

Generic substitution in the treatment of epilepsy

Case evidence of breakthrough seizures

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ABSTRACT

Objective: There are concerns that generic and brand antiepileptic drugs (AEDs) may not be therapeutically equivalent. This study investigated how generic AED substitution may have negative consequences.

Methods: Sixty-nine of 150 physicians who participated in a large survey on generic AED substitution completed a case review form regarding a patient who experienced a loss of seizure control due to a generic AED. Nineteen were excluded from analysis.

Results: Fifty patients, well-controlled on a brand AED, subsequently experienced a breakthrough seizure or increased seizure frequency after switching to a generic without other provoking factors. AEDs included phenytoin (15 cases), valproic acid (14), carbamazepine (7), gabapentin (8), and zonisamide (8). Two patients were on a combination of two AEDs, both of which were switched to generics. In 26 cases serum AED levels were known both before and after generic substitution. Twenty-one had lower levels at the time of the breakthrough seizure on the generic medication. Loss of seizure control had a negative impact on quality of life, including loss of driving privileges ($n = 30$) and missed school/work days ($n = 9$).

Conclusions: Changing from a brand antiepileptic drug (AED) to a generic may result in seizures. This raises the concern that current Food and Drug therapeutic equivalence testing regulations may not be adequate for AEDs and suggests that more clinical evidence is needed. Physicians, pharmacists, patients, and policy makers should be aware that for some patients there may be risks associated with switching from brand to generic AEDs. *Neurology*® 2008;71:525-530

GLOSSARY

AED = antiepileptic drug; FDA = Food and Drug Administration.

Health care systems have been under increasing pressure to control the costs of prescription drugs and other services. In an effort to reduce these costs, many insurance companies strongly encourage or mandate the substitution of medications with generic preparations. As of 2006, 49 states allow generic substitution by the pharmacist and 13 of those states mandate it.¹

The US Food and Drug Administration (FDA)'s position is that drugs testing as bioequivalent, according to their requirements, are approved as therapeutically equivalent and substitution can occur without concern about efficacy or toxicity. The FDA's position does not make a distinction for drugs used to treat narrow therapeutic range conditions such as epilepsy.²

Physicians and patients perceive that generic AEDs are not always equivalent to their branded counterparts, with about two-thirds of physicians reporting that they have cared for a patient who had a breakthrough seizure associated with switching to a generic AED.³⁻⁶ The American Academy of Neurology has issued two position papers^{7,8} stating that there is concern with generic AED substitution and recommends that physicians approve all generic AED substitutions when the AEDs are being used to treat epilepsy. The discordance between the

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FDA position and physician perception has led to calls for additional data⁹ and action on behalf of the FDA and the medical community, including physicians.¹⁰

Breakthrough seizures can adversely affect quality of life. Many authors advocate caution when substituting with a generic AED as adverse events have been reported,¹¹⁻¹⁵ including severe motor vehicle accidents, loss of work time, and increased doctor and hospital visits due to toxicity or increased seizure frequency, all of which have a personal and economic impact. Costs sustained from the effects of breakthrough seizures may outweigh the short-term savings that are realized by substitution with generic medications.⁷

In this study we sought to determine whether generic substitution of AEDs in the treatment of epilepsy can result in reduced seizure control and other negative consequences. Based on responses to a survey of physicians in the United States, we report 50 cases with documented seizures following the substitution of a brand AED with a generic equivalent, and the subsequent effects on quality of life.

METHODS Neurologists were recruited by e-mail and postal mail to participate in an online survey regarding epilepsy patients during May 2006.³ All neurologists were required to be in practice for at least 2 years and treat at least 50 patients per month. In addition, neurologists were required to treat at least eight patients with epilepsy per month and prescribe at least eight AEDs during that time. Neurologists were asked if they had a patient in their practice who had experienced a loss of seizure control caused by either a switch from a brand to a generic AED or from uncontrolled switching between generic forms of an AED while on the same medication regimen. Physicians were requested to exclude patients who experienced efficacy problems with generic AED medications used to treat a condition other than epilepsy. Respondents reporting this patient profile were eligible for case review. A questionnaire was sent to the neurologist to complete including a case report form (appendix e-1 on the *Neurology*[®] Web site at www.neurology.org).

