Understanding Therapeutic Equivalence in Epilepsy

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ABSTRACT

The issues surrounding generic drug substitution in patients with epilepsy are complex. The substitution of one formulation of an antiepileptic drug (AED) for another is controversial. Well-reasoned and defensible cases can be made both for and against such substitution. Although regulatory agencies require that generic and proprietary drugs have similar pharmacokinetic bioequivalence data, their therapeutic efficacy may not necessarily be identical. The paroxysmal nature of epilepsy, the narrow therapeutic index of some AEDs, the need to individualize therapy to achieve seizure control, and the negative consequences of uncontrolled epilepsy distinguishes epilepsy from other clinical conditions. Epilepsy management with AEDs requires careful dose titration and consistent drug exposure at the optimal level for each patient, which can be altered if a different formulation of the AED is substituted. Unexpected variability in plasma concentrations could occur when a patient who has been receiving one formulation of an AED (generic or brand) receives an alternate formulation. Thus, no substitutions should be made for people with epilepsy without the knowledge and approval of the prescribing physician. Patients should be consulted about the substitution, with all risks and benefits carefully explained.

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FOCUS POINTS

- Although substitution of one drug formulation for another is increasingly common, the issues surrounding antiepileptic drug (AED) substitution are complex and can be controversial.
- Bioequivalence is defined by the United States Food and Drug Administration, but bioequivalence may not translate directly into therapeutic equivalence. Whether the FDA definition of bioequivalence for extent and rate of absorption of an AED can truly be considered equivalent in practice is controversial for some clinicians.
- Exempting AEDs and epilepsy from mandatory generic substitution is reasonable. The LEAD faculty recommends that any change in AED formulation should only be allowed with the informed consent of the patient and physician.

INTRODUCTION

The issue of substituting one formulation of an antiepileptic drug (AED) for another can be controversial. Advocates for generic substitution cite strong economic rationales and the substitutes' approval by the United States Food and Drug Administration, while opponents cite the potential for adverse patient consequences (Table 1).[1-3] The interests of the authors of this review are, above all, to achieve success-

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ful patient outcomes, ideally allowing patients to live without seizures and adverse effects of therapy. We do not seek to establish branded or generic agents as the standard, but rather to bring forth issues and concerns regarding what may happen to a patient if an antiepileptic formulation is changed without the knowledge of the physician.

Since the advent of the first generic AEDs, patient advocacy associations and professional societies, such as the Epilepsy Foundation (EF) and the American Academy of Neurology (AAN), have voiced concerns regarding mandatory substitutions of generic AEDs for their branded counterparts. A growing body of evidence now bears out these concerns—that switching AED formulations may be associated with increased risk for a patient with epilepsy.[4]

The issues surrounding switching formulations (generic to generic or branded to generic) for this drug class are complex. Examining how and why substitutions are made in the pharmacy setting and specifically, the need for heightened awareness among healthcare providers regarding how AED prescriptions are filled for their patients with epilepsy is important. From the clinical perspective of these patients, substituting one AED formulation for another without the attending healthcare professional's knowledge and approval is more than a process issue. This switching/substitution may expose the patient to increased adverse events or seizures (due to a potential increase or decrease in absorbed drug), such that the patient has to cope with medical and personal issues that often result. In terms of the agents, why different AED formulations may fail to maintain seizure control involves specific pharmacokinetic properties. The distinctive physicochemical characteristics of some AEDs lend themselves to these potential problems, supporting the rationale for exempting these agents from mandatory generic substitution.

Based on these concerns, the treating healthcare professional and patient should make the final decision regarding the formulation of the agent administered. The particular agent selected by the healthcare professional and patient should then be used consistently. Further, all stakeholders in the care of patients with epilepsy—general physicians and neurologists, as well as pharmacists, nurse practitioners, physician assistants, hospitals, residential institutions, health insurance providers, employers, drug manufacturers, federal and local agencies, and legislative bodies—all need to be aware of the potential issues involved in changing antiseizure medications.

