SWITCHING AED FORMULATIONS: DEFINING THE ISSUES

William R. Garnett, PharmD*

ABSTRACT

Generic medications are less expensive than brand-name drugs, but if there is a poor response, the indirect costs associated with the use of a generic can outweigh that of the brand-name drug. Indirect costs due to loss of seizure control or medication toxicity include hospitalizations, physician office visits, serum concentration tests, quality of life, limitations on driving/job opportunities, anxiety, and depression. Despite these risks, cost continues to be a powerful driver. The stakeholders in the generic substitution debate include not only the physician, pharmacist, and patient, but also the payer, pharmaceutical manufacturer, and the US Food and Drug Administration, which takes the unequivocal position that, "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product." Payers certainly want to limit costs, while pharmaceutical companies want to protect and profit from their intellectual property; physicians and pharmacists may be rewarded by payers for lowering costs. They also may feel pressure from patients to reduce medication costs. Patients, particularly those on very limited incomes, may be forced or more tempted to choose a generic product because they cannot afford the branded drug. This article reviews the issues surrounding generic substitution of antiepileptic drugs (AEDs) from the perspective of each stakeholder. Although the literature on physician, pharmacist, or patient attitudes and experience with generic drugs is sparse, these studies highlight that the decision to switch to a generic AED is currently based more on emotion than science.

(*Adv Stud Pharm*. 2008;5(5):140-145)

Because the greatest benefit with generic drugs is lower healthcare costs, the forces that influence the decision to switch from a brand to generic drug are generally cost-driven. These forces are numerous, strong, sometimes hidden, and frequently conflicting. The stakeholders in the generic substitution debate include the physician, pharmacist, patient, payer, and pharmaceutical manufacturer. One also might argue that professional and patient societies and biomedical journals are stakeholders because of their dependence on grants from pharmaceutical manufacturers for operations (eg, education and print advertising). With regard to epilepsy, each stakeholder argues for or against the switching to a generic antiepileptic drug (AED) based on economic and scientific data and anecdotal clinical reports.

There are many misconceptions about the regulations set forth by the US Food and Drug Administration (FDA) regarding allowable variations in bioavailability of generic drugs versus their branded counterparts. As discussed in this article, these misconceptions are present among all healthcare practitioners, including physicians. In reality, the most likely greatest difference in bioavailability between 2 generics is 10% (ie, a generic that is approximately 5% less than the brand and one that is approximately 5% more than the

*Professor of Pharmacy and Neurology, Virginia Commonwealth University, Medical College of Virginia, School of Pharmacy, Richmond, Virginia.

Address correspondence to: William R. Garnett, PharmD, Professor of Pharmacy and Neurology, Virginia Commonwealth University, Medical College of Virginia, School of Pharmacy, PO Box 980583, Richmond, VA 23298. E-mail: wrgarnett@hsc.vcu.edu.

brand). But can a 10% variability in product produce a clinical difference and does it make a difference for a patient with epilepsy?

For the clinician treating a patient with epilepsy, these are difficult questions to answer. Switching to a generic statin with a 10% change in bioavailability may result in a change in cholesterol of a few mg/dL; however, the consequences of an adverse event with a similar change in AED concentration can be life changing. In fact, the consequences of a breakthrough seizure can be catastrophic, including injury to the patient or others, loss of driving privileges (up to 1 year, depending on the state), potential loss of employment or employment opportunities, depression, anxiety, and loss of self-esteem. With adverse events, patients must confront not only the unpleasantness but also the extra burden of the effects (eg, hospitalization, increased doctor visits, time off from work, and cost of other medications to address the effects). Thus, the stakes may be higher in the generic-brand debate for the individual with epilepsy.

This article reviews the issues surrounding generic substitution of AEDs from the perspective of each stakeholder and serves to make the reader aware of the influences that affect the asking and answering of the question: when is it acceptable to switch to a generic AED?