Of the 451 neurologists who completed the online survey, 293 (65%) had a patient who fit the above profile and 237 were interested in participating in a follow-up case review. A total of 150 of those neurologists were randomly selected and sent chart audit materials via postal mail. Sixty-nine chart audits were received. Nineteen of these were excluded for the following reasons: data were missing (n = 4), the patient did not meet the original criteria (n = 7), patient switched to generic of a different brand (n = 2), patient noncompliance (n = 2), or the existence of other provoking factors such as stress (n = 2) or illness (n = 2) that may have caused the breakthrough seizure.

RESULTS The reported patients were evenly divided by sex and were between the ages of 11 and 84

Table Antiepileptic drugs (AEDs) used by patients in case reports

AED before switch	n	AED at time of seizure	n
Dilantin	14	Phenytoin	15
Phenytek	1	Valproic acid	14
Depakote ER	7	Carbamazepine	7
Depakote	7	Gabapentin	8
Tegretol	5	Zonisamide	8
Carbatrol	1		
Tegretol XR	1		
Neurontin	8		
Zonegran	8		

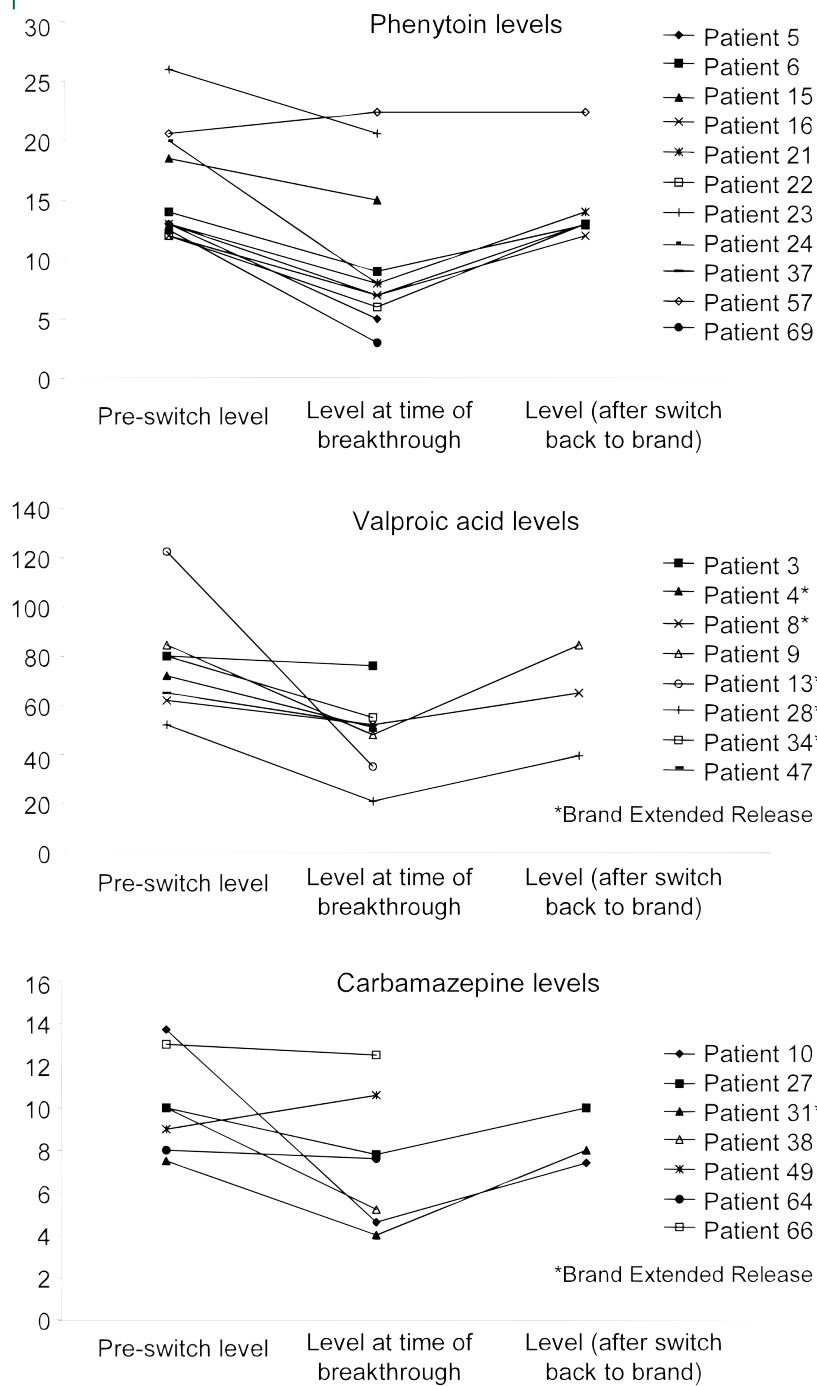
(median = 43) years old. Ninety-six percent of physicians had treated the patient for over 1 year. The most common breakthrough seizure types were complex partial in 36% and convulsive in 64%. More than one breakthrough seizure type was reported in 14%. Specific demographic and profile frequencies are in table e-1.

