

# The risks and costs of multiple-generic substitution of topiramate



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## ABSTRACT

**Objective:** To investigate clinical and economic consequences following generic substitution of one vs multiple generics of topiramate (Topamax; Ortho-McNeil Neurologics, Titusville, NJ).

**Methods:** Medical and pharmacy claims data of Régie de l'Assurance-Maladie du Québec from January 2006 to October 2007 were used. Patients with epilepsy treated with topiramate were selected. An open-cohort design was used to classify the observation period into periods of brand, single-generic, and multiple-generic use. One-year generic-switch and switchback-to-brand rates were estimated using Kaplan-Meier methodology. Medical resource utilization and costs were compared among the three periods using multivariate regression analysis.

**Results:** In total, 948 patients were observed during 1,105 person-years of brand use, 233 person-years of single-generic use, and 92 person-years of multiple-generic use. A total of 23% of generic users received at least two different generic versions. Compared to brand use, multiple-generic use was associated with higher utilization of other prescription drugs (incidence rate ratio [IRR] = 1.27, 95% confidence interval [CI] = 1.24-1.31), higher hospitalization rates (0.48 vs 0.83 visit/person-year, IRR = 1.65, 95% CI = 1.28-2.13), and longer hospital stays (2.6 vs 3.9 days/person-year, IRR = 1.43, 95% CI = 1.27-1.60), but the effect was less pronounced in single-generic use (hospitalization: IRR = 1.08, 95% CI = 0.88-1.34, length of stay: IRR = 1.12, 95% CI = 1.03-1.23). The risk of head injury or fracture was nearly three times higher (hazard ratio = 2.84, 95% CI = 1.24-6.48) following a generic-to-generic switch compared to brand use. The total annualized health care cost per patient was higher in the multiple-generic than brand periods by C\$1,716 (cost ratio = 1.21,  $p = 0.0420$ ).

**Conclusion:** Multiple-generic substitution of topiramate was significantly associated with negative outcomes, such as hospitalizations and injuries, and increased health care costs.

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## GLOSSARY

**AED** = antiepileptic drug; **C\$** = constant Canadian dollars; **CD** = cost difference; **CI** = confidence interval; **CR** = cost ratio; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **IRD** = incidence rate difference; **IRR** = incidence rate ratio; **NTI** = narrow therapeutic index; **RAMQ** = Régie de l'Assurance-Maladie du Québec.

Generic substitution policies may be controversial when applied to narrow therapeutic index (NTI) drugs, such as antiepileptic drugs (AEDs).<sup>1,2</sup> Concerns stem from small differences between therapeutic and toxic doses for NTI drugs and the need for careful dosage adjustment and patient monitoring. Recent studies reported increases in health care utilization and costs associated with the use of generic lamotrigine (Lamictal; GlaxoSmithKline, Brentford, UK) compared to branded use,<sup>3-6</sup> and higher switchback rates from generic to branded AEDs vs other chronic-disease drugs.<sup>3,4</sup> A growing number of states in the United States<sup>7-9</sup> have passed

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**Medications:** carbamazepine (Tegretol; Novartis, Basel, Switzerland); clobazam (Frisium; Sanofi-Aventis, Paris, France); clonazepam (Rivotril; Roche, F. Hoffmann-La Roche, Basel, Switzerland); divalproex (Epival) and valproate (Depakene) (Abbott Laboratories, Abbott Park, IL); fosinopril (Monopril) and pravastatin (Pravachol) (Bristol-Myers Squibb, New York, NY); gabapentin (Neurontin; Pfizer, New York, NY); isosorbide (Imdur; AstraZeneca, London, UK); lamotrigine (Lamictal; GlaxoSmithKline, Brentford, UK); topiramate (Topamax; Ortho-McNeil Neurologics, Titusville, NJ); venlafaxine (Effexor; Wyeth, Madison, NJ).

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legislation requiring physician and patient approval before a generic AED substitution is allowed.

The concern for generic substitution of AEDs is further accentuated by the availability of multiple generic versions. A change in AED therapy is typically accompanied by careful dosage titration and pharmacodynamic monitoring, thereby prolonging the time period required to reach stable doses. Thus far, to our knowledge, no scientific evidence has been reported with respect to the effects of switching between multiple generic versions of a given AED.

