

# Continuing Education for Pharmacists

## Generic Anti-Epileptic Drug Substitution: What are the Issues?

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**Goal:** The goal of this session is to discuss issues associated with generic substitution of anti-epileptic drug therapy.

**Objectives:** At the conclusion of this lesson, successful participants should be able to:

1. Recognize the FDA requirements for generic product approval
2. Identify the concerns in bioequivalence testing for AED therapies
3. Identify the clinical and economic implications of AED generic substitution

**Background:** Epilepsy affects approximately 2.5 million people in the United States.<sup>1</sup> Each year, there are roughly 200,000 new cases diagnosed, with annual direct and indirect costs amounting to \$15.5 billion. Epilepsy is characterized by recurrent seizures, defined as abnormal electrical activity in the brain. Seizures can occur in a number of settings, including metabolic, toxic, and infectious conditions<sup>2</sup>; however, seizures occurring in these conditions do not necessarily constitute a diagnosis of epilepsy. Epilepsy is defined as two or more seizures that are not provoked by other illnesses or circumstances.<sup>3</sup> Since it is difficult to capture a seizure in the healthcare setting (i.e., for a provider to witness), a thorough history of the event from the patient and any witnesses is crucial for diagnosis. Patients

experiencing recurrent seizures are at an increased risk of complications such as cognitive impairment, problems with memory, and delayed neurodevelopment and the seizures are life-threatening; therefore, chronic treatment is often needed. The ultimate goal of therapy for epilepsy is for a patient to have no seizures (i.e., be seizure-free) as well as minimal side effects from anti-epileptic drug (AED) therapy. Therapeutic doses of AED therapies are highly individualized, usually requiring careful titration with close monitoring. Despite many therapeutic options and extensive research efforts, more than one-third of epilepsy patients continue to have seizures with treatment.<sup>1</sup> This difficulty in achieving seizure control coupled with the potential complications of repeated ictal events, result in a justified reluctance to adjust therapy if a patient achieves the ideal balance of no seizures or side effects.

While there are many reasons a patient may not have adequate control (e.g., inadequate doses, noncompliance, drug interactions), one of the more recent concerns is AED generic substitution. That is, switching a patient's medication from the brand-to-generic or even generic-to-generic if there are multiple generic product manufacturers. While generic products have the potential to offer tremendous cost-savings for patients and third-party

payers, this benefit is based on the assumption that a generic product has the same pharmacokinetic and pharmacodynamic profile as that of its brand-name counterpart. Although bioequivalence may be proven when applying for generic drug approval, many clinicians question whether this translates to therapeutic equivalence. In a recent survey, neurologists were asked to complete a case review regarding a patient who experienced loss of seizure control due to a generic AED switch.<sup>4</sup> On average, serum levels were 33% lower at the time of the breakthrough seizure compared to the pre-switch level. Nearly all patients (92%) were switched back to brand AED and 96% of these patients regained seizure control after the switch back. To explore this issue further, the remainder of this lesson will review the process of generic drug approval and summarize current evidence of clinical nonequivalence as well as economic considerations with AED generic substitution.

### **FDA Generic Drug Approval:**

Currently the Food and Drug Administration (FDA) approves a generic formulation if the manufacturer can prove bioequivalence to the approved brand-name product.<sup>5</sup> The generic product must contain an identical amount of active ingredient in the same dosage form to be given by the same route. In addition, the product must be manufactured in compliance

with Good Manufacturing Practices. Finally, the rate and extent of absorption of active ingredient must not be significantly different from the brand-name medication. To measure these parameters, an *in vivo* bioequivalence test is required and is usually conducted in 24-36 healthy adults. This test is generally performed as a smaller, single-dose crossover study. The area under the curve (AUC) of the drug concentration-time curve and maximum plasma concentration (C<sub>max</sub>) must be similar, defined as the 90% confidence interval of the log-transformed ratios of AUC and C<sub>max</sub> between brand and generic products falling within 80-125% range. If these criteria are met, the product is considered bioequivalent to the brand formulation and therefore interchangeable. The actual difference in mean plasma concentrations is small. In fact, when assessing approved generics, the FDA has found a mean bioavailability difference of 3.5% between generic and brand equivalents.<sup>6</sup>

