REVIEW ARTICLE

# The Controversy over Generic Antiepileptic Drugs

*Susan J. Shaw, MD[1,2,3] and Adam L. Hartman, MD[1]*

*[1]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland; [2]Department of Neurology, University of Southern California, Keck School of Medicine, Los Angeles, California; [3]Rancho Los Amigos National Rehabilitation Center, Downey, California*

As patent protection ends for the next generation of antiepileptic drugs (AEDs), a complex debate continues over generic substitution of AEDs. On one hand, generic drug formulations provide cost savings for patients and society. On the other hand, patients with epilepsy and physicians are wary about the adequacy and efficacy of the Food and Drug Administration's (FDA) standards for generics. This article reviews current and proposed bioequivalence test procedures, summarizes new generic AED formulations and their costs, and discusses potential pitfalls in the current standards. These shortcomings include certain pharmacokinetic factors and clinical pharmacologic factors that may affect bioequivalence of generic AEDs, and statistical limitations of the standards. While the drug concentration differences between the brand name drug and each generic formulation are unlikely to be substantial, the differences with generic-to-generic switches will be greater and potentially clinically significant. Conversely, owing to their more favorable pharmacokinetic profile, newer AEDs may be less prone to problems with generic substitution than older ones. Unfortunately, very few data are available to guide decisions regarding what is best for an individual patient. Based on new prediction methods, generic substitution should be safe for many patients but identifying them ultimately requires more rigorous study.

**KEYWORDS** antiepileptic drug, child, epilepsy, generic, infant

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## INTRODUCTION

Generic formulations have been available for a decade or more for the older generation of antiepileptic drugs (AEDs), including carbamazepine, ethosuximide, phenobarbital, phenytoin, and valproic acid. As the newer generation of AEDs becomes available in generic form, a debate persists regarding the safety and efficacy of generics for treatment of epilepsy. A multinational survey of patients in 2005 found that 23% believed that generics are linked to breakthrough seizures, while 58% were uncomfortable with using a generic to treat their epilepsy.[1] In a survey of physicians, 88% reported being concerned about an increase in breakthrough seizures from generics.[2] Furthermore, the American Academy of Neurology (AAN) believes that "the Food and Drug Administration has allowed for significant differences between name-brand and generic

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**ABBREVIATIONS** AAN, American Academy of Neurology; AED, antiepileptic drugs; AES, American Epilepsy Society; ANDA, abbreviated new drug application; AUC, area under the concentration curve; BCS, Biopharmaceutics Classification System; CI, confidence interval; Cmax, maximum (peak) plasma concentration of the drug; FDA, Food and Drug Administration; NDA, new drug application; LICE, Italian League against Epilepsy; NTI, narrow therapeutic index; Tmax, amount of time that a drug is present at the maximum concentration in serum; USP, United States Pharmacopeia

Address correspondence to: Susan J. Shaw, MD, University of Southern California, Keck School of Medicine, Department of Neurology, Rancho Los Amigos National Rehabilitation Center, 7601 E. Imperial Highway, HB 145, Downey, CA 90242, email: shaws@usc.edu

drugs" that could be significant for patients with epilepsy.[3] Much of the discussion centers on whether current bioequivalence standards are adequate for this particular disease.

Epilepsy, defined as recurrent unprovoked seizures, has a prevalence of approximately 4-8 per 1,000 persons in developed countries. Estimates of age-adjusted incidence of epilepsy range from 24 to 53 per 100,000 person-years,[4] with the greatest incidence at the extremes of age. Approximately 1% of children are expected to develop epilepsy by 20 years of age.[5] Nearly half of newly diagnosed patients achieve seizure freedom with monotherapy on low to moderate doses of medication.[6] However, 30-40% of patients have seizures that are difficult to control, thus requiring multiple medications or very high doses in a carefully titrated regimen.[7] For many, seizures will be intractable despite our best medical therapy.

While generics are widely available across all drug categories, special concern has been voiced regarding their use in the treatment of epilepsy. This is due to the frequently unpredictable occurrence of seizures and the all-or-nothing nature of the disease in which a patient is either in a state of seizure-freedom or is not. Switching to a generic statin or proton pump inhibitor with a 10% change in bioavailability will likely not cause substantial changes in clinical symptoms. In contrast, a 10% decrease in AED concentration may cause a previously seizure-free patient to suffer a breakthrough seizure, which has considerable consequences such as injury or death to the patient or others, loss of driving privileges (up to one year, depending on the state), loss of employment, and emotional distress. There is also the added burden of hospitalization, increased doctor visits, time off work, and cost of other medications to address the effects. Thus, for the individual with epilepsy, the stakes are higher in the generic/brand debate.

