

Antiepileptic drugs

Are generics as effective as brand name?

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Antiepileptic drugs (AEDs) are the main treatment for seizures in people with epilepsy. The first AED, phenobarbital, was discovered in 1912 and the company that developed it gave it the brand name Luminal. Between 1938 and 2016, 25 more brand name AEDs were approved by the US Food and Drug Administration (FDA). The generic name is the chemical name for the medication. The brand name is created by the company that first discovers and patents the medication. A patent gives that company the right to be the only one that sells that drug for many years. After the patent expires, other companies can sell the generic drug. Generic drugs are usually less expensive. Today, all AEDs approved by the FDA before 2005 are available as generics.

The FDA requires that generic drugs must have the same amount of medication in them as in the brand name drug. For example, 100 mg generic lamotrigine and brand name Lamictal tablets both must contain exactly 100 mg of the drug. The FDA allows a generic company to put other ingredients in their product. These are added to make a tablet stick together, look or taste a certain way, or last longer. But they could also cause the generic pill to dissolve or be absorbed into the bloodstream differently than the brand name medication. Every company has to prove that its generic drug is bioequivalent to the brand name medication by testing the generic drug in many healthy volunteers.

Each volunteer takes one dose; then the medication blood level is measured many times afterwards. The results are compared to those from volunteers taking the brand name drug. The FDA requires that levels of the generic and brand name medication match very closely. Specifically, the statistical 90% confidence interval of these 2 results must be less than 20%. This is a statistical measure that is easily misunderstood. Many people mistakenly think that the generic is allowed to differ from the brand name drug by 20%. In fact, this statistical rule allows only small differences in levels between the brand name and the generic drug in any one volunteer.¹ Despite this strict requirement for bioequivalence in healthy volunteers, many doctors asked for more research in people who had epilepsy.

HOW DID THE RESEARCHERS STUDY THIS ISSUE? In the study by Kesselheim and others,² 2 large medical insurance databases were researched for

all patients who had been seen in a hospital for a seizure between 2000 and 2013. Over 83,000 patients were found, and they were taking any of 10 generic AEDs. The researchers looked at the type of generic AED the patient had received during a pharmacy refill in the month before their seizure. They compared this to the type of AED that they had refilled about 3 months earlier. They looked for difference in outcome if the patient got an AED refill from the same manufacturer or a refill from a different company. If it was from another company, they studied whether the pills had the same, or different, appearance from the ones the patient had been taking before.

WHAT WERE THE RESULTS? Surprisingly, the process of getting a refill raised the risk of having a seizure and needing hospital treatment by 8%. Refilling an AED with a drug from a different manufacturer had a 9% risk of needing treatment for a seizure. However, when the researchers accounted for the process of getting the refill, there was no risk in switching between different drug manufacturers. If the switch from one generic to another was for pills that looked alike, the risk was actually 8% lower.

WHAT DOES THIS MEAN? These researchers concluded that generic AEDs available to US patients appear to be safe choices. This decision was backed up by the results of 2 more recent studies done to compare bioequivalence in people with epilepsy in research centers.^{3,4} In the BEEP study, generic lamotrigine was compared to brand name Lamictal. In the EQUIGEN study, 2 generics that were expected to be quite different were compared. Both studies showed that the bioequivalence of the generics differed by less than about 3%, which was not significant. Patients and health care providers can now feel confident when switching from brand name to generic AEDs or between generic AEDs.

Patients worry about this if they previously had more seizures when they switched from brand name to generic AEDs, but there are other possible explanations. For example, a patient who has a seizure may think this is due to the switch even though it could be caused by natural fluctuation in seizure frequency. Occasionally, emotional stress about switching, or forgetting to take the AEDs due to differences in pill appearance, can cause seizures.

Patients should spend time with their health care providers discussing their concerns about generic AEDs, and how the new research is reassuring about the safety of switching from brand name to generic AEDs, and between different generic AEDs.

