. In addition, the prescription refilling process (and switching process, to the extent that switching is a subset of refilling) involves many time-sensitive steps, often beginning with a visit or telephone call to a prescribing physician or to a dispensing pharmacy, to picking up the medication from the dispensing pharmacy, to beginning the new refill on the right day. A failure or delay at any point along this chain of events could result in a brief lapse in adherence to the regimen, leading to breakthrough seizures.[19,20] The label on a newly dispensed prescription may also differ from that on the previously dispensed ones, and confusion about dosing or administration may result.[21] Between-manufacturer variation in peripheral features of the drug product may further contribute to such behavioral explanations. For example, patients whose condition is stable on particular drug products of a given size, shape, and color may regard new prescriptions that vary in one or more of these features with caution, perhaps going so far as avoiding the medication for fear of having received the wrong drug from the pharmacy, thereby increasing the likelihood of lapses in pharmacotherapy continuity. Some have suggested that variation in drug use patterns is at least as important as pharmacokinetics in explaining variation in drug response.[10,22,23]

Second, our results are consistent with hypotheses suggesting that variability in bioavailability of the AED can lead to a small increased risk of breakthrough seizures, even when the drug is made by the same manufacturer. A review of more than 2,000 clinical bioequivalence studies of orally administered generic products approved by the US Food and Drug Administration found that the average differences between generic and innovator

Table 4 Odds ratios (95% CIs) for the association between antiepileptic prescription refilling and switching and incidence of seizure-related outcomes for sensitivity analyses

No. of days in case/control periods	Refill of a prescription for the same drug, of the same strength and dosage form from the same manufacturer[a]	Switch to a different manufacturer of the same drug, of the same strength and dosage form[b]	Refill-adjusted odds ratio for switching
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Adjusted for the use of other medications and visits to general practitioners and neurologists			
21	2.31 (1.56–3.44)	2.65 (0.68–10.34)	1.15 (0.28–4.73)
28	2.08 (1.48–2.93)	3.05 (0.84–11.04)	1.46 (0.39–5.55)
Excluding diagnosis code 780.3x			
21	2.18 (1.23–3.87)	3.00 (0.81–11.08)	1.38 (0.33–5.74)
28	1.71 (1.08–2.73)	2.20 (0.76–6.33)	1.28 (0.40–4.07)
Excluding clobazam and clonazepam			
21	2.23 (1.45–3.44)	3.33 (0.92–12.11)	1.49 (0.38–5.82)
28	2.07 (1.43–3.01)	3.00 (0.97–9.30)	1.45 (0.44–4.76)
Excluding clobazam, clonazepam, gabapentin, and topiramate			
21	2.00 (1.29–3.10)	3.00 (0.81–11.08)	1.50 (0.38–5.95)
28	1.95 (1.33–2.87)	2.75 (0.88–8.64)	1.41 (0.42–4.72)
Excluding those with one or more visits to a general practitioner or neurologist			
21	2.31 (1.56–3.44)	2.00 (0.18–22.05)	0.86 (0.08–9.85)
28	2.08 (1.48–2.93)	4.00 (0.45–35.79)	1.92 (0.21–17.65)

In case–crossover studies, odds ratios are inherently adjusted for time-invariant patient factors. Sensitivity analyses assume a 1-day induction period and a 2-day grace period, consistent with primary analyses.

CI, confidence interval.

[a]Includes prescription refilling of brand-name products and of generic products. [b]Includes switching between brand-name and generic products, generic and brand-name products, and two generic products from different manufacturers.

products with respect to peak drug concentration and area under the curve were 4.4 and 3.6%, respectively.[24] Given the inherent variability in manufacturing processes, similar fluctuations in bioavailability between lots produced by the same manufacturer are expected[25–27] and have been observed.[28]

Regardless of the mechanism, we observed that the process of refilling a prescription for any antiepileptic medication was itself associated with an elevated risk of subsequent seizure-related events and that a similar risk was seen for refills that involved switching from one manufacturer to another. The refill-adjusted analysis allowed us to ascertain the extent to which switching between AED manufacturers is associated with an increased risk of seizure-related outcomes after accounting for the risk associated with within-manufacturer variability and aspects of patient behavior associated with breakthrough seizure inherent in the prescription refilling/switching process itself.