## GENERIC DRUG REGULATIONS

The FDA describes a generic drug as being "a copy that is the same as a brand name drug in dosage, safety, and strength, how it is taken, quality, performance, and intended use," and the active ingredients must be chemically identical.[8] The Drug Price Competition and Patent Term Restoration Act of 1984 regulates generic drugs. Also known as the Hatch-Waxman Act, the goal of this act was to balance the needs to support both "innovator" drug development as well as cost-saving generic drug development via abridged review and approval. The act established an abbreviated new drug application (ANDA), allowing a generic formulation to be approved if bioequivalence to the brand name drug is shown and manufacturing quality standards are met. The ANDA process enables lower-priced generics by sparing generic drug manufacturers the cost of performing the expensive efficacy and safety studies required for innovator drugs (the NDA, process).

The first approved generic formulation(s) of a drug is given 180 days of exclusive marketing. During this time, prices for generic AEDs are usually only slightly lower than for brand name formulations. Market competition usually further reduces prices as additional formulations are released, although the amount of reduction is variable.[9]

## BIOEQUIVALENCE STANDARDS

According to the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the "Orange Book"),[10] a "pharmaceutical equivalent" is a drug product that has the same active ingredient(s), strength, dosage form, route of administration, and concentration as the reference drug (usually the brand name). Allowable differences include shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, and preservatives), expiration time, and "within certain limits" labeling. In turn, "bioequivalent drug products" are defined as pharmaceutical equivalents that display comparable bioavailability when studied under similar experimental conditions. A "therapeutic equivalent" is a drug product that is expected to have the same clinical effect and safety profile when administered under the labeled specifications. Generic drugs do not need to be shown to be therapeutically equivalent; compounds that meet the bioequivalence criteria are assumed to be therapeutically equivalent and typically approved. The FDA states that "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect

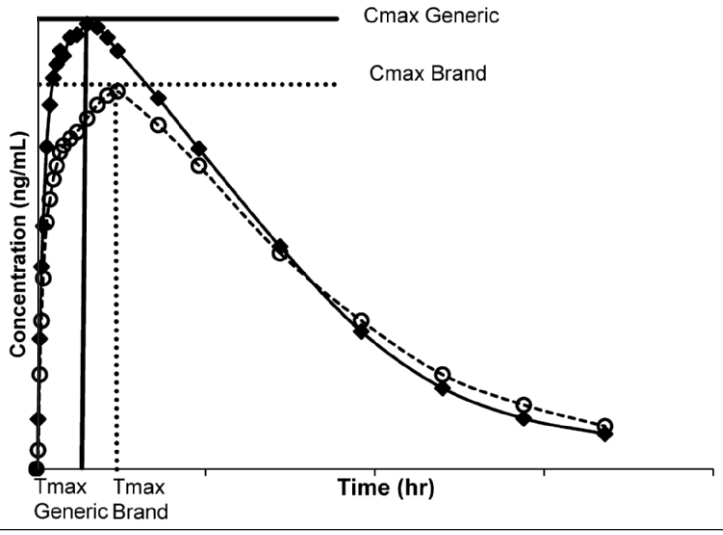


**Figure 1.** Hypothetical drug elimination curves for single doses of a brand name drug and generic formulation. Cmax and AUC are established to determine the bioequivalence of the generic formulation to brand name. Brand name medication (-○-); Generic Medication (-◆-)

and safety profile as the prescribed product." Bioequivalence is established using either an *in vitro* or an *in vivo* experiment, depending on the drug, according to guidelines set by the FDA.

### *In vivo Experiments—Average Bioequivalence*

The FDA average bioequivalence standards assess generic drug "performance," in which the rapidity and extent of absorption of the generic formulation must be similar to that of the reference (usually the brand name) drug. Small crossover studies are conducted in which single doses of test generic formulations are compared with the brand name drug in 24 to 36 adult volunteers who do not have the disease of interest.[11] Blood concentrations of test and brand name drugs are measured repeatedly, and the Cmax and AUC established. Figure 1 shows representative drug elimination curves for a hypothetical generic formulation and a brand name formulation. To be deemed bioequivalent, the curves do not need to be identical; as shown in this example, the generic drug's Cmax is higher and the Tmax earlier than those of the brand name drug.

FDA generic standards stipulate that the 90% confidence interval (CI) in analysis of variance (ANOVA) of log-transformed ratios of generic drug to brand name drug for both Cmax and AUC must be within 80% to 125% of one another. Figure 2 illustrates the AUC and Cmax 90% CI of five hypothetical generic formulations. Drug #1 would not be approved under FDA guidelines, while drugs #2 through #5 would meet these criteria.

A common misperception is that generic drug levels can vary by 20%-25% of the brand name, but in reality, to meet the 90% CI requirement, point estimates for generic drug Cmax and AUC are unlikely to be near the boundaries of the 80% to 125% acceptance standard.

