Generic Antiepileptic Drug (AED) Research Leading to Changes in Clinical Practices

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CERSI Research Impact Meeting, Silver Spring, MD

Anecdotes and Controversies on Generic Antiepileptic Drugs (AEDs)

"Physician surveys, case reports, and "switchback" rates from large-scale generic conversions imply that all generic formulations may not be equal to the brand drug for all patient groups."

Privitera MD. Generic antiepileptic drugs: current controversies and future directions. *Epilepsy Curr* 2008; 8: 113–17.

"Many physicians and patient groups are insufficiently reassured by current definitions of similarity between generics and innovator brands."

Heaney DC, Sander JW. Antiepileptic drugs: generic versus branded treatments. *Lancet Neurol* 2007; 6: 465–68.

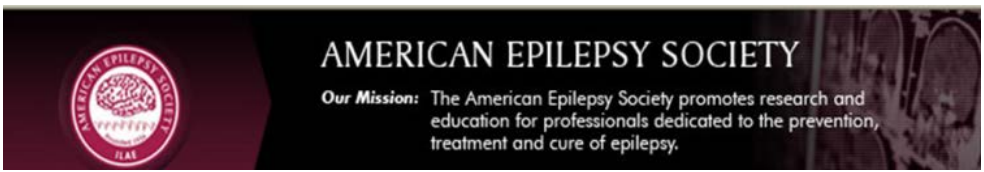
American Academy of Neurology

"The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval"

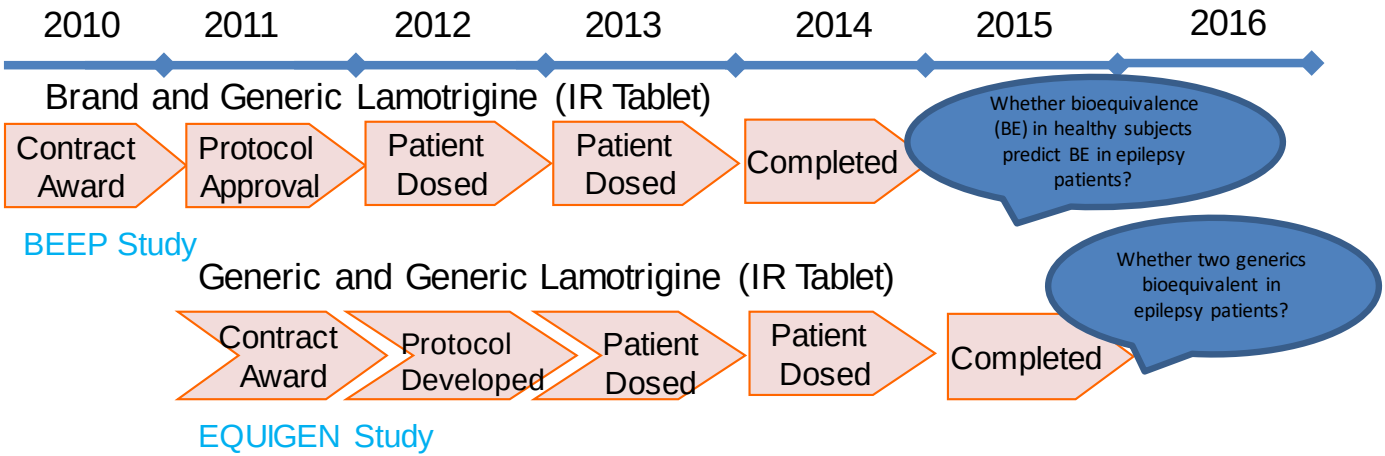
AMERICAN ACADEMY OF NEUROLOGY

American Academy of Neurology. Position Statement on the Coverage of Anticonvulsant Drugs for the Treatment of Epilepsy. November 2006.