The main objective of the present study is to investigate the impact of generic substitution of one vs multiple generics, using topiramate (Topamax, Ortho-McNeil Neurologics, Titusville, NJ, patent expiration in January 2006 in Canada) as a case study. Specifically, the study aims to analyze switching patterns of topiramate, comparing them to other AEDs and other selected chronic-disease drugs (non-AEDs) as references; and to investigate clinical and economic outcomes for patients treated with multiple versions of generic topiramate vs branded vs single-generic users.

**METHODS Data source.** We used the Régie de l'Assurance-Maladie du Québec (RAMQ) database from January 2000 to October 2007, comprising pharmacy and medical claims from Quebec, Canada. Data were drawn from four RAMQ data files: 1) information personne assurée (demographic characteristics); 2) périodes d'admissibilité (eligibility and coverage type); 3) services pharmaceutiques (outpatient prescription drug dispensings): dose, dosage form, quantity dispensed, duration, dispensing date, and specialty of 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. RAMQ databases are linked via a unique and encrypted patient identifier, allowing for longitudinal follow-up of patients.

**Study populations.** The study population was randomly selected based on the following inclusion and exclusion criteria: continuous health plan coverage, patients treated for at least 60 days with the branded version of one of the AED or non-AED study drugs before the generic entry date, or for older drugs, at least 60 days following January 1, 2000, at least one dispensing of the studied drug (brand or generic) following generic entry, and continuous use (i.e., no treatment gap >30 days) of the studied drug throughout the study period. For the AED analysis, we required at least one epilepsy diagnosis (ICD-9: 345.x: epilepsy or 780.3x: convulsions) during the study period.

The study population was stratified into monotherapy vs polytherapy, stable vs variable dose, and number of generic ver-

sions. Polytherapy was defined as patients using at least one other drug from the same therapeutic class as the studied drug during 180 days prior to generic entry. Stable dose was defined as a dosage variation within  $-2.5\%$  to  $2.5\%$  of the average dose during the first 180 days of observation. The number of generic versions was cumulated over the entire observation period.

For each patient, the study period began 180 days before generic entry or for older drugs on January 1, 2000, and lasted until the end of patient eligibility, treatment discontinuation, or the end of data availability (October 2007), whichever occurred first.

**Study design.** For objective 1, a retrospective cohort design was used to calculate various switching metrics for eight AEDs: three (topiramate, lamotrigine, gabapentin [Neurontin, Pfizer, New York, NY]) with generics that became available in 2000 or later and five with pre-2000 generic entries: divalproex (Epival, Abbott Laboratories, Abbott Park, IL), clobazam (Frisium, Sanofi-Aventis, Paris, France), clonazepam (Rivotril, Roche, F. Hoffmann-La Roche, Basel, Switzerland), valproate (Depakene, Abbott Laboratories), and carbamazepine (Tegretol, Novartis, Basel, Switzerland). Switching patterns of AEDs were compared to four other chronic-disease medications for angina (isosorbide [Imdur, AstraZeneca, London, UK]), depression (venlafaxine [Effexor, Wyeth, Madison, NJ]), hypertension (fosinopril [Monopril, Bristol-Myers Squibb, New York, NY]), and hyperlipidemia (pravastatin [Pravachol, Bristol-Myers Squibb]). All studied AEDs had full reimbursement during the study period according to the so-called 15-year rule, which allows full reimbursement of a branded drug for 15 years after being listed on the RAMQ formulary, even if a generic is available. The four non-AEDs were chosen based on their use for chronic diseases and their recent generic entry dates.

Generic switching was defined as when a patient who used a branded drug was then switched to a generic equivalent. Switch-back was defined as when a patient who used a branded compound first switched to a generic product, and then switched back to the branded drug. Generic-to-generic switching was defined as when a patient switched from one generic version to another of the same compound. Switch-in was defined as when a patient switched to the studied drug (brand or generic) after being treated with another drug of the same therapeutic class. Switch-out was defined as when a patient switched from the studied drug to another in the same class.