### *In vitro Experiments—Biopharmaceutics Classification System*

Since 2000, the FDA has allowed a waiver of the *in vivo* bioavailability and bioequivalence tests using the Biopharmaceutics Classification System (BCS) for some drugs.[12] The BCS was initially developed to correlate a drug's solubility and permeability with the rate and extent of drug absorption.[13] For the FDA, high solubility is defined as the highest dose strength being soluble in 250 mL or less of aqueous media at 37°C over a pH range of 1 to 7.5. High permeability is defined as absorption (bioavailability) of 90% or greater.[14] Drugs are classified into 4 BCS classes: high solubility/high permeability (Class I); low solubility/high permeability (Class II); high solubility/low permeability (Class III); and low solubility/low permeability (Class IV). Table 1 shows the BCS classification of the antiepileptic drugs.

Since drug dissolution and permeability across the gastrointestinal tract are the two main factors that affect drug absorption from a solid dosage form, *in vitro* dissolution is used to predict *in vivo* dissolution. The most commonly used dissolution methods are the basket and the paddle methods, which are well-standardized and widely used. Currently, the BCS can be used to waive *in vivo* bioequivalence studies for Class I drugs dosed in rapidly dissolving immediate release solid products.[12] The FDA has considered

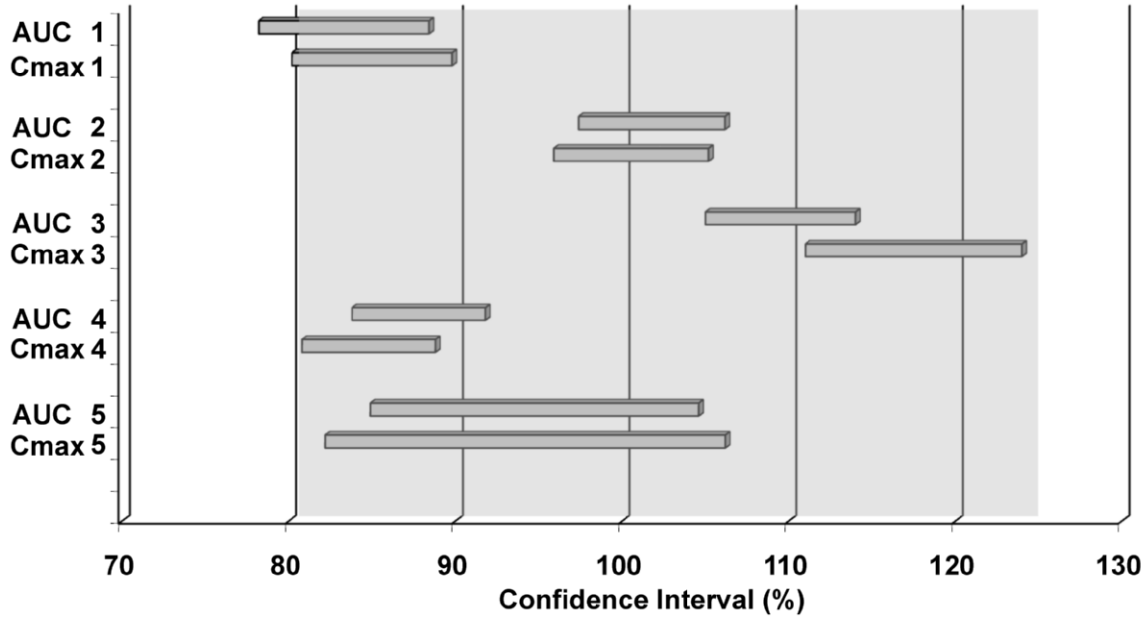


**Figure 2.** Illustration of five hypothetical generic formulations with their 90% Confidence Intervals (CI) for AUC and Cmax. The 90% CIs must fall within 80%-125% of the brand name drug (100%). Product #1 fails the criteria because the AUC 90% CI falls outside the limits. Product #2 meets the criteria and is quite comparable to the brand name product. Products #3 and #4 would also be approved, but are near the limits of the 80%-125% range and are statistically dissimilar to each other. Product #5, while fulfilling the criteria, is more variable than the other formulations.

developing additional biowaivers for Class II and Class III drugs, and developing dissolution methods that are more relevant to *in vivo* drug release and would allow comparison of dissolution performance across different products.[15]

## CONTROVERSY OVER ADEQUACY OF FDA STANDARDS

Despite the FDA's assurances that these bioequivalence standards ensure that generic and brand name formulations would be nearly identical, many patients and health care providers are concerned that significant differences may exist. Most of the concerns fall into two broad categories: whether these standards allow too much variability and whether these standards are generalizable to all clinical scenarios.

