Bioequivalence in Epilepsy Patients and Assessment of Generic Brittleness

James E. Polli, PhD
Tricia Y. Ting, MD
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Disclosures: Tricia Ting, MD

FDA
HHSF223201010244A/HHSF223201400188C

Other
GW Pharmaceuticals, Epilepsy Study Consortium (Human Epilepsy Project), Acorda, Pfizer
Scenario

• Doctor Strange:
• Mr. Brad Generik called to report the following:
  – He will be switching insurance soon. The new insurance wants him to use lamotrigine rather than Brand Lamictal.
  – He reports that he has never used the generic and recalls you sending a request for exception.
  – Is it OK for him to use the generic?
• He can be reached at 911-9111
Learning Objectives:

• To summarize BioEquivalence in Epilepsy Patients (BEEP) study findings

• To summarize current findings from an on-going BEEP2 study of generic brittle patient characterization
Background: Public unrest

Are generic and brand-name medications ever really the same? Medical historian and physician Jeremy A. Greene tackles this question in his new book, *Generic: The Unbranding of Modern Medicine*. Greene traces the development of generic medications, from suspect substances to American healthcare mainstay. He also explains how the notion and measure of "sameness" have evolved since generic drugs were first introduced. (Read an excerpt from the book [here](#).)

Produced by Becky Fogel, Production Assistant

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**GUESTS**

**Jeremy A. Greene**
Author, *Generic: The Unbranding of Modern Medicine*
(Johns Hopkins University Press, 2014)
Associate Professor, Medicine and History of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

**RELATED LINKS**

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Are Genérics the Same As Brand Name Drugs?

...from suspect substances to American healthcare mainstay.
Compulsory Generic Switching of Antiepileptic Drugs: High Switchback Rates to Branded Compounds Compared with Other Drug Classes

*Frederick Andermann, †Mei Sheng Duh, ‡Antoine Gosselin, and ‡Pierre Emmanuel Paradis

*Montreal Neurological Institute and Hospital, McGill University, Montréal, Québec, Canada; †Analysis Group, Inc., Boston, Massachusetts, U.S.A.; and ‡Groupe d’Analyse, Ltée, Montréal, Québec, Canada
Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy

K. Liow, MD; G.L. Barkley, MD; J.R. Pollard, MD; C.L. Harden, MD; and C.W. Bazil, MD, PhD

The American Academy of Neurology (AAN), representing over 20,000 neurologists and neuroscience professionals, has taken an active interest in the clinical, ethical, and policy considerations concerning the coverage of anticonvulsant drugs for people with epilepsy. The AAN has developed evidence-based guidelines that strongly support complete physician autonomy in determining the appropriate use of anticonvulsants for the patients with epilepsy. Based on this evidence, the AAN has adopted the following principles concerning coverage of anticonvulsants for adults and children with epilepsy.

The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval. The Food and Drug Administration has allowed for significant differences between name-brand and generic drugs. This variation can be highly problematic for patients with epilepsy. Even minor differences in the composition of generic and name-brand anticonvulsant drugs for the treatment of epilepsy can result in breakthrough seizures.

- Anticonvulsant drugs for the treatment of epilepsy differ from other classes of drugs in several ways that make generic substitution problematic.
- For anticonvulsant drugs, small variations in concentrations between name brands and their generic equivalents can cause toxic effects and/or seizures when taken by patients with epilepsy.

- The AAN opposes all state and federal legislation that would impede the ability of physicians to determine which anticonvulsant drugs to prescribe for the treatment of patients with epilepsy.
- The AAN believes that formulary policies should recognize and should support complete physician autonomy in prescribing, and patients in accessing, the full range of anticonvulsants for epilepsy.
- The AAN opposes policies that would result in arbitrary switching among anticonvulsants. Therefore, the AAN opposes generic substitution of anticonvulsants for patients with epilepsy at the point of sale (e.g., in the pharmacy), without prior consent of the physician and the patient.
- The AAN supports legislation that would require informed consent of physicians and patients before generic substitutions of anticonvulsants are made at the point of sale.
- The AAN believes that the use of anticonvulsant drugs in the treatment of epilepsy should be distinguished from the use of anticonvulsant drugs in treating other disorders. The AAN recognizes that different strategies may be appropriate in using anticonvulsants for the treatment of conditions other than epilepsy.

