

Generic Antiepileptic Substitution

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By 2010, four major brand-name epilepsy drugs will lose patent protection and face generic competition: Depakote, Lamictal, Keppra, and Topamax.¹ Four of these drugs generated \$5 billion in U.S. sales last year.¹ Advocacy organizations supported by the drug industry, are campaigning state legislatures to adopt bills making it harder for pharmacists to switch patients to inexpensive generic epilepsy medications. An economic report says total prescription drug costs to Medicaid and consumers would increase by \$6.2 billion and \$5.3 billion respectively over 10 years if this type of legislation were enacted.¹ None of the data published thus far are sufficient to provide definitive evidence that there is a problem with the newer generic AEDs. The FDA believes that there are no documented examples of a generic product manufactured to meet approved specifications that cannot be used interchangeably with the corresponding brand name drug.¹ This article summarizes the risks and benefits of generic AEDs.

The perception that generic products for AEDs drugs are not bioequivalent to their brand name counterparts stems from multiple sources. Problems with older generic antiepileptic drugs (AEDs), primarily phenytoin and carbamazepine, have led to opposition of generic substitution for all AEDs. The older AEDs have low water solubility, narrow therapeutic range, and unpredictable pharmacokinetics.² Monitoring therapeutic drug levels is necessary for the older agents such as phenytoin, valproic acid and carbamazepine. Data on therapeutic ranges of the new AEDs has not been well defined and many suggest that none of the new AEDs meet the criteria of a drug with a narrow therapeutic range since drug levels have not been correlated with effectiveness or toxicity.³ The new AEDs have more predictable pharmacokinetics, higher solubility and permeability, and better transporter efficiency. Many of the new AEDs are really eliminated completely unchanged (gabapentin, pregabalin and vigabatrin) or mainly unchanged (levetiracetam and topiramate), making the pharmacokinetic variability less pronounced and more predictable.³ Additionally, many of these agents are more commonly used for conditions other than seizure disorder (e.g. bipolar disorder), where targeting a narrow therapeutic drug level is not an established tenet of treatment.⁴ As such, variability between FDA approved bioequivalent versions of these newer AEDs would be expected to have no impact on the clinical effectiveness or tolerability and safety of these products.

In 2007, the FDA launched an initiative aimed at increasing the review efficiency in order to bring generic drugs to market more quickly.⁵ The FDA Office of Generic Drugs assures that the generics perform the same as the innovator compound. Thus far, this office has approved more than 7000 generic products at a current rate of more than 500 per year.⁶

The FDA's bioequivalency standards are rigorous and designed to allow for generic interchange with the same consistency as lot-to-lot variability or brand-name drugs. A major premise of the 1984 Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act established bioequivalence as the basis for approving generics. In 1986, the FDA established methodology for bioequivalency testing. Establishing

bioequivalence using two one-sided t-tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved. Based on a 90% confidence interval (CI) around the peak serum concentration (C_{max}) and areas under the curve (AUC), the generic may fall within 80-125% of the reference drug in a 2-way crossover study of between 24-36 healthy volunteers. This 80-125% range is only a probability test, not an absolute measure of the generics' bioequivalence limits. The FDA published two studies quantifying the differences between generic and brand products. In one study, they reported that the average difference between the reference and generic AUC was 3.5% in 224 approved drugs. In the past 25 years, the FDA has removed 4 generic products from the market for safety reasons compared to 21 brand name products over the same time period.⁹

Lower evidence quality, such as case reports and three retrospective economic analyses have been performed in defense of no substitution of AED policies. A Canadian study in 2008 demonstrated that switchback rates from generic to brand name are 5-10 times higher for AEDs than other classes of medications. Of 671 patients treated with brand name Lamictal, 187 switched to a generic, and 51 of these patients switched back to brand name. Rates of switchback were from 20.8%-44.1% for various AEDs and from 7.7%-9.1% for non-AED's (comparator). Generic use was associated with a 5.1% increase in mean daily dose, higher utilization rate of medical services (8.7 vs 9.8 visits per person-year, and a longer hospital length of stay (3.29 vs 4.86 days per person-years.) The generic-use period was associated with an increase in overall costs relative to brand use, despite lower cost of generic lamotrigine.¹⁰ While this study examined rates of switchbacks in other drug classes, the investigators failed to compare rates of medical service utilization in subjects with other drug switchbacks to see if their findings were a function of switching back in general or specific to lamotrigine. The study was also limited to those subjects with a diagnosis of epilepsy and therefore may not be generalizable to subjects using AEDs for mental health conditions.

In 2006, another Canadian study (by some of the same above authors) was undertaken analyzing the economic impact of switching from branded to generic lamotrigine. Using claims data among 1142 branded lamotrigine users, overall average monthly drug costs per person were expected to decrease by \$30.55 due to lower pill costs. Instead, they fell by \$11.98 from the brand to the generic periods (p<0.001). Due to dose changes, lamotrigine costs decreased by \$29.92 instead of the anticipated \$33.87 (p<0.001).¹¹ Because this study was conducted using claims data, it is subject to the usual limitations inherent to retrospective claims data analyses, including potential inaccuracies in billing, dispensing dates, drug doses, drug codes, lack of medical claims data or medical history in pharmacy claims. This prohibits a "cause and effect" relationship to be established, but does provide the impetus to perform some controlled clinical trials.¹⁰

A pilot study in Denmark looked at 9 patients reporting problems attributed to changes in preparations of lamotrigine. Lamotrigine concentrations were determined by HPLC, and pharmacokinetic parameters were measured and compared. All generics used in the investigation passed tests claiming their bioequivalence with proprietary lamotrigine according to the FDA definition, yet 5 of the 9 patients had deviations greater than 10% in at least one

December 2008 V10 Issue 9

pharmacokinetic parameter measured. The authors concluded that the deviations were not due to the formulation of the generics but due to some individual, currently undefined, factors of absorption.¹² Another study in Denmark looked at plasma concentration levels in generic and brand users of lamotrigine and found no significant differences between products.¹³ A study of generic carbamazepine showed no difference in safety or efficacy for brand-names of carbamazepine.¹⁴

Current consensus guidelines and legislative action are based on low levels of evidence and will have a dramatic impact on potential cost savings in this category. Such time intensive requirements could also cause harmful delays in the delivery of patient care and impose costly administrative burdens on prescribers and pharmacies. Physicians in all states do have a mechanism to allow the prescriber to specify the brand product using "no substitution", "dispense as written" (DAW), "do not substitute" (DNS), etc. FDA bioequivalency standards suggest generic substitution is expected to have the same bioequivalency variation as lot-to-lot variation of the same brand. However, there are clinical situations where the physician may want to eliminate all sources of potential variation and keep the patient on the same product (generic or brand) which has stabilized the patient. Additional legislation, based on dubious evidence and anecdote, would be duplicative of existing laws and automatically deprive states of important cost avoidance through off-patent medications.

Reviewed by Dr. James Proffitt MD, PharmD., Internal Medicine, Salem Hospital and Norman Muilenburg RPh, Kaiser Permanente Clinical Pharmacy Services, Portland, OR.

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