For the second objective, a retrospective open-cohort design was used to classify the observation period into mutually exclusive periods of branded topiramate only, single-generic topiramate use, and multiple-generic topiramate use. Analyses of selected clinical and economic outcomes were conducted by comparing branded and generic-use periods using a person-time approach (e.g., frequency of events per person per year [p/y] of observation). Medical claims were examined for events that could be potentially associated with negative clinical consequences of epilepsy such as head injuries, fractures, or hospitalizations.

Also, total health care costs and rates of health care utilization were analyzed in the following categories: prescriptions for topiramate, other AEDs, and non-AEDs; hospitalizations; and outpatient consultations. While claims data cannot provide a clear view of antiepileptic drug effectiveness, endpoints such as hospitalizations, head injuries, and fractures were selected as proxies for possible differences in drug effectiveness. After adjusting for differences in patient characteristics in the three

groups, costs (in 2006 constant Canadian dollars) and rates of utilization were compared between the groups.

**Statistical analysis. Population characteristics.** Frequencies and percentages were used to summarize categorical variables while means and standard deviations were used for continuous variables.

**Switching patterns.** For the eight AEDs and the four non-AED reference drugs, generic switching and switchback rates were estimated using the Kaplan-Meier method. The generic switch rate was computed as the cumulative probability of a patient switching to the generic drug given that a patient was previously using the branded drug at each time interval. To estimate switchback, time was reset at zero on the generic switch date, and the estimation calculated the cumulative probability of a patient switching back to brand after using the generic. In both cases, patients who were lost to follow-up were censored. Generic switching rates were calculated 1 year after generic entry, and switchback rates were calculated 180 days after generic entry. Generic-to-generic switching was measured with the number of generics taken by each generic user, and by calculating the share of patients who took  $\geq 2$  generic versions of the same drug among all patients. Switch-in and switch-out rates were calculated as cumulative percentages.

**Health care utilization.** Incidence rates of prescription drug dispensing, hospitalizations, and outpatient visits were calculated and compared between periods of branded vs single-generic and multiple-generic use of topiramate. Incidence rates were calculated as the number of events divided by the number of person-years observed. The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Incidence rates, i.e., frequency of events per p/y, for outcomes during the

brand period vs single-generic and multiple-generic periods were compared using incidence rate differences (IRD) and incidence rate ratios (IRR). Statistical differences among the three groups were tested using Poisson regression models, controlling for demographics (gender, age), comorbidities (brain tumors [ICD-9 191.x, 198.3, 239.6, 237.5], stroke [ICD-9 434.x to 436.x], depression [ICD-9 296.2, 296.3, 298.0, V.79.0, 311.x, 300.4, 309.0-.1], anxiety [ICD-9 300.0, 300.2, 308.0, 309.2, 293.8, 292.8], bipolar disorders [ICD-9 296.4-.9], other psychiatric conditions [ICD-9 290.x to 319.x, except above, V17.0, V71.0]), and treatment characteristics (dose change, polytherapy, presence of switch-in or of switch-out).

Cox proportional hazard models<sup>10</sup> were used to estimate the time to occurrence of possible complications following a drug switch, such as hospitalization, head injury (ICD-9 800-804, 805-854, 873, or 959.01) or fracture (V66.4, 767.2-.4, 800-839), while controlling for the type of switch (brand-to-generic, generic-to-generic, and generic-to-brand), along with the previously listed covariates.

**Health care costs.** Direct pharmacy and medical costs during the brand period vs single-generic and multiple-generic periods were compared using cost differences (CD) and cost ratios (CR). Adjusted differences in annualized health care costs per patient between periods were computed using multivariate linear regressions, controlling for the covariates listed above.

