

# Overexposed?

## The Realities of Epilepsy Treatment Failure and Generic AEDs

**It's easy to blame generic substitution for treatment failures, but the reality is that numerous other factors may influence negative outcomes.**

**By Barry E. Gidal, PharmD, RPh**

Perhaps one of the greatest controversies in medical management of epilepsy today involves the role of generic AEDs in patient care. With all the major AEDs now available in generic formulations, attention to the issue will likely increase. While there may be occasional legitimate concerns associated with certain substitutions, misunderstandings and false presumptions about substitutions abound. Neurologists seeking to provide the highest quality of care to their patients must 1.) become familiar with the realities of substitution, 2.) be able to recognize and deal with the breadth of issues that may contribute to therapeutic failure, and 3.) be prepared to effectively communicate with patients and empower them to participate in their own care. Emphasis of these points will encourage therapeutic adherence and potentially improve therapeutic outcomes.

### Substitution Realities

Generic substitution has to some extent become a scapegoat for poor therapeutic response. When a patient presents with

increased seizure frequency or breakthrough seizures after a period of seizure-freedom, one of the clinician's initial queries will almost certainly focus on generic substitution. While subtle variations in formulation between branded products and their generic counterparts may occasionally lead to substantial differences in therapeutic response, clinicians may be too quick in some cases to assign blame to the generic product. Neurologists are well aware of a range of possible contributors to apparent "therapeutic failure," the most common of which is probably non-adherence to the treatment plan. Lifestyle issues, such as sleep deprivation, may also impact seizure frequency independent of drug therapy. Yet when a generic substitution comes to the clinician's attention, many discontinue further questioning and assume they have identified the cause of the new seizure activity: an inferior drug formulation.

The issue of generic substitution has become so controversial that it can raise the ire of some clinicians, even if it has caused no complications. The prescribing physician may complain that the pharmacist has usurped the doctor's med-



ical decision making. The reality is that the pharmacist has typically acted ethically and well within his/her legal rights and in compliance with regulations set forth by the federal government via the FDA, the state, the pharmacy, and/or the patient's health insurance. According to the FDA, the generic formulation is a "therapeutic equivalent." (For more on this, see the sidebar on the next page.) Certainly substitution for a different agent is illegal and problematic; for those very reasons, such substitutions are exceedingly rare.

Insurance company formularies often require that the pharmacy substitute the generic formulation, if available, and patients who refuse the substitution face higher co-pays or responsibility for the full cost of the prescription. Given the chronic nature of epilepsy, many patients could not afford to pay for brand-name formulations month after month.

#### The Adherence Model

Therapeutic adherence in epilepsy literally can be a matter of life and death. Recently published findings from the RAN-SOM study show that patients non-adherent with the AED

regimen had more than three times the risk of death compared to adherent patients.<sup>1</sup> Non-adherence was associated with an 86 percent increase in hospital admissions and a 50 percent increase in emergency department visits compared to adherence. Non-adherent patients experienced twice as many motor vehicle accident injuries and 21 percent more fractures, compared to adherent patients. Older patients, women, African-Americans, and those with higher comorbidity scores were most likely to be non-adherent.

Improved adherence increases the likelihood of optimal seizure control, thus potentially improving the quality of life, minimizing injury, and decreasing mortality. To establish a patient-friendly treatment regimen that promotes adherence, the physician must consider, in consultation with the patient, numerous factors.

**Seek "adherence" not "compliance."** The notion of therapeutic adherence has emerged to more accurately reflect the patient's role in treatment. Rather than "comply" with instructions from the physician telling the patient what he or she has to do, the patient should be recruited to play an active

## Understanding Generic Approvals

Although the FDA maintains that approved generic formulations of AEDs are therapeutically equivalent to their branded counterparts, many neurologists express concerns about these formulations.<sup>1-3</sup> In fact, several professional societies, including the AAN,<sup>4</sup> have issued position papers expressing concern for widespread and indiscriminate substitution. The Epilepsy Foundation, for example, has posted a statement at [www.epilepsyfoundation.org/advocacy/care/genedrev.cgm](http://www.epilepsyfoundation.org/advocacy/care/genedrev.cgm). In order to better understand issues associated with substitution, it's essential to understand the approval process.

For the purposes of interchangeability in the US, a generic drug must meet a number of fairly strict criteria:

- The generic product must be pharmaceutically equivalent: It must contain the same amount of active drug as the innovator product, and must meet United States Pharmacopeia (USP) standards for purity, strength and quality.
- Inactive ingredients must be recognized as safe but do not need to be identical to those used in the innovator, or branded product.
- The generic product must also meet FDA requirements for adequate labeling, and the manufacturer of the product must be able to demonstrate to FDA that the production facility is in compliance with Good Manufacture Practices (GMP).

