Generic Antiepileptic Drugs: Fact and Fiction
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Disclosure

Commercial Interests
Lilly, Upsher Smith
UCB, Neuren, Eisai

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Learning Objectives

• State the main characteristics of current FDA regulations for approval of generic AED products
• State the main strengths and weaknesses of database studies of generic AED products
• Know that rigorous blood level sampling is critical to assess bioequivalence and performance of generic AED products
Background on the Controversy

- Every day several million tablets of generic AEDs are taken by people with epilepsy.
- Generic drugs can be an important weapon to combat health care costs.
  - FDA estimated $56.7 billion per year saved in 2002 by generic substitution.
- Advocacy groups: indiscriminate generic substitution in people with epilepsy can cause problems because FDA rules allow too much variability across formulations.
- FDA: it has no reliable documentation of generics causing problems and formulations are interchangeable without additional testing.
The AAN:
- Opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician’s approval
- For anticonvulsant drugs, small variations in concentrations between name brands and their generic equivalents can cause toxic effects and/or seizures when taken by patents with epilepsy (…evidence?)

Liow et al, Neurology 2007
US Senate:
- 2009 Appropriations Committee- Report 111-39
- FDA must report to Congress how it is funding studies to resolve questions of AED generic equivalence

For Epilepsy Community: *It is good to have friends in high places*...
Be Careful Which Term You Use

- **Bioequivalence** = pharmacokinetic parameters Cmax and AUC fall within a specified range. Usually compares the brand (reference) to a single generic.

- **Therapeutic equivalence** = two products provide equal seizure control and tolerability. Rarely tested, but inferred by bioequivalence.

- **Switchability** = there is no change in therapeutic effect when one product is switched for another. For example, indiscriminate switching among any of the approved generic products.
FDA Requires Rigorous Bioequivalence Testing

- Area under the plasma concentration time curve (AUC) and maximum concentration (Cmax) measured
- Typically 24-36 *healthy adults, single dose*
  - Subjects do not have epilepsy
  - Subjects are not taking concomitant meds or have comorbid conditions common in patients with epilepsy
- Equivalence: 90% CI of the ratio of the generic to reference compound for both AUC and Cmax fall within 80-125% range
- However: FDA analyzed 2000 BE studies pre-1997 and mean difference Cmax = 4.35% and AUC = 3.56%
*for multiple dosing, Cmin variations may have a clinical effect
FDA Sets “Goalposts” for Generics at 80-125%
BASELINE VS. SWITCHED PRODUCT COMPARISON (90% CI)

A. BRAND

B. EQUIVALENT

C. INEQUIVALENT: NOT APPROVED

D. INDETERMINATE: NOT APPROVED
<table>
<thead>
<tr>
<th></th>
<th>AUC CI</th>
<th>CMAX CI</th>
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<tbody>
<tr>
<td>Theoretical Low</td>
<td>83-90</td>
<td></td>
</tr>
<tr>
<td>Low Generic 1</td>
<td>95.48-101.43</td>
<td>93.81-100.57</td>
</tr>
<tr>
<td>Low Generic 2</td>
<td>100.0-104.54</td>
<td>91.72-103.68</td>
</tr>
<tr>
<td>Theoretical High</td>
<td>105-122</td>
<td></td>
</tr>
<tr>
<td>High Generic 1</td>
<td>102.0-113.8</td>
<td>100.8-105.8</td>
</tr>
<tr>
<td>High Generic 2</td>
<td>97.79-107.97</td>
<td>98.71-107.86</td>
</tr>
</tbody>
</table>

**Generic Products for Testing Are Close to Reference**
Literature is Full of Retrospective Studies Highlighting Generic Risks

- Physician surveys- 50% of responders saw problems
- Case series follow up from survey-random blood levels (Berg 2008)
- Generic switches associated with high switchback rate and higher costs in Canada (Andermann 2007)
- Generic use associated with higher emergency services use (Zachry 2008)
- No effect of generic use on epilepsy related events (Devine 2010)
Switchbacks on AEDs Significantly Higher than Statin or SSRI

Depakene: 20.9%
Frisium (Clobazam): 20.5%
Lamictal: 12.9%
Zocor: 1.5%
Prozac: 2.9%
Caveats to Most Retrospective Studies

