
Developing Strategies to Address Generic Substitution of Antiepileptic medications

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Generic and Brand Name AEDs: Considerations for Clinicians

Definitions

Generic drug: identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

Bioequivalence: demonstration that both the rate and extent of absorption of the active ingredient of the generic drug fall within established parameters when compared to that of the reference listed drug.

Office of Generic Drugs, <http://www.fda.gov/cder/ogd/>

History

- The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) gave generic drug companies greater access to the market for prescription drugs, and gave innovator companies greater patent life.
- The patent gives a company the sole right to sell the drug while the patent is in effect. When patents or other periods of exclusivity expire, manufacturers can apply to the FDA to sell generic versions.

History

- Drug companies must submit an abbreviated new drug application (ANDA) for approval to market a generic product.
- The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness. This applies to drugs first marketed after 1962. Therefore, generic medications are priced lower than brand name medications.

Reasons Underlying Use of Generic Medicines

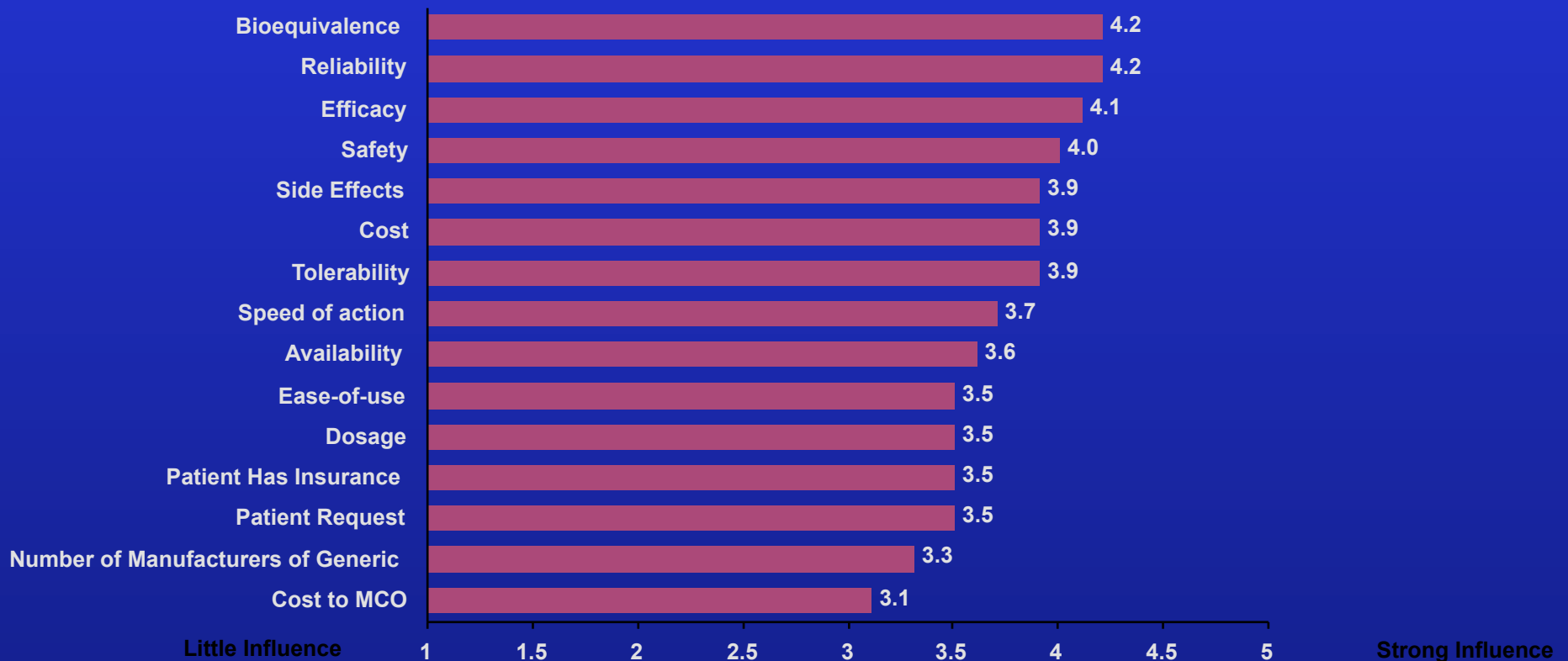
- Need by payers, including government, and formularies to reduce healthcare costs
- Congressional Budget Office estimates generics save consumers \$8 to \$10 billion a year at retail pharmacies (<http://www.fda.gov/cder/ogd/>)
- Expense of brand name drugs for patients, such as seniors on fixed income, can be substantial