"the society opposes formulation substitution of antiepileptic drugs for the treatment of epilepsy without physician and patient approval"



Brand-to-generic Switch Studies with Immediate Release (IR) Antiepileptic Drugs (AEDs)



BEEP2 Study:
Characterization of generic brittle epilepsy patients

Epilepsia
Official Journal of the International League Against Epilepsy

FULL-LENGTH ORIGINAL RESEARCH

Generic lamotrigine versus brand-name Lamictal bioequivalence in patients with epilepsy: A field test of the FDA bioequivalence standard

*Tricia Y. Ting, †Wenlei Jiang, †Robert Lionberger, ‡Jessica Wong, ‡Jace W. Jones, ‡Maureen A. Kane, *Allan Krumholz, †Robert Temple, and ‡James E. Polli

Epilepsia, 56(9):1415–1424, 2015
doi: 10.1111/epi.13095

Dr. Tricia Y. Ting is an epileptologist and associate professor of neurology at University of Maryland.

SUMMARY

Objective: To test the current U.S. Food and Drug Administration (FDA) bioequivalence standard in a comparison of generic and brand-name drug pharmacokinetic (PK) performance in "generic-brittle" patients with epilepsy under clinical use conditions.

Methods: This randomized, double-blind, multiple-dose, steady-state, fully replicated bioequivalence study compared generic lamotrigine to brand-name Lamictal in "generic-brittle" patients with epilepsy (n = 34) who were already taking lamotrigine. Patients were repeatedly switched between masked Lamictal and generic lamotrigine. Intensive PK blood sampling at the end of each 2-week treatment period yielded two 12-h PK profiles for brand-name and generic forms for each patient. Steady-state area under the curve (AUC), peak plasma concentration (C_{max}), and minimum plasma concentration (C_{min}) data were subjected to conventional average bioequivalence (ABE) analysis, reference-scaled ABE analysis, and within-subject variability (WSV) comparisons. In addition, generic-versus-brand comparisons in individual patients were performed. Secondary clinical outcomes included seizure frequency and adverse events.

Results: Generic demonstrated bioequivalence to brand. The 90% confidence intervals of the mean for steady-state AUC, C_{max}, and C_{min} for generic-versus-brand were 97.2–101.6%, 98.8–104.5%, and 93.4–101.0%, respectively. The WSV of generic and brand were also similar. Individual patient PK ratios for generic-versus-brand were similar but not identical, in part because brand-versus-brand profiles were not identical, even though subjects were rechallenged with the same product. Few subjects had seizure exacerbations or tolerability issues with product switching. One subject, however, reported 267 focal motor seizures, primarily on generic, although his brand and generic PK profiles were practically identical.

Significance: Some neurologists question whether bioequivalence in healthy volunteers ensures therapeutic equivalence of brand and generic antiepileptic drugs in patients with epilepsy, who may be at increased risk for problems with brand-to-generic switching. Bioequivalence results in "generic-brittle" patients with epilepsy under clinical conditions support the soundness of the FDA bioequivalence standards. Adverse events on generic were not related to the small, allowable PK differences between generic and brand.

KEY WORDS: Bioequivalence, Switchability, Lamotrigine, Generic-brittle, Narrow therapeutic index.

Accepted June 29, 2015; Early View publication July 23, 2015.
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EPILEPSY CURRENTS

Current Literature
In Clinical Science

Generic Substitution of AEDs: Is it Time to Put This Issue to Rest?

by Barry E. Gidal, PharmD

Epilepsy Currents, Vol. 16, No. 1 (January/February) 2016 pp. 18–20

"Clearly, this well designed study represents a major step forward in addressing the epilepsy community's concerns and provides valuable insight regarding AED PK variability."

"While encouraging, these observations do require confirmation in other patient populations. This issue of individual outliers certainly merits further study."

"Final data analysis from the EQUIGEN study group (EQUIvalence among GENeric AEDs) is near completion and should help further clarify this issue."

THE LANCET Neurology

Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial

Michael D Privitera, Timothy E Welty, Barry E Gidal, Francisco J Diaz, Ron Krebill, Jerzy P Szaflarski, Barbara A Dworetzky, John R Pollard, Edmund J Elder Jr, Wenlei Jiang, Xiaohui Jiang, Michel Berg

Summary

Background Patients and clinicians share concerns that generic drug substitution might lead to loss of efficacy or emergence of adverse events. In this trial, we assessed US Food and Drug Administration (FDA) bioequivalence standards by studying the effects of switching between two disparate generic immediate-release lamotrigine products in patients with epilepsy.