The Physician

Physicians reportedly are uncomfortable with the idea of automatic substitution of generic for branded AEDs, yet past reports suggest that physicians may be unaware of the extent to which it occurs. In general, physicians object to interference with their prescription choices for individual patients, whether that outside influence comes from payers or pharmacists. Although a physician's desire to maintain the locus of control stems from a genuine concern for what is best for his or her patient, liability concerns may also influence prescribing patterns. In 1997, 3639 physicians (25% of whom were neurologists) were surveyed, from whom 396 usable responses were received for an effective response rate of 12%. The survey results showed that fewer than 20% of respondents correctly identified the FDA's bioequivalency standards.[1] However, confusion about the FDA nomenclature in this area was highlighted by the fact that the surveyors misstated the FDA standard for bioequivalence in their survey instrument.

An oft-quoted survey of 301 neurologists found that 81.6% of those surveyed disagreed with the statement: "The FDA has determined that generic drugs must achieve 80% to 125% bioavailability compared to that of brand name. Do you feel that is sufficiently narrow to insure [sic] efficacy comparable to the brand name for your patients?" The wording of this question may have been somewhat misleading, however. The FDA does not require 80% to 125% bioavailability, but uses a more stringent and statistically robust criteria that require the ratio of the generic's maximum blood concentration and 90% confidence intervals (CIs) of the log-transformed ratio of the area under the curve to fall within 80% to 125% of those for the reference drug (ie, brand).[2] One must ask if physicians would be as uncomfortable with generic switching if he was aware of and understood this difference?

In this same survey of 301 neurologists, 67.8% of the neurologists reported breakthrough seizures and 56% reported increased adverse events that they attributed to a switch to generic drugs. Moreover, 32.5% reported breakthrough seizures and 26.6% reported increased adverse events attributable to a switch from one generic AED to another; however, it was not clear how they determined these outcomes were attributable to the generic drug and adherence was not assessed.[2] An earlier physician survey by Wilner showed that 86.4% of respondents were not comfortable with patients receiving multiple formulations of generic carbamazepine and 80.3% did not endorse generic substitution of carbamazepine.[3] In the same study, an independent audit of Tegretol (carbamazepine; Novartis Pharmaceuticals Corporation, East Hanover, NJ) prescriptions showed a substitution rate of 68%. However, only 12% to 17% of physician respondents estimated the rate of substitution as 70% and most estimated the substitution rate to be 30% to 50%.[3]

These types of discrepancies are not unique to US neurologists, however. A multinational survey of physicians in Canada, the United Kingdom, Germany, France, and Spain showed that a majority opposed generic substitution without physician consent. Moreover, 31% said they would be uncomfortable prescribing a generic medication to treat their patients' epilepsy, and 70% felt that epilepsy is a medical condition for which the universal substitution of branded medications with generics without direct approval from the physician is medically inappropriate and unacceptable. In fact, nearly all respondents (94%) felt they

should be able to override a mandatory substitution if a patient's seizure control or health might be jeopardized. Interestingly, serious concern about the level of epilepsy control with generic substitution was greater among general practitioners (57%) than for neurologists (31%).[4]

It has been my experience that misperceptions about the 80/125 bioavailability rule are pervasive among physicians. Some physicians I have spoken with thought that bioavailability among generics can vary as much as 45% and that generic drugs are more poorly made with lower manufacturing standards. It is important for physicians to realize that, in fact, generic drugs made in the United States are subject to the same Good Manufacturing Practices as all other pharmaceutical products made in the United States. Moreover, because bioavailability is not studied after phase I clinical trials, we also do not know lot-to-lot variation of brand-name drugs.

The Pharmacist and Pharmacies

Similar to physicians, pharmacists are interested in ensuring that patients receive the best drug for their medical condition. They also try to be patient advocates by working to ensure that patients receive the most economical but clinically effective drug. In many cases, this can be accomplished by simply asking the patient, are you interested in the generic version of your prescription? A pharmacist also has to address a patient's financial concerns, such as the cost of the prescribed AED, especially if it is not covered by the patient's third-party payer. Pharmacists may find themselves in the uncomfortable position of advocating for the patient in discussions with the physician and payer over this issue.

Pharmacists are also under pressure from both large retail employers and hospitals to use generic drugs as often as possible, because generic drugs maximize profit margins for the pharmacy and institution. In fact, patients may be switched between generics nearly every month as pharmacy chains frequently change generic suppliers based on pricing in bids.

