Clinical consequences of generic substitution of lamotrigine for patients with epilepsy

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ABSTRACT

Objectives: To measure the proportions of patients switching from generic to branded drugs among users of antiepileptic drugs (AED) compared to other therapeutic areas and to investigate medical services utilization associated with generic switching of lamotrigine.

Methods: Medical and pharmacy claims data from Régie de l'Assurance Maladie du Québec database from April 1998 to July 2006 were used. Patients with an epilepsy diagnosis (International Classification of Diseases-9 345) and treated with lamotrigine for >60 of the 90 days before the entry date of generic lamotrigine in Quebec (February 1, 2003) were selected. The proportion of patients switching back to brand were calculated for lamotrigine, for other AEDs (clobazam, carbamazepine CR, gabapentin) and for non-AED chronic medications (carvedilol, fosinopril, simvastatin). Medical resource utilization was compared between periods of branded vs generic use of lamotrigine.

Results: Of 671 patients treated with branded lamotrigine, 187 patients (27.9%) switched to a generic, and 51 of these patients (27.5%) switched back to the branded medication. Rates of switchback were from 20.8% to 44.1% for various AEDs and from 7.7% to 9.1% for non-AEDs. Relative to the branded lamotrigine use period, generic lamotrigine use period was associated with a 5.1% increase in mean daily dose of lamotrigine (239.1 vs 251.4 mg; $p = 0.0149$), a higher number of dispensations for other AEDs (20.4 vs 23.9 dispensations per person-year; $p < 0.001$) as well as non-AED drugs (26.4 vs 32.8 dispensations per person-year; $p < 0.0001$), a higher utilization rate of medical services (8.7 vs 9.8 visits per person-year; $p < 0.0001$), and a longer hospital length of stay (3.29 days vs 4.86 days per person-year; $p < 0.0001$).

Conclusion: A higher propensity to switch back to branded medications was observed among antiepileptic drug users compared to users of antihypertensives and antihyperlipidemics, similar to findings from Andermann et al. Switch to generic lamotrigine was significantly associated with increased physician visits and hospitalizations. *Neurology*® 2008;70:2179–2186

GLOSSARY

AED = antiepileptic drugs; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **RAMQ** = Régie de l'Assurance Maladie du Québec; **RD** = rate difference; **RR** = rate ratio.

There has been considerable debate over the appropriateness of generic substitution for drugs with a narrow therapeutic index, identified as drugs that could have subtherapeutic or toxic results by small changes in the dosage level. Food and Drug Administration surveys of both clinicians and patients have reported adverse clinical consequences following generic substitution of antiepileptic drugs (AEDs).[1,2] A recent study found that following generic substitution of AEDs, patients were more likely to switch back to their branded medications than those receiving other chronically used medications.[3] Other researchers have found that the consequences of generic AED utilization, including monitoring costs and loss of seizure control, may outweigh their lower drug price.[2,4,5]

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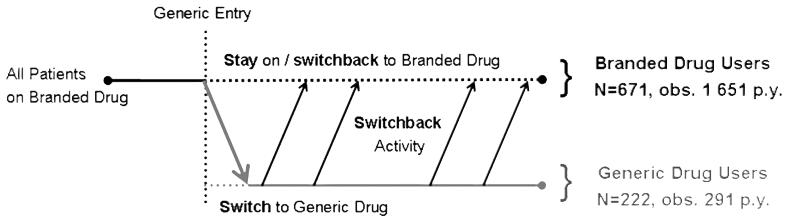
Disclosure: This study was sponsored by GlaxoSmithKline (GSK), Research Triangle Park, NC. GSK participated in the design, review, and approval of the manuscript. J. LeLorier has a consulting agreement with Analysis Group, Inc. and has received grants from GSK for other research projects in excess of $10,000. M.S. Duh, P.E. Paradis, P. Lefebvre, and J. Weiner are employees of Analysis Group, Inc., which has received research grants from GSK. R. Manjunath is an employee of GSK. O. Sheehy reports no conflict of interest.