### *Variability*

The bioequivalence standards inherently allow a certain amount of variability since the target pharmacokinetic values lie within a range. In addition, the generic formulations are allowed to be non-identical to the brand name drug, as the confidence intervals are not required to cross a point where their ratio is 1 (i.e., the point where the two drugs are identical to one another). As shown in Figure 2, the 90% CI for AUC and Cmax for the test products #2 through #5 fall within the 80%-125% acceptance standard and therefore these formulations would be approved under FDA standards; however, a patient who is switched to formulations #3 or #4 would be expected to receive a considerably increased or reduced amount of drug compared to brand name. Lastly, the bioequivalence standards do not restrict the the intra-variability of a formulation. For instance, while product #5's AUC and Cmax point estimates are close to 100%, its 90% CIs are relatively wide, and a patient on this formulation could experience clinically significant blood concentration differences from lot to lot.

The FDA's Office of Generic Drugs conducted two internal studies to assess the bioavailability differences between approved generic formulations and their brand name drugs. From 1985 to 1986, 224 approved bioequivalence studies had a 3.5% mean AUC difference between brand and generic.[16] Of studies submitted in 1997, the AUC difference was 3.5% and for Cmax was 4.29%.[17] However, 13 of the 224 (6%) generic formulations had mean AUC differences of 10% or more from the brand.[16] Even greater differences were

**Table 1.** Biopharmaceutics Classification System Classes for Antiepileptic Drugs[23]

| BCS Class | AED | Solubility | Permeability |
|---|---|---|---|
| Class I | Ethosuximide<br>Lamotrigine<br>Levetiracetam<br>Phenobarbital<br>Pregabalin<br>Tiagabine<br>Topiramate<br>Valproic acid<br>Zonisamide | High | High |
| Class II | Carbamazepine<br>Felbamate<br>Oxcarbazepine<br>Phenytoin<br>Primidone | Low | High |
| Class III | Gabapentin | High | Low |

*AED, antiepileptics drugs; BCS, Biopharmaceutics Classification System*

reported by Burkhardt et al., who described eight patients with seizure increase and an approximate 30% decrease in total and free phenytoin concentrations after switching to generic phenytoin. Concentrations returned to baseline after switching back to the brand name formulation.[18]

### *Generic-Generic Switches—Are They Equivalent?*

Further variability in drug concentrations is allowed by the bioequivalence standards because generic drugs are tested against the brand name drug but not against each other. Current standards permit a difference in bioavailability between generic formulations that is greater than the difference between the generic and brand name drugs. Formulations #3 and #4 in Figure 2 illustrate the potential difference between generic drugs when their CIs are near the limits. Once a patient is switched to a generic formulation, such generic-to-generic switching is highly likely as pharmacies often change their suppliers based on pricing. For most AEDs, a number of generic products are available, increasing the likelihood that variations will occur. Zonisamide, for instance, has 13 approved generic formulations. Whether these generic-to-generic differences are clinically relevant has not been studied rigorously.

Finally, variability is allowed among manufacturer lots due to small differences in the manufacturing process. The United States Pharmacopeia (USP) establishes standards for each medication that the manufacturer, whether brand name or generic, must follow. While some of these standards are relatively wide, (for instance, pills of valproic acid must fall between 90%-110%) the FDA has underscored that the producers are to target 100%.

### Generalizability

Another prominent concern is whether single-dose studies in 24-36 healthy volunteers adequately represents real-life medication use and whether results are generalizable to the most commonly faced patient scenarios. The bioequivalence studies are not performed in the target population of patients with epilepsy, nor in those with concomitant diseases. In addition, many clinical factors that significantly alter the pharmacokinetics of AEDs—and thus may amplify effects of formulation differences—are not examined in the ANDA process, such as patient age, drug interactions, and drug accumulation with chronic dosing.

Generic drugs are not required to undergo bioequivalence testing in the elderly or children unless they are the main target population of the drug. However, physiologic changes occur at extremes of age, including alterations in volume of distribution, protein binding, elimination rates, and oral absorption from gastric pH and gastric emptying rates.[19] Infants and elderly patients with epilepsy are particularly sensitive to AED side effects involving the central nervous system. While any absorption changes in the active ingredient would be expected in both brand and generic, small formulation differences could be

magnified in terms of efficacy and side effects. For example, one study of 23 children showed comparable seizure incidence and mean plasma concentrations of carbamazepine, carbamazepine-10,11-epoxide, and 10,11-dihydro-10,11-trans-dihydroxy-carbamazepine between brand and one generic formulation of carbamazepine, but the generic product caused significantly more neurological side effects.[20]

The current bioequivalence studies, since they are performed with single doses, may not be representative of long-term dosing and drug accumulation, especially if cytochrome isoenzyme induction and dose-dependent elimination occur. A randomized, double-blind crossover trial with chronic dosing by Oles et al. found no differences in average seizure frequencies when 40 subjects took brand name carbamazepine for 90 days compared with 90 days of a generic formulation. However, a quarter of the patients had greater than 20% difference in AUC levels and the average time to peak was earlier with the generic formulation, in pharmacokinetic studies performed at least 2 weeks after the start of each formulation.[21] Jumao-as et al. compared 5 weeks each of brand name carbamazepine versus a generic formulation in 10 subjects in a randomized, double-blind, crossover study. There were no significant differences in seizure frequency or serum carbamazepine levels drawn at the second, fourth, and fifth week of each formulation.[22] For the newer AEDs, though, which largely don't have problems of non-linear pharmacokinetics or auto-induction, single dose studies may adequately predict chronic dosing situations.

