

# *In Their Own Words:*

## **Epilepsy Patients' Experiences Changing The Formulation of The Drugs They Use to Prevent Seizures**



**EPILEPSY FOUNDATION<sup>®</sup>**  
*Not another moment lost to seizures<sup>™</sup>*

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**FINDINGS FROM THE EPILEPSY FOUNDATION'S  
SURVEY OF PATIENT EXPERIENCES  
November 2006 – March 2009**

## I. INTRODUCTION

Members of the epilepsy community have for years reported experiencing seizures and other harmful side effects after switching from one version of an anti-epileptic drug (AED) to another, whether the switch was brand-to-generic, generic-to-brand, or generic-to-generic. By law, the amount of medication delivered by one AED may differ from the amount delivered by another AED that the FDA deems “equivalent,” and it may deliver the medication at a different rate. Amid growing evidence that these variations, however slight, can mean the difference between controlled epilepsy and breakthrough seizures or other negative consequences, the Epilepsy Foundation asked to hear patients’ experiences. This Report summarizes the responses that the Foundation received, and sets out the Foundation’s related recommendations.

Patients today are most typically switched from brand-name drugs to generics, or from one generic drug to another, for a single, non-clinical reason: pressure to reduce costs.<sup>1</sup> In most states, unless a physician explicitly writes “dispense as written” or “no substitution,” pharmacists can switch a patient to a lower-cost generic drug without the consent or knowledge of either the patient or the physician.

The Epilepsy Foundation appreciates that cost-control is a worthy goal and, in general, it enthusiastically supports providing patients with greater access to generic medications. The Foundation is committed to the welfare of people with epilepsy and their families, and the high cost of many name-brand medications is a particularly significant issue for people with epilepsy, many of whom will take medication on a daily basis for the remainder of their lives. The Foundation welcomes the opportunity that generic medications present to lower the overall costs of delivering effective healthcare to individuals and society.

But the Foundation believes equally that short-sighted cost considerations should never be allowed to trump efficacy or take precedence over patient welfare. Indeed, if a patient is switched off of a well-functioning drug to avoid costs, the direct economic consequences borne by society if the cheaper drug fails—whether incurred in the form of increased ambulance rides and emergency-room admissions, greater numbers of in-patient doctor visits, or lost worker-productivity—will quickly eliminate any short-term savings occasioned by the switch. Meanwhile, the concurrent human costs borne by patients and their families can be immeasurable.

Kelly VanSingel’s recent testimony to the Michigan legislature provides a particularly vivid example. Ms. VanSingel’s 30-year old brother, Jay, had epilepsy. According to Ms. VanSingel, Jay’s seizures were under control when a pharmacist switched his anti-epileptic drug. When Jay asked his pharmacist why his pills looked different, he was told that the pills were a safe, generic form of his regular medication. Within two days, Jay was dead. Jay’s autopsy confirmed that he was an otherwise healthy individual and had died as a result of a seizure.

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<sup>1</sup> Patients may also be switched from one anti-epileptic drug to all-together different anti-epileptic drug as a result of pressures to reduce spending. Although this Report does not address the scenario (often termed “therapeutic switching”) the Foundation opposes all switching that is driven primarily by cost considerations, and therefore objects to this practice as well.

Based on evidence in the clinical literature as well as reports from physicians and patients, the Epilepsy Foundation has developed serious concerns about policies that permit or require AED-substitutions for non-therapeutic reasons. These concerns are given urgency and immediacy by stories like Jay’s—and the others collected in this Report—which demonstrate that for many patients with epilepsy, AED-substitutions have been neither effective, nor safe.

## **II. SWITCHING ANTI-EPILEPTIC DRUGS: WHEN “MORE OR LESS THE SAME” MAY NOT BE CLOSE ENOUGH**

When it comes to generic drugs, “equivalent” does not strictly mean “the same.”