Lancet Neurol 2016; 15: 365–72
Published Online
February 11, 2016
http://dx.doi.org/10.1016/S1474-4422(16)00014-4

The safety of generic substitution in epilepsy

Emilio Perucca

Lancet Neurology, Feb 2016

"The EQUIGEN trial by Michael Privitera and colleagues published in *The Lancet Neurology* provides strong evidence that, at least for lamotrigine, concerns about generic substitution are largely misplaced."

"Overall, Privitera and colleagues' findings are quite reassuring, and organisations with a negative attitude to generic antiepileptic drug substitution should consider reviewing their position."

University of Maryland Center of Excellence in Regulatory Science and Innovation
Science that speeds health innovation

Questioning the Bioequivalence Standards for Antiepileptic Drugs: Implications for Regulation of Narrow Therapeutic Index Drugs

May 12, 2014

9:00-9:15 a.m.
Opening Remarks
Janet Woodcock, MD
Director, Center for Drug Evaluation and Research
Food and Drug Administration

9:15-9:45 a.m.
Results of Bioequivalence in Epilepsy Patients (BEEP) Study
James Polli, PhD
Shangraw/Noxell Endowed Chair in Industrial Pharmaceutics
Co-Principal Investigator, M-CERSI
University of Maryland School of Pharmacy

Tricia Ting, MD
Associate Professor of Neurology
University of Maryland School of Medicine

9:45-10:15 a.m.
Equivalence Among Generic AEDs (EQUIGEN) Study
Michel Berg, MD
Associate Professor of Neurology
University of Rochester School of Medicine and Dentistry

10:15-10:45 a.m.
Ensuring Safety and Efficacy of Generic Anti-Epileptic Drugs: FDA OGD Perspectives
Wenlei Jiang, PhD
Pharmacologist
Science Staff
Office of Generic Drugs
Food and Drug Administration

11:30-12:00 p.m.
Panel Discussion
Panelists: Drs. Polli, Ting, Berg, Jiang, Clarke, and Cohen-Wolkowiez

12:00-1:00 p.m.
Lunch

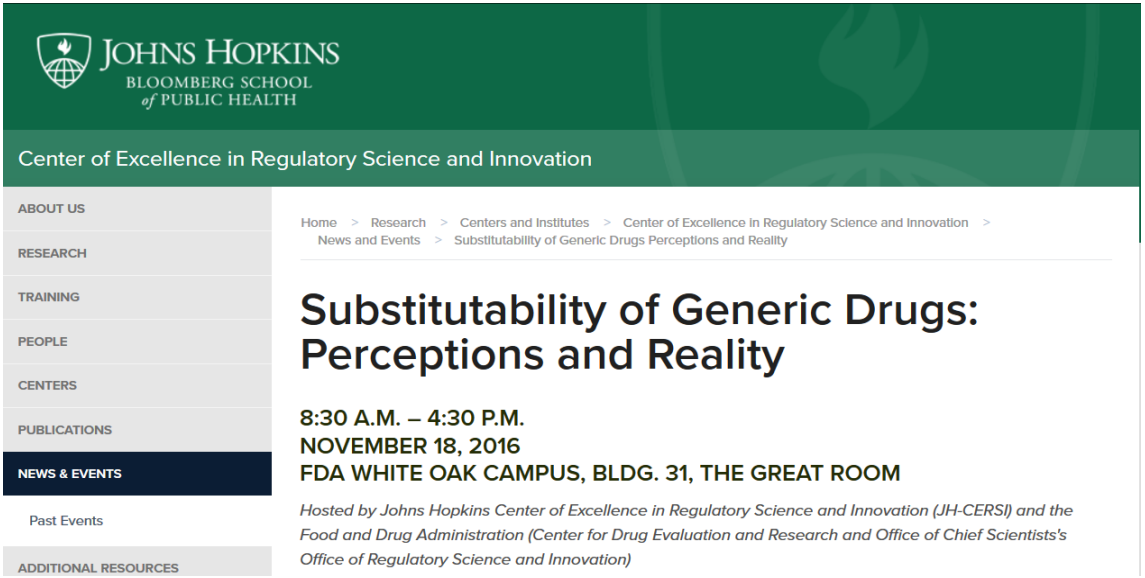
1:00-1:30 p.m.
Dose Sensitivity Considerations for AEDs
James Cloyd, PharmD
Professor of Experimental and Clinical Pharmacology
University of Minnesota College of Pharmacy

1:30-2:00 p.m.
Industrial Perspective: NTI Considerations in Ongoing Product Quality
Jack Cook, PhD
Vice President, Clinical Pharmacology Specialty Care
Pfizer, Inc.