Prior to the breakthrough seizure, the majority of neurologists (62%) saw their patient one or two times per year. Ten percent of neurologists voluntarily mentioned increasing office visits until the seizures were under control. There was a corresponding increase in patients being seen three or more times per year, from 38% to 48% (table e-2).

Most patients (86%) had taken the original AED for a year or longer before they switched to the generic AED. Seventy-eight percent of patients were on the generic AED less than 3 months before the breakthrough seizure occurred (table e-3). The AEDs before the switch and at the time of the breakthrough seizure are given in the table.

Fourteen percent of neurologists spontaneously mentioned that the patient had been switched to a generic without their consent and 16% noted that the pharmacy substituted a generic without approval. Ninety-two percent of neurologists switched patients back to the original AED after the breakthrough seizure occurred. Of those, 91% went on the same dose as originally prescribed and 9% at an increased dose. Seventy-two percent of these patients were switched back within a week of the seizure and 91% within a month (table e-4). For the four patients not switched back, two physicians mentioned it was due to cost or insurance difficulties and two increased the dosage of the generic. At the time that the case reviews were completed, 96% (n = 44) of the patients who were switched back to their original AED regained seizure control per their physician's assessment (13 with 3 months or less of follow-up and 9 with no follow-up duration provided). Of the 15 patients who have had

Figure Blood serum levels by medication



seizures since the breakthrough seizure, one reported that they have a higher frequency of seizures.

In 26 cases, the AED level was reported during the baseline phase on the brand and at the time of the breakthrough seizure (figure). In 21 of these cases the levels were lower at the time of the breakthrough seizure. Blood levels at the time of the breakthrough seizure were on average 33% lower than while on the branded AED. The blood levels of those patients who were switched to generic carbamazepine decreased by an average of 20%, which was less of a decline than those switched to phenytoin (40%) or

valproic acid (34%). In 12 of the cases, levels were also given after the patient was switched back to the brand AED. In 10 of these cases the AED level returned to within 10% of the original baseline level. In the other two cases, the AED level was higher after the switchback, but was more than 10% lower than the baseline AED level. None of the case reports with gabapentin and zonisamide switches reported level data.