Figure 1 Study design: Lamictal/lamotrigine users



Given such findings, the American Academy of Neurology has issued guidelines opposing generic substitution of AEDs without the attending physician's approval.[6,7] At the same time, other organizations such as the US Food and Drug Administration and the American Society of Health-System Pharmacists maintain that generic and branded products are therapeutically interchangeable.[8] These conflicting viewpoints regarding generic substitution underscore the importance of evidence-based research.[9,10]

The purposes of this study are to measure the proportions of patients switching from generic to branded drugs among users of AEDs compared to other therapeutic areas; and to investigate medical services utilization associated with generic switching of AEDs, using data on lamotrigine (Lamictal, GlaxoSmithKline, Brentford, Middlesex, UK), the first newer-generation AED to become generic in Canada.

METHODS

Data source. Medical and pharmacy claims data from Québec's provincial health plan, Régie de l'Assurance Maladie du Québec (RAMQ), from April 1998 to July 2006 were used for the analysis. Data elements were drawn from four RAMQ databases: 1) information personne assurée (patient demographic characteristics); 2) périodes d'admissibilité (patient eligibility dates and type of coveage); 3) services pharmaceutiques (outpatient prescription drug dispensings): dose, dosage form, quantity of drug dispensed, duration, dispensation date, and specialty of the prescribing physician; and 4) services médicaux (medical services billed): date and place of service (hospital, emergency department, or medical clinic), International Classification of Diseases (ICD)-9 diagnosis code, and physician specialty. The four RAMQ databases are linked via a unique and encrypted patient identifier, and allow longitudinal follow-up of patients.

Study populations. For each of the AED and non-AED drugs, a random sample of the study population was selected based on the following inclusion and exclusion criteria: eligible at least 180 days prior to generic entry, used the branded drug for at least 60 days in the 90 days preceding the generic entry date, had at least one drug dispensation following the generic entry date, had continuous health plan coverage, and for those in the AED study populations, were required to have at least one claim for epilepsy (ICD-9 code: 345) during the study period. The study population was further stratified into monotherapy vs polytherapy patients. Polytherapy patients were defined as those using at least one other drug from the same therapeutic class at the same time as the drug under study during the 180 days prior to generic entry. For each patient, the study period ranged from 180 days before the generic entry date until the end of the patient's eligibility, the date at which the patient discontinued treatment, or the end of data availability (August 1, 2006), whichever occurred first.

Study design. To address the first objective, a retrospective cohort design was used to calculate the switch (i.e., from a branded drug to its generic version) and switchback (i.e., from generic reverted back to its branded drug) rates for four AEDs: gabapentin (Neurontin), lamotrigine (Lamictal), carbamazepine CR (Tegretol CR), and clobazam (Frisium). AEDs switch and switchback rates were compared to those for three other commonly used chronic medications: two cardiovascular drugs, carvedilol (Coreg) and fosinopril (Monopril), and an antihyperlipidemic, simvastatin (Zocor). Drugs were selected based on whether generic entry occurred in the time frame for which RAMQ data were available and, for the non-AEDs, whether they are used to treat chronic conditions. For each of these seven drugs, switch and switchback rates were estimated among patients initially taking the branded drug when no generic version was available in Québec.

For the second objective, we examined the clinical consequences associated with generic substitution of the AED lamotrigine using a retrospective open-cohort design to classify patients' observation into periods of branded vs generic use. Figure 1 illustrates the study design for this clinical analysis.

Statistical analysis. Descriptive univariate statistics were generated for both objectives. Frequency counts and percentages were used to summarize categorical variables while means and standard deviations were used for continuous variables.

