The controversy over Generic Antiepileptic drugs

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Background
• Generic drugs turned into flashpoint for physicians, patient groups, public, and U.S. FDA
• In 2002, FDA estimated generic drug substitution saved American public $56.7 billion per year and each 1% increase in generic drug use could save additional $1.32 billion per year
• Professional and patient support organizations around world concerned about patient safety with indiscriminate generic formulation substitution and have issued statements
  ▶ Opposing replacement of prescription drugs without physician’s approval—in particular, stating that generic drug variability can be highly problematic for people with epilepsy

The U.S. Food and Drug Administration’s Position on Generic Drugs
• FDA asserts that methods used to approve generic formulations are sufficiently rigorous
• Patients and health-care providers can expect that generic equivalents will provide same therapeutic effect as brand-name drugs
• Furthermore, FDA’s contention that switches can be made between brand and generic or among generic formulations without concern about loss of therapeutic effect or enhanced toxicity and no additional testing of patients who undergo such formulation switches is necessary

The U.S. Food and Drug Administration’s Position on Generic Drugs
• These recommendations hold true for all therapeutic categories, whether the compound is used to treat a minor infection or life-threatening illnesses, such as
  ▶ Cardiac arrhythmia
  ▶ Immune suppression for organ transplantation
  ▶ Seizures
• The recommendations also apply to drugs considered to have “narrow therapeutic index” for which gap between therapeutic and toxic dose is small

FDA: BIOEQUIVALENCE STANDARDS
• According FDA Approved Drug Products with Therapeutic Equivalence Evaluations “pharmaceutical equivalent” is drug product has same active ingredient(s), strength, dosage form, route of administration, and concentration as reference drug (usually brandname)
• Allowable differences include shape, scoring configuration, release mechanisms, packaging, excipients (including color, flavors, and preservatives), expiration time,
• In turn, “bioequivalent drug products” defined as pharmaceutical equivalents display comparable bioavailability when studied under similar experimental conditions
FDA: BIOEQUIVALENCE STANDARDS

• A “therapeutic equivalent” expected to have the same clinical effect and safety profile when administered under labeled specifications

• Generic drugs do not need to be shown to be therapeutically equivalent; compounds that meet the bioequivalence criteria assumed to be therapeutically equivalent and typically approved

• In vivo Experiments—Average Bioequivalence

  • FDA average bioequivalence standards assess generic drug “performance,” in which rapidity and extent of absorption of the generic formulation must be similar to reference (usually brand name) drug

  • Small crossover studies conducted in which single doses of test generic formulations compared with brandname drug in 24 to 36 adult volunteers who do not have disease of interest

  • Blood concentrations of test and brand name drugs measured repeatedly, and the Cmax and AUC established

Controversy over adequacy of FDA standards

• FDA’s assurances that these bioequivalence standards ensure that generic and brand name formulations would be nearly identical,

• Many patients and health care providers concerned that significant differences may exist

• Most of concerns fall into two broad categories:
  • These standards allow too much variability
  • These standards generalizable to all clinical scenarios

Variability

• The bioequivalence standards inherently allow certain amount of variability since the target pharmacokinetic values lie within a range.

• In addition, generic formulations allowed to be non-identical to brand name drug, as confidence intervals are not required to cross a point where their ratio

• Switched to formulations would be expected to receive a considerably increased or reduced amount of drug compared to brand name

• Bioequivalence standards do not restrict the intra-variability of formulation
**Variability**

- FDA's Office of Generic Drugs conducted two internal studies to assess bioavailability differences between approved generic formulations and their brand name drugs.
- From 1985 to 1986, 224 approved bioequivalence studies had a 3.5% mean AUC difference between brand and generic.
- Of studies submitted in 1997, AUC difference was 3.5% and for Cmax was 4.29%.
- However, 13 of 224 (6%) generic formulations had mean AUC differences of 10% or more from the brand.

**Burkhardt et al.**, described eight patients with seizure increase and an approximate 30% decrease in total and free phenytoin concentrations after switching to generic phenytoin.