Formal surveys of pharmacists on the issue of generic substitution are virtually nonexistent. Similar to physicians, pharmacists are concerned about the safety and efficacy of narrow-therapeutic-index drugs.[5]

There is a movement within professional pharmacy organizations for pharmacists to have the right of formulation selection for 2 reasons: pharmacists typically know more about generic testing and standards than physicians and they have access to the Orange Book. It is important to remember, however, that pharmacists can always call the physician and ask, "Do you know the difference in price and/or copay between brand and generic? Does this affect your prescription?" Many physicians are not aware of these costs and the effect of this expense on their patients, thus pharmacists can be more proactive in determining formulation choice. Also, some generics are branded (eg, Epitol [carbamazepine, Novartis Pharmaceuticals Corporation, East Hanover, NJ]). Such "branded generics" are made by the manufacturer of the original brand-name drug in an effort to gain market share of the generic version as the patent for the brand-name drug is about to expire. Use of such branded generics is one way that a patient can stay on a single, generic formulation (unless the patient's pharmacy receives a lower offer and switches generics). However, the options for branded generics in the United States are quite limited.

The Patient

Several surveys have shown that patients with epilepsy are not always comfortable with the switch from branded to generic formulation. A 1996 survey of patients with epilepsy in the United Kingdom revealed several interesting trends in patient response to switching AED formulations. In this study, 1343 patients who recalled taking a different supply of AED over the last 2 years were contacted and completed a survey. Those reporting problems following a switch were classified as "switch problems validated" (ie, an increase in seizure frequency or side effects was reported with no other identifiable or medical cause, based on discussions with the physician), "switch problems unproven" (ie, an increase in seizure frequency or side effects where other likely medical or psychologic explanations were identified), and "follow-up incomplete" (ie, an increase in seizure frequency or side effects but the person did not respond to follow-up approaches or opted for no further contact on the survey). The patients in this survey were taking carbamazepine, phenytoin, or sodium valproate—all older AEDs. Overall, 251 (18.7%) had experienced a switch—from generic to brand, from brand to generic, or between generics. Of these 251, 27 had validated switch problems, 25 had unproven switch problems, and 22 had incomplete follow-up. The most common types of switches for validated problems were switching from a branded to generic (68%), followed by those switching between generics (20%), and switching from generic to brand (12%).[6]

The investigators also ascertained the patients' interest in their medications. Of those who responded to this question (n = 1288), 74.5% took a close interest in their medication, 7.1% never queried variations in the presentation of their drugs but said changes would make them anxious, 11.9% reported never querying variations and change would not make them anxious, and 6.5% said they did not pay close attention to drug presentation and would not have noticed a change. Of those with validated switch problems, 85.2% took close interest in their medication, compared with 11.1% (never query/anxious), 3.7% (never query/no worries), and 0% (does not pay close attention). The investigators noted that people who take a close interest in their medication appear to be more likely to report problems.[6]

Also from the United Kingdom, a survey of 1851 people with epilepsy showed that 33% of respondents had been switched from branded to generic AED in the past year. Of those, almost 25% stated that they had experienced an increase in seizures as a result. Also, 33% of those who had been switched experienced more or different side effects. However, it was not disclosed how the respondents knew that their seizures were the result of the switch.[7]

These studies suggest that patients are not comfortable with changing to generic AEDs because they perceive them to be associated with an increase in seizures and/or side effects. Therefore, they may be more perceptive of changes in the course of a brand-to-generic switch. The multinational survey described here showed that 23% of all patients surveyed believed that generic medication substitution is linked to breakthrough seizures, and 58% of all patients felt uncomfortable receiving a generic medication to treat their epilepsy. However, 89% said they would be more likely to report a breakthrough seizure if they thought the onset could be related to a change in their medication.[4]

The price of a medication may also influence patients' stated drug preference and expectations of therapeutic outcomes. Drug price (ie, the cost of medication borne by the patient) is determined by the health insurance payer. For coverage of prescription drugs, payers categorize drugs according to a 3-tier system in which the first tier is the preferred drug for the payer. Very often, this drug is the least expensive for the payer, based on prices negotiated with the manufacturer, although safety and efficacy are also part of the consideration. The copayments for first-tier drugs are the smallest, usually approximately $5 to $10 per month. Second- and third-tier drugs are the second and third choices, respectively, with corresponding increases in copayments, upwards of $70 or more for a 1-month supply in some cases for third-tier drugs. Thus, for a patient on a limited income or taking multiple medications, third-tier drugs can rapidly become cost prohibitive. A recent study showed that even a $5 increase in the copayment for statin prescriptions decreased adherence.[8,9] Generic formulations are almost always first-tier drugs, and are thus preferable, especially to those with limited funds to pay for healthcare.