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

**RESULTS Study population.** Table 1 shows the characteristics of 948 patients (mean ages: 33.7–37.5

**Table 1 Patient characteristics: Patients treated with topiramate**

Demographics	Brand users	Single generic users	Multiple generic users	Brand vs single generic p value*	Brand vs multiple generic p value*
No. of patients treated with topiramate, n	875	331	99	—	—
Age, y, mean (SD)	34.5 (17.0)	37.5 (16.1)	33.7 (14.7)	0.0050	0.5522
Women, n (%)	531 (60.7)	194 (58.6)	67 (67.7)	0.5113	0.1757
Mean observation period, d (SD)	665 (61)	669 (39)	676 (2)	0.6969	0.0686
Mean observation period on topiramate, d (SD) (brand or generic)	461 (204)	257 (160)	337 (128)	<.0001	<.0001
<b>Treatment characteristics</b>					
Average daily dose of topiramate, mg/d (SD)	200.5 (136.7)	197.7 (141.3)	180.1 (128.7)	0.6159	0.0845
Polytherapy, n (%)	616 (70)	234 (71)	71 (72)	0.9202	0.7853
Dosing changes, n (%)	347 (43)	123 (42)	46 (51)	0.7809	0.1235
No. of generics used, mean (SD)	—	1 (0.0)	2.8 (2.5)	—	—
<b>Comorbidity</b>					
Charlson comorbidity index, mean (SD)	0.21 (0.67)	0.21 (0.74)	0.12 (0.44)	0.8395	0.1446
Depression, n (%)	54 (6)	18 (5)	10 (10)	0.6315	0.1347
Anxiety, n (%)	60 (7)	29 (9)	5 (5)	0.2590	0.4948
Other mental disorders, n (%)	188 (21)	92 (28)	24 (24)	0.0206	0.5287

Study population: topiramate users = 2,798; eligible in 180 days prior to generic entry = 2,303; continuous users = 948. \*Statistical comparisons between cohorts of brand, single generic, and multiple generic patients were conducted using the Pearson  $\chi^2$  test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

**Table 2** Drug switching patterns

	No.	Mean observation period, d	Generic switch rate, %*	Switchback rate, %*	Generic-to-generic switching			
					No. generics	% >2 generics	Switch-in, %	Switch-out, %
<b>AEDs with generic entry date in 2000 or after</b>								
Topiramate (01/2006) <sup>†</sup>	948	665	37.8	12.5	1.4	23.0	12.7	11.3
Lamotrigine (02/2003)	1,046	1,795	18.3	12.4	1.8	36.7	30.5	19.3
Gabapentin (07/2001)	1,673	2,236	35.4	19.5	1.7	32.1	60.5	32.8
Weighted average <sup>‡</sup>			30.5	14.7	1.7	31.6	39.6	23.4
<b>AEDs with generic entry before 2000</b>								
Divalproex (01/1999)	5,474	2,625	34.4	14.0	2.0	35.7	58.9	23.4
Clobazam (01/1999)	4,786	2,609	12.5	23.0	1.9	40.6	62.9	25.3
Clonazepam (01/1999)	3,175	2,733	10.8	30.8	2.1	40.3	56.9	40.4
Valproate (01/1996)	912	2,684	22.9	23.9	2.8	48.7	44.0	41.7
Carbamazepine (01/1994)	2,434	2,709	10.9	12.2	1.8	37.2	51.1	34.3
Weighted average <sup>‡</sup>			18.2	19.2	2.0	38.8	57.7	29.7
<b>Non-AEDs with generic entry date in 2000 or after</b>								
Isosorbide (10/2006)	2,094	533	28.2	8.7	1.0	0.0	6.5	3.2
Venlafaxine (10/2006)	1,494	295	30.3	4.5	1.0	0.0	10.5	1.9
Fosinopril (06/2004)	2,314	1,286	28.8	7.2	2.5	28.9	12.4	2.5
Pravastatin (01/2001)	3,914	2,442	53.5	8.8	2.1	48.6	38.1	32.0
Weighted average <sup>‡</sup>			35.9	7.8	2.0	34.7	21.1	14.3

\*Generic switch rates were calculated for 1 year following generic entry, while switchback rates were computed for the first 180 days following a generic switch.

<sup>†</sup>The date in brackets (MM/YYYY) indicates the generic entry date in Quebec.

<sup>‡</sup>The weights used to compute these averages were 1) the number of brand users for the generic switch rate, 2) the number of brand-to-generic users for the switchback rate, 3) the number of generic users for generic-to-generic switching, and 4) the total study population for each drug for switch-in and switch-out.