**Concentrations returned to baseline after switching back to the brand name formulation.**

**Generic-Generic Switches—Are They Equivalent?**

- Further variability in drug concentrations is allowed by the bioequivalence standards because generic drugs are tested against brand name drug but not against each other.
- Once switched to generic formulation, such generic-to-generic switching is highly likely as pharmacies often change their suppliers based on pricing.
- For most AEDs, a number of generic products available, increasing likelihood that variations will occur.

**Generic-Generic Switches—Are They Equivalent?**

- Current bioequivalence studies, performed with single doses, may not be representative of long-term dosing and drug accumulation, especially.
- If cytochrome P450 enzyme induction
- Drug-dependent elimination occurs.
- A randomized, double-blind crossover trial with chronic dosing by Oles et al. found no differences in average seizure frequencies when 40 subjects took brand name carbamazepine for 90 days compared with 90 days of generic formulation.
- However, a decrease of 30% differences in AUC levels and overall time to peak earlier with generic formulation, in pharmacokinetic studies performed 2 weeks after start of each formulation.

**Generalizability**

- Generalizability of current bioequivalence studies is limited due to single-dose studies performed in healthy volunteers. Bioavailability may differ in patients with epilepsy, as well as those with concomitant diseases.
- Variations may occur across different formulations and patient populations.

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Clinicians Question Whether AED Therapeutic Equivalence Actually Exists

- Many health-care providers, patient support organizations, and professional organizations believe that:
  - People with epilepsy have an unacceptable incidence of seizures or side effects when switching to generic formulations
  - Walker reported on survey results from 301 responding neurologists:
    - 68% reported breakthrough seizure
    - 56% reported increased side effects after a switch from a brand name to a generic AED

Clinicians Question Whether AED Therapeutic Equivalence Actually Exists

- An electronic survey with 480 responding physicians in Germany, Austria, and Switzerland (23.6% response rate) found:
  - 49% reported problems when switching from a brand to a generic AED
  - Survey data do not provide evidence for generic failure, but rather document rough estimates of physician concern
  - Case reports document problems related to generic AED substitution in individual patients
  - Jain et al. reported 16 out of 133 cases of carbamazepine failure reported associated with seizure increases occurring with switching to generic formulation and seizure control returned to baseline when the brand formulation was reinstated

Clinicians Question Whether AED Therapeutic Equivalence Actually Exists

- More indirect evidence of generic formulation inequivalence reported for large numbers of patients who had brand-name products substituted for generic formulations:
  - An electronic survey with 301 responding neurologists: switching for people with epilepsy receiving lamotrigine after the Canadian health system urged providers to switch to generic formulations of lamotrigine citrate, sodium valproate, and two antidepressants fluoxetine and clomipramine.
  - Among 1,354 patients prescribed generic lamotrigine:
    - 98% switched back to the branded name
    - 98% continued to use the medication
    - In the switch group, seizure control only 1.3-2.0%

Clinicians Question Whether AED Therapeutic Equivalence Actually Exists

- Significant increases in lamotrigine doses observed among those who did not switch back to brand formulation
- The primary criticism of Andermann et al. study is nonrandomized and unblinded methods used, which could allow substantial contribution of physician and patient bias against generics to potentially influence outcome.
- However, it is unclear why such bias more influence in people with epilepsy as compared to those with depression or hyperlipidemia

Clinicians Question Whether AED Therapeutic Equivalence Actually Exists

- Subtle differences in pharmacokinetic parameters between two formulations could produce clinically important differences:
  - Adverse effects
  - Absorption
  - Metabolism
  - Elimination
  - Fisher et al. reported subjects who received extended-release formulation of carbamazepine in an open-label trial had significantly lower scores on an inventory of adverse effects as well as an improved quality of life

Clinicians Question Whether AED Therapeutic Equivalence Actually Exists

- Oling et al. compared pharmacokinetic parameters and side effects among three generic carbamazepine formulations approved in the Netherlands with a brand formulation:
  - The occurrence of side effects, especially dizziness, associated with differences in absorption rates of products
  - Mayer et al. compared patients who received a generic extended-release carbamazepine formulation with patients taking a brand formulation in an unblinded trial and found:
    - 9 of 13 subjects experienced adverse effects on the generic formulation, with AUC fluctuations that were acceptable within current FDA guidelines
    - Mayer et al. also reported a single subject who experienced carbamazepine adverse effects with an increase in Crm of less than 10%
Clinicians Question Whether AED Therapeutic Equivalence Actually Exists

