

Compulsory Generic Switching of Antiepileptic Drugs: High Switchback Rates to Branded Compounds Compared with Other Drug Classes

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Summary: *Purpose:* Compulsory generic substitution of antiepileptic drugs (AEDs) may lead to adverse effects in epilepsy patients because of seizure recurrence or increased toxicity. The study objectives were (a) to quantify and compare the switchback rates from generic to brand-name AEDs versus non-AEDs, and (b) to assess clinical implications of switching from branded Lamictal to generic lamotrigine (LTG) and whether signals exist suggesting outcome worsening.

Methods: By using a public-payer pharmacy-claims database from Ontario, Canada, switchback rates from generic to branded AEDs [Lamictal, Frisium (clobazam; CLB), and Depakene (VPA; divalproex)] were calculated and compared with non-AED long-term therapies, antihyperlipidemics and antidepressants, in January 2002 through March 2006. We then assessed pharmacy utilization and AED dosage among LTG patients switching back to branded Lamictal compared with those staying on generic formulation.

Results: The 1,354 patients (403 monotherapy, 951 polytherapy) were prescribed generic LTG, of whom 12.9% switched back to Lamictal (11.7% monotherapy, 13.4% polytherapy). Switchback rates of other AEDs were ~20% for CLB and VPA. The switchback rates for AEDs were substantially higher than for non-AEDs (1.5–2.9%). Significant increases in LTG doses were observed after generic substitution for those who did not switch back (6.2%; $p < 0.0001$). The average number of codispensed AEDs and non-AED drugs significantly increased ($p < 0.0001$) after LTG generic entry, especially in the generic group.

Conclusions: These results reflect poor acceptance of switching AEDs to generic compounds. They may also indicate increased toxicity and/or loss of seizure control associated with generic AED use. **Key Words:** Epilepsy—Antiepileptic drugs—Generic substitution—Lamictal—Lamotrigine.

In recent years, increasing medical costs have forced healthcare systems to adopt measures to limit expenditure and maximize cost savings. A common example has been the encouragement or mandatory requirement for the use of cheaper generic medicines instead of branded products. However, as generic medications are required to demonstrate only short-term bioequivalence to be granted product license, their bioavailability may differ from that of their branded counterparts, which could lead to decreased efficacy and/or tolerability. Specifically, the U.S. Food and Drug Administration (FDA) criteria for bioequivalence are designed to achieve 90% confidence that the ratios of the test to reference log-transformed mean values for area under the plasma concentration–time curve

(AUC) and peak plasma concentration (C_{\max}) lie within an interval of 80% to 125% (Borgherini, 2003). The FDA accepts –20% to 25% variation in AUC and C_{\max} that are considered bioequivalent, whereas the brand standard ranges from –5% to +5% (Borgherini, 2003). Therefore it is theoretically possible for a patient to receive an almost 50% increase in serum concentration if switched from a low-bioavailability generic formulation to a high-bioavailability one (Feely et al., 2005). An additional concern is that bioavailability studies are carried out on a small number of healthy volunteers by using single doses of a drug. These studies may not represent a clinical practice setting, where patients have a wide range of characteristics, may have other concomitant diseases, and can use potentially interacting drugs (Besag, 2000).

In medication classes in which a “narrow therapeutic index” is present, such as antiepileptic drugs (AEDs), generic substitution raises particular concern. In addition to individual response, tolerability and toxicity are important considerations when selecting an AED therapy.

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Many AEDs are CNS depressants and may produce undesirable sedation impact on activities requiring skilled coordination and alertness (Sander, 2004). Discontinuation of or changeover from one AED to another must be done gradually to avoid precipitating seizures. For a patient in stable long-term control, prevention of seizure recurrence is paramount, as even a single breakthrough seizure could have serious consequences, on both a personal (loss of driver's license, employment, injury to self, etc.) and a social level (injury to others, increased health cost to society) (Feely, 2005; Crawford, 2006). As short-term bioequivalence may not translate to equivalent efficacy with respect to long-term seizure control, generic AEDs may be less acceptable and paradoxically increase healthcare costs.