2:00-2:30 p.m.
Extrapolating Efficacy of AEDs from Adults to Pediatrics: An Ongoing Critical Path Project
Angela Men, MD, PhD
Clinical Pharmacology Team Leader for Neurology Products
Food and Drug Administration

2:30-2:45 p.m.
Break

2:45-3:15 p.m.
Modified Release AED Generic Standards
Gregory Krauss, MD



Welcome and Introduction
Robert M. Califf, M.D., MACC
Commissioner
Food and Drug Administration (FDA)

Closing remarks
Caleb Alexander, M.D., M.P.H.
Johns Hopkins University

Session 3: Generic Substitution Studies in Patients [Recording]

Moderator: Jodi Segal, M.D., M.P.H.
Johns Hopkins University

Bioequivalence in Epilepsy Patients and Assessment of Generic Brittleness
Jim Polli, Ph.D.
University of Maryland School of Pharmacy, Baltimore

Tricia Ting, M.D.
University of Maryland Medical Center, Baltimore
Slides

Pharmacokinetic Studies of Epileptic Drugs in Patients [EQUIGEN], Multiple-dose Studies and Single Dose Studies
Timothy Welty, Pharm.D.
Drake University
Slides

Clinical Neurology News

CONFERENCE COVERAGE

AES: Three studies show generic lamotrigine equals Lamictal

Publish date: December 18, 2015

By Mitchel L. Zoler; Clinical Neurology News

AT AES 2015

PHILADELPHIA – Several different generic lamotrigine products proved pharmacologically and clinically equivalent to Lamictal <http://www.drugs.com/lamictal.html> , the brand-name, reference form of lamotrigine, in three separate, prospective, randomized trials run by two independent groups. These results that should lay to rest lingering concerns by physicians and patients that generic lamotrigine poses any risk to patients, agreed a panel of experts speaking at a session at the annual meeting of the American Epilepsy Society.

FDA

September 22, 2017

Impact Story: Addressing Concerns About the Quality of Generic Drugs for Treating Epilepsy

Back to Regulatory Science In Action (/drugs/science-research-drugs/regulatory-science-action)

When concerns arose in the medical community that generic versions of drugs used to treat epilepsy were not as effective as the brand name versions, FDA conducted groundbreaking clinical trials to address this issue.

The Scientific Challenge

Learn More

FDA-initiated research facilitates the availability of high-quality, affordable generic drug products. (/drugs/science-research-drugs/impact-story-overcoming-challenges-evaluating-bioequivalence-complex-drugs)

Overview and basics (/drugs/generic-drugs/overview-basics) related to the Generic Drugs Program at FDA

https://www.fda.gov/drugs/science-research-drugs/impact-story-addressing-concerns-about-quality-generic-drugs-treating-epilepsy

FDA Town Hall Update
Generic Antiepileptic Drug Bioequivalence in Epilepsy Patients: From Anecdotes to Evidence

AES Position on the Substitution of Different Formulations of Antiepileptic Drugs for the Treatment of Epilepsy

There is equipoise about the therapeutic equivalence of the various formulations of Antiepileptic Drugs (AEDs) when used to treat people with epilepsy. The U.S. Food and Drug Administration (U.S. FDA) states that the current regulations guarantee that the approved AED formulations of each specific AED can be used interchangeably without concern for safety or efficacy and that no additional testing is needed when formulations of the same AED are interchanged. However, physicians and patients, in several surveys including one performed of AES members in 2007, express a majority opinion that the various formulations of the same AED are not always therapeutically equivalent in every patient. Positions taken by several organizations including the American Academy of Neurology, the Epilepsy Foundation and the International League Against Epilepsy (French Chapter) reflect this equipoise and advocate for physician and patient consent prior to switching formulations. The AES recognizes that controlled, prospective data on therapeutic equivalence of different AED formulations in people with epilepsy is not available because appropriate studies have not been conducted.