Reasons Underlying Use of Generic Medicines

- FDA's commitment to generic medicines
 - “FDA will continue to make the generic drug approval process more efficient with the goal of lowering national health care costs by reducing the cost of bringing safe and effective generic drugs to market.” FDA press release August 8, 2003
- Belief by payers, some physicians and some patients that brand products and generic versions are entirely equivalent and interchangeable

Decision-Influencers on Prescribing Brand vs Generic

- For most physicians, bioequivalence, reliability, efficacy and safety are the key influencers on whether to prescribe a branded versus generic drug
- However, these factors are close in terms of the degree of their influence



Base: All Physicians – 150.

**Bick J, Simmons E. GFK Martin Hamblin Market Research Presentation:
*Understanding the Impact of Generic Zonegran on the Current AED Market.***

Physician Beliefs on Prescribing Generics

- Neurologists believe that generics are not comparable to branded AEDs in terms of efficacy
 - PCPs disagree somewhat
- Generic safety profiles are not as good
- Poor bioequivalence and multiple generic manufacturers are also concerns
- Lowered cost to patient is main advantage of generics
 - However, physicians feel pressured to prescribe generics to save costs for patients and MCOs

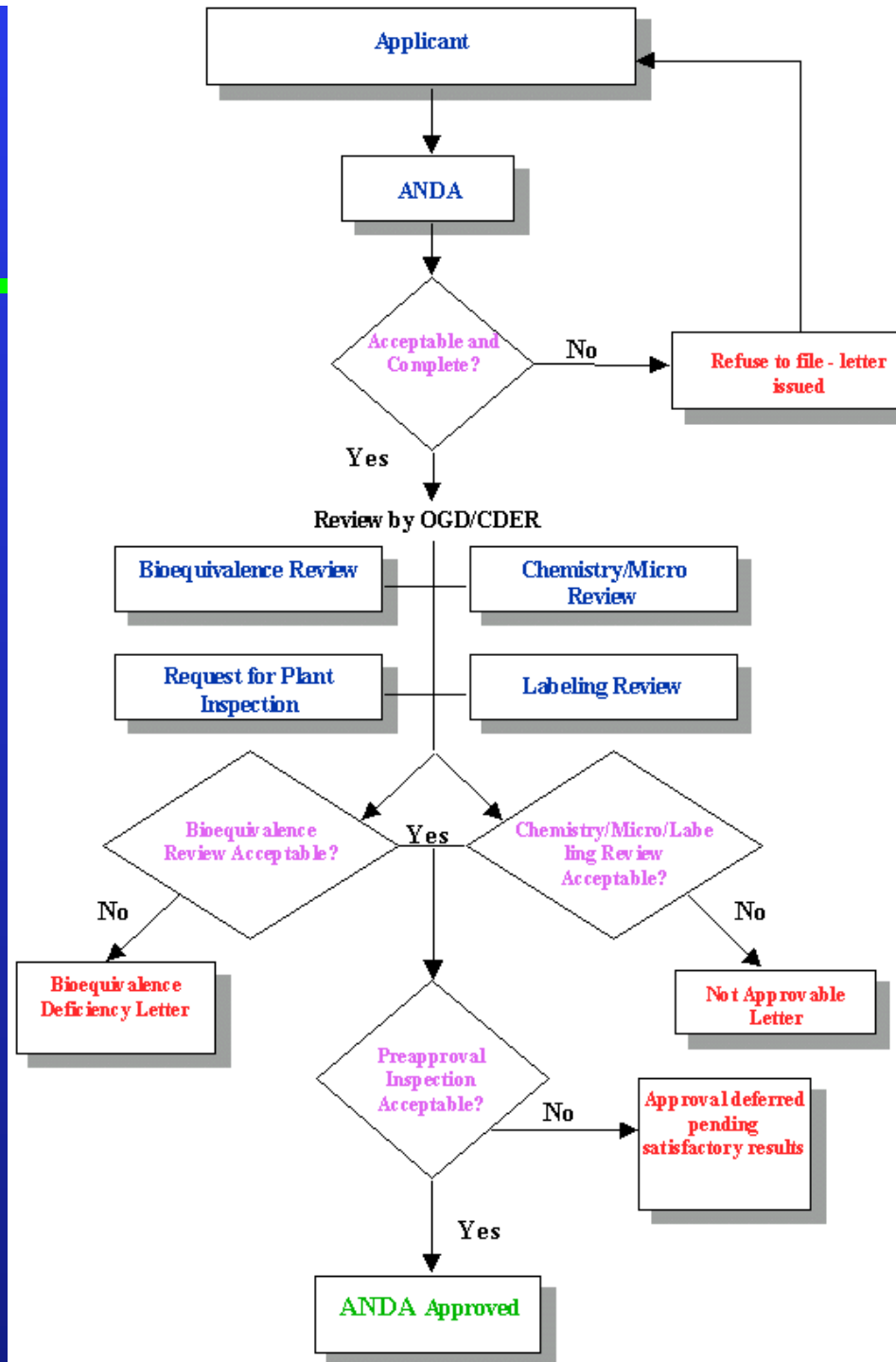
Regulatory Process for Generics in U.S.