Increased toxicity or intolerance and/or breakthrough seizures have been reported after generic substitutions of AEDs, including phenytoin (PHT) (Tyrer et al., 1970), valproic acid (VPA) (Macdonald, 1987), primidone (PRM) (Wyllie et al., 1987) and carbamazepine (CBZ) (Gilman et al., 1993). In a survey of 301 neurologists in the United States, 67.8% reported breakthrough seizures, and 56% reported increased side effects in their patients after a switch from brand-name to generic AEDs (Wilner, 2004). In the largest patient survey reported to date, involving 251 patients who had been switched to generic AEDs, 10.8% experienced a confirmed breakthrough seizure or toxicity attributable to the substitution (Crawford et al., 1996).

Analyses have suggested that the cost saved by generic switching of AEDs could be outweighed by the price of increased monitoring and loss of seizure control. (Crawford et al., 1996; Jobst and Holmes, 2004). Another problem is that physicians typically underestimate the frequency of generic substitution taking place at the pharmacy (Guberman and Corman, 2000; Wilner, 2004). Consequently, many recommend that physicians be more vigilant in their prescription-writing practices to prevent unwarranted generic substitution (Wilner, 2004). The American Academy of Neurology has issued a guideline recommending that switching between proprietary and generic formulations of AEDs be avoided unless medically indicated (American Academy of Neurology, 1990).

Lamotrigine [(LTG) Lamictal, GlaxoSmithKline, Brentford, Middlesex, U.K.] is a newer drug in the AED formulary that has a narrow therapeutic index, but better toxicity profile and less drug interaction compared with older AEDs. It is one of the first of the new-generation AEDs to have a generic version, and understanding the effect of substitution of branded Lamictal to generic LTG would further the knowledge in the generic substitution of new AEDs. Starting in January 2003, the province of Ontario required that all branded prescriptions of Lamictal be switched to its generic version. In this study, we assess the impact of generic substitution by comparing pharmacy claims data on cohorts of epilepsy patients receiving AEDs

in Ontario before and after the government-mandated switch, by using LTG as a case-study example.

METHODS

Data source

We used a public-payer database from Ontario, Canada, comprising patient-level prescription drug dispensing claims paid for by the Ontario Drug Benefit (ODB) Formulary. Data elements included patient demographics, drug use, product manufacturer, strength, form, and treatment duration.

Study design

The objectives of the study were twofold. First, we aimed to quantify the switchback rates from generic to brand-name AEDs in comparison with other drugs used over the long term. Second, we documented the potential adverse clinical consequences of generic switching, focusing on the case of Lamictal.

To address the first objective, the switchback rates were calculated from generic to three branded AEDs: Lamictal, Frisium, and Depakene, in comparison with other commonly used long-term medications, antihyperlipidemics (Statin 1: simvastatin, Zocor) and antidepressants [selective serotonin reuptake inhibitor (SSRI) 1: fluoxetine, Prozac; and SSRI 2, citalopram, Celexa]. In every case, only one brand name was available for each of these products, whereas five different generic formulations exist for Lamictal, six for Frisium, 15 for Depakene, and >10 generic formulations for other non-AEDs. To be selected in this study, the drug had to be on the market only as a branded version in 1995 or later, and then a generic formulation had to be introduced in 2004 or before. Of all the possible AED candidates, only Neurontin (gabapentin) was excluded, as it is also widely used for indications other than epilepsy.

"Switchback" was defined as switching a patient from the branded drug to the generic, and then back to the branded drug. Switchback rates were estimated for patients initially taking the branded drug during a time when no generic version was available in Ontario and who were then switched to a generic formulation. Among those patients, those who were converted back to the branded drug were considered switchback patients. Figure 1 lists the drugs under study, their therapeutic class, and the date (quarter/year) of generic entry on the Ontario market.