### *The New Generation of AEDs*

Some experts have pointed out that the history of problems with generic formulations of the older AEDs, especially carbamazepine and phenytoin, can be explained by their pharmacokinetic properties,[23] and thus the newer generation of AEDs would not be expected to have such problems. As described by Nuwer et al., these properties are low water solubility, non-linear pharmacokinetics, narrow therapeutic index.[24]

#### Low Water Solubility

The FDA considers solubility and permeability as the sole critical factors in determining generic bioequivalence, as *in vivo* bioavailability tests may be waived based on BCS Class I status alone.[12] While most of the older AEDs (including carbamazepine, phenytoin, and primidone) have low solubility, most of the newer AEDs (including lamotrigine, levetiracetam, pregabalin, topiramate, zonisamide, and gabapentin) are highly water soluble. Oxcarbazepine and felbamate are poorly soluble, which could contribute to a higher risk of problems with their generics.

#### Non-linear Pharmacokinetics

Phenytoin's nonlinear (Michaelis-Menton) kinetics has been identified as a complicating factor for generics because small differences in the amount absorbed (which subsequently affects metabolism and elimination) could result in relatively large changes in the serum concentration, depending on where the patient's concentrations fall on the concentration-over-time curve.[25] Additionally, carbamazepine exhibits dose-dependent autoinduction, and valproic acid has saturable binding to plasma proteins. Of the newer generation AEDs, gabapentin exhibits definite nonlinear pharmacokinetics, as its transporter-mediated intestinal absorption system is saturable, resulting in reduced oral bioavailability as the dose is increased. However, because transport processes occur after dissolution, and gabapentin is highly soluble, transporter efficiency should not be different for generic products of gabapentin. Zonisamide has shown some evidence of Michaelis-Menten kinetics in previous reports.[26] Otherwise all the other newer generation AEDs possess linear pharmacokinetics.

#### Narrow Therapeutic Index (NTI)

The FDA defines NTI as less than a 2-fold difference in ratio between the median minimum toxic concentration and the minimum effective blood concentration. Thus, small changes in the dose and blood concentration may result in toxicity or breakthrough seizure. Most of the older generation AEDs have been identified as NTI, including carbamazepine, phenytoin, valproic acid, and divalproex.[27] In contrast, most of the newer generation AEDs are not NTI.

Based on the properties of non-linear pharmacokinetics, narrow therapeutic index, and low water solubility, the newer AEDs could theoretically be expected to have less problems with generics than the older AEDs[23]; whether this is true in clinical practice remains to be determined. Exceptions to this hypothesis could

include felbamate, gabapentin, oxcarbazepine, and zonisamide.

In the end, whether the standards allow too much variability or whether the more favorable pharmacokinetic profile of most of the new AEDs sufficiently decreases potential intra-subject variability, a more fundamental question is how much variability is tolerable for a particular individual. Some patients retain seizure control and do not experience side effects despite large variations in their AED dose, while others have "brittle" control and do not tolerate small changes in dose. These might be patients already at doses near toxicity thresholds, those taking multiple medications, or those whose seizure control was difficult to achieve. Unfortunately, the current bioequivalence standards do not test these patients who are at higher risk of sensitivity to a change, and the current standards allow large changes with generic-to-generic switches. Nevertheless, such patients with a personal narrow therapeutic range are likely in the minority, and generic-to-generic-switching problems are not expected to occur in most patients.

## FUTURE DIRECTIONS IN PHARMACOKINETIC ANALYSIS—THEORETICAL CONSIDERATIONS

The FDA's current analysis of average bioequivalence (that is, the effects on a population of patients, rather than an individual) focuses on a decision-making outcome, rather than an analysis of the evidence from a given trial.[28] The current approach requires that both means and variances of the two drugs are within a defined range of one another. Data are log-transformed partly because AUC is based on skewed data (Figure 1) and a logarithmic 2 transformation "linearizes" the data for an analysis that is easier to perform. AUC is actually a product of drug absorption, apparent volume of distribution, and the elimination rate constant - it is not a sum, meaning that log-transformed deviations become additive, rather than multiplicative, and thus, differences between drugs are mathematically easier to analyze. The current standard, the "two one-sided test" approach suggested by Schuirmann (simplistically, where two independent one-sided hypotheses are tested) is carried out at the 5 percent level of significance, effectively yielding a 90 percent confidence interval (90% confidence intervals are narrower, for example, than 95% confidence intervals and thus are more conservative).[29] Both AUC and Cmax are evaluated this way, with both means and variances "aggregated" together in the same analysis. These standards have been accepted internationally, but ongoing literature suggests this is not the end of the debate because of a concern that valuable information may be obscured in the latter analysis.[28] The issues of "switchability" and "prescribability" are critical when considering whether to dispense a given formulation to a specific patient or to the population at large, respectively, although attempts to model variability between formulations has not been successful thus far.[28,29] The debate over which parameters should be compared continues. Other approaches that compare a test formulation to some reference have been suggested, such as those that "disaggregate" means, variability, and interactions. One technique, which makes more use of maximal likelihood estimates (i.e., a method that determines where the true values actually lie) than the current paradigm, appears to be more sensitive to differences between formulations than current approaches and may better define bio-inequivalence.[28] Further work should determine whether this approach more closely captures sources of variation between formulations and within an individual patient.