Switch and switchback rates. Switch rates were estimated using the Kaplan-Meier method, which is a conditional probability approach based on the subjects who were on the branded drug at the beginning of the interval. The switch rate was calculated as the cumulative probability of a patient switching to the generic drug given that he was on the branded drug at each time interval. Switchback rates were also computed using the Kaplan-Meier method, thus yielding the cumulative probability that a patient will eventually switch back to brand after using the generic at each time interval. In both cases, patients who were lost to follow-up were censored. To harmonize the duration of the switch and switchback analyses, both rates were calculated for the first 2 years following generic entry. In addition, the hazard ratios (HR) associated with the impact of AED's therapeutic class (vs non-AED) in switch and switchback occurrences were computed using Cox proportional hazards regressions after controlling for demographics and treatment characteristics.[11]

Health care utilization. Mean daily doses of lamotrigine, as well as incidence rates of dispensations, inpatient hospitalizations, and outpatient visits, were calculated and compared between periods of branded vs generic use of lamotrigine. Incidence rates were calculated as the number

Table 1 Patient characteristics

	Lamotrigine	Clobazam	Gabapentin	Carbamazepine CR	Simvastatin	Fosinopril	Carvedilol
Generic entry date in Québec (MM/DD/YYYY)	2/1/2003	1/1/1999	7/1/2001	10/1/1998	6/1/2003	6/30/2004	4/28/2004
Study population	671	1,060	202	851	6,760	7,299	1,703
Mean age (SD)	39 (18.7)	38 (18.5)	49 (18.5)	40 (17.3)	71 (10.1)	73 (11.3)	72 (11.3)
Women, n (%)	377 (56.2)	557 (52.6)	122 (60.4)	420 (49.4)	3,495 (51.7)	3,958 (54.2)	497 (29.2)
Mean observation period, days (SD)*	1,098 (327.9)	1,090 (329.4)	1,019 (351.5)	1,117 (307.6)	1,067 (336.5)	827 (202.2)	842 (243.8)
Study population stratifications, n (%)							
Monotherapy	116 (17.3)	65 (6.1)	34 (16.3)	410 (48.2)	6,562 (97.1)	7,081 (97.0)	1,666 (97.8)
Polytherapy	555 (82.7)	995 (93.9)	168 (83.2)	441 (51.8)	198 (2.9)	218 (3.0)	37 (2.2)

*Defined as 180 days baseline prior to generic entry until end of eligibility, discontinued treatment (>90 days), or August 1, 2006, whichever ends first.

of events divided by the number of person-years of observation. To account for varying days of supply associated with different dispensations, the dispensation length was set to 28 days. For each outcome, the incidence rates for the brand and generic periods were compared using rate differences (RD) and rate ratios (RR). Statistical differences between the two groups were tested using a Wald χ^2 statistic with Poisson density function. In this analysis, we adjusted for potential differences in population characteristics, including gender, age, other comorbidities (angina, high blood pressure, diabetes, asthma, and depression), and polytherapy.

Statistical significance was defined as a two-sided α-level of 0.05 or less. All statistical analyses were performed using SAS release 9.1 or newer (SAS Institute, Inc., Cary, NC) and Microsoft Office Excel 2003 (Microsoft Corporation, Redmond, WA).

RESULTS

Study population. Table 1 shows the demographic characteristics for the study populations for the seven studied AED and non-AED drugs. A total of 671 patients were available for analysis in the lamotrigine study population. Patients treated with AEDs were younger (mean age of 38 to 49 years) than those treated with other chronically used drugs (mean age of 71 to 73 years). The gabapentin study population had the largest percentage of women (60.4%), while the carvedilol study population had the smallest (29.2%). The mean number of days in the observation period ranged from 827 for fosinopril to 1,117 for carbamazepine CR, with 1,098 days for the lamotrigine patients. Three of the four AED groups comprised 82.7% or more polytherapy patients, while the fourth one, carbamazepine CR, numbered 51.8% of them. In contrast, polytherapy users represented 2.2% to 3.0% of patients for non-AED study populations. Table 2 shows more detailed baseline characteristics of the Lamictal/lamotrigine patients under study. About two thirds of all patients remained on the branded Lamictal medication throughout the study period, and more than a quarter of patients who were treated with generic lamotrigine switched back to the branded drug. The most prevalent comorbidity was high blood pressure, followed by depression, asthma, diabetes, and angina.