- To gain FDA approval, a generic drug must:
 - contain the same active ingredients as the innovator drug (inactive ingredients may vary)
 - be identical in strength, dosage form, and route of administration
 - have the same use indications

Regulatory Process for Generics in U.S.

- To gain FDA approval, a generic drug must:
 - be bioequivalent
 - meet the same batch requirements for identity, strength, purity, and quality
 - be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products

Regulatory Process for Generics in U.S.



Regulatory Process for Generics in U.S.

- Bioequivalence is a key requirement
- Bioavailability and Bioequivalence Requirements of FDA are codified under Title 21, Chapter 21, Subchapter D, Part 320 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320>)

Regulatory Process for Generics in U.S.

- Part 320, Subpart B – Procedures for Determining the Bioavailability or Bioequivalence of Drug Products
 - The in vivo bioavailability of a drug product is . . . [accepted] if the product's rate and extent of absorption, as determined by comparison of measured parameters, e.g., concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption.

Regulatory Process for Generics in U.S.

- Two formulations of the same drug or two drug products are claimed **bioequivalent** if the ratio of means of the primary PK responses such as AUC and C_{max} between the two formulations of the same drug or the two drug products is within (80%, 125%) with 90% assurance.
- A generic drug product can substitute for the brand name drug product if it has been shown to be bioequivalent to the brand name drug.

Regulatory Process for Generics in U.S.

- The FDA, however, does not indicate that a generic drug can be substituted by another generic drug for a brand name drug product even though both of the generic drugs have been shown to be bioequivalent to the same brand name drug.
- Bioequivalence studies are generally performed on a limited number of healthy volunteers, and not on patients. Further, doses used may not yield clinically relevant ranges of serum concentrations
 - Bioequivalence of AED generics are not tested on patients with epilepsy

Potential Disadvantages of Generic Medicines

- Rate and extent of absorption (bioavailability) differs between different generic versions of branded products
- Generic names are not as easy to remember, spell or pronounce as branded names
- Generic products usually differ in appearance from the brand and from other generic versions of the same product, leading to patient confusion and anxiety
- Excipients and colorants used in generic products may differ from the brand, potentially causing problems

Issues for Generics Specific to Epilepsy

- Characteristics of epilepsy / seriousness of therapy failure
 - Epilepsy is unlike other medical conditions, such as elevated cholesterol, because of the seriousness of its episodic symptoms (seizures)
 - Breakthrough seizure after long remission can have significant psychosocial and physical consequences
 - Driving/employment
 - Injury