The FDA has rated all generic drugs “A” or “B”.<sup>7</sup> “A” drugs are considered bioequivalent to the brand-name product, either because they have demonstrated equivalence in human bioavailability studies (“AB”) or are unlikely to have bioavailability problems (“AA”). “B” drugs have not demonstrated bioequivalence by an *in vivo* test; examples include extended release dosage forms, drugs with known differences in bioequivalence, as well as products with unavailable or insufficient bioequivalence information. Only A-rated products are interchangeable with their brand-name equivalents.

Given these requirements, how might

brand-name and generic antiepileptic drugs differ? First, bioequivalence tests for AED medications are performed as single-dose tests and they are not conducted in patients with epilepsy, the group of patients who will be using these medications long-term. Differences in drug absorption, distribution, metabolism, and excretion may differ based on age, sex, ethnicity, smoking status, genetic variation and concomitant medication use. These variants may be highly significant in patients with epilepsy. For example, the studies are not conducted in children or older adults, which are two groups identified as having a higher risk of developing epilepsy. Age-related declines in absorption time and excretion due to physiologic changes in the intestine, liver, and kidney, may have a significant impact on the plasma levels of medications. In addition, stomach and intestinal pH vary depending on concurrent therapy (i.e., proton pump inhibitor) and age, as organs develop in the young child and tend to slow acid production with age. For medications that need to be absorbed in a particular form (ionized or non-ionized), the pH can be an important factor in the ultimate level of drug that reaches systemic circulation. Phenytoin is one such example, as it must be in the ionized form for absorption; therefore, alterations in the stomach pH and/or product formulation (salt, acid) may significantly impact the extent of absorption. Such differences in age and concomitant medications, along with other factors, cannot be accounted for in the bioequivalence testing conducted in healthy adults.

Furthermore, for a drug to circulate in the plasma after oral administration,

drug disintegration, dissolution, and absorption across mucosal membranes in the intestine or lymph must occur in a timely fashion. One concern regarding bioequivalence is that the excipients (i.e., any inactive ingredient in the formulation) of the generic product do not need to be the same as the brand-name counterpart. Changes in excipient identity or amount may alter those pharmacokinetic parameters not measured for in bioequivalence testing. For many drugs, these variations make little or no difference in the therapeutic affect of the medication. However, for drugs with narrow therapeutic indices, including AED therapies, subtle differences in formulation may result in pharmacokinetic disparities that put patients at an increased risk of breakthrough seizures or side effects. Specifically, drug formulations with low solubility and absorption (i.e., phenytoin and carbamazepine) are perhaps the most threatened group regarding bioequivalence, as subtle changes in absorption can cause significant differences in plasma concentrations.

Moreover, perhaps the most important issue is that the FDA does not require any testing to prove bioequivalence among the generic products. Based on this information, two generic drug products may each be bioequivalent to the brand-name medication, but may fall on opposite ends of the ranges and be different enough from each other to cause problems. A major concern surrounding this issue is that pharmacies often switch generic product manufacturers and are not required to inform the patient or provider of this switch.<sup>8</sup> As of 2009, in the United States there were 17

brand-name AEDs available (excluding benzodiazepines), with 11 available generically.<sup>9</sup> The generic manufacturers for each medication ranged from 3 to 42. This kind of data has prompted several national organizations, including the American Academy of Neurology, American Epilepsy Society, and Epilepsy Foundation, to draft position statements recommending that patients and providers be notified and consent given before switching a patient's AED therapy.<sup>10,11,12</sup>

**Clinical Evidence:** Evidence supporting the concern of AED generic substitution is found in several recently published case-control studies and surveys. First, in a retrospective analysis, switchback rates of several classes of medications, including AEDs, antidepressants, and cholesterol-lowering drugs, were assessed to compare switchback rates of AEDs versus non-AEDs.<sup>13</sup> For all medications, patients were taking branded drugs for at least 3 months before switching to a generic equivalent. A switchback was then defined as converting back to the branded drug. Between January 2002 and March 2006, data collected revealed a high switchback rate for AEDs (12.9%-20.9%) as compared to the non-AED classes of drugs (1.5-2.9%). In addition, a specific analysis was conducted looking at dosages of brand and generic lamotrigine, which found that for patients who remained on generic lamotrigine, a dose change of +6.2% was required ( $p < 0.0001$ ). Limitations to this study include that it was retrospective, and reasons for switchbacks were not specifically assessed.