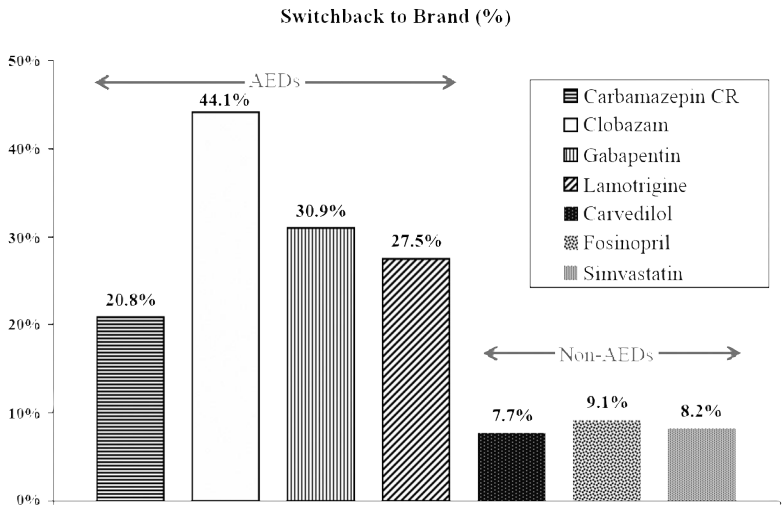
Switch and switchback rates. Among the AEDs, lamotrigine (27.9%) and clobazam (18.9%) exhibited much lower switch rates than gabapentin (45.0%) and carbamazepine CR (72.3%). Among

Table 2 Baseline characteristics: Lamictal/lamotrigine patients

	Study population
No. of patients	671
Mean duration of observation, d (SD)	1,098 (327.9)
Mean age, y (SD)	39 (18.7)
Women, n (%)	377 (56.2)
Polytherapy (%)	555 (82.7)
Average lamotrigine dose (mg/day)	239.1
Co-prescribed AEDs (% other AED prescriptions)	
Carbamazepine	19.2%
Clobazam	16.9%
Valproic acid	15.2%
Comorbidities, n (%)	
Angina	25 (3.7)
High blood pressure	91 (13.6)
Diabetes	51 (7.6)
Asthma	56 (8.3)
Depression	80 (11.9)
Patients who switched to generic, n (%)	222 (33.1)
Person-years of observation	
Branded use of lamotrigine	1,650.9
Generic use of lamotrigine	291.2

AED = antiepileptic drug.

Figure 2 Switchback rates estimated with a Kaplan-Meier conditional probability approach and calculated for the first 2 years following generic entry



non-AEDs switch rates ranged from 40.8% to 90.2%. Figure 2 shows switchback rates for each of the seven drugs of interest after 2 years of generic entry. AEDs exhibited substantially higher switchback (20.8–44.1%) rates from generic to branded medication than non-AEDs (7.7–9.1%).

Table 3 presents the multivariate analysis of switch and switchback patterns for AEDs and non-AEDs using Cox regressions. After controlling for demographics and treatment characteristics, patients treated with AEDs (all combined) were less likely to switch from brand to generic (HR = 0.737; CI = [0.666, 0.815]; $p < 0.0001$) than those treated with non-AED drugs. Among patients switching to generic, those receiving AEDs were nearly two and a half times more likely to revert back to the branded medication (HR = 2.461; CI = [1.930, 3.136]; $p < 0.0001$) than non-AEDs users. Patients receiving polytherapy were less likely to switch to generic (HR = 0.755; CI = [0.688, 0.830]; $p < 0.0001$), but no more or less likely to switch back to brand (HR = 1.227; CI = [0.995, 1.515]; $p = 0.056$). Younger patients and those who experienced a dose increase in the generic period were more likely to require a switchback to brand the branded medication (HR = 0.993, CI = [0.988, 0.997], $p = 0.002$).