Unlike other diseases, a single breakthrough
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.
Understanding the issue with generic AEDs: the BEEP studies

• Can approved generic AEDs be trusted?
  • Approval process
  • Relevance to patients with epilepsy

• Is the issue **drug quality**?

• Is the issue **drug bioavailability**?
  – Is there significant difference with generic switch?

• Is it the patient? “**generic-brittle**”
  – Perception (blame the generic)
  – Special cases (SxF interaction, excipient sensitivity, etc)
  – Nocebo effect
Pharmaceutical Quality Tests

• BIOPHARMACEUTIC RISK ASSESSMENT OF BRAND AND GENERIC LAMOTRIGINE TABLETS

Vaithianathan, Soundarya; Raman, Siddarth; Jiang, W; Ting, Tricia; Kane, Maureen; Polli, James

• All brand name and generic lamotrigine 100mg tablets passed all tests and showed acceptable pharmaceutical quality and low biopharmaceutic risk
# Excipients

<table>
<thead>
<tr>
<th>Lamictal</th>
<th>Teva lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamotrigine</td>
<td>lamotrigine</td>
</tr>
<tr>
<td>lactose</td>
<td>lactose monohydrate</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>magnesium stearate</td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
<td>microcrystalline cellulose</td>
</tr>
<tr>
<td>povidone</td>
<td>povidone</td>
</tr>
<tr>
<td>sodium starch glycolate</td>
<td>sodium starch glycolate</td>
</tr>
<tr>
<td>FD&amp;C yellow #6 (100mg), ferric</td>
<td>FD&amp;C yellow #6 (100mg), ferric</td>
</tr>
<tr>
<td>oxide yellow (150mg), and FD&amp;C</td>
<td>oxide yellow (150mg), and FD&amp;C</td>
</tr>
<tr>
<td>blue #2 aluminum lake (200mg)</td>
<td>blue #2 aluminum lake (200mg)</td>
</tr>
<tr>
<td>-</td>
<td>colloidal silicon dioxide;</td>
</tr>
<tr>
<td></td>
<td>pregelatinized starch</td>
</tr>
</tbody>
</table>
Bioequivalence in Epilepsy Patients (BEEP1) Study

BEEP Study
at University of Maryland

Generic vs BRAND lamotrigine bioequivalence in epilepsy patients:
a field test of the public bioequivalence standard
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

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 (Cmax), and minimum plasma concentration (Cmin) 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, Cmax, and Cmin 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 367 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.
BEEP study objectives
Bioequivalence in Epilepsy Patients (BEEP1) Study

• *Is bioequivalence the same in patients as in healthy volunteers?*

• **Primary objective**: To assess whether generic Teva lamotrigine tablets are *bioequivalent* to Lamictal

• **Secondary objective**: To assess incidence of seizure and (non-seizure) adverse effects on each formulation
Innovative Bioequivalence Study Design

• "Generic brittle" epilepsy patients and not healthy volunteers
  – Already taking lamotrigine BID for epilepsy
  – Evidence of (potential) sensitivity to switching
• Double-blind, multiple-dose, fully replicated design
  – Outpatient (e.g. self-dosing)
• Average bioequivalence
  (brand versus generic at steady-state)
BEEP Study: Brand-Generic AED

Bioequivalence in Epilepsy Patients 1 (BEEP1) Study

OUTPATIENTS

Randomization

Baseline compliance

8 wk 2 wk 2 wk 2 wk 2 wk

Generic Brand Generic Brand

12 hr PK 12 hr PK 12 hr PK 12 hr PK

Two levels to assure steady state

Single site at University of Maryland
Initiated 2010 - completed 2013
# Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Male N=20</th>
<th>Female N=15</th>
<th>N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age Range (Mean years)</strong></td>
<td>19-66 (44)</td>
<td>20-63 (39)</td>
<td>19-66 (42)</td>
</tr>
<tr>
<td><strong>Epilepsy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>17</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Generalized</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td><strong>AED concomitant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid (inhibitor)</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Inducer</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td><strong>Smoking (inducer)</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>One or more</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>
Average profiles