For all these medications, the study populations comprised patients who continuously used the branded drugs for ≥ 3 months in the 6 months preceding generic entry. "Continuous use" was defined as drug supplies without a gap of >30 days, or a time interval between two dispensing dates of ≤ 60 days. The study period ranged from 1 year before generic entry until March 2006. Because generic substitution is compulsory in Ontario, the use of a branded medication is not allowed without a physician

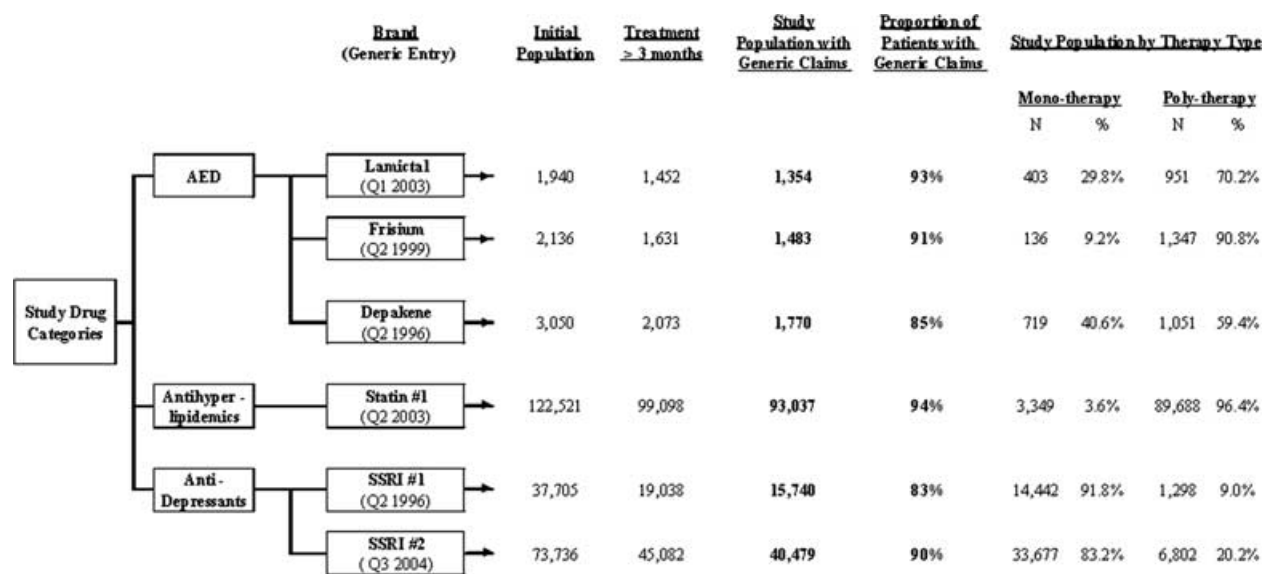


FIG. 1. Patient disposition. SSRI, selective serotonin reuptake inhibitor.

letter of medical necessity. Therefore we did not use the few patients who remained taking their branded medication after generic entry as a comparator group, as it was too small (~2%) for a reliable statistical analysis.

For the second objective, we assessed the potential clinical consequences of switching from branded Lamictal to generic LTG by using two cohorts of patients: (a) those switching back to branded Lamictal after being converted to generic LTG (switchback group), and (b) those staying with generic LTG after generic entry (generic group) as of January 1, 2003. The baseline dosages and number of entities for this case study were calculated by using a 90-day period of Lamictal use before generic substitution occurred. Similar to the switchback analysis, the follow-up period lasted until March 2006. A stratified analysis was conducted on Lamictal patients receiving monotherapy versus polytherapy of AEDs. Monotherapy was defined as patients taking only Lamictal during the 90 days before generic entry, whereas polytherapy referred to Lamictal patient using at least one other AED at the baseline period.

Outcome measures

Switchback rates

Switchback rates were estimated by using the Kaplan-Meier method, which is a conditional probability approach based on the subjects who were on the generic drug at the beginning of the interval. This calculation yields the probability that a patient will eventually switch back to the branded drug after being switched to the generic. Patients who were lost to follow-up were censored. The switchback rate was calculated as the cumulative probability of a patient switching back to the branded drug, given that he was on the generic drug at each time interval.