Generic drugs contain the same amount and type of medical ingredients as their name-brand equivalents, but they contain different inactive ingredients, and need not deliver precisely the same amount of medicine to the needed location in the body, nor do so at precisely the same rate.<sup>2</sup> By law, the amount of medication delivered by a generic pill may differ from the amount delivered by the name-brand “equivalent,” so long as the differences between the generic and name-brand drugs’ effects in the body are not considered by the FDA to be “significant.”<sup>3</sup>

For most individuals and conditions, this regime has worked. Many patients have switched from name-brand to generic medications to control high cholesterol or blood pressure, for instance, with little or no problems—and at significant cost savings.

But a growing volume of evidence suggests that, for at least some individuals, the same has not been true for anti-epileptic drugs. The scientific literature now contains:

- clinical confirmation that switching between “equivalent” formulations of the same anti-epileptic drug, whose differing effects in the body are not considered “significant” by the FDA, caused serious adverse consequences in patients,<sup>4</sup>
- case studies affirmatively establishing that switching between “equivalent” AEDs can lead to breakthrough seizures,<sup>5</sup>

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<sup>2</sup> See 21 C.F.R. § 320.23 *Basis for measuring in vivo bioavailability or demonstrating bioequivalence* (allowing a generic drug to be deemed “bioequivalent” to a brand-name drug despite differences in the “rate and extent of absorption” of the drug’s active ingredient in the body).

<sup>3</sup> See *id.* (“bioavailability is measured if the product’s rate and extent of absorption, as determined by comparison of measured parameters, . . . do not indicate a significant difference from the reference material’s”) (emphasis added).

<sup>4</sup> See, e.g., Nielson KA, Dahl M, Tømmerup E, Wolf P. *Comparative daily profiles with different preparations of lamotrigine: A pilot investigation*. *Epilepsy and Behavior*. 2008;13(1):127-130.

<sup>5</sup> See Berg MJ, Gross RA, Tomaszewski KJ, Zingaro WM, Haskins LS. *Generic substitution in the treatment of epilepsy: Case evidence of breakthrough seizures*. *Neurology*. 2008;71:525-520.

- statistical analysis showing that persons with epilepsy who recently switched between “equivalent” AEDs sought more in-patient and emergency care than those that did not,<sup>6</sup>
- case studies documenting that epilepsy patients on the brand name and generic versions of “equivalent” AED medications had different levels of therapeutic medication in their blood,<sup>7</sup> and
- population data revealing that epilepsy patients have “switch[ed] back” to brand-name medication at significantly higher rates than patients who have switched to generic drugs to treat other long-term conditions.<sup>8</sup>

Two distinguishing features of epilepsy further suggest that AED-switching should be approached with special caution.

First, seizure control can be an all-or-nothing proposition. Slight changes in the amount of medication received by a person with epilepsy can mean the difference between a fully controlled condition and breakthrough seizures. By comparison, slight changes in the amount of medication received by patients being treated for hypertension or high cholesterol, for example, may cause undesirable changes in the patients’ blood pressure or triglycerides levels, but the resulting changes will be incremental—the patient’s levels may change by 10 or 15 points. Critically—and unlike the patient with cholesterol or blood-pressure problems, whose condition can become incrementally better or worse—the patient with epilepsy exists in either of only two states: the patient is either seizure-free, or is not. In some patients, there may be correspondingly little room for error when changing the patient’s dosage or prescription.

Second, the consequences of a breakdown in a well-functioning seizure-control regimen can be catastrophic. A change in cholesterol or blood-pressure levels may leave a patient marginally worse off, but the consequences of a breakthrough seizure can be extreme: seizures increase the likelihood of serious bodily injury and death, and, even when no physical injury occurs, seizures often result in significant social, legal and developmental consequences, including loss of the patient’s driver’s license, loss of employment, and loss of self-esteem.

Many now question whether the range of difference that the FDA allows for different formulations of anti-epileptic drugs is too expansive, and draw attention to the number of

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<sup>6</sup> See Zachry III WM, Doan QD, Clewell JD, Smith BJ. *Case-control analysis of ambulance, emergency room, or inpatient hospital events for epilepsy and antiepileptic drug formulation changes*. *Epilepsia*. 2009;50(3):493-500.