Of the 34 patients who had driving privileges, 88% had those privileges restricted for some period of time after the breakthrough seizure. Other consequences on quality of life included job loss (n = 1), fear of job loss (n = 2), missed school/work days (n = 9), increased anxiety (n = 5), and inconvenience/effect on family members (n = 4) (table e-5).

ILLUSTRATIVE CASES Below are four exemplar cases. All other cases can be reviewed in appendix e-2.

Patient 21. A 43-year-old man had a history of complex partial and secondarily generalized convulsive seizures that began at age 30 years. He was started on phenobarbital but was not controlled and experienced somnolence. Phenobarbital was discontinued and Dilantin 400 mg/day was prescribed. He remained seizure free for 11 years on Dilantin. While on Dilantin he had stable phenytoin concentrations of 12–14 $\mu\text{g}/\text{mL}$. He switched to generic phenytoin 400 mg/day due to a change in his health plan. Two months after the switch, he had a breakthrough secondarily generalized convulsion in his sleep. Phenytoin level was 8 $\mu\text{g}/\text{mL}$ in the emergency room. He received a loading dose of Dilantin in the emergency room and was restarted on Dilantin 400 mg/day within 1 week of the breakthrough seizure and has been seizure free for approximately 2 years and 1 month. After the patient was switched back to Dilantin, the phenytoin concentration was 14 $\mu\text{g}/\text{mL}$. He experienced anxiety about the breakthrough seizure and had restricted driving privileges for 6 months. This greatly inconvenienced his spouse who had to drive for him. The patient also reported that he had lost all confidence in generic medications.

Patient 37. A 75-year-old man had a history of nocturnal complex partial seizures, which were diagnosed at age 71 years after a 7-year history of infrequent (two to three times per year) episodes of confusion and verbal unresponsiveness followed by 12 to 24 hours of confusion. He was prescribed Dilantin 300 mg per day and had serum phenytoin concentrations of 12–14 $\mu\text{g}/\text{mL}$ and was seizure free for 2½ years. He was switched to generic phenytoin due to cost. He had a breakthrough seizure 2 months

after the switch. At the time of the breakthrough seizure, the phenytoin level was 7 $\mu\text{g}/\text{mL}$. He switched back to Dilantin at the same dose as before within 1 week and has been seizure free for approximately 1 year and 9 months with phenytoin levels of 12–14 $\mu\text{g}/\text{mL}$. He lost his driving privileges for 3 months which was very stressful and inconvenient. His wife was on dialysis and he was unable to drive her there.

Patient 47. A 36-year-old man had his first generalized seizure at age 32 years, at which time a head CT and MRI of the brain with gadolinium were normal. He was discharged without treatment. One week later he had a similar episode that lasted for 1 minute, with a postictal state lasting for 2 hours. His neurologic examination and an EEG were normal. He was started on Depakote, eventually achieving a dose of 500 mg BID. His valproic acid trough level was 62 $\mu\text{g}/\text{mL}$. He remained seizure free for 1 year. He changed jobs and was changed to a new insurance policy. His Depakote was switched to generic valproic acid at the same dose. One month later he had a breakthrough seizure. His valproic acid level at the time of the seizure was 52 $\mu\text{g}/\text{mL}$. His valproic acid dose was increased to 750 mg BID. He had difficulty tolerating this dose due to tremor and sedation. A follow-up level was 72 $\mu\text{g}/\text{mL}$. He was decreased to generic valproic acid 500 mg QAM and 750 mg QHS. He tolerated this dose better than but not as well as the brand name drug. He had a follow-up EEG that was normal. Two months later he had a second recurrent generalized seizure. A third EEG was done and again was normal as was a 48-hour ambulatory EEG. His trough valproic acid level at this time was 68 $\mu\text{g}/\text{mL}$. He was switched back to brand name Depakote with his insurance company's approval and has been seizure free for approximately 1 year and 7 months. The patient lost his driving privileges for more than 3 months and had to take time off from work, almost losing his job.