The results of our refill-adjusted analyses are consistent with a recent meta-analysis of bioequivalence trials that reported the incidence of seizure outcomes[17] and with a recent case–control study.[16] Other case–control studies suggest that the increased risk of seizure-related outcomes associated with switching vs. not switching ranges between 78 and 84%.[13–15] However, these studies did not consider the effect of within-manufacturer variability in bioavailability or other factors inherent in the refilling and switching process, which probably inflated their findings. Furthermore, confounding on account of the severity of epilepsy may limit these studies, because epilepsy that is not well controlled would predispose to seizure and would also be associated with the use of multiple AEDs, thus increasing the probability that there would be at least one medication switch. Hansen *et al.* partly adjusted for this confounding bias by adjusting for the number of AEDs dispensed, which reduced the primary effect from 1.78 (95% CI 1.35–2.36) to 1.57 (95% CI 1.17–2.10) and suggested that the number of AEDs was a strong predictor of seizure-related events.[15] Indeed, the one case–control study in which the results were consistent with our findings adjusted for several potential confounders, including total number of AEDs and use of interacting medications, although conditioning on intermediates may be a concern in that study.[16] The case–crossover approach is valid regardless of the number of drugs used because the frequency of refills and switches would be expected to be uniformly distributed across case and control periods of short duration, in the absence of both true effect and bias.

To assess the validity of the duration of the pre-defined case and control periods, we plotted the distributions of exposures (both refills and switches) over the 8 weeks immediately preceding the index event for each patient. Both refills and switches were largely clustered within the 21 days preceding the index events, substantiating the use of the 21-day periods and suggesting that the risk of seizure-related events may be greatest in the 3 weeks after an AED prescription refill or switch. Furthermore, case periods of greater than 21 days would have led to misclassification of the exposure. This explains why the

effect estimates for analyses using 28-day periods are somewhat smaller than those using 21-day periods. Several important limitations of this study should be noted. First, we identified seizures using inpatient and emergency room ICD codes. The accuracy of ICD codes for identifying seizure is not known, and many patients do not seek emergency treatment for seizure; as a result, our study population represents a select sample of patients who experience a seizure of severity great enough to warrant emergency care or hospitalization. Although this highly specific outcome definition may limit the generalizability of the results, it preserves the internal validity of ratio effect measures.[29] We probably further improved the specificity of the outcome by requiring current AED use and an outpatient diagnosis of epilepsy in the year prior to the outcome.

A second limitation is that, should a bioavailability mechanism be implicated, focusing on seizure-related outcomes ignores the other end of the adverse event spectrum—namely, toxicities resulting from exceeding the upper limit of the therapeutic window for plasma drug levels. Nevertheless, such adverse events would be difficult to capture in administrative data and are less important than breakthrough seizures, given the clinical ramifications of seizures.[30] Another limitation of this analysis is the small number of cases on which it is based, particularly in subgroups of types of prescription refilling or switching. However, because seizure-related emergency treatment is fairly rare, and because only those with an exposure in either the case or the control period, but not both, contribute to the analyses of case–crossover studies, this represents a rare disease–rare exposure scenario. The fact that a sizable proportion of prescriptions dispensed in British Columbia are for 90 days rather than for 30 days further reduces the total number of possible exposures.

We expect that the implications of this study can be extended beyond Canada and that the association between AED switching and seizure-related events may be smaller in other countries, given that the bioequivalence requirements of the European Medicines Agency and the US Food and Drug Administration are more stringent than those of Health Canada.[1–3] Requirements established by the Food and Drug Administration, which are identical to those of its European counterpart, are intended to ensure that differences in bioavailability between bioequivalent products are no greater than between-lot variations from a single manufacturer.[31] This study is the first to describe an association between refilling a prescription for the same AED and seizure-related events; we also found that the magnitude of this association is similar to that for prescription switching. Nevertheless, some advocacy groups,[32] professional organizations,[6] and legislators[33] oppose AED substitution, and at least one US state prevents substitution by pharmacists.[34]Although our results do not completely rule out the possibility that switching between antiepileptic medications produced by different manufacturers may contribute to loss of seizure control in some patients, our findings indicate that, after adjustment for the risk associated with refilling a prescription for the same agent, the residual harmful effect of switching between two generic formulations of the same medication or between a brand-name and a generic version (or vice versa) of the same drug is either negligible or much smaller than that reported in previous studies, which had not properly adjusted for the effect of prescription refilling *per se*.