AED = antiepileptic drug.

years; 59%–68% women) treated with topiramate observed for an average of 665 days. The cohorts presented similar demographic characteristics, treatment patterns, and comorbidities, except for duration of topiramate use, and some age and comorbidity differences between brand and single-generic users. While nearly all patients (92%) had received  $\geq 1$  prescription for branded topiramate, close to half (45%) had  $\geq 1$  prescription for generic topiramate. Generic patients used on average 1.4 versions of generic topiramate (seven versions available), with 23% of them receiving two versions or more. The frequent occurrence of polytherapy (70%–72%) and dosing changes (43%–51%) underscores the complexities of epilepsy medication management.

**Switching patterns.** Table 2 shows switching rates for the AED and non-AED products studied. For the eight AEDs, study populations ranged from 912 to 5,474 patients and were observed for 665 to 2,733 days, while non-AED users (1,494 to 3,914 patients) were observed for 295 to 2,442 days. After 1 year of

observation, AEDs showed lower generic substitution rates (weighted average: 30.5% for generic entry after 2000; 18.2% for generic entry before 2000) than non-AEDs (35.9%). Users of generic AEDs were more likely to switch back to branded drugs, especially those taking older AEDs (weighted average: 14.7% for generic entry after 2000; 19.2% for generic entry before 2000) compared to patients taking other chronic disease drugs (7.8%).

Also in table 2, generic AED patients received 1.4 to 2.8 different generic versions, with 23%–49% of generic users receiving two versions or more during the study period. In contrast, two of the non-AEDs were available in one generic version, while the two others showed similar generic-to-generic switching frequencies (2.1–2.5 versions per patient). Switch-in and switch-out rates were higher for AEDs and tended to increase with the length of observation.

**Health care utilization.** Table 3 shows incidence rates of health care utilization for patients using topiramate during the brand, single-generic, and multiple-

**Table 3 Pharmacy and medical service utilization: Patients treated with topiramate**

	Incidence rate (no. events/person-year)			Incidence rate difference*		Adjusted incidence rate ratio (95% CI)†	
	Brand	Single generic	Multiple generics	Single generic vs brand	Multiple generics vs brand	Single generic vs brand	Multiple generics vs brand
<b>Prescription drugs‡</b>							
Other AED prescriptions	11.76	12.78	13.39	1.01	1.63	1.11 (1.06; 1.15)	1.16 (1.09; 1.23)
Non-AED prescriptions	44.38	58.38	57.14	14.00	12.75	1.24 (1.22; 1.27)	1.31 (1.28; 1.35)
<b>Medical services</b>							
Hospitalizations	0.48	0.52	0.83	0.04	0.35	1.08 (0.88; 1.34)	1.65 (1.28; 2.13)
Outpatient visits	9.07	9.48	8.74	0.41	-0.33	0.99 (0.94; 1.04)	0.95 (0.88; 1.02)
Mean length of hospital stays, d	2.55	3.22	3.88	0.67	1.34	1.12 (1.03; 1.23)	1.43 (1.27; 1.60)

\*Incidence rate (single-generic or multiple-generics) – incidence rate (brand).

†Incidence rate (single-generic or multiple-generics)/incidence rate (brand). This adjusted rate ratio and its CI were estimated using a multivariate Poisson regression, with the following covariates: demographics (gender, age), comorbidities (brain tumors, stroke, depression, anxiety, bipolar, other psychiatric conditions), and treatment characteristics (dose change, polytherapy, presence of switch-in or switch-out).

‡Prescription length was harmonized to 28 days.

CI = confidence interval; AED = antiepileptic drug.

generic period. Single and multiple-generic use periods presented more prescriptions per year for both AEDs and non-AEDs compared to brand use period. After adjusting for covariates, multiple-generic topiramate use was associated with significantly higher utilization of other AEDs (IRR = 1.16, 95% CI = 1.09–1.23) and of non-AED products (IRR = 1.31, 95% CI = 1.28–1.35).