Switching Between Generics Carries Risks: Consistency of Supply

- Repeated substitution with generics from different manufacturers is likely¹
- Once a number of generic products are on the market, pharmacists may change their supplier according to price and availability²
- The FDA's bioequivalence requirement implies that the plasma levels of a bioequivalent generic will not differ by more than 5% to 7% from those observed with brand product¹
 - Switching between generic formulations is riskier than switching from brand name to generic, because the bioequivalence of the generic AED was most likely determined using the brand AED; the bioequivalence of 2 generics may vary when using a generic formulation as the base¹

Drug	No. of Manufacturers ^{3,4}
Carbamazepine	14
Gabapentin	19
Lamotrigine	2
Levetiracetam	12
Oxcarbazepine	9
Phenytoin	13
Valproates	19
Zonisamide	16

1. Bialer M. *Epilepsia*. 2007;48:1825-1832. 2. Crawford P, et al. *Seizure*. 2006;15:165-176. 3. IMS National Prescription Audit; February 2009.

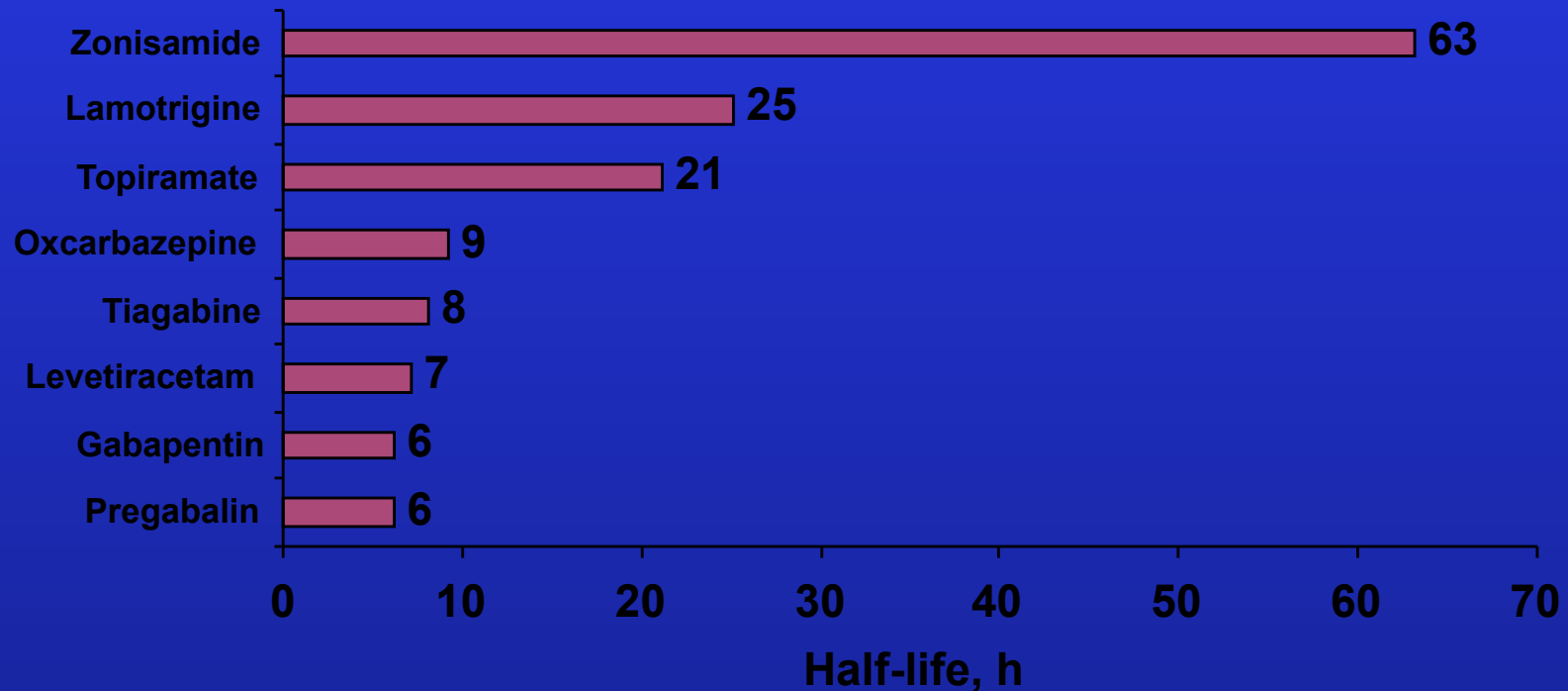
4. Levetiracetam. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed December 1, 2008.