- Open label
  - Any problem with seizure control or adverse effects could have been attributed to generic, causing physician and patient to desire switchback, or visit emergency room
  - No control for stress, sleep deprivation, or adherence (compliance)
  - *Nocebo* effect (opposite of placebo) where an inactive treatment causes negative outcomes

- No rigorous blood levels of AEDs
- No rigorous assessment of seizure frequency
- So... evidence is sparse and equipoise exists
Generic Carbamazepine Products May Show Large Variations

- Five generic CBZ formulation-FDA-approval packets were assessed, using the Freedom of Information Act
- The AUC & Cmax of three generics were accurate copies of Tegretol®
- For two generics, the mean AUC & $C_{max}$ values were near the acceptance range of Tegretol®
- Switches between two generic CBZ formulations produced AUC variations up to 21% & Cmax variations up to 40%

Krauss et al., Ann Neurology, August 2011
Summary of Generic Background Issues

- **Criticisms of FDA testing**
  - Not on people with epilepsy
  - Single dose
  - No concomitant meds
  - No seizure or adverse event outcomes
  - Same rules for any drug—ignores narrow therapeutic index drug differences. FDA advisory committee suggests changing this and definition is forthcoming

- **Criticisms of Anti-generic literature**
  - Uncontrolled
  - Retrospective
  - No rigorous blood levels
What study design can assess the risk of generic substitution?

- First choose the “most disparate” generic products for LTG using the ANDA data plus dissolution characteristics.
- Study 1. Chronic dosing in people with epilepsy, taking LTG comparing “high range” generic vs. “low range” generic.
- Study 2. Single dose study, people with epilepsy, not taking LTG of “high range” generic vs. “low range” generic vs. brand.
- Study 3. Chronic dosing in people with epilepsy taking LTG comparing brand vs. single generic.
EQUIGEN-Chronic Dose Study

MEMS Baseline compliance

randomization

Two levels to assure steady state
randomization

EQUIGEN-single dose STUDY

96 hr PK

Brand 1 dose

High Generic 1 dose

2 wk

washout

96 hr PK

Low Generic 1 dose

2 wk

washout

96 hr PK

Brand 1 dose

2 wk

washout

96 hr PK

Low Generic 1 dose

2 wk

washout

96 hr PK

High Generic 1 dose

2 wk

washout

FINAL PROTOCOL
EQUIGEN Study Group

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BEEP Study Design

- **Patients** not healthy volunteers
- **Clinical use setting**
- **Compliance issue**
  - Nocebo effect concern
- **Blinding** study drugs by **Overencapsulation**
  - In vitro dissolution testing

James Polli, Pharm D
Tricia Ting, MD
University of Maryland
BEEP STUDY: Brand-Generic AED

Randomization

2 wk

Baseline compliance

2 wk

12 hr PK

2 wk

Generic

12 hr PK

2 wk

Brand

12 hr PK

2 wk

Generic

12 hr PK

2 wk

Brand

Three levels to assure steady state

ONGOING PROTOCOL
Generic Drugs: Conclusions

- Indirect evidence that product switches with antiepileptic drugs are associated with more problems
- No prospective, adequately designed studies support this
- Three studies are planned: two chronic dosing and one single dose in people with epilepsy taking concomitant AEDs
My Suggestions for Your Patients

- Discuss with patients the option of generic substitution and encourage them to research the cost difference.
- Identify higher risk groups: pregnant, history of status epilepticus, seizure free and driving.
- Counsel patients about unauthorized formulation substitution. If the pills look different, call us.
- Use the opportunity to counsel patients on compliance/adherence and avoid triggers (alcohol, sleep deprivation).
- Help support the proposed studies.
Annual Fundamentals
Optimal Use of the Newest AEDs and Generics
November 30, 2012

Discussion & Conclusions
Impact on Clinical Care and Practice

• Many new AEDs have been approved in the past several years with new mechanisms of action that should be considered when prescribing. The role of potassium channels is intriguing.
• Pharmacokinetics and drug interactions of the newest AEDs do not present major obstacles.
• Newest AEDs have indications for medication resistant partial seizures or Lennox Gastaut Syndrome
• Evidence is accumulating for use of newest AEDs in pediatrics, status epilepticus and idiopathic generalized epilepsy
• Generic drugs are here to stay and several ongoing studies will add new evidence to help determine optimal use, especially with generic to generic switches.
Thank you!