Potential adverse clinical consequences associated with switching from Lamictal to lamotrigine

The following outcomes were used as proxies for possible adverse clinical consequences: mean and median daily Lamictal or LTG doses and utilization of concomitant AED and non-AED medications. These outcomes were compared in the following time periods: 90-day baseline branded Lamictal period, generic LTG period, and switchback to branded Lamictal period among those who switched back from generic LTG.

Statistical analysis

Univariate statistics were calculated to describe population characteristics, switchback rates, and dosages. Statistical comparisons of means of continuous variables before and after generic entry were conducted by using paired Student's *t*-tests. Comparisons of medians were tested based on Signed Rank tests. Linear regressions were used to measure changes occurring during the generic period. Statistical significance was defined at a two-sided 0.05 α level. All statistical analyses were performed by using SAS release 9.1.3 (SAS Institute, Inc., Cary, NC, U.S.A.).

RESULTS

Patient characteristics

Figure 1 depicts the patient disposition and sample size for each of the seven drugs under study, stratified by monotherapy and polytherapy. A large share of branded products users (83% to 93%) received generic dispensings after generic availability. Most AED patients were polytherapy users (59% to 91%), meaning that they also received another AED during the baseline period. Almost all patients taking Statin 1 were receiving polytherapy

TABLE 1. Baseline characteristics of study populations

	Age ^a			Gender ^b			
				Female		Male	
	Mean	SD	Median	No.	%	No.	%
Lamictal	38.9	20.8	38.9	773	53.5%	672	46.5%
Frisium	38.5	20.5	37.0	787	49.2%	813	50.8%
Depakene	44.4	18.2	40.4	1,049	52.0%	968	48.0%
Statin 1	73.8	8.1	74.2	50,099	50.6%	48,846	49.4%
SSRI 1	56.0	19.0	56.0	12,773	68.0%	6,018	32.0%
SSRI 2	69.0	18.5	74.7	30,963	67.9%	14,671	32.1%

SSRI, selective serotonin reuptake inhibitor.

^aAs of January 1, 2003.

^bSum could differ from patient disposition because of unknown gender.

(96%), whereas a majority of SSRI 1 (9%) and SSRI 2 (20%) users were not.

Table 1 describes the age and gender distributions of patients in each drug-user cohort. Compared with other AED users, Depakene patients were older (mean age, 44.4 years), whereas Lamictal was used by more female patients (53.5%). In the other three non-AED groups, Statin 1 and SSRI 2 patients were older than SSRI 1 patients (73.8 years, 69.0 years, and 56.0 years, respectively), and the proportion of female patients was higher for SSRI 1 (68.0%) and SSRI 2 (67.9%).

Table 2 describes the patient disposition and characteristics of patients in the Lamictal case study. Because this was a large subset of the previous Lamictal cohort, their age and gender characteristics were almost identical (mean age, 38.5 years; 53.2% female patients).

Switchback rates

Figure 2 compares the switchback rates from generic to branded drugs under study. AEDs had much higher switchback rates compared with other long-term drugs. Depakene (20.9%) and Frisium (20.7%) patients experienced the highest switchback rates, followed by 12.9% for Lamictal patients. In the case of Lamictal, the switchback

TABLE 2. Patient disposition and baseline characteristics of the Lamictal case study

	No.	%
Initial population of Lamictal users	1,940	169.9%
Treatment >3 mo	1,452	127.2%
Patients in 90-day baseline with at least one generic claim (study population)	1,142	100.0%
Therapy type		
Monotherapy	330	28.9%
Polytherapy	812	71.1%
Switchback or not		
Switchback to brand medication	149	13.0%
Stayed on generic	993	87.0%
Age (yr) (mean; median)	38.5	37.0
Male (yr) (mean; median)	35.6	35.0
Female (yr) (mean; median)	40.0	39.0
Female gender (no., %)	608	53.2%

rate was higher among those taking polytherapy of AEDs compared with monotherapy (13.4 vs. 11.7%). A larger share of polytherapy patients switched back in the case for Depakene (21.3 vs. 20.6%), but not for Frisium (19.8 vs. 27.1%). In contrast, the switchback rates for non-NTI drugs were substantially lower at 1.5–2.9% for the statins and SSRIs under study.