Table 3 Cox regressions on predictors for generic switch and switch back

Variable	Hazard ratio	95% Confidence limit	*p* Value
Switching from brand to generic			
Demographics			
Age (continuous variable)	0.999	0.998, 1.001	0.2849
Women (ref: men)	0.948	0.913, 0.985	0.0057
Treatment characteristics			
Polytherapy (ref: monotherapy)	0.755	0.688, 0.830	<0.0001
Drug type			
AED (ref: non-AED)	0.737	0.666, 0.815	<0.0001
Switching back to brand from generic			
Demographics			
Age (continuous variable)	0.993	0.988, 0.997	0.002
Women (ref: men)	1.097	0.973, 1.237	0.130
Treatment characteristics			
Dose increase (ref: dose decrease)	1.229	1.074, 1.406	0.003
Polytherapy (ref: monotherapy)	1.227	0.995, 1.515	0.056
Drug type			
AED (ref: non-AED)	2.461	1.930, 3.136	<0.0001

AED = antiepileptic drug.

Health care utilization. Among patients who used both branded and generic lamotrigine during the study period, the dose difference was significant during brand use (239.1 mg/day during brand use vs 251.4 mg/day during generic use; +5.1%; $p < 0.0001$).

Table 4 presents annualized per-patient frequency for pharmacy and medical service utilization. On average, patients were dispensed 20.4 dispensations per person-year for other AEDs during the branded lamotrigine use period vs 23.9 while receiving generic lamotrigine (RR = 1.17; CI = [1.14, 1.20]; $p < 0.001$). The three most commonly co-prescribed AEDs were the same in both periods, namely carbamazepine, clobazam, and valproic acid. The number of non-AED dispensations was also significantly higher during the periods of generic use, compared to branded use (32.8 vs 26.4 per person per year; RR = 1.30; CI = [1.27, 1.33]; $p < 0.0001$). The five most prescribed non-AEDs during the brand period were, in descending order, levothyroxine, acetylsalicylic acid, folic acid, risperidone, and lorazepam, and in the generic period, levothyroxine followed by risperidone, lorazepam, acetaminophen, and sodium docusate.

Total medical service visits (inpatient plus outpatient visits) were higher during generic use period compared to brand use (9.81 vs 8.73 visits per patient per year; RR = 1.13; CI = [1.09, 1.18]; $p < 0.0001$). Rates of inpatient hospitalizations were not statistically different between the generic and brand periods (0.56 vs 0.49 visits per person per year, RR = 1.14; CI = [0.96, 1.35]; $p = 0.1264$); however, the average length of hospital stay was longer during the generic period (4.86 vs 3.29 days per patient per year; RR = 1.48; $p < 0.0001$). The top three

Table 4 Pharmacy and medical service utilization: Lamictal/lamotrigine patients*

	Brand use	Generic use	Rate difference	Rate ratio	CI		p Value†
					Lower	Upper	
Pharmacy utilization							
No. of other AED dispensations (per patient per year)	20.40	23.86	3.47	1.17	1.14	1.20	<0.0001
No. of non-AED dispensations (per patient per year)	26.37	32.76	6.38	1.30	1.27	1.33	<0.0001
Frequency of medical services							
Mean no. of inpatient visits (per patient per year)‡	0.49	0.56	0.07	1.14	0.96	1.35	0.1264
Mean no. of outpatient visits (per patient per year)‡	8.24	9.25	1.01	1.13	1.09	1.18	<0.0001
Total (inpatient + outpatient)	8.73	9.81	1.08	1.13	1.09	1.18	<0.0001
Mean length of hospital stay (days) (per patient per year)§	3.29	4.86	1.56	1.44	NA	NA	<0.0001

Dosing patterns are measured in mg per day. The statistical significance of the difference between brand and generic periods is verified using a paired *t* test (switching patients only). The average branded dose for patients who eventually used generic lamotrigine was 239.1 mg/day.

*The brand period refers to brand use only by all patients, while the generic period refers to generic use only. A total of 671 patients were observed during 1,650.9 and 291.2 person-years of branded and generic use of lamotrigine.