Issues for Generics Specific to Epilepsy

- Characteristics of AEDs
 - High potential for CNS-related adverse events
 - Usually related to serum concentration
 - Some AEDs have narrow therapeutic index
 - Defined by FDA as less than two-fold difference between the minimum toxic concentration and the minimum effective concentration
 - Particularly true for CBZ, PHT and VPA
 - Individual patients may have even narrower differences between efficacy and toxicity

Crawford et al. Seizure 2006;15:168-176

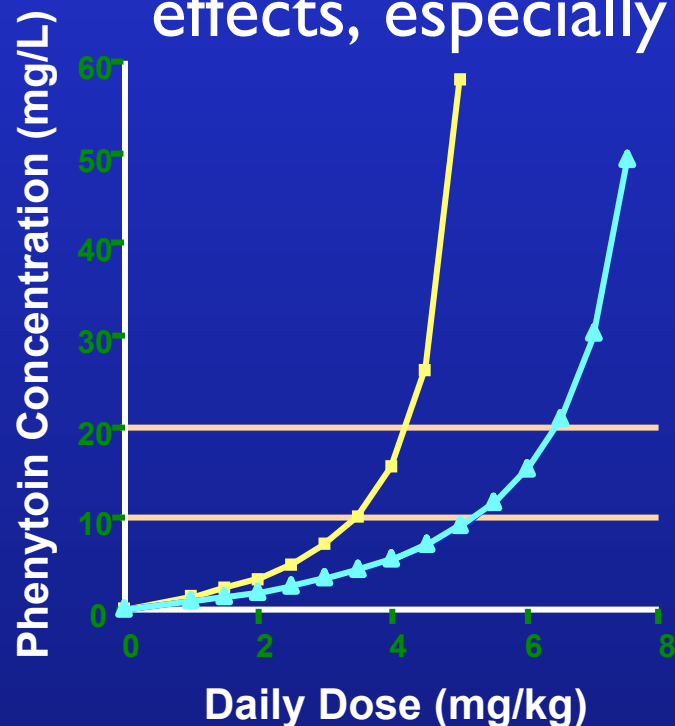
Half-lives of Newer AEDs: Summary



Zonegran® (zonisamide) package insert.
Lamictal® (lamotrigine) package insert.
Topamax® (topiramate) package insert.
Trileptal® (oxcarbazepine) package insert.
Gabitril® (tiagabine) package insert.
Keppra® (levetiracetam) package insert.
Neurontin® (gabapentin) package insert.
Lyrica® (pregabalin) package insert.

Issues for Generics Specific to Epilepsy

- Characteristics of AEDs
 - Non-linearity: slight increase in PHT bioavailability can lead to marked increase in serum level and adverse effects, especially when level is over 15 mg/L



Crawford et al. Seizure 2006;15:168-176

Issues for Generics Specific to Epilepsy

- Complexity of management regimens
 - May need titration over weeks to avoid side effects
 - Need for consistency of product during titration so that prescribed changes of dose have predictable consequences; this is a potentially a problem if there is a switch of product during titration

Issues for Generics Specific to Epilepsy

- Complexity of management regimens
 - Drug interactions
 - Change in serum concentration of one drug may lead to changes in serum concentrations of co-medications

Issues for Generics Specific to Epilepsy

- Continuity of supply/ changes in suppliers over time
 - Several products have multiple suppliers
 - Pharmacies change their supplier according to price and availability
 - Patients can not usually identify the source of a generic product, and may be unaware that the supplier has changed from one refill to the next
 - In 2000, there were over 26 different generic preparations for five brand name AEDs

Issues for Generics Specific to Epilepsy

- Initial prescribing vs. switching
 - Use of a single-source generic during initiation, titration and maintenance of AED therapy would be cost-effective and would avoid concerns about generics
 - However, switching from brand to generic, or one generic to another manufacturer's generic can potentially lead to adverse effects or seizures

Issues for Generics Specific to Epilepsy

- Potential savings vs. potential costs
 - Savings associated with a generic may be offset by costs associated with office visits, lab tests, emergency room visits or hospitalizations
- Legal situation and informed consent, implications for generic substitution without informed consent
 - Who is responsible?