- Concentration changes capable of producing adverse clinical symptoms likely to depend on plasma concentration range
- For example, patient who experiences 10% increase in Cmax with formulation change more likely to experience adverse effects if initial concentration is 12 mg/mL as compared with patient whose initial concentration is 6 mg/mL.

Potential Factors Contributing to the Lack of AED Therapeutic Equivalence

- Health care providers and patients concerned because even a single seizure could have on quality of life
- People with well-controlled epilepsy may be most vulnerable
  - A single seizure could jeopardize driving privileges or work
  - A person who has not had seizure in several years may be more likely to be engaged in potentially dangerous activities (e.g., driving) when seizure occurs.

Potential Factors Contributing to the Lack of AED Therapeutic Equivalence

- If there are truly bioequivalence and therapeutic equivalence among branded and approved generic formulations
- Why would health care providers and patients be reporting so many problems?
  - A nocebo effect (i.e., negative symptoms from an inert treatment) involving generic substitutions might be involved
  - If patients warned by caregivers or via other medical information sources that generic formulations may be less effective than brand-name product, patients may experience adverse effects.

Potential Factors Contributing to the Lack of AED Therapeutic Equivalence

- If generic AED formulations sometimes not bioequivalent to the brand or other generic formulations, might there be subgroups of epileptic patients more at risk?
- Drug–drug interactions, especially interactions that trigger induction of AED metabolism, could be cause of bio-inequivalence.

Potential Factors Contributing to the Lack of AED Therapeutic Equivalence

- A recent study compared a lamotrigine immediate-release formulation to an extended-release formulation
  - AUCs equal for subjects not receiving concomitant medication that induces hepatic enzyme
  - However, AUCs were 20% lower with extended-release formulation
  - Cmax lower for all subjects with extended release compared with the immediate-release formulation
Potential Factors Contributing to the Lack of AED Therapeutic Equivalence

- Possibly that people with epilepsy who receive enzyme-inducing medications may be more likely to show bio-inequivalence with generic formulation substitution.
- This is a concern because many people with epilepsy taking multiple AEDs, and incidence of concomitant medications for comorbid conditions, like depression, is high.

Looking Forward: Research Needed on Brand and Generic AED Formulations

- Studies needed to determine whether many complaints about
  - Seizures and side effects associated with generic AED formulations are due to bio-inequivalence
  - Therapeutic inequivalence
  - Other factors (e.g., placebo/nocebo effects, stress, presence of concomitant illness, or progression of underlying neurological brain)

Looking Forward: Research Needed on Brand and Generic AED Formulations

- First step is to assess whether problems occurring after generic AED formulations switches related to bio-inequivalence between formulations,
- Such a study might use an enriched population of people with epilepsy who experienced either an increase in seizure frequency or unexpected adverse effects following initiation of a generic AED formulation.
- Study participants might undergo a single-dose pharmacokinetic trial that involved taking each of the exact same formulations.
- Any concomitant medications and their dosages need to be kept stable.

Looking Forward: Research Needed on Brand and Generic AED Formulations

- Further studies to identify patient subgroups or specific factors that may increase risk of bio-inequivalence with generic formulation substitution be valuable.
- If none of subjects shows Cmax or AUC falling outside FDA guidelines, then other causes of many complaints by health-care providers and patients could be evaluated in a randomized, controlled trial designed to test therapeutic equivalence with additional outcomes of adverse effects and seizure frequency.