<sup>7</sup> See Burkhardt RT, Leppik IE, Blesi K, Scott S, Gapany SR, Cloyd JC. *Lower phenytoin serum levels in persons switched from brand to generic phenytoin*. *Neurology*. 2004;63:1494-6

<sup>8</sup> See Andermann F, Duh MS, Gosselin A, Paradis PE. *Compulsory Generic Switching of Antiepileptic Drugs: Higher Switchback Rates to Branded Compounds Compared with Other Drug Classes*. *Epilepsia*. 2007;48(3):464-469.

European nations that specifically exempt some or all AEDs from their mandatory-substitution laws.<sup>9</sup>

### **III. THE EPILEPSY FOUNDATION'S SURVEY ON PATIENTS' EXPERIENCES SWITCHING ANTI-EPILEPTIC MEDICATIONS**

Underlying the scientific data are the stories of individual patients.

To collect these stories, and as part of the Epilepsy Foundation's on-going efforts to evaluate the safety of AED-switching, the Foundation posted a survey on its website ([www.epilepsyfoundation.org](http://www.epilepsyfoundation.org)). The survey asked patients (and parents of children with epilepsy) about their experiences with brand-to-generic, generic-to-brand and generic-to-generic AED substitutions.

Although not representative of all persons with epilepsy, the findings from the Epilepsy Foundation's survey reflect a wide array of patient experiences. A total of 1085 people responded to the survey between November 2006 and March 2009.

In addition to asking respondents whether they had ever switched AEDs (and, if so, whether they suffered any adverse consequences resulting from the switch), the survey asked respondents to provide comments about their experiences. More than half did.

### **IV. FINDINGS FROM THE FOUNDATION'S SURVEY**

In the collected responses to the Epilepsy Foundation's survey, many respondents reported problems after switching between brand-name and generic AEDs, or from one generic to another:

- Of respondents that had switched from a brand-name to a generic AED, seizures worsened for 59 percent of patients, and medication side effects worsened for 49 percent of patients.
- Of respondents that had switched from a generic to a brand-name AED, seizures worsened for 15 percent of patients, and medication side effects worsened for 18 percent of patients.
- More than a quarter of respondents reported experiencing problems after switching between different generic formulations of an AED.

In addition to reporting whether they had problems switching medications, many survey respondents offered narrative responses about their experiences with AED-switching. In their comments, they:

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<sup>9</sup> See, e.g., Feely M, Crawford P, Kramer F, Guberman A. *Risk Management in epilepsy: generic substitution and continuity of supply*. *European Journal of Hospital Pharmacy Science* 2005;11(4):83-87.

- A. Provided examples of increases in seizures or adverse events following a medication substitution,
- B. Described the problems obtaining adequate health-insurance coverage for the anti-epileptic drugs prescribed to them, and
- C. Reported occasions in which medications were changed without notice to the patient or the patient's physician.

Comments illustrative of each finding are set out below.

**A. PATIENTS EXPERIENCED INCREASED SEIZURES AND ADVERSE EVENTS AFTER SWITCHING ANTI-EPILEPTIC DRUGS**

***(1) Many respondents reported breakthrough seizures or increased frequency of seizures after switching from name-brand to generic AEDs.***

“I am now 39 years old and have had epilepsy since age 6. Many times I have tried the generic equivalents only to have my seizures worsen or to have side effects that were intolerable.” – *Oxford, Alabama*

“When switching from brand name Dilantin to generic, I had the first breakthrough seizure in many years (I believe 10 [years]). The seizure happened two weeks after I began taking the medicine.” – *Venice, Florida*

“Our neuro[logist] has insisted that we maintain brand name medications. However, both the local pharmacy and the mail order pharmacy have at one time mistakenly dispensed the generic of Zonegran, zonisamide. Because of time issues, daughter has taken that generic for a few days and definitely had increase in seizures. We're all for saving with generics, but only when not at expense of efficacy. I don't understand why the FDA allows 20% variance in bioequivalence for generics.” – *Houston, Texas*

