

# Generic Antiseizure Drugs Similar to Brand Names

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San Diego, California — A new study shows generic extended-release formulations of several antiepileptic drugs (AEDs) generally have the same drug plasma concentrations as their brand-name counterparts, which suggests that patients can change to these drugs without compromising safety or efficacy.

The study is one more piece of evidence indicating that brand name and generic AEDs are "switchable" — at least in healthy persons, researchers say.

But the controversy over whether generic AEDs are a relatively cheap but safe and effective option in the "real world" probably won't be resolved until results of studies investigating the bioequivalence of generics and brand-name drugs in patients with epilepsy are completed, possibly some time next year.

"The generic extended-release or modified-release products are the bioequivalent to the brand-name product," said one of the study authors, Gregory Krauss, MD, professor, neurology, Johns Hopkins University, Baltimore, Maryland. However, he stressed that it's probably not a good idea to switch between generics because variability for 2 drugs in relation to a brand-name product could be greater than expected.

Most of the advantages of once-a-day extended-release products relate to adherence or convenience, he said.

The study was presented here at the American Epilepsy Society (AES) 66th Annual Meeting.

## Breakthrough Seizures



**Dr. Gregory Krauss**

A wide array of generic formulations of brand-name AEDs are used by patients with epilepsy across the United States, but more reports of adverse events and breakthrough seizures have been associated with these agents than with brand-name products.

Generic AEDs are approved through bioequivalence studies, in which about 25 to 35 paid volunteers without epilepsy take a single dose of test and reference brand-name formulations. Researchers use measurements of C<sub>max</sub> (maximum plasma concentrations) and area under the curve (AUC) of drug

concentrations (an estimate of total drug exposure) to determine bioequivalence, which is defined as a 90% confidence interval (CI) of the ratio of the generic to reference compound within the range of 80% to 125%.

Dr. Krauss and his colleagues are carrying out bioequivalence studies to assess pharmacokinetics of generics compared with brand-name agents using data submitted by the generic manufacturers to the US Food and Drug Administration (FDA). They first compared immediate-release formulations and found that these were about equivalent to their brand name products ( *Ann Neurol.* 2011;70:221-228).

The current study evaluated bioequivalence measures in the clinical studies submitted to the FDA to support marketing approval of 25 generic modified-release (MR) AEDs. MR formulations of the AEDs carbamazepine, phenytoin sodium, divalproex sodium, and levetiracetam are currently marketed in the United States.

The study included data on Cmax and AUC from 53 bioequivalence studies that included 1570 patients. It found that the 90% CIs of the generic/brand AUC and Cmax ratios differed by less than 15% in 86.8% and 77.4% of the bioequivalence studies, respectively. The 90% CIs of the generic/brand AUC and Cmax ratios differed by 15% to 25% in 13.2% and 22.6% of the studies, respectively.

### **Poorly Soluble Drugs**

MR AED formulations of poorly soluble drugs demonstrated higher rates of variability irrespective of whether the formulation was generic or brand, the study found. With drugs such as carbamazepine that are "fairly insoluble," it's a "real advantage" to have an extended-release product, commented Dr. Krauss.

"We recommend that most patients be on extended-release carbamazepine rather than immediate release," said Dr. Krauss. "So you'd want that generic extended release to be available." He added that less dizziness and other adverse effects are associated with extended-release formulations of carbamazepine, which is a sodium channel drug.

Although the study found bioequivalence measures were generally more variable for MR AEDs compared with previous observations for immediate-release formulations, all MR AED products surveyed were well within the bioequivalence acceptance limits of 80% to 125% (90% CIs), noted Dr. Krauss.

With some drugs — for example, levetiracetam — the variability is limited across the generics, but with others, including divalproex and carbamazepine, there are more fluctuations across the products, noted Dr. Krauss.

Because of this variability, it's probably a good idea to stick with the same agent, he said. "For example, if one generic product is 15% below the reference drug and another is 15% above, you could potentially have a 30% swing, so we think in general it's better to stick with one generic product if possible."

One of the advantages of MR formulations is better patient adherence. "Young people and college students often miss their pill at night, so there are advantages to taking a pill once a day, but for many

patients, the twice a day products are fine and provide the same sort of delivery patterns as the once a day."

In a previous study, Dr. Kraus and his colleagues found that the smoother drug release provided by an MR AED formulation decreased serum fluctuations, leading to fewer breakthrough seizures.

Dr. Krauss noted that extended-release products often have different release technologies; for example, carbamazepine extended release comes in matrix dissolving tablets, osmotic release tablets, and microgranule release products.

### **Standards Too Broad?**

Many neurologists are concerned that the current bioequivalence standards are too broad, that a narrower range — perhaps 90% to 110% — might be more appropriate, said Dr. Krauss. An FDA advisory board recently decided in favor of considering having a narrower range of acceptance standards for what it calls "critical dose" drugs.

The FDA is funding studies comparing brand-name and generic lamotrigine in patients with epilepsy. "People have said that patients with epilepsy may be different," said Dr. Krauss. "Generic studies have largely been done on average-aged adults, often men; they don't include the elderly, they don't include young people, and they don't include people taking other medicines."

Dr. Krauss noted that lamotrigine is coming off patent, so an extended-release lamotrigine generic formulation is expected to enter the market soon.

Asked to comment on this most recent bioequivalence study, Michael Privitera, MD, professor, and director, Cincinnati Epilepsy Center, University of Cincinnati, Ohio, said it is "still limited because the data are all from single doses of these products in normal volunteers," which is the method currently used by the FDA.

Dr. Privitera is conducting one of the studies in people with epilepsy who are taking other medications — in other words, testing bioequivalency in a "real world" setting.

"This is an important topic that has the potential to have a major impact on how the FDA approves generic AED products," said Dr. Privitera. "We estimate that every day, more than 1 million tablets of generic AED are taken by people with epilepsy in the US."

He expects that the studies that he and his colleagues are currently carrying out will generate new data during the next year.

*Dr. Krauss reports he is an investigator with Eisai, UCB Pharma, Sunovion, Upsher Smith, and Vertex and on a safety committee for Lundbeck. Dr. Privitera has a research grant from the FDA, has research support from Eisai and UCB for trials of new AEDs. The study he is doing is with lamotrigine; he has no conflicts with GSK, the company that markets lamotrigine. .*

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