Clinical Experience: the Literature

- Most papers are case reports or case series
 - Majority concern CBZ, PHT or VPA
 - Reports document breakthrough seizures or adverse events when switching from branded AED to generic
 - Limited because reports are retrospective, anecdotal
- In a survey of neurologists, 56% of the 301 respondents reported adverse events, and 68% reported breakthrough seizures in at least one patient switched from branded to generic AED

Clinical Experience: the Literature

- Burkhardt et al identified 8 adult patients whose seizures worsened after switching from brand PHT to generic PHT
 - Mean total PHT concentration
 - on brand (before generic): 17.1 + 5.3 mg/L
 - after switch to generic: 12.5 + 2.7 mg/L
 - after switch back to brand: 17.8 + 3.9 mg/L
 - They concluded brand and generic PHT do not yield equivalent concentrations in some patients

Clinical Experience: the Literature

- Very few blinded, controlled studies compare generic to brand versions
 - Only factor evaluated, however, is relative pharmacokinetics, and only one generic version is studied
- No controlled studies have mirrored clinical practice by evaluating safety, efficacy and compliance with multiple generic versions used in succession

AAN Recommendations on AED Generics

- Generic substitution can be approved only if safety and efficacy are not compromised
- Physicians should avoid switching between formulations of AEDs
- Specific pharmacokinetic information about each AED generic should be made available to physicians
- Pharmacists should be required to inform patients and physicians when switching a patient between manufacturers

AAN Recommendations on AED Generics (cont)

- Labeling should identify specific manufacturers
- Organizations that encourage or mandate substitution of AEDs should evaluate their responsibility for problems arising from their policies
- Further research on the impact of generic substitution is required

Epilepsy Foundation Policy on Generic AEDs

- The Epilepsy Foundation is seriously concerned about mandatory substitution of generic antiepileptic drugs without prior approval of the patient and treating physician.
- Because changing from one formulation of an AED to another can usually be accomplished, and risks minimized, if physicians and patients monitor blood levels, seizures and toxicity, the Foundation maintains that the individual and physician should be notified and give their consent before a switch in medications is made, whether it involves generic substitution for brand name products, or generic to generic substitutions.

<http://www.epilepsyfoundation.org/advocacy/care/genedrev.cfm>

What Clinicians Can Do

- The FDA encourages people with epilepsy and physicians to report any breakthrough seizures resulting from switching formulations of a product to the FDA's MedWatch program. For information, call 1-800-FDA-1088 or visit the web site at <http://www.fda.gov/medwatch>

Summary

- The potential financial savings of generic AEDs to consumers and insurers need to be balanced against the possibility of:
 - Serious consequences of breakthrough seizures
 - Adverse events
 - Unpredictable effects on levels of other AEDs
 - Patient confusion and errors in compliance

Summary

- Further controlled studies are needed to better understand these risks, and to determine which patients are particularly vulnerable
- Physicians and patients should be informed and communicate with each other when a product change is made, such as brand to generic, generic to brand, one generic to another

Thank you!

DISCUSSION

Key Questions

- What are your thoughts about prescribing generic AEDs for epilepsy?
- Is there a significant difference in therapeutic range between a particular branded AED and its generic equivalent?
- Is there any difference in the prevalence or degree of side effects when you compare branded AEDs to generics?

Key Questions

- Is tablet switching a significant problem? What can physicians do to minimize this practice?
- Does overseas manufacturing of generic drugs influence your prescribing decisions on brand vs. generic?
- What is the effect of a new AED formulation on prescribing habits?