The FDA recently considered a new Individual Bioequivalence standard, in which the subject would receive a dose of the brand name drug two separate times. The two concentration-time curves, which reflect average bioavailability, intra-subject variability and lot-to-lot variation, would be the "goalposts" within which the generic formulation must fall.[30] This would require generic AEDs to have identical bioavailability, and variability that is no greater than the brand name drug. This would theoretically lead to generics that perform as well, or even better than, the original brand name drug. However, the FDA moved away from the Individual Bioequivalence paradigm, in part because they felt current parameters were adequate and that there was a lack of serious safety concerns.[31]

## STUDIES

The FDA bioequivalence standards have not been evaluated objectively. No large, prospective, blinded, randomized controlled trials have

been performed to validate the safety of switching between different formulations of generic or brand AEDs. Available data have shown variable results; some have been discussed above. A recent survey of pharmacists in Ontario, Canada, identified 11 patients who lost seizure control after switching to generic lamotrigine; eight patients regained control when switched back to the brand name drug.[32] Andermann et al. found that of Canadian patients switched from brand name AED to generic, 13% of lamotrigine, 20% of clobazam, and 20% of valproic acid users switched back to brand name. In comparison, only 1.5% to 2.9% of patients on non-AED comparison drugs (simvastatin, fluoxetine, and citalopram) switched back. The reasons for "switchbacks" were unknown, but the authors suggested that the high rate for AEDs may have been due to adverse clinical consequences from generic switch.[33] Oles et al. reported similar average seizure frequencies in a crossover study between brand name and generic carbamazepine. However, eight individuals had a greater than 50% change in seizure frequency between the two regimens, though this did not correlate with large changes in their AUC. In addition, nine out of 36 subjects experienced a greater than 20% change in AUC, with breakthrough seizures occurring in two of them.[21] Another study using a randomized, crossover, double-baseline design demonstrated similar AUC, peak, and trough concentrations for brand name and two generic formulations of carbamazepine after three days on each. The authors noted these conclusions cannot be applied to other formulations or other types of antiepileptic drugs not tested.[34]

After reviewing the limited series and studies available, the Italian League against Epilepsy (LICE) working group concluded that there are no adequately powered randomized controlled trials that assess the risk-to-benefit ratio of generic AEDs and that the safety of switching between brand name and generic AED formulations is therefore unknown. They recommended against generic substitution in patients who achieved seizure remission, and against switches between generics. They felt generic AEDs should be limited to monotherapy initiation, adjunctive treatment and use in patients with persistent seizures despite the use of a brand name product.[25] The American Epilepsy Society (AES) agrees that "controlled, prospective data on therapeutic equivalence of different AED formulations in people with epilepsy is not available because appropriate studies have not been conducted."[35]

## CLINICAL PRACTICE

Several major scientific associations, including AES, LICE, the AAN, and the French Chapter of the International League Against Epilepsy, have published statements articulating concerns about generic substitution of AEDs, arguing that epilepsy is a unique disease and AEDs are a special class of drugs such that their substitution is problematic when used for this indication.[3,25,35,36] The issue is not generics *per se*, but that the criteria appear too wide[3] and are not adequately substantiated.[25,36] Due to the fact that generics are *similar*, not *identical*, to the brand name, and even less similar to one another, these differences could be clinically significant when a patient is switched. If a patient could always remain on the same formulation from the same manufacturer, whether brand or generic, then this would eliminate such concerns.[36] However, this is not easily accomplished in our current system, in which pharmacies frequently change suppliers based on price.

### *Drug Substitution Legislation*

Pharmacists are often under pressure to use generic alternatives instead of brand name whenever possible, as profit margins are larger for pharmacy retailers and cost savings are higher for health insurers. Currently, the brand name drug is often automatically substituted if a generic formulation is available, unless the prescription contains state-specific "Dispense As Written" or "Do Not Substitute" language. In their position statements, the AAN,[3] the AES,[35] and patient-advocate group Epilepsy Foundation[37] all oppose generic substitution of antiepileptic drugs for the treatment of epilepsy without the prior consent of the patient and the prescribing physician.