METHODS

Data source. We used data from British Columbia, Canada, covering the period 1996 to 2005. Patients were identified in the Ministry of Health inpatient administrative database, which contains data such as diagnostic codes, admission dates, and dates of service, related to all hospitalizations in British Columbia. The hospital data of patients were linked to data on physician services and to the PharmaNet database through a personal health number unique to each British Columbia resident. The PharmaNet database captures all records of prescriptions dispensed at community pharmacies in the province. No traceable individual identifiers were used in the analyses, so as to protect patient confidentiality. The institutional review board of Brigham and Women's Hospital approved this study, and signed data-use agreements were in place.

Design. We used a case–crossover design to assess the relationship between seizure-related outcomes and refilling of AED prescriptions with and without switching to the same product from a different manufacturer.[35] Case–crossover studies are the observation-based analogs of crossover clinical trials that are used to experimentally test bioequivalence of two drug preparations. They can be conceptualized as case–control studies that, rather than selecting separate individuals as controls, use an antecedent period in each case's history (i.e., the control period) to ascertain the exposure distribution in the person-time prior to the case-defining event (**Figure 1**).

By using each subject as his or her own control, the case–crossover design inherently adjusts for potential confounding (both measured and unmeasured) by time-invariant factors.[35,36] Case–crossover studies are well suited to study relationships between transient exposures, such as medication switching and prescription refilling, and acute outcomes, such as seizure-related events, using short study periods within which confounding by time-varying factors is limited or unlikely.[35]

Case ascertainment. Cases were identified using the inpatient data file, as patients with an emergency room visit or hospitalization related to epileptic seizure between 1997 and 2005. We used *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) codes 345.xx (epilepsy and recurrent seizures) or 780.3x (convulsions) to define seizure-related events but excluded code 345.6x, which indicates infantile spasms. The index date (**Figure 1**) was defined as the date of first occurrence in the inpatient file of one of the codes of interest in the primary-diagnosis position. We further required individuals to have at least one diagnosis of epilepsy or seizure recorded in their outpatient file in the year preceding the index date. Thus, we excluded events that occurred in 1996 in order to ensure that exposure and covariate data were available for the 365 days prior to the index date for each case. If a patient had more than one seizure-related event during the study period, only the first event was included in the analysis.

Exposure and covariate assessment. We defined etiologically relevant exposure risk windows and induction periods that preceded the index event.[37] For both refilling and switching, we chose a 1-day induction period and a 21-day exposure window (i.e., case period) for primary analyses (**Figure 1**), consistent with observations and hypotheses surrounding the pharmacokinetics of the association of interest.[38,39] The control period was then defined as the 21 days immediately preceding the case period in primary analyses (**Figure 1**). As with matched case–control studies, only discordant pairs contribute information to the analysis of case–crossover studies,[18] so that only those with variation in exposure status between the case and control periods contributed information to the analysis of data in this study.

We operationalized the exposure definitions by identifying cases with at least two occasions of AED dispensing in the 365 days prior to the index date because a minimum of two dispensings are required to define

at least one refill or switch (**Figure 1**). Brand-name and generic drugs are distinguishable from each other in the PharmaNet database using the drug identification numbers (DINs), which are specific to each drug product marketed by each manufacturer; however, DINs cannot distinguish between individual lots. We included the following AEDs for which both brand-name and generic versions were already available in British Columbia or became available during the study period: carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, phenytoin, topiramate, and valproic acid.

A refill of the same product was defined as a filled prescription for a given AED that was preceded by a filled prescription for the same DIN, indicating dispensing of the same dose of the same drug product manufactured by the same company. A switch was defined as a filled prescription for a drug with a given DIN that was preceded by a filled prescription for the same medication but with a different DIN, indicating a different manufacturer. No "switches" between different chemical entities were considered. We also excluded switches between DINs with different strengths or dosage forms (e.g., immediate- vs. extended-release carbamazepine formulations) and excluded data for patients who had a subsequent dispensing of the first DIN, which would also indicate a dose change by the addition of the second prescription. The date of the refill or switch was defined as the date of the second prescription in the respective sequence, which, for the purposes of the study, was required to have occurred within the coverage days of the first prescription (as defined by the prescription fill date plus the days of supply for that dispensing, plus a 2-day grace period).