Multiple-generic periods showed higher hospitalization rates than brand periods (0.83 vs 0.48 visit per p/y). After covariate adjustment, multiple-generic use was associated with a significantly higher incidence of hospitalization relative to brand-only use (IRR = 1.65, 95% CI = 1.28–2.13), while the difference between single-generic and brand periods (IRR = 1.08, 95% CI = 0.88–1.34) was not significant. Longer mean hospital lengths of stay were also observed for multiple-generic period than for branded period (3.88 vs 2.55 days per p/y; adjusted IRR = 1.43, 95% CI = 1.27–1.60) and for single-generic period (3.22 vs 2.55 days per p/y; adjusted IRR = 1.12, 95% CI = 1.03–1.23). Outpatient visits showed no significant differences among the three studied periods.

For both branded and single-generic periods, the top three inpatient diagnoses were epilepsy (ICD-9 345), schizophrenia (ICD-9 295), and anxiety (ICD-9 300), whereas for multiple-generic users, the top inpatient diagnosis was episodic mood disorders (ICD-9 296), followed by epilepsy and schizophrenia. The most frequent outpatient consultations were general symptoms (ICD-9 780) and epilepsy for all three groups, followed by abdomen and pelvis symptoms for branded patients (ICD-9 789), chest and

respiratory symptoms for single-generic users (ICD-9 786), and anxiety for multiple-generic patients.

Table 4 presents the association of generic-to-generic switching and other types of drug switches to time to first occurrence of 1) hospitalization and 2) fracture or head injury relative to continuous brand therapy. The risk of hospitalization following generic-to-generic substitution was close to two times higher (HR = 1.62, 95% CI = 1.05–2.50) compared with brand use. While switchback was associated with higher risk of hospitalizations relative to brand (HR = 1.91, 95% CI = 1.03–3.53), single generic switch did not exhibit risks that were significantly different from the brand period. The risk of fracture or head injury was nearly three times greater following generic-to-generic substitution (HR = 2.84, 95% CI = 1.24–6.48), but not significantly larger for any other type of switch relative to brand use. The relatively common practice of polytherapy was significantly associated with risk of fracture or head injury relative to monotherapy (HR = 2.16, 95% CI = 1.19–3.95).

**Health care costs.** Table 5 compares annualized health care costs per patient during the three periods. Relative to brand use, the observed annual cost of topiramate therapy was lower for single-generic use (–\$677) and multiple-generic use (–\$690) periods. In contrast, the observed medical services costs and total health care costs were higher for single generic (+\$592 and +\$410) and multiple-generic (+\$997 and \$1,716) than for brand.

After adjustment, multiple-generic use was associated with 21% higher total health care costs (adjusted CR = 1.21, adjusted *p* = 0.0420),

**Table 4** Cox regressions on time to event: Patients treated with topiramate

	Time to first hospitalization from date of drug switching			Time to first fracture or head injury from date of drug switching		
	Adjusted HR	(95% CI)	p Value	Adjusted HR	(95% CI)	p Value
<b>Cohort</b>						
Generic-to-generic	1.62	(1.05; 2.50)	0.0303	2.84	(1.24; 6.48)	0.0133
Generic switch	1.03	(0.78; 1.35)	0.8418	1.10	(0.62; 1.96)	0.7382
Switchback	1.91	(1.03; 3.53)	0.0393	2.52	(0.77; 8.28)	0.1274
Generic*	0.96	(0.44; 2.13)	0.9241	1.24	(0.11; 13.95)	0.8606
<b>Brand (Reference)*</b>						
<b>Demographics</b>						
<b>Gender</b>						
Women	0.86	(0.69; 1.06)	0.1626	0.94	(0.60; 1.46)	0.7780
<b>Men (Reference)</b>						
Age	1.01	(1.00; 1.01)	0.1425	1.00	(0.99; 1.02)	0.7980
<b>Treatment characteristics</b>						
Dose change	1.46	(1.17; 1.82)	0.0008	0.96	(0.61; 1.51)	0.8655
<b>Stable dose (Reference)</b>						
Polytherapy	1.36	(1.05; 1.76)	0.0197	2.16	(1.19; 3.95)	0.0118
<b>Monotherapy (Reference)</b>						
Switch-in	1.15	(0.70; 1.88)	0.5900	0.64	(0.15; 2.68)	0.5450
Switch-out	1.37	(0.96; 1.95)	0.0834	0.92	(0.36; 2.33)	0.8580
<b>Comorbidities</b>						
Depression	1.91	(1.31; 2.76)	0.0007	0.60	(0.18; 2.00)	0.4081
Anxiety	1.43	(0.98; 2.08)	0.0647	0.41	(0.10; 1.77)	0.2335
Bipolar	1.55	(0.85; 2.82)	0.1552	0.76	(0.10; 5.72)	0.7901
Other psychiatric conditions	1.40	(1.10; 1.79)	0.0073	1.81	(1.11; 2.93)	0.0166
Charlson Comorbidity Index	1.32	(1.19; 1.47)	<0.0001	1.22	(0.96; 1.55)	0.1115

\*Generic is the period without a switch when the patient starts using a generic.