Dosing patterns

Table 3 shows the dosing patterns of Lamictal and LTG, before and after generic entry. Among the switchback group, the average daily prescription dose of Lamictal was at 252.2 mg during the baseline period before generic entry, and this average dosage barely increased to 254.6 mg (0.9% increase; $p = 0.6925$) during the generic period, followed by a decrease to 250.7 mg when switched back to branded Lamictal (-1.5% ; $p = 0.8836$). The median daily prescription dose remained constant at 200 mg during the three periods.

Among the generic group, the average daily dispensed dose of Lamictal was 255.3 mg at baseline, with a significant dose increase to 271.1 mg (6.2% increase;

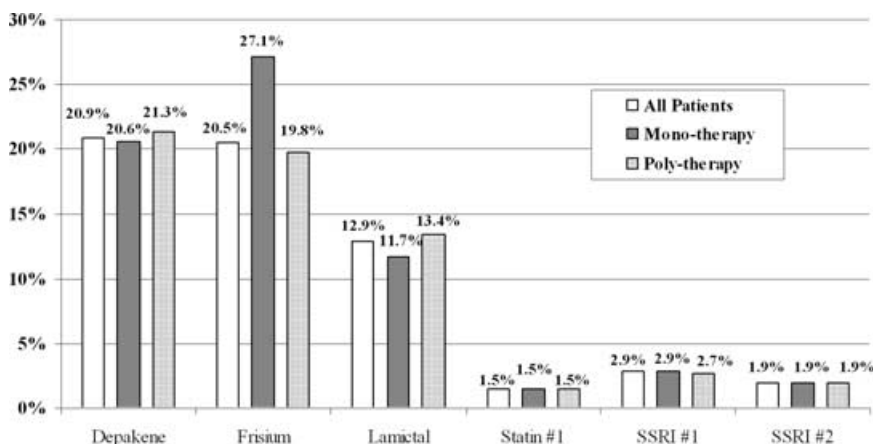
**FIG. 2.** Switchback rates: Kaplan-Meier estimations. SSRI, selective serotonin reuptake inhibitor.

TABLE 3. Dosing patterns of branded Lamictal and generic lamotrigine

Switchback group	Daily dosage (mg/day)			Statistics
	Baseline branded period	Generic period	Switchback period	
Lamictal				
Mean	252.2	254.6	250.7	p = 0.6925
Median	200.0	200.0	200.0	p = 0.0668
Generic group				
Lamictal				
Mean	255.3	271.1	NA	p < 0.0001
Median	200.0	232.5	NA	p < 0.0001
Switchback group	Percentage of initial branded dose (%)			Statistics
	Baseline branded period	Generic period	Switchback period	
Lamictal				
Mean	100.0	100.9	99.4	
Median	100.0	100.0	100.0	
Generic group				
Lamictal				
Mean	100.0	106.2	NA	
Median	100.0	116.3	NA	

Mean, Paired *t* test testing whether the dose change when switching from brand to generic is significantly different from zero; median, signed rank test.

NA = non-applicable

$p < 0.0001$) during the generic period. The corresponding median dose also increased from a baseline of 200 mg to 232.5 mg after the generic switch (16.3%; $p < 0.0001$). To further characterize the dosage pattern for the generic group, a regression analysis was performed. The regression coefficient suggested that the dose increase was at 15.4mg/day ($p < 0.0001$) at generic entry, with an average trend increase of 0.43 mg/day ($p < 0.0001$) during the following 3 years.