In addition to AED refills and switches, other drug-related covariates were collected for all study subjects. We ascertained whether patients initiated other medications during either the case or control period so that we could adjust for the possibility of drug–drug interactions. We also measured the number of physician visits to general practitioners and neurologists during both periods.

Statistical analysis. Data were analyzed using standard methods for matched case–crossover data.[40,41] ORs and 95% CIs for seizure-related events were estimated using separate conditional logistic regression models for both exposure types: refilling and switching. OR estimates were based on the ratio of the observed frequency of prescription refills or switches in the case period compared with the respective frequency in the control period. We adjusted the conditional logistic regression models for the time-related factors, number of visits to general practice physicians or neurologists in either the case or control period, and the addition of other medications during either period, under the assumption that these factors were not affected by previous exposures.[42]

We conducted analyses stratified by the type of prescription refill or switch. Specifically, we examined whether outcomes varied depending on whether patients refilled a prescription for a brand-name product or a generic one and examined switches from brand-name to generic products, and vice versa, as well as switches between generic products from different manufacturers.

We used the case–crossover analog of the difference-in-differences study design to define the risk of seizure-related outcomes after drug switching, relative to that seen after refilling of a prescription for the same medication from the same manufacturer. Difference-in-differences, or ratio-of-ratios, analyses have long been in use in the literature dealing with economics[43] and are commonly used in controlled time-series analyses to evaluate drug policy changes.[44] We conducted a conditional logistic regression analysis among all the cases, including those in both the refilling and the switching analyses. Independent variables included a binary indicator for exposure status ("exposure"), defined as exposure = 1 for a refill or a switch and exposure = 0 otherwise, and a product term for "exposure × group", where "group" is a binary indicator for switching agents (group = 1) or refilling a prescription for the same agent (group = 0). The antilogarithm of the coefficient for the product term obtained from the model can be interpreted as the increase in the odds of a seizure-related outcome associated with switching between AEDs, beyond that associated with refilling a prescription for an AED. This approach enabled adjustment for inherent within-manufacturer and between-lot variability and factors involved in the prescription refilling or switching process (the "refill-adjusted OR for switching"). Our implementation of this approach is similar to the case–time-control design to adjust for confounding due to exposure time trends.[45,46] However, it avoids certain assumptions by using other cases that had the event of interest—rather than controls that did not experience the event—to ascertain the magnitude of adjustment required for the primary-effect measure.[47] **Supplementary Figure S1** online demonstrates the method of calculation of the crude OR from the case–crossover analyses and the refill-adjusted OR from the difference-in-difference analysis.

Sensitivity analyses. We conducted sensitivity analyses to assess the robustness of the results by varying the durations of the case and control periods, the induction period, and the grace period used in primary analyses. We extended case and control periods to 28 days and extended induction periods to 2 days and 5 days. In primary analyses, we allowed a 2-day grace period at the end of the number of days of supply of the first dispensing occurrence in the sequence, so as to define coverage days. In sensitivity analyses, we considered grace periods of 0 and 5 days added to the number of days of supply; we did not consider longer grace periods because these likely indicate gaps in pharmacotherapy, which may themselves be risk factors for seizure.[19]

We also conducted two separate sensitivity analyses by excluding from the primary analyses data related to prescription refilling and switching of drugs that are frequently used for other indications. The first sensitivity analysis excluded users of the anxiolytics clobazam and clonazepam, and the second excluded users of clobazam, clonazepam, gabapentin, and topiramate. Additionally, we excluded cases of patients with primary diagnoses of 780.3x (convulsions), which have been excluded in some[13–15] but not all[19,48] studies that have used claims databases to identify seizure-related outcomes. Finally, we excluded those with one or more visits to a general practitioner or neurologist during either the case or control period, under the assumption that these factors were not affected by previous exposures.[41]

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

ACKNOWLEDGMENTS

J.J.G. is supported by a National Institute on Aging training grant (T32 AG000158). We thank Claire Canning for help in data management and programming.

CONFLICT OF INTEREST

J.J.G. participated in a research fellowship administered by Jefferson Medical College and sponsored by Ortho-McNeil Janssen Scientific Affairs, L.L.C., which ended in 2007. S.S. received an investigator-initiated grant from Pfizer to study the safety of COX-2 inhibitors. The other authors declared no conflict of interest.