\*Brand is the period without a switch when the patient starts using the brand.

CI = confidence interval.

whereas the difference between single-generic and brand periods was not significant. The lower costs of generic topiramate compared to the brand were counterbalanced by higher costs for other drugs (single-generic vs brand: adjusted CR = 0.95, adjusted  $p = 0.3053$ ; multiple-generic vs brand: adjusted CR = 1.14, adjusted  $p = 0.0926$ ) and nominally higher, although not significant, costs for medical services.

**DISCUSSION** The results of this study are consistent with previous research associating increased health care utilization and costs with brand to generic switching of AEDs. Recent research reported that patients during the time period of receiving generic lamotrigine incurred significant increases in dispensings (other AEDs: +17% per p/y; non-AEDs: +30% per p/y), medical visits (+13% per p/y), mean hospital length of stay (+44%),<sup>4</sup> and health care costs (+22% per p/y)<sup>6</sup> compared to when

treated with branded lamotrigine. In addition, as in this study, lower generic substitution rates and higher switchback rates to branded drugs among AEDs compared to other drugs used to treat chronic diseases were found.<sup>3,4</sup>

We expanded on previous efforts by providing a detailed portrait of switching across several AEDs and non-AED reference drugs. Furthermore, we examined separately the clinical and economic outcomes of single-generic and multiple-generic use, exposing a set of potentially higher risks with the latter group.

Compared to branded use, multiple-generic use was associated with a 65% higher hospitalization rate and 43% longer length of hospital stays. Multiple-generic patients also received more AED and non-AED medications than single-generic and brand users. The multivariate analysis of the occurrence of medical services following drug switches further re-

**Table 5** Health care costs: Patients treated with topiramate

	Cost rate (\$/person-year)			Cost difference*		Adjusted cost ratio (p value) <sup>†</sup>	
	Brand	Single generic	Multiple-generics	Single generic vs brand	Multiple generics vs brand	Single generic vs brand	Multiple generics vs brand
<b>Prescription drugs</b>							
Topiramate	\$1,976	\$1,299	\$1,286	-\$677	-\$690	0.68 (<0.0001)	0.66 (<0.0001)
Other AED prescriptions	\$661	\$610	\$728	-\$51	\$67	0.97 (0.7495)	1.1 (0.5483)
Non-AED prescriptions	\$2,594	\$3,140	\$3,935	\$546	\$1,341	1.14 (0.1461)	1.52 (0.0007)
Total prescription drugs	\$5,231	\$5,049	\$5,949	-\$182	\$718	0.95 (0.3053)	1.14 (0.0926)
<b>Medical services</b>							
Hospitalizations	\$1,851	\$2,392	\$2,780	\$541	\$930	1.13 (0.5863)	1.45 (0.1651)
Outpatient visits	\$773	\$824	\$840	\$51	\$67	1.02 (0.8115)	1.06 (0.6342)
Total medical services	\$2,624	\$3,216	\$3,621	\$592	\$997	1.10 (0.5823)	1.34 (0.1675)
<b>Total costs</b>							
With topiramate	\$7,854	\$8,265	\$9,570	\$410	\$1,716	1.00 (0.9715)	1.21 (0.042)
Without topiramate	\$5,879	\$6,966	\$8,284	\$1,087	\$2,405	1.10 (0.2842)	1.39 (0.0033)

\*Cost rate (single-generic or multiple-generics) – cost rate (brand).