“I was switched by my insurance carrier from Dilantin to a generic. My neurologist warned me never to do this, but it was the weekend and I was low on pills and had to take them. I thought I would be able to rectify the problem by the beginning of the week. Within 36 hours I had a grand-mal and a visit to the ER for some stitches.” – *Chandler, Arizona*

“I've been taking Dilantin for my seizures since I was first diagnosed, some 25+ years ago. In that time[,] I have been switched to generic form of Dilantin by several doctors. Each time I have had seizures (grand mals) [and] I have vowed NEVER to take generic again.” – *Astoria, New York*

“I have been taking Dilantin for over 30 years. I at my doctor’s suggestion[, I] switched to generic. I had 3 seizures in 1 month. While I am sure some people are not affected[, I] think [generics] should be used on an individual basis.”  
– *Harwood Heights, Illinois*

“Both my sister-in-law and mother have epilepsy. Both have tried unsuccessfully to switch from a brand-name medication to a generic because of insurance issues. Both have suffered breakthrough events within a month to 6 weeks.”  
– *Anonymous*

“In 2004, I had my first grand mal seizure in 18 years three weeks after the pharmacy switched me from brand name Dilantin to generic phenytoin. The pharmacist told me that although these two drugs had previously not been interchangeable, they now were.” – *Anonymous*

“I am completing this survey for an adult child. The switch to generic medication caused a seizure after many years of being seizure free. . . . The seizure required a 3-day hospital visit for tests. There were 4 other patients in the neurology department who experienced break-through seizures after taking generic medicine.” – *Upper Saddle River, New Jersey*

“My husband switch[ed] and had a breakthrough seizure [that] caused sudden death. This is serious.” – *Dorchester, Massachusetts*

**(2) Respondents reported adverse side effects after switching from generic and name-brand AEDs.**

“The generic had given me a problem with having headaches. . . . After returning to name brand [my] headaches disappeared.” – *Anonymous*

“While I did not have any breakthrough seizures from taking a generic, I had increased frequency of seizure auras and sensitivity to triggers. In my case, my doctor did not prescribe the generic, the pharmacy made a mistake and filled the prescription with generic.” – *Anonymous*

“I have tried several times to switch to the generic Tegretol. It does not work the same on me[.] [I]t makes me dizzy, light-headed and I have breakthrough seizures. I may have to pay more for the other[,] but it is worth it to me.”  
– *Anonymous*

“Within a month of my insurance company automatically switching us to the generic form of Zonegran when it became available[, ] my daughter began to have seizure activity again. Her seizure control has increasingly worsened over the last year, and her quality of life is severely impaired to the point she is now having difficulty finishing her bachelors degree (less than 20 credits to go): depression, tooth and bodily injuries, employment uncertainty, etc.” – *Fort Wayne, Indiana*

“My daughter was recently put on generic Trileptal and experienced really bad side effects. We had to take her to the ER twice within one week because of severe ataxia. She was unable to walk, sit up or eat. After running many tests and blood work it was believed by her neurologist that it was the generic Trileptal. Once we switched her to the brand name Trileptal her condition improved! Her neurologist stated that he had other patients experiencing similar side effects.”

– *St. Clair Shores, Michigan*

“This past month my [prescription] for Lamictal was filled with generic. I have taken Lamictal for 6 years. I had my 1st seizure in 1999 at the age of 37. My seizures have never been completely controlled, but the intensity of them has been greatly reduced. After taking the generic version of Lamictal for 2 weeks I had 4 grand mal seizures in a 24 hour period. This has never happened before except when I was a patient at the epilepsy unit and taken off my meds to have my seizures monitored.” – *Waynesville, North Carolina*

“I recently was switched from my regular Depakote to the generic[;] within 3 weeks I had the wors[t] seizure I have had in about 5 years. And in the 3 weeks leading up to the seizure the side effects were dramati[c]. It was really bad, back on brand name for 2 wks now & finally back to myself.” – *Anonymous*

**(3) Several respondents reported that the adverse events they associated with an AED substitution resolved after switching back to the original drug.**

“[I] had a seizure when I went on [a] generic drug. I ended up in the hospital overnight. [The doctor] switched me back to brand name. No problems since.”