BACKGROUND: *ALL BIOEQUIVALENT AGENTS MAY NOT BE EQUAL*

Historically, the FDA has not had a role in determining how doctors manage specific clinical circumstances. The early governmental role in the regulation of pharmaceutical products began in 1862 when Abraham Lincoln established the Bureau of Chemistry, the predecessor of the FDA, to check products for purity. At the turn of the 20th century, Theodore Roosevelt addressed the broader problem of misbranded and adulterated food and drink products by signing the Food and Drugs Act, and the agency later became the FDA. By the 1930s, toxicity became recognized as a major issue through problems with early antibiotics and the FDA began testing products for safety. In 1962, the Kefauver-Harris Amendment was put in place expanding the FDA

TABLE 1.
Factors Favoring Generic Substitution and Potential Issues of Concern With AED Substitution[1-3]

Pros	*Cons*
• Potential cost savings	• Potential recurrent seizures
• Convenience – simply always write the same generic name	• AED low therapeutic index; variability of individual patient responses
• FDA-approved product	• Need for slow titration, serum level monitoring
	• Complex risk of drug interactions
	• Bioequivalence vs therapeutic equivalence
	• Inability to ensure continuing refills from the same manufacturer
	• Impact on adherence

This table was published in Crawford P, Feely M, Guberman A, Kramer G. Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. *Seizure.* 2006;15:165-176. Copyright Elsevier/Epilepsy Action. Reprinted with permission from Pharma Publishing and Media Europe. *Eur J Hosp Pharm Sci.* 2005;11(4):83-7. Copyright 2005 Pharma Publishing and Media Europe. All rights reserved.

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

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mandate to include both safety and efficacy.[5] It was only in 1968 that FDA formed the Drug Efficacy Study Implementation to investigate the efficacy of these early drugs and the first patient package insert was mandated in 1970.

In more recent years, streamlined procedures at the FDA have been put in place allowing generic products to be rapidly approved to meet the demand of patients and payers for more cost-effective therapy options.[6] Generic products have the same medicinal ingredient(s) in comparable dosage forms as their branded counterparts.[7,8] However, a generic formulation may contain a different salt or ester of the active ingredient, with chemical and biological properties distinct from those of the branded product.[6,7] As shown in Figure 1, the differences in excipients, binders, tablet hardness, film coating, and manufacturing processes may produce a generic product that appears different and may also have shelf life, taste, or in vivo pharmacokinetic characteristics different from those of the other generic formulations despite bioequivalency to the branded formulation.[7]

Bioequivalence and Therapeutic Equivalence

Under the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, manufacturers seeking approval to market a generic drug must submit data demonstrating that the drug is bioequivalent to the pioneer drug. A major premise underlying this 1984 statute is that bioequivalent drugs are therapeutically equivalent and therefore interchangeable.[9] In the US, generic bioequivalence to a branded drug is established in studies with healthy volunteers, and is based on the rate and extent to which the therapeutic ingredient is absorbed from a drug. The mean area under the plasma concentration-time curve (AUC) measures the extent of absorption and the peak plasma concentration (C_{max}) measures rate of absorption.[9]

Bioequivalence exists when the 90% confidence intervals (CI) of the log-transformed ratios of the generic to reference compound for the AUC and C_{max} fall within an 80% to 125% range. Whether this possibly broad FDA definition of bioequivalence for both extent and rate of absorption of an AED can truly be considered equivalent in practice is controversial for some clinicians. Studies of bioequivalence typically include 24–36 healthy adults and are also intended to control for intersubject variability in pharmacokinetic parameters.[9,10] The width in the confidence interval in part also reflects the within-subject variability and the ability of a generic product to meet bioequivalence criteria may be affected when somewhat larger differences in average subject responses exist.

Moving from pharmacokinetics to clinical effects, therapeutic equivalence of a generic agent with established bioequivalence to its branded counterpart is assumed. This assumption is valid for many generic agents.[1] However, bioequivalence is not a guarantee of similar efficacy or side effects in every instance (ie, therapeutic equivalence in every case).[1] Within the permitted bioequivalence measures, the AUC and/or C_{max} of a generic may differ slightly from the reference compound, which along with additional variation introduced by substituting one formulation for another, may result in a clinically significant difference in the attainment of needed blood levels for a patient.

FIGURE 1.
Variability in appearance of different AED product formulations

Zonisamide 100-mg capsule (APOTEX CORP)



ZONEGRAN® 100-mg capsule (EISAI INC)



Zonisamide 100-mg capsule (MYLAN)



Zonisamide 100-mg capsule (Sun Pharmaceutical Industries LTD)



Differences in manufacturing processes can create final products with significant differences in appearance, even though the active ingredient is the same.