Use of concomitant medications

Table 4 presents the impact of generic entry on the use of AED and non-AED medications, both of which increased significantly for all patients (AED, 11.0%; $p < 0.0001$; non-AED, +15.6%; $p < 0.0001$). The number of codispensed entities decreased in the switchback group (AEDs,

–4.6%; $p = 0.125$; non-AEDs, –8.8%; $p = 0.042$). In the generic group, both numbers of entities increased and were statistically significant (AED, 13.4%; $p < 0.0001$; non-AED, +19.3%; $p < 0.0001$).

DISCUSSION

We addressed an important and often underrated issue regarding generic prescribing. The findings illustrate how and why AEDs are different from other medications when it comes to the desirability of switching to generic equivalents. To the best of our knowledge, the present study is the first to assess the switchback rates from generic to branded AEDs compared with switchback rates for non-AEDs. The high rate of switchback to branded AEDs (12.9 to 20.9%) compared with non-AEDs (1.5 to 2.9%) observed in this study is particularly impressive in light of the strict Ontario rules favoring generics and the fact that the switchback to branded medications is not allowed without a physician letter of medical necessity.

The ODB imposes a steep hurdle to prevent patients from switching back to a brand-name drug without documented medical necessity from the attending physician. Taking LTG as an example: since generic LTG was available in the ODB formulary in January 2003, all branded Lamictal prescriptions had to be switched to generic LTG at the pharmacy level, even if the prescription mentioned “do not substitute.” Doctors would have to petition to let a patient continue to take Lamictal by filing an adverse drug reaction form to Health Canada with all the required documentation, for the plan to pay for the brand medication. Therefore the fact that such a significant proportion

TABLE 4. Use of concomitant medications: branded Lamictal and generic lamotrigine

All patients	Baseline branded period	Generic period	Variation (%)	Statistics
No. AED entities/mo	0.92	1.02	11.0	$p < 0.0001$
Non-AED entities/mo	2.78	3.22	15.6	$p < 0.0001$
Switchback group				
No. AED entities/mo	0.96	0.92	–4.6	$p = 0.125$
No. non-AED entities/mo	2.77	2.52	–8.8	$p = 0.042$
Generic group				
No. AED entities/mo	0.91	1.03	13.4	$p < 0.0001$
No. non-AED entities/mo	2.79	3.33	19.3	$p < 0.0001$

Paired *t*-test testing indicated whether the change in the number of entities when switching from brand to generic is significantly different from zero.

of patients and physicians would go to these extents to switch back to the original branded AED reflects both their experience and their sentiments toward generic AEDs. These high switchback rates may reflect a common attitude among patients with epilepsy who are anxious to avoid having a recurrence, actual loss of seizure control, or other side effects.

Our findings add to the literature surrounding generic switching of AEDs and support prior studies demonstrating that generic AEDs could be less effective or tolerable compared with their branded counterparts (MacDonald, 1987; Welty, 1992; Jain, 1993; Wyllie, 2004; Crawford et al., 2006).

Although results based on claims data must be interpreted with caution, this significant increase in AED and non-AED drug dispensing after the generic switch is nonetheless intriguing and could potentially reflect adverse effects associated with generic LTG. Regardless of the pharmacokinetic data for generic versus brand-name preparations of AEDs, this study shows that patients with epilepsy are less likely to be satisfied with generic switches than are patients with other long-term medical conditions. The reasons for this phenomenon are beyond the data available in this article, but on this issue, the motivation is less important than the fact that, when it comes to AEDs, forced generic substitution is less likely to be well tolerated and may lead therefore to more medical and social complications.

The statistically significant increase in dosage from baseline to the generic period observed in LTG is also noteworthy. In patients who stayed with the generic, an absolute dosage increase of +6.2% ($p < 0.0001$) was observed. This suggests that bioavailability of the generic product may be decreased relative to the branded formulation, and a higher dose of the generic compound may be needed to maintain therapeutic efficacy. In a regression analysis, we found a significant initial dose increment of 15.4 mg/day and a trend increase of 0.43 mg/day for every month during the following 3 years. In other words, an increase in generic LTG dosage was observed from the moment of generic entry, and this dose escalation persisted through the end of the study period. This increased dosage requirement in patients receiving generic LTG, based on our regression results, could also factor into significant increased costs in the long term.