– *Anonymous*

“When I was switched to the generic last year, in a 6-8 month period, I had 3 grand mal seizure[s] and many petit [mal] seizure[s]. [Since] I was put back on the brand name, I have not had one.” – *Phoenix, Arizona*

“Taking generic Dilantin was a terrible mistake for me. I was controlled on Dilantin for a few years before switching to the generic. After a week or so on the generic, I had several violent seizures that landed me in the hospital. Upon returning to the name-brand, I have been seizure free for quite some time. I can’t *prove* the generic was the problem, but I certainly believe it.” – *Anonymous*

“After switching to a generic seizure medicine, I had two seizures in one day and wound up in the hospital emergency room and had to spend the night in the hospital. I had injuries from the seizure. That was 6 years ago. Since switching back to my brand name, I have had no further problems.” – *Anonymous*

“My son was taking Dilantin for his seizures and the drug store filled his prescription with a generic. Shortly after the medication was switched he had a breakthrough seizure. Once he was switched back to the brand name he did not have any further problems.” – *Houston, Texas*

“After a change in medical coverage, only generic drugs were covered. During this time my son’s seizures increased. ([F]rom average of 2 per year to 2–3 per quarter.) After switching medical plans again and resuming non-generic medications, his seizure activity returned to the average of 2 per year.”

– *Sacramento, California*

“I switched from brand name Trileptal to generic Trileptal and within days had several grand mal seizures. Although my seizures are frequent, even on medication, I do not have grand mals. They stopped as soon as I started to take the brand name Trileptal again the next day.” – *Winthrop, Washington*

“Our daughter switched to the generic Zonegran and within 1 month was having numerous breakthrough seizures. We switched her back and the breakthrough seizures went back to the usual number [and] regularity.” – *Farmville, North Carolina*

“My daughter was switched from brand name Lamictal to generic due to insurance requirements. Within 3 days, she had 5 seizures (normally she would have had none). Pharmacy switched her back to brand and seizures stopped.”

– *Chapel Hill, North Carolina*

“I also had an significant increase in seizures when I was put on the generic form of Synthroid. Thankfully, my neurologist was able to switch me back to the brand name. I still have to fight this with my insurance company every time I refill the prescription, though!” – *Anonymous*

**(4) A few respondents reported problems with changes in formulations (i.e., generic-to-generic switches).**

“I am a physician and I have always tried to be open about generics. But when Neurontin went generic, I found that almost each time I went to get my prescription, it would be a different generic. I didn’t know there were that many companies out there making [generic] gabapentin. [O]ne generic . . . definitely ha[s] a negative effect on my seizure control. Now I always ask to get the same generic as last time!” – *Prospect, Kentucky*

“When switching from [generic] zonisamide 100mg, made by Apotex, to [generic] zonisamide 100mg by Mutual there was a tremendous increase in seizures after about 1 week.” – *Neenah, Wisconsin*

“Our pharmacy has been switching from generic manufacturer to generic manufacturer. They have even filled a prescription with medications from two different manufacturers. This has gone on for about the last six months. My daughter [had] 3 ‘unexpected’ seizures. . . .” – *Ashland, Kentucky*

“I was switched from the brand name Tegretol to a generic form . . . I experienced an increase in seizures do to my receiving multiple generic forms. The level of the medication I took was no longer remained consistent.” – *Rancho Cordova, California*

“My daughter’s seizures always worsen with a change in formula with the same drug. She returns to normal after about 2 weeks. Because of this her doctor prescribed name brand only.” – *Marlboro, Massachusetts*