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AED=antiepileptic drug.

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BIOEQUIVALENCE ISSUES WITH AEDS

Some of the assumptions regarding bioequivalence and therapeutic equivalence for brand-name and generic AED formulations may not be true. First, single-dose and steady-state pharma-

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cokinetic profiles of the brand-name and generic AEDs are presumed to be similar, with a strong correlation between single-dose pharmacokinetic and therapeutic effects. The allowed difference in the extent and rate of absorption (90% CI from -20% to +25% of branded standard) is thought to have no effect on therapeutic outcomes. In addition, similar performance in healthy volunteers is assumed to imply similar performance in diseased patients.[2,11]

The variability of pharmacokinetic parameters in patients may be greater than in healthy volunteers due to drug interactions and other disease-related factors. Three characteristics of drugs make bioavailability a particular concern: low water solubility, a low therapeutic index, and nonlinear pharmacokinetics.[2,11,12] Commonly used AEDs exhibit some of these characteristics and have significant interactions with other AEDs (Table 2).[13-19] These characteristics of AEDs may contribute to the variations in bioavailability that may result when switching formulations. Thus, clinical events potentially arising from therapeutic variability may not only arise from patient and disease state factors, but also from physicochemical properties of AEDs.

Variability Among Generic AEDs

Healthcare providers should consider the comparative bioequivalence among generic AEDs. Generic agents are not tested against other generics for bioequivalence but rather against their branded counterparts. Two generic formulations with established bioequivalence to a reference drug may vary considerably at the low and high ends of the therapeutic range. With generic-to-generic substitutions, greater variations in bioavailability are possible than when branded and generic agents are substituted.[2] For example, if a formulation with lower bioavailability than brand is switched to a formulation with higher bioavailability than brand, an average patient may experience an increase in serum concentration. Conversely, a switch from the higher- to the lower-bioavailability generic may result in a decrease in bioavailability.[2,3]

The Office of Generic Drugs of the US FDA has conducted two surveys to quantify the differences between generic and brand name products. The first survey included 224 bioequivalence studies submitted in approved applications. The observed average differences between reference and generic products for AUC was 3.5%.[20] The second survey included the 127 bioequivalence studies in the 273 generic drug applications approved in 1997. The three measures reviewed included area under the plasma concentration-time curve from time zero to last measurable (AUC_{0-t}), area under the plasma concentration-time curve from time zero to infinity (AUC_{0-inf}), and C_{max}. The observed average differences between the reference and generic products were ±3.47% (SD=2.84) for AUC_{0-t}, ±3.25% (SD=2.97) for AUC_{0-inf}, and ±4.29% (SD=3.72) for C_{max}.[21] Although these FDA surveys revealed that generics generally varied from the reference product by <4%, the FDA bioequivalence standard allows much greater variability. Whether these results are generalizable to AEDs, particularly those with a narrow therapeutic window, is unclear.

Because multiple generic agents are available for a given reference AED, patients may receive a different generic preparation with each refill. In fact, generic-to-generic substitution is the most frequent form of substitution and one that often goes unnoticed by the dispensing pharmacist and the patient unless the products have readily apparent differentiating characteristics.[22] Table 3 lists the multiple generic formulations that are available as of October 2009 for proprietary AED agents.[9,23] Poor visual differentiation between generics may also lead to problems for patients. References such as the *Physician's Desk Reference* for generic drugs may not be widely known or available, making verification that the formulation

TABLE 2.
Pharmacokinetic Characteristics of AEDs That May Suggest Potential Risk Associated With Formulation Substitution[13-19]

AED	Low Water Solubility	Nonlinear Pharmacokinetics	Drug Interactions with AEDs
Carbamazepine	Yes	No	Yes
Gabapentin	No	Yes	No
Lamotrigine	Yes	No	Yes
Phenytoin	Yes	Yes	Yes
Topiramate	No	No	Yes
Valproate	N/A	Yes	Yes

AED=antiepileptic drug; N/A=not available.