Cmax 90% CI: (98.8%, 104.5%) with ratio = 101.6%
AUC 90% CI: (97.2%, 101.6%) with ratio = 99.4%
## NTI Drug BE Evaluation

<table>
<thead>
<tr>
<th>Computed reference-scaled ABE confidence interval limits</th>
<th>Observed WSV of generic</th>
<th>Observed WSV of brand</th>
<th>Observed ratio of WSV</th>
<th>Observed confidence interval for ratio of WSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>93.65-106.78%</td>
<td>8.26%</td>
<td>6.38%</td>
<td>1.29</td>
<td>0.96-1.74</td>
</tr>
<tr>
<td>91.85-108.88%</td>
<td>11.38%</td>
<td>8.27%</td>
<td>1.38</td>
<td>1.02-1.85</td>
</tr>
<tr>
<td>90.80-110.14%</td>
<td>13.55%</td>
<td>9.39%</td>
<td>1.44</td>
<td>1.08-1.94</td>
</tr>
</tbody>
</table>
Individual subject PK ratios:
Cmax and AUC ratios of generic vs brand
Individual subject PK ratios:
Individual AUC ratios for each generic and brand
Individual subject PK ratios:
Individual Cmax ratios for each generic and brand
Special Cases in BEEP1

Subject 026

Subject 024
Brand and generic was essentially identical in subject 026, although subject experienced 19, 93, 40, and 115 focal motor seizures during period 1 brand, period 2 generic, period 3 brand, and period 4 generic, respectively.
### Secondary outcomes: Seizure frequency

<table>
<thead>
<tr>
<th></th>
<th>Number of seizures on brand [AUC]</th>
<th>Number of seizures on generic [AUC]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total seizures in ITT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=35)</td>
<td>108</td>
<td>262</td>
</tr>
<tr>
<td><strong>Subject 026</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 1</td>
<td>59</td>
<td>208</td>
</tr>
<tr>
<td></td>
<td>19 [99,317 ng/ml hr]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>93 [99,673 ng/ml hr]</td>
<td></td>
</tr>
<tr>
<td>Period 2</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[98,613 ng/ml hr]</td>
<td></td>
</tr>
<tr>
<td>Period 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total seizures in ITT</strong></td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>without subject 026</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=34)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BEEP Subject 026

- Subject 026 had 267 seizures (19, **93G**, 40, **115G**)
- PK profiles of 026 for generic and brand *practically identical*
- Small difference (~3%), but generic provided both highest and lowest AUC in periods 2 and 4, respectively
- Increased seizure frequency with generic *did not correlate with LTG exposure.*
- 026 had no other AEs during the study
- Reason other than lack of BE as cause for seizures?
  - 026 theorized that increased seizure frequency may have been due to increased physical activity
BEEP1 Conclusions

• Passed conventional BE (Bioequivalence)
  – validating testing in healthy volunteers
  – passed scaled BE for NTI drugs

• BEEP Study: Unique design
  – Randomized, double-blind, multiple-dose, steady-state, fully replicated BE study in “generic-brittle” epilepsy patients
  – First to demonstrate feasibility of performing BE evaluations in epilepsy patients
  – First to assess BE in “generic brittle” patients
BEEP1 Conclusions

• Lamictal and Teva generic lamotrigine tablets are bioequivalent in epilepsy patients.
  – Supports healthy volunteer results (current standard)

• As may be noted in clinical practice, individual patient circumstances were observed, although are not attributed to product quality issues or bioinequivalence.
Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial

Prof Michael D Privitera, MD✉, Prof Timothy E Welty, PharmD, Prof Barry E Gidal, PharmD, Francisco J Diaz, PhD, Ron Krebill, MPH, Prof Jerzy P Szafarski, MD, Barbara A Dworetzky, MD, John R Pollard, MD, Prof Edmund J Elder Jr, PhD, Wenlei Jiang, PhD, Xiaohui Jiang, PhD, Michel Berg, MD

Published: 11 February 2016
The results of these two BE studies, done in patients with epilepsy under clinical conditions, support the validity of the FDA BE standards. As a consequence, the board of directors of the AES has approved a new position statement (Appendix) regarding generic switching of AEDs.
What about “Mrs. Jones”? What about “outliers”?