1. Health Canada. Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies: Part A: Oral Dosage Formulations Used for Systemic Effects <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/bio-a-eng.php> (1997). Accessed 10 October 2009.
2. US Food and Drug Administration. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf> (2003). Accessed 20 May 2008.
3. European Medicines Agency. Guideline on the Investigation of Bioequivalence <http://www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf> (2008). Accessed 10 October 2009.
4. Andermann, F., Duh, M.S., Gosselin, A. & Paradis, P.E. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. *Epilepsia* **48**, 464–469 (2007).

5. Berg, M.J. What's the problem with generic antiepileptic drugs?: a call to action. *Neurology* **68**, 1245–1246 (2007).
6. Liow, K., Barkley, G.L., Pollard, J.R., Harden, C.L. & Bazil, C.W.; American Academy of Neurology. Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. *Neurology* **68**, 1249–1250 (2007).
7. Berg, M.J., Gross, R.A., Haskins, L.S., Zingaro, W.M. & Tomaszewski, K.J. Generic substitution in the treatment of epilepsy: patient and physician perceptions. *Epilepsy Behav.* **13**, 693–699 (2008).
8. Papsdorf, T.B., Ablah, E., Ram, S., Sadler, T. & Liow, K. Patient perception of generic antiepileptic drugs in the Midwestern United States. *Epilepsy Behav.* **14**, 150–153 (2009).
9. McAuley, J.W., Chen, A.Y., Elliott, J.O. & Shneker, B.F. An assessment of patient and pharmacist knowledge of and attitudes toward reporting adverse drug events due to formulation switching in patients with epilepsy. *Epilepsy Behav.* **14**, 113–117 (2009).
10. Urquhart, J. The odds of the three nons when an aptly prescribed medicine isn't working: non-compliance, non-absorption, non-response. *Br. J. Clin. Pharmacol.* **54**, 212–220 (2002).
11. MacDonald, J.T. Breakthrough seizure following substitution of Depakene capsules (Abbott) with a generic product. *Neurology* **37**, 1885 (1987).
12. Besag, F.M. Is generic prescribing acceptable in epilepsy? *Drug Saf.* **23**, 173–182 (2000).
13. Zachry, W.M. 3rd, Doan, Q.D., Clewell, J.D. & Smith, B.J. Case-control analysis of ambulance, emergency room, or inpatient hospital events for epilepsy and antiepileptic drug formulation changes. *Epilepsia* **50**, 493–500 (2009).
14. Rascati, K.L., Richards, K.M., Johnsrud, M.T. & Mann, T.A. Effects of antiepileptic drug substitutions on epileptic events requiring acute care. *Pharmacotherapy* **29**, 769–774 (2009).
15. Hansen, R.N., Campbell, J.D. & Sullivan, S.D. Association between antiepileptic drug switching and epilepsy-related events. *Epilepsy Behav.* **15**, 481–485 (2009).
16. Devine, S.T., Weisbart, E., Barron, J. & Behm, A. Acute epilepsy exacerbations in patients switched between A-rated anti-epileptic drugs. *Curr. Med. Res. Opin.* **26**, 455–463 (2010).
17. Kesselheim, A.S. *et al*. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis. *Drugs* **70**, 605–621 (2010).
18. Schneeweiss, S., Stürmer, T. & Maclure, M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. *Pharmacoepidemiol. Drug Saf.* **6** (suppl. 3), S51–S59 (1997).
19. Manjunath, R., Davis, K.L., Candrilli, S.D. & Ettinger, A.B. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. *Epilepsy Behav.* **14**, 372–378 (2009).
20. Cramer, J.A., Glassman, M. & Rienzi, V. The relationship between poor medication compliance and seizures. *Epilepsy Behav.* **3**, 338–342 (2002).
21. Shrank, W.H. *et al*. The variability and quality of medication container labels. *Arch. Intern. Med.* **167**, 1760–1765 (2007).
22. Harter, J.G. & Peck, C.C. Chronobiology. Suggestions for integrating it into drug development. *Ann. NY Acad. Sci.* **618**, 563–571 (1991).
23. Burnier, M., Schneider, M.P., Chioléro, A., Stubi, C.L. & Brunner, H.R. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. *J. Hypertens.* **19**, 335–341 (2001).