Prescription drug substitution is addressed in state legislatures. While some legislation seeks to facilitate or support use of generic alternatives, recently many bills have been filed seeking to restrict substitution of certain classes of drugs, notably antiepileptic drugs and immunosuppressants commonly used for transplant patients. Variations exist, but typically these bills would prohibit a pharmacist from substituting or in-

**Table 2.** Antiepileptic Drug Substitution Legislation

| State | Summary | Enacted |
|---|---|---|
| Hawaii | "The pharmacist shall not substitute an equivalent generic drug product for any prescription for an anti-epileptic drug, except upon the consent of the practitioner and the patient or the patient's parent or guardian. This narrow exception for epileptic patients shall not be construed as a policy decision to make exceptions for any other conditions."[40] | §328-92<br>2003 |
| Illinois | "When the prescribing physician has indicated on the original prescription 'may not substitute,' a pharmacist may not interchange an anti-epileptic drug or formulation of an anti-epileptic drug for the treatment of epilepsy without notification and the documented consent of the prescribing physician and the patient or the patient's parent, legal guardian, or spouse."[41] | Public Act 095-0689<br>Effective 10/29/07 |
| Tennessee | "A pharmacist, pharmacy intern or pharmacy technician must provide notification to the patient, a family member, other relative, or a close personal friend of the individual or any other person identified by the patient before interchanging one manufacturer of an anti-epileptic drug for another manufacturer of an anti-epileptic drug in instances where said patient's epilepsy or seizures is currently being controlled on a specific drug, strength, dosage form, and dosing regimen from a specific manufacturer. The prescriber of said medication must also be notified prior to the interchange."[42] | Public Chapter No. 370<br>Effective 7/1/07 |
| Utah | "Requires a pharmacist or pharmacy intern who substitutes a drug product equivalent for an epilepsy drug prescribed to a patient to treat or prevent seizures to notify the prescribing practitioner prior to the substitution, regardless of whether the substitution is a substitution of a generic drug for another generic drug, a generic for a nongeneric drug, a nongeneric drug for another nongeneric drug, or a nongeneric drug for a generic drug."[43] | Session Law Chapter: 205<br>Effective 5/5/08 |

terchanging any AED (or immunosuppressant), without prior notification and/or written consent and/or signed consent from the prescriber and/or patient. According to the National Conference of State Legislatures, in 2007-2008 at least 24 states had such bills for AEDs; in 2009 legislation (as of April 1), 13 bills in 8 states (CT, GA, IA, MA, MI, MN, NJ and NY) had been filed to restrict substitution of brand name epilepsy drugs, while similar bills specific to immunosuppressant drugs were filed in five states (FL, GA, IL, MA and TN).[38] The National Association of Chain Drug Stores opposes such legislation, arguing that prescribers already indicate their determination regarding generics on the prescription, and therefore this requirement would create unnecessary extra work and delays.[39]

So far, epilepsy-specific drug substitution legislation has passed in Connecticut, Hawaii, Illinois and Tennessee (Table 2). In addition, a few states restrict substitution of narrow therapeutic index drugs, which includes some AEDs. For instance, under North Carolina law, a drug classified by the North Carolina Board of Pharmacy as NTI may not be substituted unless the pharmacist obtains documented consent of the prescriber and the patient. The 2009 list includes carbamazepine, ethosuximide, and phenytoin.[44] Kentucky and Pennsylvania have laws with similar negative formularies and restrictions.[45,46] Pharmacists are advised to check their specific state generic substitution laws.

### *Role of the Pharmacist*

Pharmacists play a key role in ensuring that generic substitutions are used when possible and when appropriate. They may need to identify situations where substitution is not in the patient's best medical interest. The American Pharmacists Association (APhA) published a special feature with resources and a patient-centered 18 box step-by-step flow chart to help make dispensing decisions, as well as a monograph focused on critical dose (NTI) drugs with its own algorithm for generic substitution of NTI drugs in specific situations.[47,48]

As the professional at the point of sale, the pharmacist fields questions from the patients or the patients' families, and can often answer better than prescribers, who may be unfamiliar with bioequivalence standards. The pharmacist may need to counsel on the potential benefits and risks of brand-to-generic switching and generic-to-generic switching and help the patient