The next hurdle for a formulation is to demonstrate bioequivalence. The FDA defines bioequivalence as: "The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" [Federal Register (21 CFR 320.1)].

To be accepted as bioequivalent, new oral drug formulations must:

- Be compared to the branded product in relatively small (typically 24-36 healthy adult volunteers) single-dose crossover studies.
- Bioequivalence is evaluated by comparison of the area under the concentration-time curve (AUC), a measure of systemic exposure, and peak plasma concentration (C<sub>max</sub>), a measure of absorption rate. For a generic product to be considered equivalent, the 90% confidence interval of the log-transformed ratios of AUC and C<sub>max</sub> between brand and

generic product fall between goal-posts of 80-125%. This has been commonly been misinterpreted to mean that the FDA will accept a difference in AUC of 20-25% for a generic product, which is incorrect. Under current rules, this does not mean that there can be a 20% to 25% difference between the mean pharmacokinetic parameters of the two products.

- Regulations are intended to ensure interchangeability between a brand/innovator product and an individual generic formulation.
- Generic products need not be tested to prove bioequivalence with another generic formulation. Equivalence is assumed.

Numerous factors can influence the bioavailability of a drug product, such as aqueous solubility, membrane permeability, and presystemic metabolism. For a generic drug product that contains the same active ingredient, pharmaceutical characteristics such as solubility and permeability of the compound are likely to be the most important predictors of bioequivalence. Non-active ingredients, such as excipients, binders, fillers, lubricants, etc. can differ between the innovator and the generic. Variances in these factors may be only modestly important for many drugs, but drugs such as phenytoin, carbamazepine, lamotrigine, and oxcarbazepine have poor aqueous solubility, so formulation changes that affect dissolution may ultimately impact oral absorption.

Well-documented reports suggest that there may be problems with generic formulations of some AEDs.<sup>5</sup> In addition, anecdotal reports suggest problems associated with generic formulations. It seems clear that in certain cases, generic formulations contribute to poor seizure control for some patients. Future research may help identify specific characteristics of formulations or patients that may help predict poor performance of formulations.

*For more detail on these issues and counterarguments, see the Epilepsia article from which the author adapted this sidebar: "Debate: Substitution of generic drugs in epilepsy: Is there cause for concern?" available at [www3.interscience.wiley.com/journal/117957420/home](http://www3.interscience.wiley.com/journal/117957420/home)*

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4. Liow K, Barkley G, Pollard J, et al. Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. *Neurology.* 2007 Apr 17;68(16):1249-50.
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role in developing a treatment strategy that he or she is willing to “adhere” to.

**Minimize the administration schedule.** The administration schedule is a key issue to consider when selecting a therapeutic agent. Studies and clinical experience confirm that as the number of daily doses increases, adherence decreases. In other words, once-daily formulations tend to be associated with highest levels of adherence while agents administered two or three times a day present more opportunities for missed doses.

**Consider the impact of possible side effects.** Closely related to administration are side effects, and the two can be related. For example, a patient may have a higher tolerance for side effects from a drug he takes once each day, but the same side effects compounded by multiple daily administrations could lead to non-adherence.

**Assess lifestyle factors.** A fourth critical element is the patient’s lifestyle: personal preferences, professional/scholastic schedules, etc. There may be a tendency to instruct patients to take a once-daily medication “each morning”—an arbitrary but generally reasonable recommendation for most patients. However, if the patient is a college student whose daily wake-up times vary significantly from day-to-day or a laborer who works through the morning, then this seemingly straightforward recommendation does not apply. In fact, such a recommendation fosters non-adherence by establishing an unattainable goal from the start.

**Avoid well-intentioned but arbitrary and meaningless instructions.** Similarly, avoid making arbitrary recommendations, such as “take the pill with breakfast each morning.” While this may intuitively seem like a way to make the regimen seem simple and patient-friendly, it can actually create unnecessary confusion. Does this mean the patient must take the medication with food? If the patient skips breakfast or forgets to take the pill with breakfast, should he or she skip the dose entirely or take it with lunch?

If a medication should be taken with food or at a particular time of the day, state this and explain why. Otherwise,

encourage the patient to select a specific time of day that is convenient and easy to remember.