A retrospective case control analysis was conducted utilizing health claims

data of cases ( $n=416$ ) receiving care in an ambulance, emergency room, or inpatient hospital with a primary epilepsy diagnosis between July 1, 2006 and December 31, 2006.<sup>14</sup> The control group ( $n=1248$ ) had a primary epilepsy diagnosis in a physician's office during the same date range. Cases were eligible if they included stable patients (i.e., had not been hospitalized in the last 6 months with a primary epilepsy diagnosis) between ages 12-64 years old, and had continuous insurance eligibility for 6 months prior to the date of hospitalization or clinic visit. Cases and controls were matched in a 1:3 ratio by age and epilepsy diagnosis. These dates were chosen because the range was shortly after a generic version of zonisamide became available. There were no significant differences between groups regarding demographics or diagnosis. Results demonstrated cases were significantly more likely to have an A-rated AED formulation switch than controls (odds ratio [OR] 1.81, 95% confidence interval [CI] 1.25-2.63). This analysis found an association between recent AED formulation switching and obtaining care in an inpatient or emergency care setting. Limitations include the fact that concomitant medications, which may have introduced drug interactions with the AED therapy, as well as patients experiencing breakthrough seizures who did not seek medical care were not accounted for. So, this study may in fact under-report the problem.

In a separate case-control analysis, cases of patients having an epileptic event requiring acute care were compared to control patients to determine the odds of having an AED substitution with an acute event.<sup>15</sup>

Cases ( $n=991$ ) of patients receiving care in an ambulance, emergency department, or hospital with a primary epilepsy diagnosis between October 1, 2005 and December 31, 2006 were matched in 1:3 for gender, age, and epilepsy diagnosis to controls (patients with epilepsy who did not have an event,  $n=2973$ ). AED substitution rates for the cases and controls were found to be 11% and 6%, respectively. Cases were significantly more likely to have an A-rated AED formulation substitution than controls (OR 1.84, 95% CI 1.44-2.36). This analysis concluded that patients having an event were 80% more likely to have had a recent AED substitution compared to matched controls not having an event. Similar to the previous study, limitations include lack of information regarding concomitant medications and patients experiencing seizures or side effects who did not seek medical care.

Finally, a more recent case-control study was conducted in the United States which looked at the potential association of A-rated switching of AED therapy and breakthrough seizures.<sup>16</sup> Using claims data between January 2005 and December 2007, individuals with a documented exacerbation of epilepsy ( $n=2949$ ) were compared to those with the same baseline epilepsy diagnosis who did not have an exacerbation ( $n=8847$ ) to determine whether there was a difference in switch rates between A-rated AEDs within 90 days. In unadjusted data, cases were significantly more likely to be associated with an A-rated AED switch than controls (OR 1.51, 95% CI 1.29-1.76). However, when potential confounders including patient age, 2005 Charlson comorbidity index, total number of AEDs, number

of new interacting drugs, new AEDs in the 90 days prior to the exacerbation, and change in epilepsy diagnosis in 6 months prior to the exacerbation were accounted for, the adjusted odds ratio became nonsignificant (OR 1.08, 95% CI 0.91-1.29). Results of this study revealed that the potential for breakthrough seizures occurring due to an A-rated AED switch depends on many factors including overall control of disease during the switch as well as other variables that can affect AED plasma levels.

Taken together, these studies suggest that a correlation exists between acute events requiring medical care and recent AED substitution. However, when accounting for potential confounders such as age, number of AEDs, number of new interacting drugs, or a recent change in epilepsy diagnosis, there was no significant association in the number of breakthrough seizures or adverse events with a recent AED switch. Thus, it may be that only certain populations are at significant risk for having an acute event due to an AED switch.

