Generic substitution of antiepileptic drugs

What's a clinician to do?

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Summary

Generic substitution of antiepileptic drugs remains a controversial area without a clear consensus to guide clinicians. The US Food and Drug Administration (FDA) requires rigorous testing of generic products and states that all approved products are interchangeable. FDA studies involve single doses in normal subjects so may not represent the performance of generic products in people with epilepsy. Physician surveys, case reports, and retrospective pharmacy database analyses suggest that antiepileptic drug generic substitution is associated with more health problems and high switchback rates, but these studies have insufficient detail on seizure control and blood levels. Several ongoing prospective randomized trials with rigorous pharmacokinetic methods aim to provide more data for decision-making.

Every day in the United States, it is likely that more than 1 million tablets of generic antiepileptic drug (AED) are taken by people with epilepsy. Many of these generic AED products have been on the market for several years, yet much controversy remains about equivalence and “switchability” between brand and generic products or among different generic products. Clinicians are faced with conflicting publications, editorials, and statements from the Food and Drug Administration (FDA), and patients are concerned. Most everyone agrees that widespread generic drug substitution is an important weapon to tame the growth of the multibillion-dollar prescription drug bill borne by the health care system.¹ Retrospective studies and case series raise questions about how closely the generic AEDs match the brand name AEDs in efficacy and adverse effects. The FDA states that it has no reliable documentation that generic drugs have ever caused problems for people with epilepsy.² Even the US Senate has stepped in—in 2009, the Appropriations Committee directed the FDA to provide a report on how it would fund research to resolve

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questions of generic AED equivalence.³ What are the bases of these claims and how can the controversy be resolved?

The FDA believes that the methods it uses to approve generic products are sufficiently rigorous that patients and health care providers can expect that generic equivalents will provide the same therapeutic effect as brand name drugs.² An approvable generic product must contain an identical amount of active ingredient in the same dosage form as the reference drug. Two pharmacokinetic measures, the area under the curve (AUC) of the drug concentration time (an estimate of total drug exposure) and the maximum plasma concentration (C_{max}), are used to determine bioequivalence. Equivalence is established when the 90% confidence interval of the ratio of the generic to reference compound for the AUC and C_{max} falls within an 80% to 125% range. The in vivo bioequivalence testing is typically performed on 24–36 healthy adults.⁴ The FDA analyzed over 2,000 bioequivalence studies carried out up to 1997 and reported that the mean difference between the reference and generic compounds was only 4.35% for C_{max} and 3.56% for AUC.⁵ Based on this rigorous testing, the FDA contends that switches can be made between brand and generic or among generic products without concern about loss of therapeutic effect or enhanced toxicity and that no additional testing of patients who have undergone such product switches is necessary. Critics point out that generic AED testing is not done on people with epilepsy, the test population is not taking other medications that could interact with AEDs, only a single dose of the generic AED is taken, and outcomes like seizure control or adverse effects are not measured.⁶

Another concern is that these generic approval rules apply to any therapeutic category, whether the compound is used to treat a minor infection or life-threatening illnesses, such as cardiac arrhythmias, immunosuppression for organ transplantation, or seizures. However, the FDA has asked an advisory committee to assist in defining “narrow therapeutic index” drugs for which the gap between the therapeutic and toxic dose is small, and may consider changing standards for this drug category. One suggested option is to use a scaled average bioequivalence method, which could make the 80%–125% range smaller if the brand product shows low variability in pharmacokinetic testing.⁷

What data indicate that generic substitution causes problems? Many reports have suggested that seizure control and adverse effects may change after generic AED substitution. These studies have for the most part been carefully done, but have relied on retrospective data from large patient databases or open-label case series and have not rigorously documented AED blood levels. A Canadian study in 2007 demonstrated that switchback rates from generic to brand are 5–10 times higher for AEDs than other classes of medications.⁸ In a United States case-controlled database analysis of epilepsy and AED product changes, there was an 81% greater probability of an AED product switch compared to controls in those who had ambulance or emergency room care.⁹ In contrast, another database trial reported no significant effect of switching AED products on epilepsy-related events.¹⁰ Generic to generic product switches also commonly occur and could potentially be associated with shifts in AED concentrations. Krauss et al.¹¹ used data from generic approval studies to model AED generic to generic switches and found that switches among different manufacturers’ products could produce much larger swings than allowed by current FDA regulations for testing brand to generic switches.

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If there truly is bioequivalence and therapeutic equivalence among brand and approved generic products, why would health care providers and patients report so many problems? A nocebo effect (i.e., negative symptoms from an inert treatment) involving generic substitutions might be involved. If patients are warned by caregivers or other medical information sources that generic products may be less effective than the brand name product, patients may be more attentive to adverse effects, more diligent about counting or reporting seizures, or more apt to attribute an unrelated or coincidental symptom to the generic substitution.

It is generally agreed that prospective randomized trials in people with epilepsy are needed, and the FDA has funded 3 ongoing studies to address questions beyond the standard FDA bioequivalence studies. Instead of single doses in normal volunteers, these new studies will employ rigorous pharmacokinetic methods in people with epilepsy taking adjunctive AEDs. Two of the three studies will be in people taking the medication chronically. To address questions of generic–generic switches, 2 studies will also use an innovative selection method to test 2 different AED generic products against one another, choosing AED generics with pharmacokinetic properties of the low vs high end of the approvable range. These studies will help establish whether or not there is a problem in the “real world” with product switches. If so, then additional studies may be necessary to provide an evidence base to the FDA in changing generic approval guidelines.

Until these studies are completed, clinicians should encourage patients to look carefully at pills each time they get pharmacy refills and, if they are receiving an AED generic product, endeavor to stay on a single generic product. To minimize generic to generic switching, we often request pharmacies to maintain a patient on a single generic AED manufacturer by writing this on the prescription, but pharmacies have no legal obligation to follow this directive. Switches in more vulnerable patients, for example during pregnancy, in the patient who has been seizure-free for a long interval and is driving, or in a patient with a history of seizure increases or status epilepticus after small changes in AED doses, should be avoided if possible.

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