Patient 13. A 53-year-old man had a history of simple partial seizures that began at age 52 years. He had several other health problems including diabetes, hypertension, hypovolemia, and potassium wasting syndrome. While on Depakote ER he had stable valproic acid concentrations of 110–135 $\mu\text{g}/\text{mL}$ and was seizure free for 9 months. He was switched to generic valproic acid. He experienced a breakthrough seizure 1 month after the switch occurred. At the time of the breakthrough seizure, valproic acid level was 35 $\mu\text{g}/\text{mL}$. He switched back to the same dose of Depakote ER prior to the substitution within 1 week of the breakthrough seizure and has been seizure free at follow-up at 4 months. After his breakthrough seizure the patient lost his driving privileges for 1 year.

DISCUSSION We report 50 patients whose seizures were previously well-controlled while on a brand AED, who experienced a breakthrough seizure or an increase in seizure frequency when switched to the corresponding generic AED on the same dosing regimen. The physicians treating these patients believed that the change to the generic was the reason for the loss of seizure control.

Several other smaller case reports offer similar, albeit anecdotal, evidence that generic substitution can lead to breakthrough seizures. In one report, eight patients had increased seizures after being switched from brand Dilantin to generic phenytoin.¹¹ The mean phenytoin level was 17.7 on brand Dilantin and fell to a mean of 12.5 on generic phenytoin with increased seizures. The levels returned to the pre-switch range with switchback to brand Dilantin. In another report, a switch from brand Tegretol to generic carbamazepine resulted in a decrease in carbamazepine levels and a loss in seizure control in two patients.¹² In a separate report, a woman who was seizure free for 3 years while on Depakene experienced a breakthrough seizure 3 days after being switched to generic valproic acid.¹³

Toxicity has also been reported with generic substitution. A patient was hospitalized due to ataxia with a phenytoin level of 44.2, 10 days after being changed to generic phenytoin.¹⁴ After switchback to Dilantin the patient's phenytoin level returned to within the normal therapeutic range. Carbamazepine level elevations of 22% and 41% were reported after Epitol was substituted for Tegretol in two children.¹⁵

In a large Canadian claims database study spanning over 4 years, the rate of patients switching back to a brand medication from a generic were substantially higher for AEDs (lamotrigine, carbamazepine, and valproic acid) than for non-AED long-term therapies (antihyperlipidemics and antidepressants).¹⁶ Thirteen percent of those switched to lamotrigine and 20% of those switched to carbamazepine and valproic acid were switched back to the brand medication. In contrast, non-AED long-term therapies had switchback rates of 1.5–2.9%.¹⁶ As these data were obtained through payor claims, reasons for the switchback were not available. However, the authors speculated that patients may have experienced increased toxicity or loss of seizure control while on a generic AED which led to the high rate of switchback to brand AEDs.

Our study has the advantage of a nationally drawn sample, but it is limited in several respects including that it is semiquantitative. The overall proportion of cases received that met the inclusion criteria was 72%. We received viable case reports from 50 neurologists, or 33% of those randomly selected for

participation. Caution is always needed in interpreting self-reported data. However, given the clarity of the instructions and the request to complete an actual chart audit for each case, we expect more valid data than from an unaided recall approach, as would be obtained in a standard survey.

Another limitation to our study is that it was retrospective. There is the possibility that the timing of the breakthrough seizures was coincidental and not causally related to the switch to a generic medication. However, the large number of cases and the documentation of lower drug serum levels in some of the cases that returned to the previous baseline after switchback favor the attribution of the breakthrough seizures to the generic substitution. This notion is supported by the cases in which breakthrough seizures were associated with the substitution of standard release generics (valproic acid) from extended release compounds (divalproex sodium extended release). In such instances, lower trough levels might be related to seizure recurrence. The breakthrough seizures occurred at doses of the generics identical to those of the brand. In a few of the cases, the formulation was changed from divalproex sodium to valproic acid at equal doses, which should result in similar efficacy although less tolerability. To limit the number of variables, we excluded cases without confirmation of compliance and with any other recognized factors that may have contributed to a seizure.