†The *p* value tested the null hypothesis that the frequency of event was equal between periods of brand and generic use based on a multivariate Poisson regression model. In this model, the control variables were gender, age, polytherapy, and other comorbidities.

‡Inpatient hospitalizations refer to all hospitalizations and emergency room visits lasting more than 1 day. Outpatient consultations refer to all hospitalizations and emergency room visits lasting less than 1 day, as well as all physician visits.

§The statistical significance of the difference in lengths of stay was tested with a Cox regression, which provides CIs for hazard ratios, but not for the rate ratio.

AED = antiepileptic drug.

inpatient diagnoses during the brand period were, in descending order, epilepsy (ICD-9 345), neurotic disorder (ICD-9 300), and bipolar affective psychosis (ICD-9 296), while in the generic period, the first two diagnoses were the same followed by personality disorder (ICD-9 301) in the third position. Outpatient visits were more frequent during the generic period compared to the brand periods (9.25 vs 8.24 visits per person per year; RR = 1.13; CI = [1.09, 1.18]; $p < 0.0001$). The top five most frequent diagnoses associated with outpatient visits during the brand period were neurotic disorder (ICD-9 300), epilepsy (ICD-9 345), bipolar affective psychosis (ICD-9 296), moderate mental retardation (ICD-9 318), and pneumonia with unspecified organism (ICD-9 486). During the generic period, the same five diagnoses occupied the top five positions, except that epilepsy and bipolar switched ranks. The top outpatient specialty visits were made to neurologists, radiologists, and psychiatrists.

DISCUSSION The authors of a recent Ontario study found that, despite compulsory generic substitution policy and a requirement of documented medical necessity prior to switchback, the rates of switchback from generic to branded drugs were significantly higher for AEDs than for antidepressants and antihyperlipidemics.[3] They also showed that patients who switched from branded to generic lamotrigine experienced significantly higher average daily doses of lamotrigine and increased utilization of both other AED and non-AED products based on prescription drug dispensing claims. While these findings may signal reduced clinical effectiveness or increased side effects associated with generic lamotrigine use, this study lacked access to medical claims data to evaluate the impact on medical services.

The present study aimed to investigate generic switching patterns and pharmacy and medical care utilization in Québec. Again, more resistance to generic switching and higher switchback rates were observed for AEDs than for other chronically used drugs for the treatment of hypertension and hyperlipidemia. The switchback rates found in this study (AEDs: 20.8% to 44.1%; non-AEDs: 7.7% to 9.1%) were higher than in the earlier Ontario study (AEDs: 12.9% to 20.9%; non-AEDs: 1.5% to 2.9%).[3]

These differences in switchback rates stem in part from Québec's greater permissiveness in al-

lowing individuals to switch between brand and generic medications compared to Ontario, where generic substitution is compulsory, and a letter of medical necessity is required for patients to switch back to brand from generic product. In 1994, Québec implemented the so-called "15-year rule," which stipulates that a branded drug will be fully reimbursed for 15 years after its first listing on the formulary for the province's basic prescription drug insurance plan (Régime Général d'Assurance Médicaments), even if a generic version of this drug is available at a lower price.[12] Therefore, the higher switchback rates observed in both jurisdictions among AED users relative to those treated with other chronically used drugs, despite the marked divergence in the freedom to switch or switch back, may signal clinical advantages of branded AEDs that drive patient and physician preferences. In the United States, each state has its own rules concerning generic substitution, which vary from the obligation to use generic drugs to mandated use of certain branded drugs. Several states recognize that epilepsy is different from other medical conditions because of seriousness of breakthrough seizure and have developed laws to prohibit substitution or interchanging of any antiepileptic drug, prescribed for the treatment of seizures, without the written consent of the prescribing physicians (In 2006: Illinois, signed into law; In 2007: Tennessee, signed into law; Wyoming, filed, not passed; Alabama, bill drafted).[13-15]

Also unlike the Ontario study,[3] which relied solely on pharmacy claims data, the present study further investigates medical service utilization for both branded and generic lamotrigine treatment. The increased pharmacy utilization of other AEDs and non-AEDs support the findings from the Ontario study. However, this study also demonstrates a greater number of total medical visits and lengthier hospital stays during generic use period, suggesting potential differences in clinical effectiveness between brand and generic lamotrigine treatments.