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TABLE 3.
Multiple Generic AEDs: Approved Drug Product List[9,23]

Branded AED	Generic Manufacturer(s)
Carbamazepine	
Oral suspension	Morton Grove
Tablet	Actavis Elizabeth, Apotex, Inwood Labs, Taro, Torrent
Tablet, ER	Taro
Chewable tab	Cadista, Taro, Torrent
Ethosuximide	
Capsule	Banner Pharmacaps, Covenant
Syrup	Mikart, Pharmaceutical Associates, Teva
Fosphenytoin	
Injection	Akorn-Strides, Apotex, APP, Baxter, Bedford, Hikma, Hospira, IV Therapy, Sun, Teva, Wockhardt
Gabapentin	
Capsule	Actavis Elizabeth, Amneal, Apotex, Aurobindo, Hikma, Ivax, Ranbaxy, Sandoz, Sun, Teva, Watson Labs
Tablet	Actavis Elizabeth, Apotex, Glenmark, Ivax, Sandoz, Sun, Teva
Lamotrigine	
Tablet	Apotex, Aurobindo, Cadista, Dr Reddy's Labs, Matrix Labs, Mylan, Roxane, Sandoz, Taro, Teva, Torrent, Upsher-Smith, Wockhardt, Zydus
Chewable tab	Aurobindo, Cobalt Labs, Dr Reddy's Labs, Glenmark, Mylan, Sandoz, Taro, Teva, Zydus
Levetiracetam	
Tablet	Apotex, Aurobindo, Cipla, Cobalt Labs, InvaGen, Lupin, Mylan, Orchid Healthcare, Roxane, Sandoz, Solco Healthcare, Teva, Torrent, Watson Labs, Wockhardt, Zydus
Oral solution	Activus Mid Atlantic, Amneal, Aurobindo, Cypress, Roxane, Silarx, Taro, Tolmar
Oxcarbazepine	
Oral suspension	Ranbaxy
Tablet	Apotex, Breckenridge, Glenmark, Roxane, Sun, Taro, Teva
Phenytoin	
Oral suspension	Actavis Mid Atlantic, Taro, VistaPharm, Wockhardt
Capsule ER	Amneal, Mylan, Sun, Taro, Wockhardt
Injection	Baxter, Hikma, Hospira, Pharmaforce
Primidone	
Tablet	Amneal, Dr Reddy's Labs, IMPAX, Lannett, Mutual, Vintage, Watson Labs, West, Ward
Valproate	
Injectable	APP, Bedford
Valproic Acid	
Capsule	Banner Pharmacaps, Catalent
Syrup	Alpharma, Apotex, Hi-Tech, Morton Grove, Pharmaceutical Associates, Teva, Vintage
Zonisamide	
Capsule	Alphapharm, Apotex, Banner Pharmacaps, Barr, CorePharma, Dr Reddy's Labs, Glenmark Generics, InvaGen, Mylan, Sandoz, Sun, Teva, Wockhardt, Zydus

This information was updated according to the US Food and Drug Administration Center for Drug Evaluation and Research. Approved Drug Products With Therapeutic Equivalence Evaluations, current through October 2009. (http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm)

AED=antiepileptic drug; ER=extended release.

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is indeed the correct one potentially difficult for both patients and pharmacists. A useful resource may be the FDA orange book which lists essentially all approved generics. (http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm)

GENERICS AND THEIR ROLE IN EPILEPSY

Generic drugs are widely advocated as a means of containing healthcare costs, and mounting pressures from healthcare systems and third-party payers strongly encourage their use.[1,24,25] For many patients, the cost saving with generics is the prime consideration, but this may not be true for patients with epilepsy being treated with AEDs. In the case of epilepsy, the goal of treatment is for the patient to have no seizures and no adverse events due to their therapy. To achieve this goal, the treating healthcare professional needs to make the decision regarding which agent a given patient consistently receives.[2] Epilepsy is a paroxysmal disorder very different from others such as hypertension, hyperlipidemia, allergic rhinitis, or diabetes. For example, for the latter conditions, the effect of changing a dose brought about by a different formulation of an agent can be assessed by monitoring blood pressure or routine blood chemistries. Patients with epilepsy have an "all or none" problem; either seizures occur or they do not.[26]

Additionally, many people with epilepsy can achieve seizure control on an AED with a low therapeutic index (eg, carbamazepine or phenytoin). Clinically, this means that there is a small difference between the effective and toxic dose. Patients achieving seizure control on an AED with a low therapeutic index who are given a substitute agent may be at heightened risk for adverse events, seizure recurrence, injury, hospitalization, or death. In terms of quality of life, these patients could lose their driver's license, or their ability to live productively or independently.[11,27,28] Given what could be at stake for a patient should seizure control be lost, carefully assessing the potential risk-benefit ratio associated with the use of various formulations of a prescribed AED is especially important.