Subject 026?

http://thecanberran.com/2012/11/16/me-mrs-jones/
“Generic brittleness” (GB) concerns the familiar notion of individual patient sensitivity to generics.

The objective was to identify causes and predictors of GB:

- **Working definition of GB**
- **Frequency** of generic brittleness (GB) in epilepsy patients at a tertiary care center.
- **Factors** associated with GB.
- **Test GB criteria** with generic-brand AED product switch in a subsequent PK study.
BEEP2: Basis of Generic Brittleness

Natural Fluctuation
Regression to the mean

Perception

Physiologic

Psychological

Clinical factors
Genetic
Subject-by-formulation interaction

Nocebo
Expectation
Biased opinion

Named by *Fortune* ONE OF THE SMARTEST BOOKS OF ALL TIME

*FOOLED BY RANDOMNESS*

The Hidden Role of Chance in Life and in the Markets
What defines a GB patient?

History of switch problem

Taking Brand or Generic?

Opinion against generic

Having Seizures or AEs?
“Classic GB” vs “Classic Not GB” working definitions

• Classic GB
  – History of problem with formulation
  – Ongoing seizures or AE problem
  – Opinion generics problematic
  – Taking brand

• Classic Not GB
  – No history of switch problem
  – No seizures or AEs
  – Opinion generics not problematic
  – Taking generic
BEEP2 methods to characterize GB

- Single center U MD outpatient epilepsy clinic
- Adult epilepsy patients
- Consented for history, blood draw and neuropsych testing
- Analysis of associated factors based on GB classification (GB vs Not GB)
BEEP2 study GB factors

- Demographic and clinical
- Physiologic markers
- Neuropsychological profile
- Genetic testing

GB Patients selected for individual PK testing
BEEP2: Testing the Definition with Individual PK testing

Patients will be switched on one of their own brand vs generic AED
Secondary clinical outcome measures of Szs and AEs
Results

• **N=148** patients completed. N=60 subjects were GB (40.5%), with n=88 were not GB (59.5%).

• A vast majority had **focal epilepsy**. There were about equal numbers of men and women and about equal racial distribution between white and African American subjects.

• Factors **did not anticipate GB**: sex, age, race, type of epilepsy, number of AEDs, number of problem AEDs, presence of an AED allergy, previous epilepsy surgery, number of co-morbidities, and number of auto-immune co-morbidities
Percentages of GB and Not GB subjects: Number of comorbidities
Percentages of GB and Not GB subjects: Number of medications
Number of Subjects taking Brand or Generic AEDs Currently.

<table>
<thead>
<tr>
<th>Currently Taking Brand/ Generic AED</th>
<th>GB Subjects (N=60)</th>
<th>Not GB Subjects (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Generic</td>
<td>31</td>
<td>86</td>
</tr>
</tbody>
</table>
Conclusion

• **Frequency**: About 40% of epilepsy patients in this sample at a tertiary care center were found to be generic brittle.

• **Factors** that did not explain which subjects were GB or not GB: sex, age, race, type of epilepsy, number of AEDs, number of problem AEDs, presence of an AED allergy, previous epilepsy surgery, number of co-morbidities, number of auto-immune co-morbidities, and total number of medications.

• Patients who took brand name AEDs had a propensity to be more GB than patients who took generic AEDs currently.
BEEP 2
Characterization of GB Epilepsy Patients ("BEEP2") Study

Supported by FDA HHSF223201400188C
Thanks to Wenlei Jiang, Xiaohui Jiang, Xia Pu,
Sharmila Das

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