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PATIENT MONEY

Not All Drugs Are the Same After All

By LESLEY ALDERMAN

LET me start by saying I'm a fan of generic drugs. They save Americans billions of dollars each year and give us access to wonderful drugs at affordable prices. I've recommended generics in this column many times and use them myself when possible.

But there is a gnawing concern among some doctors and researchers that certain prescription generic drugs may not work as well as their brand-name counterparts. The problem is not pervasive, but it's something consumers should be aware of — especially now that more insurers insist that patients take generic medications when they are available.

Let me also prepare the groundwork for what I hope will be full and frank reader comments, by acknowledging that this issue is controversial.

Joe Graedon, who has been writing about [pharmaceuticals](#) for three decades and runs a consumer advocacy Web site, the People's Pharmacy (peoplespharmacy.com), was 100 percent behind generics for many years.

"We were the country's leading generic enthusiasts," he told me recently. But over the last eight or nine years, Mr. Graedon began hearing about "misadventures" from people who read his syndicated newspaper column, also called The People's Pharmacy.

The stories were typically from patients who were switched from a brand name drug to a generic one and had side effects or found that their symptoms returned — or even became worse than before they were medicated. Most recently Mr. Graedon has been hearing complaints on his Web site about generic forms of the antidepressant Wellbutrin XL 300 (known as Budeprion XL 300 in one generic form), the heart medicine Toprol XL (metoprolol succinate) and the antiseizure medicine Keppra (levetiracetam).

"Consumers are told generics are identical to brand name drugs, but that is clearly not always the case," Mr. Graedon said.

Some specialists, particularly cardiologists and neurologists, are concerned about generic formulations of drugs in which a slight variation could have a serious effect on a patient's health. The American Academy of Neurology has [a position paper](#) that says, in part, "The A.A.N. opposes generic substitution of anticonvulsant drugs for the treatment of [epilepsy](#) without the attending physician's approval."

But insurers tend to argue otherwise. On Thursday, ExpressScripts, which handles drug insurance for big employers, put out [a news release](#) announcing results of a study it sponsored that found no difference in hospitalizations or emergency-room visits for people on brand-name epilepsy drugs compared with those taking generics.

The [Food and Drug Administration](#), meanwhile, says it stands behind generic medications and its methods for approving them.

“We have not seen any scientific studies that show generics do not hold up as well as brand name drugs,” says Gary J. Buehler, director of the agency’s office of generic drugs. “We believe the generic drugs we approve work in everyone.”

The [American Medical Association](#) concurs. A spokeswoman for the group told me in an e-mail message, “the A.M.A. position is that as a whole generic drugs do work as well as name-brand drugs.”

Yet, after hundreds of consumers posted messages about problems with the generic drug Budeprion XL 300 on the People’s Pharmacy Web site, Mr. Graedon worked with an independent laboratory, ConsumerLab.com, to test the drug, which in other generic versions is typically known as bupropion.

The [lab found](#) that Budeprion XL 300 released the active drug at a different rate than the brand name Wellbutrin XL 300. Mr. Graedon and the lab conjecture that the different dissolution rates might be to blame for the reported side effects and lower effectiveness of Budeprion.

But Mr. Buehler at the F.D.A. explained to me that over the course of 24 hours a patient ends up with the same amount of the drug in the bloodstream, so there should be no reason for a variation in effectiveness. “We remain puzzled,” he said.

The maker of Budeprion XL 300, [Teva Pharmaceutical Industries](#), recently announced that it would conduct a clinical trial comparing its product against the original, Wellbutrin XL.

A Teva spokeswoman said in an e-mail message that the company was working with the F.D.A. on a study “specifically designed to answer the questions raised following the recent anecdotal commentary on generic budeprion.”

“We believe the study and the resulting data will provide further scientific support for the product’s bioequivalence to the innovator drug,” she said.

To parse that statement — or at least understand “bioequivalence” — it is worth taking a step back to consider what a generic drug is and how it gets approved.

When a name-brand drug’s patent expires, other manufacturers are generally free to create their own version of that product. If a drug is popular, a dozen or more companies may rush in to create a copy of it.

According to F.D.A. rules, the new generic version must “have the same active ingredient, strength and dosage form” as the brand name or reference product.

A generic medication must also be bioequivalent to the brand name drug, meaning that it must “be shown to give blood levels that are very similar to” the brand name product, according to a [fact sheet on the F.D.A.’s Web site](#). Generally, the only test that a maker of a generic medication must perform to receive F.D.A. approval is one that establishes the “bioequivalence” of the product. This test is done on healthy volunteers and compares the blood levels of the reference drug to the generic one.

According to Mr. Buehler of the F.D.A., to be considered bioequivalent, the generic drug must reach a blood serum level that is 80 to 125 percent of what the reference product achieves. But Mr. Buehler said that in reality the spread was not nearly that large. He noted that the F.D.A. conducted a large study and found that the average difference in absorption into the body between a generic and brand name drug was only 3.5 percent.

Some specialists, though, worry that the allowable range for bioequivalence is too wide, especially for patients who are taking medication to control problems like [arrhythmias](#) or [seizures](#).

If a patient with the heart arrhythmia known as [atrial fibrillation](#) who also has risk markers for [stroke](#) gets a blood thinner for which the levels are too low, “there is risk for stroke, and if the levels are too high it could result in bleeding,” says James A. Reiffel, a cardiologist and professor of clinical medicine at Columbia.

Neurologists who treat epilepsy have similar concerns. Two studies published last year in the journal *Neurology* found that patients who switched from a brand-name product to a generic one had more seizures or higher hospitalization rates.

“For many drugs, generics are just fine,” said Kimford Meador, a professor of neurology at [Emory University](#).

“But when you’re taking a [seizure](#) medication, the therapeutic window is narrow,” Dr. Meador said. “If the absorption of the drug is slightly different between brand and generic or between generics, then the patient could have a seizure, and that seizure could lead to serious injury or perhaps even death.”

The problem is not just in changing from a name-brand drug to a generic, Dr. Meador said, but also switching from generic to generic. And the patient may not even know the change is happening.

When patients are on maintenance medication for which a generic is available, they might be given a different version of the generic drug when refilling their [prescriptions](#). A pharmacy might stock one generic for a few months, and then switch to another a few months later, if the store is offered a better deal on it.

A pharmacist is not required to notify the patient of the change, although some choose to do so.

So for a few months you might receive a drug that was on the low side in the bioequivalence test, and then be switched to one on the high side of the test.

Stephanie Ford, 29, who spoke on condition that she not be otherwise identified, had been taking Lamictal to control her [bipolar disorder](#). When a generic version came out two years ago, her insurer switched her to it.

Ms. Ford found that the generic drug, lamotrigine, worked just as well as the name brand and cost her just \$10 a month instead of the \$45 copayment she had been spending on the brand name. (For a person without insurance, Lamictal can cost about \$300 a month, depending on the dosage.)

But when her insurer then urged her to order her medication by mail, she received another generic version of Lamictal and her symptoms returned.

“After about a week,” she wrote in an e-mail message, “I noticed a difference in my emotional state (and nothing changed in my life) and by a week and a half, I had digressed to the state I had been before being on medication.”

Ms. Ford has found a local pharmacy that carries the original generic. She now buys the medication directly from that store. Because her insurer charges her a \$5 penalty for not using mail order, her copayment is now \$15.

She says her condition has once again stabilized.