The unique concerns facing the patient with epilepsy have prompted expert healthcare professional groups and medical societies to examine mandatory generic substitution of AEDs. Organizations such as the AAN and EF have adopted a position that patients with good seizure control should not be given a substitute AED formulation unless both patient and healthcare professional are fully informed about the substitution, and the treating physician deems it acceptable.[29,30]

WHAT HEALTHCARE PROVIDERS SHOULD KNOW ABOUT GENERIC SUBSTITUTION IN EPILEPSY

A "substitution" occurs when a pharmacist fills or refills a prescription with a different formulation from the one prescribed or previously dispensed—generic to generic, generic to brand, or brand to generic.[22] Substitutions occur for numerous reasons: generic products from a specific manufacturer are not consistently available[11] or the pharmacy has switched manufacturers due to negotiated costs. Third-party payers may mandate that the least expensive formulation be dispensed. A lack of consistency in the formulation dispensed to the patient results. Moreover, each payer has its own criteria for handling no-substitution requests.

Substitution occurs routinely in most pharmacies, but healthcare providers may underestimate its frequency.[7,31,32] In 2001, physicians attending meetings of the American Epilepsy Society (AES) and the AAN were asked the question, "What percentage of patients are substituted with a generic short-acting carbamazepine in the US annually?"[31] In this AES survey, 55% of respondents estimated a <30% rate of substitutions, while 15% estimated a 70% substitution rate. The actual substitution rate was much higher than most physicians estimated—68%, as determined by an independent audit of 1.04 million prescriptions.

According to a recent online survey of 606 US physicians and 550 adult patients, one quarter of physicians treating epilepsy—and 38% of their patients—were not aware that a branded AED may be substituted with a generic without their consent.[32] More than half the physicians (57%) did not know about mandatory generic substitution laws for prescription medications.[7] This is particularly concerning with respect to long-term consistency in patient management, since the physician needs to control and manage the actual AEDs that a patient with epilepsy is receiving.

Reported Patient Outcomes

The potential impact of switches to generics

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from branded agents, particularly those with a narrow therapeutic index, has been the subject of a number of review articles.[1,6,12] Clinical experience highlights the potential problems with switching to generic AEDs. Some authors suggest that even slight variations in drug bioavailability can diminish efficacy or promote toxicity for the patient with epilepsy.[27,33-35] Increased seizure activity and side effects following generic AED substitution have been reported in several surveys of patients and healthcare providers (Table 4).[7,32,36-39] In addition, increased cases of adverse events, including dizziness, nausea, ataxia, diplopia, and nystagmus, have been documented.[34,35,40] Emergency department visits, hospitalizations, patient injuries, and missed workdays also occurred, according to a survey of 301 US neurologists (Figure 2).[36]

Most recently, results from a study of associations between AED formulation switching and epilepsy-related adverse events have been reported. In this case-controlled study, people diagnosed with epilepsy had 81% greater probability of receiving ambulance, emergency room, or inpatient care if they had switched between AEDs considered therapeutically equivalent by the FDA ("A-Rated Drugs") within the past 6 months than if they had not recently switched A-Rated AEDs.[4] Taken together, these surveys and data from the case-controlled study suggest that, in the case of epilepsy, switching formulations, even if bioequivalent according to FDA criteria, may lead to increased seizures and side effects, and poorer therapeutic outcomes.

The Canadian Experience With Generic Substitution

A Canadian study offers some insights into the effects of substituting generic AEDs for newer AEDs. Makus and colleagues[41,42] reviewed the public databases of patients with epilepsy before and after the availability of generic lamotrigine. Findings showed that not only did the number of reported AED-related adverse reactions increase with the availability of the generics but, in the case of lamotrigine, more than half were generic-related, and nearly 50% of these involved loss of seizure control. Most patients who switched back to the branded product specifically did so to regain seizure control, which proved successful in the majority of cases.