24. Davit, B.M. *et al*. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. *Ann. Pharmacother.* **43**, 1583–1597 (2009).
25. Perucca, E., Albani, F., Capovilla, G., Bernardina, B.D., Michelucci, R. & Zaccara, G. Recommendations of the Italian League against Epilepsy working group on generic products of antiepileptic drugs. *Epilepsia* **47** (suppl. 5), 16–20 (2006).
26. Bialer, M. Generic products of antiepileptic drugs (AEDs): is it an issue? *Epilepsia* **48**, 1825–1832 (2007).
27. Boylan, L.S. Clinical consequences of generic substitution of lamotrigine for patients with epilepsy. *Neurology* **72**, 1876; author reply 1876–1876; author reply 1877 (2009).
28. Meyer, M.C. *et al*. Variability in the bioavailability of phenytoin capsules in males and females. *Pharm. Res.* **18**, 394–397 (2001).
29. Measurement error. In *Methods in Observational Epidemiology* 2nd edn. (eds. Kelsey, J.L., Whittemore, A.S., Evans, A.S. & Thompson, W.D.) 341–363 (Oxford University Press, New York, 1996).
30. Liow, K. Understanding patients' perspective in the use of generic antiepileptic drugs: compelling lessons for physicians to improve physician/patient communication. *BMC Neurol.* **9**, 11 (2009).
31. Williams, R.L. Therapeutic equivalence of generic drugs: response to the National Association of Boards of Pharmacy (letter) <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm073224.htm> (16 April 1997).
32. Epilepsy Foundation. Statement on generic substitution of AEDshttp://www.epilepsyfoundation.org/advocacy/care/genedrev.cfm>. Accessed 12 October 2009.
33. National Black Caucus of State Legislators. Resolution HHS-07-19. Epilepsy patient prescription drug safety <http://www.nbcsl.org>. Accessed 12 October 2009.
34. Hawaii revised statutes <http://www.capitol.hawaii.gov/hrscurrent/Vol06_Ch0321-0344/HRS0328/HRS_0328-0092.HTM>. Accessed 12 October 2009.
35. Maclure, M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am. J. Epidemiol.* **133**, 144–153 (1991).
36. Schneeweiss, S. Developments in post-marketing comparative effectiveness research. *Clin. Pharmacol. Ther.* **82**, 143–156 (2007).
37. Schneeweiss, S. & Avorn, J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J. Clin. Epidemiol.* **58**, 323–337 (2005).
38. Di Bonaventura, C., Fattouch, J., Fabbrini, G., Manfredi, M., Prencipe, M. & Giallonardo, T.A. Switching from branded to generic antiepileptic drugs as a confounding factor and unpredictable diagnostic pitfall in epilepsy management. *Epileptic Disord.* **9**, 465–466 (2007).
39. Crawford, P., Feely, M., Guberman, A. & Kramer, G. Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. *Seizure* **15**, 165–176 (2006).
40. Mittleman, M.A., Maclure, M. & Robins, J.M. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am. J. Epidemiol.* **142**, 91–98 (1995).
41. Schelleman, H., Bilker, W.B., Brensinger, C.M., Han, X., Kimmel, S.E. & Hennessy, S. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin. Pharmacol. Ther.* **84**, 581–588 (2008).
42. Robins, J.M., Hernán, M.A. & Brumback, B. Marginal structural models and causal inference in epidemiology. *Epidemiology* **11**, 550–560 (2000).
43. Abadie, A. Semiparametric difference-in-differences estimators. *Rev. Econ. Stud.* **72**, 1–19 (2005).
44. Schneeweiss, S., Maclure, M., Soumerai, S.B., Walker, A.M. & Glynn, R.J. Quasi-experimental longitudinal designs to evaluate drug benefit policy changes with low policy compliance. *J. Clin. Epidemiol.* **55**, 833–841 (2002).
45. Suissa, S. The case-time-control design. *Epidemiology* **6**, 248–253 (1995).
46. Suissa, S. The case-time-control design: further assumptions and conditions. *Epidemiology* **9**, 441–445 (1998).
47. Greenland, S. Confounding and exposure trends in case-crossover and case-time-control designs. *Epidemiology* **7**, 231–239 (1996).
48. Davis, K.L., Candrilli, S.D. & Edin, H.M. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. *Epilepsia* **49**, 446–454 (2008).