Most AEDs with available generics are represented in our case series. Although some have argued¹⁷ that more difficult to make compounds with low water solubility or saturation kinetics, such as phenytoin, are the major concern, our data on zonisamide and gabapentin, which are water soluble, pharmacokinetically well-behaved compounds, suggest that the narrow therapeutic range may be the major factor.

Although the criteria for case submission were that patients must have experienced a loss of seizure control caused by either a switch from a brand to a generic AED or from uncontrolled switching between generic forms of an AED, we did not receive any cases with the latter type of substitution. This raises the concern that physicians are not aware of generic to generic switching within pharmacies. If a patient is well-controlled on one generic AED and experiences a breakthrough seizure when switched to a second generic manufacturer, neither the physician nor patient may be aware of this possible causative factor and it could be the reason why some patients are unable to achieve seizure control.

The FDA considers drugs to be therapeutically equivalent when they meet bioequivalence criteria based on *in vitro* and *in vivo* studies. The drugs may

differ in certain characteristics, such as shape, release mechanisms, and excipients, but are considered to have the same effectiveness and safety. The bioequivalence testing for generic AEDs is done *in vivo* in 24 to 36 healthy volunteers. The FDA requires that the 90% CI for the area under the curve and concentration maximum on the concentration–time plot be within 80–125% of the reference compound (usually the brand). They use two one-sided *t* tests at the 0.05 level of significance which “ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved.”¹⁸ The FDA states that the prescription of a brand should be considered a medical necessity only when non-bioequivalence differences (such as shape or color) are important to a particular patient.¹⁸

A variety of concerns have been raised about the FDA requirements for bioequivalence: the number of individuals tested is relatively small; the individuals tested are not affected by the medical condition being treated (in our situation, epilepsy), or by the spectrum of medical illnesses that affect a typical individual with the condition; and that the bioequivalence testing is done in the absence of other, potentially confounding, medications.¹⁹ The small numbers of subjects tested make it probable that infrequent metabolic, genetic, or biologic variations are unlikely to be detected. Clinicians commonly believe that the 80–125% range is too broad for narrow therapeutic range conditions.²⁰ These and other individual factors potentially amplify small differences in bioequivalence, raising the possibility that some patients with epilepsy are being put at risk for more seizures or adverse effects with generic substitution.²¹

The FDA relies on postmarketing physician reporting of adverse events to identify drugs that may pose a safety risk. They recognize limitations of adverse event reporting including underreporting.²² While estimates vary, it is thought that fewer than 10% of adverse events are reported.²² The FDA states that there are no adequate data indicating that the current testing for generic medications is faulty, even for narrow therapeutic range conditions.² It is unclear if the problem is underreporting or if there is actually no problem with generic preparations of AEDs, a crucial issue that requires further study. Ideally, double-blind placebo-controlled trials should be done in a large population of people with epilepsy for each generic preparation to determine therapeutic equivalence and to assess the frequency of non-equivalence on clinical grounds. These studies would address whether it is sensible from a financial and public health perspective to change existing policy.

Unfortunately, such studies are costly and impractical. Alternatively, performing a bioequivalence study on an enriched population, those who previously reported a problem with generic substitution, and using drug levels as a surrogate measure of therapeutic equivalence, could serve as a means to assess if there is excessive variability. Additionally, it is appropriate to continue to accumulate postmarketing case-report data carefully.

Given the current uncertainty, and the potential negative effect on quality of life from seizure recurrence, we believe that in a seizure-free, fully compliant patient, it is prudent for the physician to ensure that the AED preparation does not vary. Since a definitive evidence base on the effects of generic AED substitution is lacking, we advocate that physicians report cases in which generic AED substitution is associated with breakthrough seizures or medication toxicity to the FDA using the MedWatch system (<http://www.fda.gov/medwatch/>). Physicians should make every effort to document levels at the time of the seizure or other adverse event as well as in the baseline state and confirm compliance to maximize the validity of the data.