Price can also affect patients' expected outcomes (eg, "you get what you pay for"). In one study, patients received placebo pills but were told they were receiving an analgesic that was described as FDA-approved and similar to codeine with faster onset time. Half the participants were told that the drug had a regular price of $2.50 per pill and the other 50% was told that the pills had been discounted to $0.10 each. The results showed a greater number of patients experiencing reduced pain (measured with a visual-analog scale) among those in the regular price group (85.4%; 95% CI, 74.6%–96.2%) than those in the discount price group (61%; 95% CI, 46.1%–75.9%; P = .02.)[10] Although pain and epilepsy differ substantially in the overall effect of the placebo response in their treatments, these findings warrant consideration of a price effect on sensitivity to efficacy with AEDs.

A recent case series studied switching from branded lamotrigine to generic. In this study, a survey of adverse reaction forms submitted to pharmacists (71 pharmacists responded) by physicians revealed that 11 of 14 forms described patients with epilepsy who experienced loss of seizure control when generic lamotrigine was substituted for branded drug. Of note, seizure control was regained in 80% of patients when they were switched back to brand lamotrigine, and, in 1 case, anxiety, mood swings, and dizziness were cited as additional reasons for the switch back to brand lamotrigine. In this same report, a physician audit and survey revealed that, of 9 patients who experienced adverse reactions with a brand-to-generic switch, 8 were due to loss of seizure control, which was regained in all but 1 case when they were switched back to brand lamotrigine. It should be noted, however, that this study was supported by a grant from GlaxoSmithKline, the manufacturer of lamotrigine.[11]

Given patients' reported uncertainty and discomfort associated with a switch to generic AEDs, once the

issues are settled amongst the medical community, patient education will be essential. Direct-to-consumer (DTC) advertising may provide an effective venue. Studies conducted soon after DTC advertising was permitted in the United States showed not only that these campaigns influenced patient requests for specific drugs but also that patients are interested in learning about generic drugs through advertising and that when patients learn more about generic drugs, they are more willing to accept them.[12,13] If we are to give patients informed consent for switching to generic formulations, they should be able to make informed choices.

The Payer

In the end, generic substitution is always driven by economics, thus payers are interested in substituting with generic medications whenever possible. In fact, switching to generics is now virtually mandated by health insurers, and many computer systems require multiple steps to override the substitution with generic when the prescription indicates "dispense as written." According to the Centers for Medicare and Medicaid Services, the Omnibus Budget Reconciliation Action of 1990 (OBRA '90) established criteria for federal upper limits on what Medicaid could reimburse for drugs when generic versions are available. The criteria state that a federal upper limit is permitted for a drug product if there are 3 (or more) versions of the product rated therapeutically equivalent regardless of the rating of other versions and at least 3 suppliers are listed in the current editions of published national compendia.

However, payers, in their strong push to convert all prescriptions to generic formulations when possible, in the name of improving the bottom line, may ultimately "cut off their nose to spite their face." For example, several years ago, third-party payers sent "Dear Doctor" letters asking physicians if they realized that by switching their prescriptions from a brand-name AED (Dilantin, phenytoin; Pfizer Inc, New York, NY) to a generic, they could save money. This is a shortsighted initiative, with no regard for the cost of side effects with using phenytoin or the difficulty in using phenytoin (eg, titration), let alone the risk of breakthrough seizures. Of note, this is a frequently cited, but not the best, example of the risks of generic substitution because of the proposed risk of switching to a different AED along with the non-linear pharmacokinetics with phenytoin.