### **Economic Implications:**

Generic drugs have tremendous cost-savings potential. Generic medications generally cost 80-85% less than brand-name medications.<sup>17</sup> The FDA has estimated that if the use of generic medications was increased to reduce total prescription costs by just 10%, this would amount to an estimated \$14 billion in savings. However, such cost-savings is negligible if the switch leads to expensive consequences, such as hospitalizations, provider office visits, or days of work lost. In fact, these cost implications have been assessed

in recent reports. Using health claims data from Quebec's provincial health plan, 671 patients using branded lamotrigine to treat their epilepsy were followed.<sup>18</sup> Authors projected Canadian costs of treatment into the United States setting and found that overall healthcare costs would be 6-9% higher during generic AED use compared to brand AED use. Specifically, when comparing periods of branded and generic use, significant total projected health costs during the time patients received the generic product were found (\$1750-2500 per person-year,  $p < 0.01$ ). These excessive costs were attributed to the probability of increased physician visits, hospitalizations, and utility of pharmacy services.

A more recent review discussed economic implications of generic substitution of all AEDs.<sup>19</sup> In addition to summarizing data from Lelorier et al., authors discussed the outcomes of a review of claims data in the United States for more than 33,600 patients from 2000-2007. In this assessment, periods of generic AED treatment were associated with higher annual medical costs (adjusted cost difference [CD] \$3186, 95% CI 2359-4012) and total costs (adjusted CD \$3254, 95% CI 2403-4105). Considering the data from these economic analyses, authors drafted an expert opinion recommending that (1) patients stable on a branded AED should not be switched to a generic without patient and provider consent, (2) patients should not be switched from one generic AED formulation to another, and (3) generic versions of branded AEDs can be used to initiate monotherapy if their supply can be guaranteed for the duration of the patient's therapy.

### **Summary and Conclusions:**

Patients with epilepsy often require chronic therapy to control their condition. The ultimate treatment goal, which is difficult to achieve, is for the patient to be seizure-free with no side effects from drug therapy. Recent evidence suggests that AED generic substitution may place patients at an increased risk for seeking medical attention due to breakthrough seizures and/or side effects. However, research efforts should focus on whether there are certain high-risk groups of patients, as one study found that an A-rated AED switch was not associated with breakthrough seizures when confounding factors were accounted for. Preliminary economic evaluations demonstrate that generic AED drug use results in cheaper drug cost but is associated with higher total medical costs when compared to brand-name AED drug use. Pharmacies should inform patients and providers of AED generic substitutions so a decision can be made about whether the substitution would pose a significant risk to the patient. In addition, all healthcare providers should make an effort to report cases in which generic AED substitution is related to breakthrough seizures or side effects to the FDA using the MedWatch system. Finally, close monitoring, which may include blood levels, should be considered during a necessary switch.

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# Continuing Education for Pharmacists