Another analysis followed a Canadian population of 1,354 patients receiving branded lamotrigine who were mandated to switch because the area's drug benefit formulary had adopted compulsory conversion to generic lamotrigine. Of these, 12.9% switched back to the branded product. The authors suggest that switching back was influenced by patient desire to avoid seizures or side effects. Switching from other AED generics occurred about 20% of the time. Comparatively, agents used chronically to treat other diseases (eg, statins and selective serotonin reuptake inhibitors) had much lower rates of switching back to branded products, with ranges from 1.5% to 2.9%.[43,44]

Patients who continued on the generic AED required more concomitant AEDs and non-AEDs than those who switched back to the brand-name drug (P=.042). This could have reflected adverse effects associated with generic lamotrigine, although this was not specifically studied.[44] Higher doses of generic lamotrigine (+6.2%; P<.0001) were required compared with the branded agent, suggesting decreased bioavailability of the generic relative to the branded formulation.[44] This report suggests that generic substitution of newer agents such as lamotrigine can lead to poorer outcomes even though they possess parallel pharmacokinetic profiles and higher therapeutic indices than older agents. However, these studies were unblinded and retrospective, therefore ruling out variables other than the drugs themselves that might have influenced outcomes is difficult.

OTHER ISSUES REGARDING GENERIC SUBSTITUTION

It is also important to recognize other limitations of the existing data, including potential bias against generic AEDs. Further, the studies often do not include a control group or directly asses the breakthrough seizure rates of branded versus generic version. Other practical concerns regarding generic substitution include patient compliance and economics. Because generic agents may not carry identifying marks or characteristics, patients may be confused if their medicine looks different or, more importantly, if they experience unusual side effects. As a result, patients may be more likely to be only partially adherent to their medication regimen, which is often cited as a factor relevant to inadequate seizure control.[2]

In terms of economics, in epilepsy, any potential savings afforded by generics may be outweighed by the switch-related expenses to

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treat adverse events or therapy failure.[45,46] In a report issued by the Therapeutics and Technology Assessment Subcommittee of the AAN, in which issues relating to generic substitution of AEDs were discussed, the authors stated, "These hidden costs [after a single recurrent seizure] represent a serious flaw in the economic incentive for generic substitution, which can result in additional costs that far outweigh any small cost saving accruing from use of generic medications."[28] A single sei-

TABLE 4.
Selected Results From Patient and Healthcare Professional Surveys Regarding Generic AEDs

Location	Population	Generic Substitution	Seizure Activity or Toxicity After Generic Substitution	Other Results
Canada[7]	83 patients	17% had switched; 22% did not know if they had ever been switched from brand name to generic	• 14% reported no problems	
USA[36]	301 neurologists		• Brand-to-Generic – 68% reported breakthrough seizures – 56% reported increased AEs • Generic-to-Generic – 33% reported breakthrough seizures – 27% reported increased AEs	• Additional consequences reported included increased need for consultation, greater number of sick days, higher incidence of injury to patients • 10% of neurologists noted that their relationship with the patients had been undermined by the change to a generic AED • 82% considered FDA standards for AED bioequivalence not sufficiently narrow
International[37]	974 patients		• 23% attributed breakthrough seizures to generic medication	• 52% aware of the term "generic" • 34% aware that substitution could occur without healthcare professional consent • 58% uncomfortable about generic AEDs
USA[32]	550 patients 606 physicians		• 65% of physicians reported having a patient experience breakthrough seizures • 35% of patients think substitution is linked to breakthrough seizures	• 81% of patients and 87% of physicians agreed that substitution should occur only with physician consent
International[38,39]	602 physicians	About 80% had experience with generic substitution		• ~50% reported problems including additional telephone contacts/office visits, emergency department visits, disturbance of physician-patient relationship, sick days, injuries

AED=antiepileptic drug; AE=adverse effect; FDA=Food and Drug Administration.