Looking Forward: Research Needed on Brand and Generic AED Formulations

- Investigators could collect data on adverse effects and seizure frequency,
- However, primary outcome would be comparison of pharmacokinetic parameters (i.e., Cmax and AUC)
- If a substantial number of subjects have Cmax or AUC outside the ranges mandated by the FDA, then FDA might reconsider its current policy.
Looking Forward: Research Needed on Brand and Generic AED Formulations
• Such a study might determine that some people with epilepsy experience seizures or adverse effects with small variations in plasma concentration currently allowed by the FDA
• The American Epilepsy Society statement on AED formulations generally supports research

Generic Antiepileptic Drugs and Associated Medical Resource Utilization in the United States

- To evaluate whether generic substitution associated with any difference in medical resource utilization for 5 widely used antiepileptic drugs (AEDs) in U.S.A.
- METHODS: Health insurance claims from PharMetrics Database, representing over 90 health plans between January 2000 and October 2007 analyzed.
- Adult patients with epilepsy, continuously treated with carbamazepine, gabapentin, phenytoin, primidone, or zonisamide, selected
- An open cohort design used to classify patients into mutually exclusive periods of brand vs. generic use of AEDs
- Pharmacy and medical utilization compared between 2 periods with multivariate regression analyses
- Results stratified into epilepsy-related medical services, and stable (≥ 2 outpatient visits per year and no emergency room visit) vs unstable epilepsy. Time-to-event analysis performed

Objective
• It was to identify potential problems arising from the generic substitution of AEDs by systematic review
  • Pharmacokinetic parameters
  • Desired outcomes
  • Recommendation

Method – Systemic Review

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1980–April 2015
Method

Method

Results

Hypothesis of risk arising due to the generic substitution of AEDs

Pharmacokinetics characteristics of AEDs

• Therapeutic dose of almost all AEDs vary across patients → Individualised dose is needed

• Narrow therapeutic index of AEDs results in doctors to continuously monitor the plasma level of these drugs
Wide ranging bioequivalence criteria

- **Therapeutic equivalence**
  - Acceptance range for bioequivalence
    - General: AUC, Cmax 80–125%
  - Narrow therapeutic: 90–111,11%

- The frequency change in the supply source of medicine

High-risk patient groups

- **High risk patients**
  - Pregnant women
  - Patients with multiple disorders being treated with several drugs
  - History of medication

- **High risk diseases**
  - Chronic disease
  - Disease aggravated after the administration of drugs prescribed for comorbid condition

- **High risk drugs**
  - Rare therapeutic, side drug
  - Drug requiring individualization of dose
  - Drugs with severe drug-drug interaction
  - Drugs with the complex therapeutic regimen
  - Drugs altering the preceding outcome

Use of Generic Medicines in the Treatment of Epilepsy Using Topiramate as an Example

- Quantitative analysis of causes of termination of pharmaceutical remission lasting > 1 year in 220 adult patients with epilepsy

- Most frequent cause of loss of seizure control was switching from original medicine to generic analog (60.4%)
  - 28.2% switched to generic topiramate

- Topamax were increased in 58.0%, 60.0% of patients transferred from monotherapy to polytherapy, and seizure control achieved in only 32.9% of patients

Use of Generic Medicines in the Treatment of Epilepsy Using Topiramate as an Example

- Comparative analysis switching of 160 patients from original topiramate (Topamax) to its generics, control group consisted of 52 patients continuing original formulation

- Switching led to loss of remission in 75.6% of patients, with
  - Status epilepticus 3.75%
  - Emergency care or hospitalization 51.9%
  - Switching back to original formulation performed in 86.2% of patients
  - Topamax were increased in 58.0%, 60.0% of patients transferred from monotherapy to polytherapy, and seizure control achieved in only 32.9% of patients

Take home message

- Until such studies completed, health-care providers and people with epilepsy would do well to proceed cautiously when switching to generic formulations with
  - Health-care providers communicating to patients potential risks
  - Benefits of substitution

- Extra caution may be needed for patients at highest risk of seizure complications, such as
  - Pregnant patient
  - Patients with recurrent status epilepticus
  - Patients who have been seizure-free for long periods of time and driving
Take home message

• Advise patients to adhere to AED schedules and timing, avoid seizure triggers (such as alcohol or sleep deprivation), and report to health-care providers any changes in concomitant medication.

• The American Epilepsy Society’s position that formulation substitution should not take place without the physician and patient approval supports this practice.