As a study based on a drug-claims database, the extent to which firm conclusions can be drawn is limited by several factors. First, we did not have access to information on patient diagnosis or medical history, which prevented further investigation into the factors that could have influenced switchback activity, both overall and within categories of mono- and polytherapy patients. Although the second part of this study aimed to investigate the clinical effects of generic substitution of Lamictal with epilepsy patients, other users of AEDs for conditions such as bipolar disorder

or neuropathic pain may also have been included in the study population, which may explain the relatively large share of polytherapy users in this study (Sander, 2004). Second, the motive for drug selection cannot be determined from claims data. It is possible that the decision process to switch to generic or back to brand was driven by nontherapeutic factors, such as inability to afford the branded drug, provincial rules governing generic substitution, or absence of a particular drug in the pharmacy stock. Finally, our study is subject to limitations inherent to claims data, including potential inaccuracies in billing, dispensing dates, drug doses, and drug codes.

The high switchback rates and dosing changes found in this study may be associated with adverse clinical consequences due to compulsory switching of branded AEDs to generic. These findings further abet the guidelines set by the American Academy of Neurology to avoid switching between proprietary and generic formulations of AEDs unless medically indicated.

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REFERENCES

- American Academy of Neurology. (1990) Assessment: generic substitution for antiepileptic medication. *Neurology* 40:1641–1643.
- Besag FM. (2000) Is generic prescribing acceptable in epilepsy? *Drug Safety* 23:173–182.
- Borgherini G. (2003) The bioequivalence and therapeutic efficacy of generic versus brand-name psychoactive drugs. *Clinical Therapeutics* 25:1578–1592.
- Crawford P, Hall WW, Chappell B, Collings J, Stewart A. (1996) Generic prescribing for epilepsy: is it safe? *Seizure* 5:1–5.
- Crawford P, Feely M, Guberman A, Kramer G. (2006) Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. *Seizure* 15:165–176.
- Feely M, Crawford P, Kramer G, Guberman A. (2005) Risk management in epilepsy: generic substitution and continuity of supply. *The European Journal of Hospital Pharmacy Science* 11:83–87.
- Gilman JT, Alvarez LA, Duchowny M. (1993) Carbamazepine toxicity resulting from generic substitution. *Neurology* 43:2696–2697.
- Guberman A, Corman C. (200) Generic substitution for brand name antiepileptic drugs: a survey. *The Canadian Journal of Neurological Sciences* 27:37–43.
- Jain KK. (1993) Investigation and management of loss of efficacy of an antiepileptic medication using carbamazepine as an example. *Journal of the Royal Society of Medicine* 86:133–136.
- Jobst BC, Holmes GL. (2004) Prescribing antiepileptic drugs: should patients be switched on the basis of cost? *CNS Drugs* 18:617–628.
- MacDonald JT. (1987) Breakthrough seizure following substitution of Depakene capsules (Abbott) with a generic product. *Neurology* 37:1885.
- Sander JW. (2004) The use of antiepileptic drugs: principles and practice. *Epilepsia* 45(suppl 6):28–34.
- Tyrer JH, Eadie MJ, Sutherland JM, Hooper WD. (1970) Outbreak of anticonvulsant intoxication in an Australian city. *British Medical Journal* 4:271–273.
- Welty TE, Pickering PR, Hale BC, Arazi R. (1992) Loss of seizure control associated with generic substitution of carbamazepine. *Annals of Pharmacotherapy* 26:775–777.
- Wilner AN. (2004) Therapeutic equivalency of generic antiepileptic drugs: results of a survey. *Epilepsy & Behavior* 5:995–998.
- Wyllie E, Pippenger CE, Rothner AD. (1987) Increased seizure frequency with generic primidone. *JAMA* 258:1216–1217.