The Manufacturer

Clearly, manufacturers of brand-name drugs have a vested interest in protecting their intellectual property and avoiding the promotion of generic formulations whenever possible. Some of the ways pharmaceutical brand manufacturers seek to protect their intellectual property are to buy outright the companies that manufacture generic drugs, create extended- and controlled-release versions of their own brand-name drugs just before the patents expire, create their own generic formulations (ie, branded generics), and on the judicial front, challenge patent infringements by generic manufacturers in court. In response to concern about abuse of the judicial tactics, the FDA announced in 2003 the Final Rule regarding generic drugs (http://www.fda.gov/oc/initiatives/generics/fs_rule.html). In brief, the Final Rule states that brand-name manufacturers will be limited to one 30-month stay to resolve allegations that a generic drug maker is infringing on a listed drug patent and the Rule tightens patent submissions and Orange Book listing requirements to avoid manufacturers submitting additional patents for changes in drug packaging or other minor changes not related to effectiveness.

Because patient safety is not at risk (with the FDA's assurances on bioequivalence), pharmaceutical manufacturers have a fiduciary duty to protect their investors' money. This is understandable, but it also creates a bias. Although this may be intuitively obvious to some, it is worth noting because this influence can affect other areas of healthcare, such as patient and professional societies. One example of this was drug company-sponsored campaigning by the Epilepsy Foundation in specific states for bills to make it harder for pharmacists to switch patients to generic epilepsy drugs.[14]

Conclusions

Although the literature on physician, pharmacist, or patient attitudes and experience with generic drugs is sparse, these studies highlight that there is currently more emotion than science in the debate. Payers and pharmaceutical manufacturers have responsibilities to their own stakeholders (the stockholders) to maximize financial returns. Government agencies have similar obligations in the allocation of limited financial resources. Although none of the parties may be acting inappropriately, their collective influence can make it difficult to answer the question, "When is it acceptable to switch to a generic AED?" For all stakeholders, it is important to be aware of these influences.

REFERENCES

1. Banahan BF, Kolassa EM. A physician survey on generic drugs and substitution of critical dose medications. *Arch Intern Med*. 1997;157:2080-2088.
2. Wilner AN. Therapeutic equivalency of generic antiepileptic drugs: results of a survey. *Epilepsy Behav*. 2004;5:995-998.
3. Wilner AN. Physicians underestimate the frequency of generic carbamazepine substitution: results of a survey and review of the problem. *Epilepsy Behav*. 2002;3:522-525.
4. Haskins LS, Tomaszewski KJ, Crawford P. Patient and physician reactions to generic antiepileptic substitution in the treatment of epilepsy. *Epilepsy Behav*. 2005;7:98-105.
5. Kirking DM, Ascione FJ. Perspectives on generic pharmaceuticals: some conclusions. *J Am Pharm Assoc* (Wash). 2001;41:826-828.
6. Crawford P, Hall WW, Chappell B, et al. Generic prescribing for epilepsy. Is it safe? *Seizure*. 1996;5:1-5.
7. Goodwin M. The importance of brand continuity in epilepsy drugs. *Nurs Times*. 2005;101:26-27.
8. Doshi JA. Impact of prescription copayment increase on lipid lowering medication adherence in elderly patients. Presented at: 2008 American Geriatric Society Annual Scientific Meeting; April 30-May 4, 2008; Washington, DC. Abstract P8.
9. Hartung DM, Carlson MJ, Kraemer DF, et al. Impact of a Medicaid copayment policy on prescription drug and health services utilization in a fee-for-service Medicaid population. *Med Care*. 2008;46:565-572.
10. Waber RL, Shiv B, Carmon Z, Ariely D. Commercial features of placebo and therapeutic efficacy. *JAMA*. 2008; 299:1016-1017.
11. Makus KG, McCormick J. Identification of adverse reactions that can occur on substitution of generic for branded lamotrigine in patients with epilepsy. *Clin Ther*. 2007;29:334-341.
12. Peyrot M, Alperstein NM, Van Doren D, Poli LG. Direct-to-consumer ads can influence behavior. Advertising increases consumer knowledge and prescription drug requests. *Mark Health Serv*. 1998;18:26-32.
13. Perri M, 3rd. An experimental intervention: stimulating patient requests for generic prescription medications. *J Pharm Mark Manage*. 1989;3:21-36.
14. Rubenstein S. Industry fights switch to generics for epilepsy. Big drug makers help patient groups lobby; more attention to states. *Wall Street Journal*. July 13, 2007.