**(5) Respondents reported that their AED blood levels changed after switching between generic and name-brand AEDs.**

“The blood levels obtained between the same doses of the generic and brand name drug varied wildly.” – *Anonymous*

“I don’t think generic drugs should be given as each time my son took generic he had seizures and pretty quick. The hospital said his blood work showed he had extremely low levels that probably triggered the seizures.” – *Anonymous*

“After being on generic Dilantin for over a year my levels were constantly low, and my doctor was not aware I was taking the generic. When he found out, he switched me right away to name brand. Within weeks of the switch my levels were toxic at the same dose on the name brand as I was on the generic. I had my blood drawn EVERYDAY when I would begin to have side effects. At the highest level, my Dilantin was 37.5. TOXIC!!” – *Cincinnati, Ohio*

“I am filling this out for my brother who had a breakthrough [grand mal] seizure Jan 2009. He had no seizures in the 10 years prior. A few weeks before seizure the pharmacist had given him generic drug even though prescription was [dispense as written]. While at work (and driving) he went into a [grand mal] seizure[,] was in a bad car accident and crushed 5 vertebrae. His blood level was tested and was at ½ of therapeutic level. Now my brother is recuperating[,] he will not be able to do his job anymore and is in constant pain. – *Anonymous*

“[My] child was switched from generic carbamazepine to brand [name] Tegretol and had more seizures and problems. The brand product achieves lower levels than the generic . . . never had any problems with the generic!” – *Anonymous*

**B. PATIENTS HAD PROBLEMS OBTAINING ADEQUATE HEALTH INSURANCE COVERAGE FOR THE AED PRESCRIBED TO THEM.**

***(1) Respondents reported problems obtaining health insurance coverage for name-brand AEDs.***

“Major problem with insurance coverage. My Mom’s insurance will only cover cost of available generics, even though my doctors provided evidence that I had breakthrough seizures in 4 days when switched to generics.” – *Cypress, Texas*

“Because I’m disabled my insurance wouldn’t pay for [brand-name] Dilantin, the pharmacist gave me [generic] phenytoin. At the time I was having seizures once a month. I started having seizures daily [after] the switch.” – *East Troy, Wisconsin*

“[My] daughter died after having a grand mal seizure in October. She was on 4 different anti-convulsants...one of them was switched from [a “dispense as written”] brand to a generic by my insurance. She hadn’t had a grand mal in 4 years!” – *East Grand Rapids, Michigan*

***(2) Several respondents with name-brand drug coverage reported that higher costs and penalties compelled them to abandon well-functioning medications.***

“Switched from [branded Clobazam] Frisium (Canadian) to a generic Clobazam a few years ago and seizures got worse almost immediately so switched back. It is getting so expensive now that we are trying [generic] again.” – *Springfield, Oregon*

“I experienced some difficulties when switching to generics but as with everything else I could not afford to comment in order to be able to survive.” – *Birmingham, Alabama*

“[M]y Goodness, why am I charged [extra] for . . . medication I have to take. I should not be penalized if [a doctor] writes [dispense as proscribed] and I can’t take generic [anti-epileptic drug]. This should be a law.” – *Saginaw, Michigan*

“Under the State of [Missouri] Insurance[,] my Lamictal costs went from \$50 to \$187.50. Now the costs are being changed from \$187.50 to \$934.00. My neurologist does not want me taking generics, but my insurance company is forcing their hand by raising the cost to a price I can’t afford. I fear having another seizure and the effects it will have on my life.” – *Jefferson City, Missouri*

**C. PATIENTS’ MEDICATIONS WERE CHANGED WITHOUT NOTICE TO THE PATIENT OR THE PATIENT’S PHYSICIAN.**

***(1) Several respondents discovered that their medications had been changed only after they developed problems.***

“Our pharmacy was changing from one manufacturer to another without notifying us. When Sam went from 7 weeks seizure free to a bad breakthrough, they were very difficult with our request to call around for what we had been using.”