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About epilepsy

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WHAT IS EPILEPSY? Epilepsy is a brain condition that causes seizures from time to time. There is not just one type of epilepsy, but rather there are about 40 different types of epilepsy. Doctors use several pieces of information to determine the type of epilepsy:

1. Age at seizure onset
2. Seizure types
3. Pattern on brain wave electrical recording (EEG)
4. Findings from brain imaging using MRI
5. Abnormalities in the person's neurologic examination
6. Family medical history of epilepsy
7. Presence of any other brain or general physical condition
8. Results of memory and intelligence tests
9. Identification of things that trigger seizures
10. Assessment of which medications help or worsen the seizures and help define the epilepsy type

Epilepsy is common. It is present in 1 of 120 people around the world. It affects all races and sexes equally. By age 80 years, 1 in 26 people will have had epilepsy and 1 in 10 will have had at least 1 seizure. Epilepsy is sometimes called a seizure disorder by patients and general doctors. Some persons with epilepsy like to use that term when they tell friends, coworkers, or family about their condition. The more accurate term is epilepsy. This term recognizes that there often are other problems besides the seizures. Having epilepsy almost always means the patient has to take medications, which may have side effects including tiredness, dizziness, and others.

Persons with epilepsy also often have other concerns such as depression, anxiety, and stress. Memory problems, job difficulties, dating/marriage/fertility issues, social isolation, inability to drive under state laws, and limited finances are among other common concerns in people with epilepsy. Thus epilepsy is more than a seizure disorder for most people.

WHAT IS A SEIZURE? A seizure is a temporary episode in which the person feels symptoms or shows outward physical signs that are caused by abnormal firing of brain cells. There are 2 major classes of seizures:

1. Focal seizures that start in a localized part of the brain
2. Generalized seizures that begin over both sides of the brain simultaneously

The mildest form of focal seizures does not affect the person's awareness. They produce symptoms or signs that depend on which part of the brain is causing the seizure. If the seizure focus is in a part of the brain that controls movement, then stiffening or jerking may occur. If the seizure is in the temporal lobe, symptoms can include odd memories, smells, or tastes, or emotional feelings.

If the seizure is in the occipital lobe, the person will have visual symptoms. Stronger forms of focal seizures alter awareness, sometimes causing unconscious behaviors, and can progress to full tonic-clonic convulsions (in the past called grand mal seizures). Generalized seizures include single muscle jerks (myoclonic seizures), motionless unawareness (absence seizures), tonic-clonic convulsions (with no initial focal portion), and others.

WHAT CAUSES EPILEPSY? There are many causes of epilepsy, but one of the most common is genetics (heredity, family history). It is complex to explain, but many people have genetic forms of epilepsy even though they may not be aware of anyone in the family who had epilepsy. There are also many neurologic disorders that can cause epilepsy or that occur with epilepsy. These include stroke, significant head injuries, meningitis, encephalitis, intellectual developmental disabilities, tuberous sclerosis, tumors, congenital brain malformations, and others. It is also common that no cause is found.

HOW IS EPILEPSY DIAGNOSED? Epilepsy is usually diagnosed by neurologists. In some cases, neurologists specializing in epilepsy (epileptologists) are asked to evaluate people with epilepsy. Most importantly, doctors get a thorough history from the patient and family. They do a careful neurologic physical examination. Then they normally get an EEG and an MRI. In some cases they order neuropsychological testing of memory and thinking. Bring detailed seizure descriptions and videos, dates of seizures, and related medical records to your first visit with the neurologist.

HOW ARE EPILEPSY AND SEIZURES TREATED?

AEDs are the main treatment for seizures in people with epilepsy. The AEDs developed between 1912 and 1978 to treat epilepsy in the United States were phenobarbital, phenytoin, ethosuximide, carbamazepine, clonazepam, and valproic acid. Since 1993, 20 more AEDs have been approved by the US FDA. Some of the newer AEDs have fewer side effects than some of the older ones, but the newer medications are not necessarily more effective. Some can be used alone, and all can be used in combination.

About 2/3 of patients have complete freedom from seizures, but 1/3 of patients are not seizure-free with AEDs. Other treatments include the ketogenic diet or modified Atkins diet, vagus nerve

stimulator, responsive neurostimulation, or one of many different types of brain surgeries. The treatment choices depend on which of the 40 types of epilepsy the patient has. For example, in temporal lobe epilepsy, surgery has a very good chance of seizure freedom when AEDs have not worked.

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