**Table 3.** Generic and Brand-Name Antiepileptic Drug Formulations: Price of One Tablet

| Antiepileptic Drug, Dose (Brand Name, Manufacturer) | Generic | Brand Name |
|---|---|---|
| Carbamazepine 200 mg (Tegretol, Novartis Pharmaceuticals Corporation) | $0.16 | $1.10 |
| Ethosuximide 250 mg (Zarontin, Pfizer Inc.) | $1.18 | $1.49 |
| Gabapentin 600 mg (Neurontin, Pfizer Inc.) | $1.03 | $3.48 |
| Lamotrigine 100 mg (Lamictal, GlaxoSmithKline) | $4.00 | $5.33 |
| Levetiracetam 500 mg (Keppra, UCB) | $2.67 | $3.67 |
| Oxcarbazepine 600 mg (Trileptal, Novartis Pharmaceuticals Corporation) | $4.33 | $6.04 |
| Phenytoin Sodium Extended 100 mg (Dilantin, Pfizer) | $0.36 | $0.52 |
| Topiramate 100 mg (Topamax, Ortho-McNeil Neurologics) | $0.83 | $7.24 |
| Valproic Acid 250 mg (Depakene, Abbott Laboratories) | $0.30 | $2.53 |
| Zonisamide 100 mg (Zonegran, Eisai Inc.) | $1.89 | $2.85 |

*Prices from drugstore.com, based on a prescription of 100 tablets, as of September 20, 2009*[50]

make an informed decision. Often patients and their prescribers are unaware that a substitution has occurred. The Pharmacist's Letter encourages pharmacists to inform the patient and prescriber of switches, noting that pharmacists and physicians could potentially be held legally liable for serious adverse events attributable to a generic substitution in which the patient was not informed.[49] Moreover, the pharmacist should inform the physician, or advise the patient to do so, because the physician may want to check serum drug concentrations or ensure sooner follow-up. He or she may also suggest the patient keep a diary of seizures and side effects, to help determine whether a new event is due to the switch or not.

For epilepsy patients who are already on generic and thus will be exposed to generic-to-generic switches, the pharmacist can inform the patient if the manufacturer is different from the previous refill, and can teach the patient how to identify the manufacturer on the prescription label. For certain patients who may not tolerate brand-to-generic or generic-to-generic switches, such as children or the elderly, those with brittle control, or those on high doses or polytherapy,[50] it may be helpful to keep track of manufacturers and potential corresponding seizures and side effects.

### *Cost Savings*

Generic formulations provide significant cost savings for patients and society. To demonstrate the prices a patient may encounter, Table 3 compares the cost of one tablet of a generic drug to one tablet of the brand name formulation, with a prescription of 100 tablets from an internet retailer. The cost for a typical year of treatment with oxcarbazepine (600 mg twice daily) is 28% less with a generic formulation ($4409 vs $3160), and for zonisamide (400 mg daily) is 34% less ($4161 vs $2759) from an internet retailer.[51]

Whether any, and how much, additional clinical vigilance or laboratory assessments are needed when switching to generic formulations is unclear. Many experts recommend obtaining blood concentrations of the drug before and after the switch, in order to adjust the dose as necessary.[52] After brand-to-generic switch, though, blood levels may vary even more from refill to refill due to generic-to-generic switches. In higher-risk patients, whether to check blood levels after every new generic switch becomes a quandary. LeLorier et al. found that of 187 patients in Quebec on lamotrigine, the mean daily dose increased by 5.1% and medical service utilization increased (8.7 vs 9.8 visits per person-year) during the generic use period compared with the brand use period.[53] A recent database study compared the economic outcomes of 948 patients in Quebec who took either brand name, a single generic formulation, or multiple generic formulations of topiramate. More prescriptions per year for both AEDs and non-AEDs occurred in single and multiple-generic users compared to brand name users. Hospitalization rates were similar in brand name and single-generic users, but were higher in multiple-generic users. Overall, while annual costs of topiramate therapy was lower using generics than brand name, total annual health care costs (prescription drugs, hospitalizations, and outpatient visits) were $410 higher for single-generic users and $1716 higher for multiple-generic users.[54] Such outcomes negate some of the cost-savings of generics, although it is difficult to determine

how much of this increased resource utilization is due to perceptions of problems, rather than actual seizures or adverse events.

Besides blood concentrations, patient diaries documenting medication adherence, seizures, and side effects, also would help determine whether a breakthrough seizure or toxicity is attributable to generic switch. A report should be filed with FDA using the MedWatch system (http://www.fda.gov/medwatch).

## CONCLUSIONS

Generic AEDs provide substantial reduction in cost of epilepsy treatment. However, uncertainty still exists regarding the adequacy of the current bioequivalence standards to ensure identical performance and adverse event profile. More data are needed to determine the efficacy or pitfalls of generic substitution, and to guide treatment decisions. Since generic formulations are not required to be bioequivalent to one another, generic-to-generic switches can potentially cause clinically significant changes in blood concentration levels. In general, the pharmacokinetic profiles of the newer generation of AEDs are more favorable to creating generic equivalents, and thus are expected to have fewer problems than older AEDs. Patients who are at higher risk for problems with generics include children and the elderly, those whose seizure control was difficult to achieve, those with the risk of drug interactions, and those taking large doses near toxicity thresholds. That said, most people with epilepsy could probably successfully switch to generic antiepileptic drug formulations.

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