– *Dayville, Connecticut*

“My seizures were under control for 15 years with Tegretol. One month after my druggist switched my prescription without my knowledge or the knowledge of my physician I had a breakthrough seizure. I was admitted to the hospital for 3 days and underwent expensive testing. I do not want this to happen to any other patient.” – *Anonymous*

“My neurologist and surgeon are trying to figure out if my seizures have been caused by my switch from the name brand Zonegran, to the generic brand. I am not exactly sure of when my seizures worsened because I was not informed by my pharmacy of the switch from name brand to generic. I do know that it was somewhere around the time of the switch though. Because I am having all of these seizures my doctors have been discussing second possible brain surgery, which could all be due to the switch.” – *East Lansing, Michigan*

“My 1st seizure in eight years occurred after taking generic Dilantin for 2 weeks. I had been on brand name Dilantin since I had a brain tumor removed with no [breakthrough seizures]. The pharmacist switched to generic and I did not realize the difference when he did it. Two weeks later I had a grand mal while driving and almost lost my life, needless to say I am very careful about the prescription now.” – *Punta Gorda, Florida*

## **V. CONCLUSIONS AND RECOMMENDATIONS**

The results from the Epilepsy Foundation’s survey mirror longstanding concerns within the medical community regarding patient safety when substituting AEDs for non-clinical reasons.

Epilepsy is unique among chronic conditions in the multitude of ways in which the disease affects patients medically, socially, economically, emotionally and psychologically, and the degree to which medical therapy must be individualized. Physicians routinely witness the fact that patients with similar clinical presentations do not respond in similar ways to the same AED. To be effective, treatment must be customized for each patient to achieve maximum seizure control and minimal adverse side effects. Patients may face significant challenges achieving effective treatment, and treatment failure following AED substitution can be devastating.

To help reduce the risk associated with AED substitutions, the Epilepsy Foundation provides the following recommendations related to its survey findings. These recommendations are part of a larger set that the Epilepsy Foundation’s Advisory Committee on the Substitution of

Epilepsy Medications completed after a recent review of the evidence regarding AED substitutions.<sup>10</sup>

**A. RECOMMENDATIONS FOR FEDERAL POLICYMAKERS:**

- The Food and Drug Administration (FDA) should conduct research to determine the best method for ensuring that brand-name and generic AEDs are truly therapeutically equivalent. Considerations in improving the methodology should include whether: (1) test groups appropriately represent the patient population; (2) sample sizes are adequate; (3) individual bioequivalence measures should be required; (4) population bioequivalence measures should be required; and (5) different testing methodologies should be developed for different types of medications.
- The FDA should require drug manufacturers to make all the bioequivalence information of their generic and brand-name AED products available to physicians and the scientific community.
- The FDA should carry out post-marketing surveillance for all generic and brand-name AEDs, and should take all necessary steps to ensure broader reporting of adverse reactions to switching.
- The FDA should immediately notify doctors and pharmacists about the retrospective data on switching, and should ensure consent and oversight of doctors prior to any switching among different formulations or versions of the same AED.
- Congress should conduct oversight review of the FDA's practices and steps taken to ensure safety and efficacy of all AEDs, including the safety of substitutions of different formulations of the same therapeutic agent.

**B. RECOMMENDATIONS FOR PATIENTS, PHARMACISTS, AND PROVIDERS:**

- Patients should be informed of the risks of switching between different versions of the same AEDs, and instructed to be aware both of their AED's manufacturer and the look of their medications so that they can monitor for unanticipated substitutions.
- Patients and pharmacists should discuss with patients' physicians the appropriateness of substitution before switching among different versions of the same AEDs.
- Patients should provide informed consent prior to any change in medication.
- Pharmacists should be educated on the unique nature of epilepsy and AEDs, and the need for caution when switching AEDs.

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<sup>10</sup> For more information about the full set of recommendations, please contact Sandy Finucane at the Epilepsy Foundation ([afinucane@efa.org](mailto:afinucane@efa.org)).