<sup>†</sup>Cost rate (single-generic or multiple-generics)/cost rate (brand). This adjusted cost ratio was estimated using a multivariate linear regression, with the following covariates: demographics (gender, age), comorbidities (brain tumors, stroke, depression, anxiety, bipolar, other psychiatric conditions), and treatment characteristics (dose change, polytherapy, presence of switch-in or of switch-out).

AED = antiepileptic drug.

vealed that after a generic-to-generic switch, the risk of hospitalization was significantly higher than during continuous brand use, while fractures or head injuries occurred three times more frequently.

In addition to these adverse clinical effects, the economic impact of generic substitution was found in this study to be counterproductive as a cost-saving strategy. While the single-generic group appeared to be cost neutral to brand on total health care costs, a shift in expenditures was observed from pharmacy to medical services, particularly hospitalizations. More concerning is multiple-generic use, as even with the lower topiramate therapy costs for multiple-generic periods, the total cost for multiple-generic users was significantly higher (\$1,716 per patient per year) than for brand users.

While physicians prescribing AEDs typically select and titrate these products carefully to control seizures without causing adverse effects,<sup>11</sup> they are not directly involved in the generic substitution that occurs at the pharmacy level. This research highlights the frequency of substitution between generic versions of the same compound, as well as the associated heightened risks of clinical consequences such as hospitalizations, fractures, and injuries associated with this pattern. In our study, 31% of patients using generic versions of newer AEDs received two or more

different generic versions, as did 38.7% of those treated with generics of older AEDs.

Neurologists may be aware of the potential risks due to changes in serum concentration accompanying generic substitution, but our findings highlight the particular risk of generic-to-generic switches. Pharmacists dispensing generic AEDs may be able to mitigate that risk by consistently providing a given patient the same generic version.

There are limitations to the conclusions that can be drawn from this study. This research is based on administrative claims data that do not include relevant factors such as severity, family history, or other risk factors and may also present inaccuracies in coding of diagnoses and procedures. Also, this retrospective analysis found significant relationships or associations, which should not be interpreted as causes and effects. In addition, the magnitude of these effects may vary in other jurisdictions, given possible differences in the provision of services in Quebec (e.g., nature and intensity of epilepsy care, health systems, insurance) vs other Canadian provinces and the United States. Finally, the effects of time are difficult to parse out, especially for the analysis of drug switching patterns. The health care system has evolved from 2000—the earliest data point observed—to 2007, potentially affecting results from

different time points. Product-level comparisons may be impacted by both the state of health care system upon generic entry and by the duration of time available since generic availability.

The findings of this study, namely that patients receiving multiple-generic versions of topiramate had higher risks of negative clinical events and incurred health care costs compared to patients receiving branded topiramate, have particular relevance for policy makers. While similar increases in risk and cost were not found for patients receiving a single generic version of topiramate, these results call into question the effectiveness of generic substitution policies pertaining to AEDs as a means to control costs, under the assumption that bioequivalence standards result in comparable clinical effectiveness.

### AUTHOR CONTRIBUTIONS

Statistical analyses were performed by P.E.P. and D.L.-V.

### DISCLOSURE

This study was sponsored by a research grant to Analysis Group, Inc., from Ortho-McNeil Janssen Scientific Affairs (OMJSA), LLC, Titusville, NJ. Employees of Johnson & Johnson participated in the design, review, and approval of the manuscript. Dr. Duh is an employee of Analysis Group, Inc.; P.E. Paradis is an employee of Groupe d'Analyse, Ltée, which is the Canadian office of Analysis Group, Inc.; D. Latrémouille-Viau is an employee of Groupe d'Analyse, Ltée; Dr. Greenberg is an employee of Analysis Group, Inc.; Dr. Lee was an employee of OMJSA during the conduct of the study, is now an employee of Johnson & Johnson Pharmaceutical Services, LLC, and holds equity interest in Johnson & Johnson; Mr. Durkin is an employee of OMJSA and holds equity interest in Johnson & Johnson; Dr. Wan is an employee of OMJSA and holds equity interest in Johnson & Johnson; Dr. Rupnow was an employee of OMJSA during the conduct of the study, is now an employee of Ethicon, Inc., a Johnson & Johnson company, and holds equity interest in Johnson & Johnson; and Dr. LeLorier has a consulting agreement with Analysis Group, Inc.

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