**Rely on local pharmacists.** Neurologists should seek to work more closely with pharmacists and encourage patients to rely on these professionals for information about their medications and answers to questions about side effects, dosing, potential interactions, and more. The pharmacist is prepared to answer most drug-related questions efficiently with access to an assortment of informational resources.

Similarly, neurologists should not hesitate to contact pharmacists directly to ask questions or to discuss any apparent problems with a drug. A pharmacist can provide important information about therapeutic failure and adherence by, for example, verifying whether a patient has refilled prescriptions as often as indicated. A collaborative rather than adversarial relationship will be most productive for all involved.

**Don't ignore drug costs and their impact.** As noted above, insurers or pharmacies stipulate a generic substitution, and failure to substitute incurs higher costs for patients. While costs theoretically should not influence treatment decisions, the realities of practice dictate that they do. A drug won't work if the patient doesn't fill the prescription due to lack of funds. According to one recently reported survey, over a

three-month period in fall 2008, one in five US adults on long-term therapies skipped or reduced doses of medications to save money (International Communications Research, icr-survey.com).

Ascertain the patient's drug coverage and determine whether or not he or she can afford the brand name agent. If you firmly believe that the patient must receive the brand name formulation rather than a therapeutic equivalent, discuss this with the patient and describe your rationale.

**Weigh other important factors.** Other important issues to consider and discuss with the patient include dosage forms. Like side effects, this consideration also ties into the medication administration schedule. A once-daily extended relief capsule may encourage adherence, but if the patient

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# Generic AEDs

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cannot swallow a large capsule, then opting for a liquid formulation—even if administered more frequently—is a better option.

## Empower Patients

Inherent in the “adherence” model is the notion that patients not only provide input into therapeutic planning but that they take greater responsibility for their own medical care. The physician encourages the patient to “buy into” the treatment plan, thus improving the likelihood of therapeutic success.

The physician has responsibilities, too. Perhaps most important is to actively seek out potential problems associated with a therapy and/or related to adherence. If the patient has had a breakthrough, appropriate and sufficient questioning should help determine why. It takes a bit of detective work.

Question the patient about adherence, changes to his/her lifestyle, alterations to his/her schedule, stress at work or

home, lack of sleep, dietary changes, or other factors that might give a clue to the cause of seizures.

Determine whether the patient has experienced troublesome side effects that have led to drug avoidance. Avoid the temptation to indict substitution, if identified, without exploring other possible factors.

Keep in mind that therapeutic success can present its own challenges. A well-controlled patient may see no reason to maintain therapy or may decide on his/her own to decrease the dose or administration schedule. Patient counseling and meaningful dialogue will help patients understand the need for continued therapy.

Encourage patients to take an active role in monitoring the medications they receive from their pharmacies. When a patient receives a generic agent, he or she should obtain from the pharmacist information regarding the manufacturer and lot number. In the event that there truly is an issue associated with the formulation, this information will be essential for reporting the problem.

## No Generic Response

In its non-pharmaceutical use, a synonym for generic is “non-specific.” Ironically, in this sense, substitution has in some cases become the generic excuse for poor therapeutic response to AED therapy. The controversies associated with generic substitution have been covered extensively in various presentations and publications, and there are valid concerns in some instances.

Generic formulations vary slightly from innovator formulations and from other generics, and these differences may on occasion explain differences in therapeutic response. In such instances, neurologists should document problems with the formulation to the best of their ability and report them to the FDA.

In a number of cases, substitutions are blamed for suboptimal therapeutic responses with little evidence. In fact, careful questioning of patients might determine that other factors related to adherence may, in fact, explain the apparent treatment failure. By taking steps to empower patients to take greater responsibility for their own care, actively involving them in therapeutic decision-making, and thoughtfully assessing various relevant issues, neurologists can improve adherence and decrease the incidence and sub-optimal therapeutic response. **PN**

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## How to Report Suspected Formulation Problems

When there is a strong suspicion that a generic formulation has not demonstrated therapeutic equivalence (the patient experiences new or increased seizure activity that cannot be attributed to any other factors), consider obtaining blood levels. These can easily be compared to historic levels from the time the patient was using the innovator drug to determine whether there may, in fact, be an issue related to the generic formulation. Of course, careful questioning of the patient is essential to ensure that the drug was taken as directed prior to the blood draw. Any strongly suspected problem with a drug should be reported to the FDA's MedWatch.



1. Fought E, Duh MS, Weiner JR, et al. Nonadherence to antiepileptic drugs and increased mortality: Findings from the RANSOM study. *Neurology* 2008. 71(20):1572-8.