- Health care providers should receive education on the issues associated with AED substitution and ensure substitutions are medically appropriate on a case-by-case basis.

**B. RECOMMENDATIONS FOR HEALTH INSURERS:**

- Health insurers should develop policies that recognize and support physician discretion, and which permit the physician to proscribe the AED that the physician believes will provide the patient with the best results.
- Health insurers should ensure that there are no restrictions on prescribing brand-name AEDs for patients with epilepsy.
- Health insurers should ensure adequate protections are in place to prevent the mandatory substitution of an AED for individuals with epilepsy.
- Health insurers should provide safeguards to ensure that patients who experience a treatment failure following an AED substitution are not penalized for switching-back to their earlier-prescribed AED, either financially or by having to comply with onerous administrative burdens.

**C. RECOMMENDATIONS FOR STATE POLICYMAKERS:**

- State laws should be strengthened to ensure that patients have their AEDs switched only when medically appropriate.
- States should require that pharmacists obtain physician and patient consent before switching AEDs for epilepsy patients.
- State laws should ensure that pharmacy-bottle labels clearly identify a drug's manufacturer, and indicate if an AED substitution has been made.

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## APPENDIX A: Consumer-Survey Response Data

The Epilepsy Foundation posted a survey on its website that asked patients (and parents of children with epilepsy) about their experiences with brand-to-generic, generic-to-brand and generic-to-generic AED substitutions. A total of 1086 people responded to the survey between November 2006 and March 2009. The limitations of this survey include the use of self-reported data; and that persons with epilepsy who completed this survey may differ from patients who do not visit the Epilepsy Foundation website or who choose not to complete the survey. Nonetheless, this survey provides a valuable snapshot of a wide array of patient experiences following AED substitutions. Following is a summary of these survey results.

| <b>Question</b>  | <b>Yes</b><br>Percent of answering<br>respondents (n =<br>number of<br>respondents) | <b>No</b><br>Percent of answering<br>respondents (n =<br>number of<br>respondents) | <b>Proportion<br/>Responding</b><br>Percent of total<br>respondents (n = number<br>of respondents) |
|--|---|--|--|
| <b>Question 1:</b> While taking a prescribed dose of an AED, have you ever had a breakthrough seizure?   | 74 percent<br>(n=804)   | 26 percent<br>(n=281)  | 100 percent<br>(n=1085)  |
| <b>Question 2:</b> Have you ever switched from a brand to a generic seizure medication?  | 67 percent<br>(n=724)   | 33 percent<br>(n=361)  | 100 percent<br>(n=1085)  |
| <b>Question 3:</b> Did your seizure control worsen at the time (within a month) of the switch to a generic seizure medication from a brand name seizure medication?  | 59 percent<br>(n=446)   | 41 percent<br>(n=273)  | 66 percent<br>(n=719)  |
| <b>Question 4:</b> Did your side effects worsen at the time (within a month) of this switch to a generic medication?   | 49 percent<br>(n=361)   | 51 percent<br>(n=356)  | 66 percent<br>(n=717)  |
| <b>Question 5:</b> Have you ever switched from a generic to a brand name seizure medication?   | 40 percent<br>(n=439)   | 60 percent<br>(n=646)  | 100 percent<br>(n=1085)  |
| <b>Question 6:</b> Did your seizure control worsen at the time (within a month) of this switch from a generic seizure medication to a brand name seizure medication? | 15 percent<br>(n=72)  | 85 percent<br>(n=356)  | 39 percent<br>(n=428)  |
| <b>Question 7:</b> Did your side effects worsen at the time of this switch from a generic seizure medication to a brand seizure medication?                          | 18 percent<br>(n=87)  | 82 percent<br>(n=337)  | 39 percent<br>(n=424)  |
| <b>Question 8:</b> Have your seizures ever worsened when switching from one generic drug to another generic drug?  | 25 percent<br>(n=273)   | 75 percent<br>(n=812)  | 100 percent<br>(n=1085)  |