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FIGURE 2.
Consequences of generic AED substitution[36]

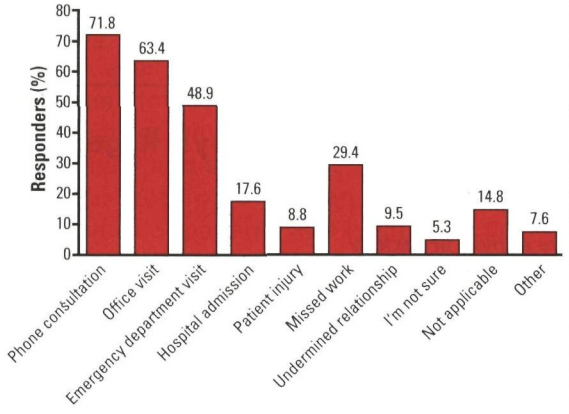


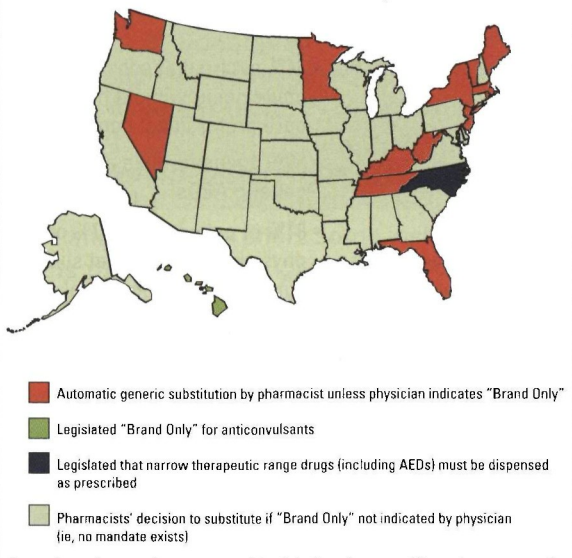
Figure depicts 301 US neurologists' answers to the question, "In cases where generic substitution occurred, did the substitution result in any of the following? (Indicate all that apply.)"

Reprinted from: Wilner AN. Therapeutic equivalency of generic antiepileptic drugs: results of a survey. *Epilepsy Behav.* 2004;5:995-998, with permission from Elsevier.

AED=antiepileptic drug.

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FIGURE 3.
State laws or statutes governing generic substitution by pharmacists[47]



A number of states have enacted legislation that specifies when a generic substitution may be made at the pharmacy level. In all states, if a physician designates "brand only," the medicine will be dispensed with the formulation specified.

AED=antiepileptic drug.

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zure can cause injury, hospitalization, and even death. Table 5 summarizes these and other direct and indirect costs to consider before a generic substitution is made, especially for patients who are seizure free on their current AED. Switching to a generic AED for the sake of economy may not, in fact, be cost-effective overall.[45]

Although the FDA sets the standards for bioequivalence, the laws and statutes for generic substitution vary among the states. Currently, all states mandate "Brand Only" if indicated by the healthcare professional. However, as shown in Figure 3, a number of states mandate generic substitution by the pharmacist if "Brand Only" is not indicated by the healthcare professional. Notably, Hawaii mandates "Brand Only" for anticonvulsants, and in North Carolina, narrow-therapeutic-range drugs, which include AEDs, must be dispensed as originally prescribed.[47] In Tennessee, where substitution is mandated if "Brand Name" is not specified, pharmacists

TABLE 5.
Direct and Indirect Costs of Epilepsy Treatment[45]

Direct Costs

- Drug acquisition
- Outpatient visits
- Emergency department visits
- Inpatient hospitalizations
- Nursing care
- Diagnostic testing (EEG, neuroimaging)
- Antiepileptic plasma drug concentration and other laboratory monitoring (complete blood count, liver function tests)
- Transportation costs
- Epilepsy surgery cost

Indirect Costs

- Earning loss and economic production loss
- Household production loss
- Special education costs
- Institutionalization costs
- Increased mortality costs
- Adverse effects costs and related returns to healthcare professionals

Reproduced with permission from: Jobst BC, Holmes GL. Prescribing antiepileptic drugs: should patients be switched on the basis of cost? *CNS Drugs.* 2004;18:617-628.

EEG=electroencephalogram.

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must inform patients or their designates, as well as the prescribing physician, before substituting one AED for another.[48-50] The responsibility for informing patients, in many cases, may fall to the pharmacist because the other healthcare providers treating a patient with epilepsy may not be aware of the generic substitution nor do they have access to the exact bioavailability data for a given generic product.[11]

EXEMPTING AEDS FROM MANDATORY GENERIC SUBSTITUTION

Expecting that certain agents, patient groups, and chronic diseases would be exempt from mandatory generic substitution is reasonable. The most likely candidates for such an exemption are drugs with complex regimens, narrow therapeutic indices, or a high probability of interactions, patients at particular risk for adverse events, and medical conditions with potentially serious outcomes.[1,2,51] AEDs and epilepsy meet these criteria.