The American Epilepsy Society offers its support of the following principles concerning the continuity of Antiepileptic Drugs for adults and children with epilepsy:

- The American Epilepsy Society supports the development and completion of a valid controlled, prospective clinical trial, with protocol approval by the U.S. FDA, studying the impact of differences between the same AED formulations of different manufacturers. Until such data becomes available, the following positions are adopted:
- Physicians who treat people with epilepsy are skilled in choosing appropriate AEDs at appropriate dosages to reduce or eliminate seizures and avoid adverse effects. Physicians are trained to do this by using the best available scientific evidence in combination with clinical expertise. As such, the Society opposes formulation substitution of antiepileptic drugs for the treatment of epilepsy without physician and patient approval.

EPILEPSY CURRENTS

It's Current
Epilepsy Resources and Updates

AES Position Statement on Generic Substitution of Antiepileptic Drugs

David G. Vossler, MD, FAAN,[1*] Gail D. Anderson, PhD,[2] and Jacquelyn Bainbridge, PharmD[3]
[1]Department of Neurology, University of Washington, Seattle, and UW Medicine, Valley Medical Center, Renton, WA
[2]Department of Pharmacy, University of Washington, Seattle
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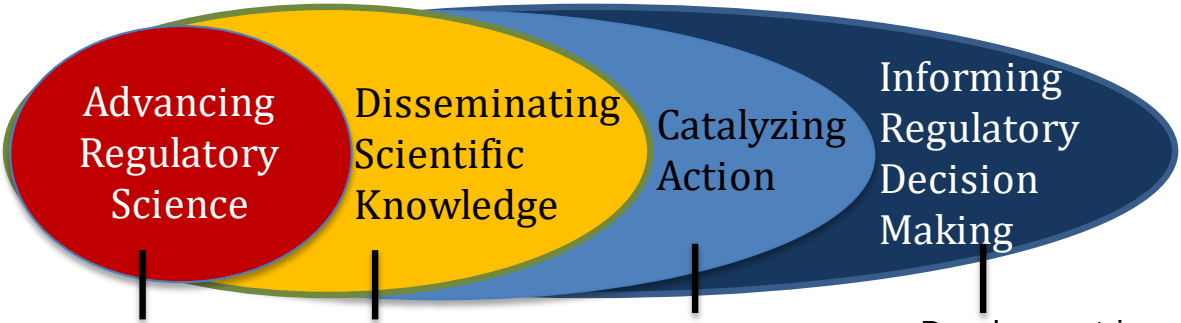
*Address correspondence to David G. Vossler, MD, Neuroscience Institute, UW Medicine | Valley Medical Center, 400 S. 43rd St., Renton, WA 98055. E-mail: david_vossler@valleymed.org

- The AES acknowledges that drug formulation substitution with FDA-approved generic products usually reduces cost, and does not compromise efficacy.
- The AES supports ongoing research by the FDA to study factors (e.g., extended-release products, tablet or capsule color and shape, nocebo effect) related to the generic substitution of AEDs in adults and children.
- When dispensing medications to patients, healthcare professionals should ensure that a bioequivalent FDA-approved generic product is substituted for the brand or another generic AED. For example, an immediate-release generic product should not be dispensed as a substitute for a delayed-release or an extended-release product.



Advancing Public Health

Enhancement of FDA expertise in addressing generic skepticism

Facilitation of strategic relationships with epilepsy community

Presentations at American Epilepsy Society and American Academy of Neurology Annual meetings

2 Public workshops

7 scientific publications

Media coverage

FDA Townhall topic at American Epilepsy Society Annual meetings

Position statement change about generic AEDs

Adoption of generic AED use in medical practice

Development in Surveillance strategies

Communication strategies

Confirmation of generic approval standards

Acknowledgements

BEEP Team
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- Tricia Ting

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University of Rochester
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- Jill Coker

FDA-University of Maryland CERSI

FDA- Johns Hopkins University CERSI