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REFERENCES

1. National Association of Boards of Pharmacy. Survey of pharmacy law. Mount Prospect, IL; 2006.
2. Nightingale SL. Therapeutic equivalence of generic drugs letter to health practitioners. 1998. Available at: <http://www.fda.gov/cder/news/nightgenlett.htm>. Accessed July 29, 2007.
3. Berg MJ, Gross R. Physician and patients perceive that generic drug substitution of antiepileptic drugs can cause break through seizures: results form a US survey. *Epilepsia* 2006;47(suppl 4):155 Abstract.
4. Wilner AN. Therapeutic equivalency of generic antiepileptic drugs: results of a survey. *Epilepsy Behav* 2004;5:995–998.
5. Guberman A, Corman C. Generic substitution for brand name antiepileptic drugs: a survey. *Can J Neurol Sci* 2000; 27:37–43.
6. Haskins LS, Tomaszewski KJ, Crawford P. Patient and physician reactions to generic antiepileptic substitution in the treatment of epilepsy. *Epilepsy Behav* 2005;7:98–105.
7. Therapeutics and Technology Assessment Subcommittee, American Academy of Neurology. Assessment: generic substitution for antiepileptic medication. *Neurology* 1990; 40:1641–1643.
8. Liow K, Barkley GL, Pollard JR, Harden CL, Bazil CW. Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. *Neurology* 2007;68:1249–1250.
9. Cassels C. Mandatory generic substitution of antiepileptic drugs raises concerns. 2006. Available at: <http://www.medscape.com/viewarticle/548860>. Accessed May 22, 2007.
10. Berg M. What's the problem with generic antiepileptic drugs? A call to action. *Neurology* 2007;68:1245–1246.
11. Burkhardt RT, Leppik IE, Blesi K, Scott S, Gapany SR, Cloyd JC. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. *Neurology* 2004;63:1494–1496.
12. Welty TE, Pickering PR, Hale BC, Arazi R. Loss of seizure control associated with generic substitution of carbamazepine. *Ann Pharmacother* 1992;26:775–777.
13. MacDonald JT. Breakthrough seizure following substitution of Depakene capsules (Abbott) with a generic product. *Neurology* 1987;37:1885.
14. Finestone AJ, Williams FF. Generic substitution resulting in toxicity. *PA Med* 1985;88:34.
15. Gilman JT, Alvarez LA, Duchowny M. Carbamazepine toxicity resulting from generic substitution. *Neurology* 1993;43:2696–2697.
16. Andermann F, Duh MS, Gosselin A, Paradis PE. Compulsory generic switching of antiepileptic drugs: high switch-back rates to brand compounds compared with other drug classes. *Epilepsia* 2007;48:464–469.
17. Besag FM. Is generic prescribing acceptable in epilepsy? *Drug Saf* 2000;23:173–182.
18. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Generic Drugs. Approved drug products with therapeutic equivalence evaluations. 2007 (27th ed.) Available at: <http://www.fda.gov/cder/orange/obannual.pdf>. Accessed March 4, 2007.
19. Crawford P, Feely M, Guberman A, Kramer G. Are there potential problems with generic substitution of antiepileptic drugs? *Seizure* 2006;15:165–176.
20. Banahan BF, Kolassa EM. A physician survey on generic drugs and substitution of critical dose medications. *Arch Intern Med* 1997;157:2080–2088.
21. Meyer MC, Straughn AB. Biopharmaceutical factors in seizure control and drug toxicity. *Am J Hosp Pharm* 1993; 50(12 suppl 5):S17–22.
22. Food and Drug Administration. The clinical impact of adverse event reporting. Available at: <http://www.fda.gov/medwatch/articles/med.pdf>. Accessed February 27, 2007.