## Quiz and Evaluation

### Anti-Epileptic Drug Subscription: What are the Issues?

- Which of the following is required by the FDA for a generic drug to be approved?
  - Manufactured in compliance with Good Manufacturing Practices
  - Identical excipient content and concentration
  - Bioequivalence
  - All of the above
  - A and C
  - A and B
- According to the FDA, what defines bioequivalence?
  - 90% confidence interval of AUC and Cmax between brand and generic falling between 80-125%
  - AUC and Cmax between brand and generic falling between 80-125%
  - 90% confidence interval of log-transformed ratios of AUC and Cmax between brand and generic falling between 80-125%
  - 95% confidence interval of AUC and Cmax between brand and generic falling between 80-125%
- Which of the following most accurately describes how a bioequivalence test is usually conducted?
  - Large single-dose crossover study in healthy subjects
  - Small single-dose crossover study in healthy subjects
  - Small multiple-dose crossover study in healthy subjects
  - Small single-dose crossover study in subjects with the condition the medication treats
- Which of the following is not considered in bioequivalence tests?
  - Concomitant medications
  - Smoking status
  - Genetic variation
  - Age
  - All of the above
- How does the FDA test for bioequivalence between generic products (i.e., from various manufacturers) of the same active medication?
  - Small single-dose crossover study in healthy subjects
  - Small multiple-dose crossover study in healthy subjects
  - Small single-dose crossover study in subjects with the condition the medication treats
  - The FDA does not test for bioequivalence among generic products
- Which group of medications is most likely to have significant changes in plasma concentrations with altered absorption?
  - Narrow therapeutic index drugs with low solubility
  - Wide therapeutic index drugs with high solubility
  - Narrow therapeutic index drugs with high solubility
  - Wide therapeutic index drugs with low solubility
- Results from a recent case-control study revealed that, after changing from a brand product to generic formulation, which of the following classes of medications was significantly associated with higher switchback rates?
  - Antidepressants
  - Antiepileptic drugs
  - Cholesterol-lowering drugs
  - A and B
- Which of the following was identified as a potential confounder when assessing AED switchback rates?
  - Gender
  - Number of new interacting medications
  - Dose of antiepileptic drug
  - All of the above
- Which of the following is a conclusion that Canadian authors made after retrospective assessment of claims data in Canada for patients using lamotrigine to treat their epilepsy?
  - Overall healthcare costs in the US would be higher during generic AED use than brand AED use
  - Overall healthcare costs in the US would be lower during generic AED use than brand AED use
  - Generic AED use would be associated with an increased probability of hospitalizations and physician visits
  - A and C
- Which of the following is a disadvantage of the currently available literature regarding AED generic substitution?
  - All studies analyze insurance claims data or doctors' reporting, which limit results to those who seek medical attention
  - There are no economical analyses available to date
  - There is no reporting that switching back to the original brand resulted in regaining of seizure control
  - No study has assessed for a required change in dosage when switching from a brand to generic AED product



# Journal CPE Answer Sheet

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## Genetic Anti-Epileptic Drug Subscription: What are the Issues?

This lesson is a knowledge-based CPE activity and is targeted to pharmacists.

GPhA code: J10-06

ACPE#: 0142-0000-10-006-H01-P

Contact Hours: 1.5 (0.15 CEU)

Release Date: 06/01/2010

Expiration Date: 06/01/2013

1. Select one correct answer per question and circle the appropriate letter below using blue or black ink (no red ink or pencil.)

2. Members submit \$4.00, Non-members must include \$10.00 to cover the cost of grading and issuing statements of credit/ Please send check or money order only. Note: GPhA members will receive priority in processing CE.

Statements of credit for GPhA members will be emailed or mailed within four weeks of receipt of the course quiz.

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|------------|-------------|
| 1. A B C D | 6. A B C D  |
| 2. A B C D | 7. A B C D  |
| 3. A B C D | 8. A B C D  |
| 4. A B C D | 9. A B C D  |
| 5. A B C D | 10. A B C D |

### Activity Evaluation: must be completed for credit

Please rate the following items on a scale from 1 (poor) to 5 (excellent) as to how well the activity:

- |  |       |   |   |   |   |
|--|-------|---|---|---|---|
| 1. Met my educational needs:                                 | 1     | 2 | 3 | 4 | 5 |
| 2. Relates to pharmacy practice:                             | 1     | 2 | 3 | 4 | 5 |
| 3. Achieves the stated learning objectives:                  | 1     | 2 | 3 | 4 | 5 |
| 4. Faculty presented the information:                        | 1     | 2 | 3 | 4 | 5 |
| 5. Teaching methods conveyed information:                    | 1     | 2 | 3 | 4 | 5 |
| 6. Post-test aided in assessing my grasp of the information: | 1     | 2 | 3 | 4 | 5 |
| 7. Avoided any bias or commercial bias:                      | 1     | 2 | 3 | 4 | 5 |
| 8. How long did it take to complete this activity?           | _____ |   |   |   |   |

A passing grade of 70% is required for each examination. A person who fails the exam may resubmit the quiz only once at no additional charge.

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Remove this page from the Journal and mail this completed quiz and evaluation to: GPhA, 50 Lenox Pointe NE, Atlanta, GA 30324.