The case for exempting AEDs from mandatory generic substitution is centered on the premise that establishing and maintaining seizure control in the absence of unacceptable adverse events is a complex, carefully orchestrated, individualized effort that frequently requires more than a single dose adjustment to establish optimal outcomes.[2] Optimizing epilepsy therapy is a challenge because the metabolism of AEDs may affect the metabolism of concomitant drugs the patient may be taking to manage coexisting conditions. Furthermore, no simple measurements (such as blood glucose in diabetes) can predict the appropriateness of an epilepsy regimen. Since safe and effective use of these agents frequently requires careful titration and monitoring, even slight variations in their absorption can potentially impact health outcomes negatively.[2]

Epilepsy as a disease state could also be considered for exemption from mandatory generic substitution based on its status as a critical disease. A single seizure has a dramatic impact on the patient, ranging from social stigma and loss of confidence to hospitalization and even death.[2] At the very least, a seizure recurrence means having to reestablish seizure control.

RECOMMENDATIONS FROM EPILEPSY ASSOCIATIONS AND SOCIETIES

Societies and specialty associations agree that formulation substitution of AEDs in epilepsy requires careful consideration. The EF has recommended that extreme caution be exercised when switching among different formulations and that policies be in place that allow physicians or patients to override mandatory substitution of AED generics for brand-name drugs due to concerns about breakthrough seizures.[30] The AAN opposes generic substitution of AEDs without the approval of the attending healthcare professional. The AAN takes the position that the significant, FDA-permitted variations between generic and branded AEDs could be problematic because even minor differences can negatively impact seizure control.[29] The AAN position is that:

- AEDs differ from other drug classes in several ways, making generic substitution problematic
- Healthcare providers should have complete autonomy in prescribing AEDs
- Patients should have access to all anticonvulsants
- No point-of-sale generic substitution should occur without consent
- Informed consent should be given prior to any change in formulation
- Unlike other diseases, a single breakthrough seizure can have severe consequences, ranging from loss of driver's license to injury and even death, due to the change in delivered dose

Other groups such as the AES, the National Institute for Health and Clinical Excellence, which is an independent organization in the United Kingdom responsible for providing national guidance on clinical practices, and the International League Against Epilepsy have cautioned against AED substitution without a healthcare professional's approval.[52-57]

CONCLUSION

The use of lower-priced generic products is an established component of healthcare cost containment and in many instances represents the most cost-effective patient management option. However, once a patient has begun epilepsy management, switching between AED formulations leads to important clinical concerns. Therefore the LEAD faculty (please see acknowledgements) recommends that any change in AED formulation, whether from a branded product to a generic product or from one generic to another generic formulation, should only be allowed with the

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informed consent of the patient and physician.

Switching AED formulations without the approval of the healthcare professional should be avoided. Remembering that in the case of epilepsy, switching from one AED formulation to another is potentially associated with severe effects for the patient, both clinically and socially, is important. Therefore informed consent of the patient should also be obtained. The decision to switch formulations in attempts to lower costs should take into account the potential expense of adverse events and lost seizure control that may occur with AED substitution.

The lessons learned from Canada's mandatory generic substitution and evidence from surveys of US healthcare providers and patients provide important background for those who treat patients with epilepsy and for pharmacists who dispense AEDs. Generic-related adverse events or seizures should be reported to MedWatch (http://www.fda.gov/medwatch), including information on the patient's AED blood level when the side effect or seizure has occurred, as well as when the patient is restabilized on their prior AED.[10]

The continued watchfulness and event reporting by the healthcare community can help increase awareness of the possible need to institute more stringent AED generic bioequivalence requirements and to take appropriate steps to ensure the continuity of pharmacotherapy for patients with epilepsy. Additional clinical data on the potential adversities associated with generic switching of AEDs may provide evidence suggesting to healthcare plans and other providers, as well as formularies used by health insurance plans, hospitals, and residential institutions, that patients with epilepsy might be exempted from the process of mandatory AED generic substitution. Indeed, at least one insurance company has decided to rescind its requirement that patients pay the difference in cost between brand name AEDs and the generic for these medications, according to a letter from Wellmark BlueCross Shield in December 2009. ***CNS***

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