Furthermore, our results demonstrate that switching from a branded medication to a generic may lead to unfavorable clinical consequences, including longer inpatient length of stay, increase in number of outpatient visits, and higher dosing regimens. Generic substitution is generally considered a sensible treatment alternative, as it is believed to deliver an equivalent treatment at a reduced cost compared to innovator drugs. However, it raises particular concerns for AEDs used for the treatment of epilepsy. Physicians have to carefully choose and titrate the appropriate AED or combination of AEDs based on the nature of seizure or symptoms, in order to both maximize expected efficacy and minimize the risk of adverse events.

Because generic products are approved based on their short term bioequivalence to the brand,[16,17] and because short-term bioequivalence may not translate into equivalent efficacy in controlling seizures over the long term in a clinical setting, generic AEDs may in fact be less favorable than branded ones. Several studies have observed increased toxicity, intolerance, and breakthrough seizures following the generic substitution of older AEDs, including phenytoin,[18] valproic acid,[19] primidone,[20] and carbamazepine,[21] as has recent research concerning the newer-generation AED lamotrigine.[22,23]

In the clinical analysis of lamotrigine users, we aggregated health care utilization results into broad categories (pharmacy, inpatient and outpatient services), hence countering the inherent difficulty in isolating the medical effects of epilepsy. This difficulty was identified in an economic analysis, which found that considering only the costs of epilepsy drugs, ambulatory care, and hospitalizations specifically coded with an epilepsy diagnosis severely understated the overall costs associated with providing medical care to patients with epilepsy.[24] As many consequences of epilepsy may not be coded with an epilepsy diagnosis (e.g., fractures, motor vehicle accident injuries), a patient-based rather than diagnosis-based approach was deemed more appropriate in estimating the true effect of generic AED use for patients with epilepsy.

These observed clinical consequences have led several physicians and patients to express concerns over the generic substitution of AEDs, specifically related to seizure control,[25] breakthrough seizures, and increased side effects.[1,26] Our findings on switch patterns of AEDs are consistent with these concerns. Patients receiving AEDs were less likely to switch to a generic drug than patients receiving medications for other chronic illnesses. As we are aware of no extraordinary technical barriers (e.g., cost, access, availability) to explain this, the finding seems to imply an existing cognizance that generic substitution of AEDs may be disadvantageous. Our results also indicate that these beliefs are actually rooted on concrete and statistically significant evidence.

While claims data are a rich source for examining health care utilization and costs, there are

some inherent limitations. First, claims data are subject to inaccuracies in coding diagnoses and procedures. They do not provide detailed clinical information regarding reasons for generic substitution or drug switchings, or information on potentially relevant disease risk factors such as family history or tobacco use. Additionally, pharmacy claims data do not provide any information on whether drugs dispensed were actually taken according to prescribed instructions. Also, claims data limit the possibility of precisely assessing disease severity. It should be noted that these limitations are present in any study conducted with claims data and are not specific to the present study.

Medical records review could complement claims data analysis by providing more detailed information on the clinical factors driving the reasons for generic substitution or switching back from generic to branded drugs, as well as health care utilization. This type of analysis could improve our understanding of the nature of clinical implications of generic AED use that are suggested in the present study.

These findings have implications for clinicians treating patients with epilepsy, as they lend further support to the hypothesis that generic AEDs may not, in practice, be clinically equivalent to their branded counterparts. Physicians are urged to consider all existing evidence when making treatment decisions, as even a single breakthrough seizure can have serious consequences, both on a personal (loss of driver's license, injury, loss of employment, hospitalization, death) and social level (injury to others, increased health cost to society),[26,27] while additional side effects can also have considerable impact on patient quality of life.

Received May 16, 2007. Accepted in final form August 28, 2007.

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