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Factors associated with poor seizure control and increased side effects after switching to generic antiepileptic drugs

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Summary
Objective: To determine those factors associated with increased seizures and side effects after switching from brand name to generic antiepileptic drugs (AEDs).
Methods: We surveyed adult epilepsy patients and obtained demographic, clinical, and psychosocial data. We inquired whether they switched from brand name to generic AEDs, and whether they experienced poorer seizure control and increased side effects. Using univariate analysis, we determined those variables significantly associated with increased seizures and side effects. We applied binary logistic regression to determine those independently associated with these target variables.
Results: One hundred and twenty-one subjects completed the questionnaire. Seventy-one switched to generic AEDs. Of these, 18 subjects (25.7%) reported increased seizure frequency. This was associated with high seizure count ($p = 0.03$) and scores on the Beliefs About Medicines-General (BMQ-G) questionnaire ($p = 0.04$). On multivariate analysis, these variables were not independently significant.

Fourteen subjects (20.6%) reported increased side effects. This was associated with being African-American ($p = 0.04$), and high scores on the BMQ-G ($p = 0.01$). On multivariate analysis, BMQ-G scores were independently associated with increased adverse effects.
Interpretation: High baseline seizure count is associated with increased seizure frequency while high BMQ-G scores are associated with increased seizure frequency and adverse effects when patients switch from brand name to generic AEDs.

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Introduction

Cost control is an important facet of modern health care delivery. Substituting brand name medications with cheaper generic alternatives is one means of reducing health care costs and the practice has now become widespread in the United States.

In theory, generic drugs should work similarly to their corresponding brand name equivalents. They must contain the same active ingredient and be available at the same dose and by the same route of administration. Manufacturers of generic drugs are required to demonstrate bioequivalence of their product with the original brand. The World Health Organization (WHO) recommends that ''the 90% confidence interval of the ratios between the pharmacokinetic parameters of generic and brand name equivalents must fall within the acceptance range of 80—125% AUC and Cmax'' (Kramer et al., 2007).

Despite this bioequivalence, many observational studies have indicated an increase in seizure occurrence (Welty et al., 1992; Berg et al., 2008a; Papsdorf et al., 2009) and adverse effects (Gilman et al., 1993; Brown et al., 1998) after switching to generic AEDs. Several authors have also reported an increased in switchback rates from generic to brand name AEDs (Andermann et al., 2007; LeLorier et al., 2008) as well as an increase in health resource utilization (Helmers et al., 2010; Labiner et al., 2010). A considerable number of physicians and patients continue to maintain an unfavorable attitude towards the use of generic AEDs (Berg et al., 2008b; McAuley et al., 2009).

These observational studies appear to contradict the findings of randomized clinical trials that have not identified any significant differences in seizure control when comparing brand name and generic AEDs, particularly phenytoin (Hodges et al., 1986; Kishore et al., 1986; Soryal and Richens, 1992), carbamazepine (Hartley et al., 1991; Wolf et al., 1992; Oles et al., 1992; Sipalkit et al., 1997), and valproate (Vandney and Kraushaar, 1997).

One aspect of the debate that has not been addressed is determining those factors associated with the occurrence of increased seizures and adverse effects when switching from generic to brand name AEDs. This information can aid clinicians and health policy-makers in identifying those instances where prescribing brand name AEDs would improve patient outcomes.

In this study we surveyed a group of epilepsy patients followed at a tertiary (level four) epilepsy center who were switched from brand name to generic AEDs. We determined the prevalence of those who experienced increased seizures and adverse effects. We then identified those demographic, clinical, and psychosocial variables that were associated with these occurrences.

Methods

This study was approved by the Institutional Review Board of the University of Florida Health Sciences Center/Jacksonville (UFHSCJ). A written consent was obtained from all patients who participated in the study. We performed a direct survey of consenting patients followed at the UFHSCJ-Comprehensive Epilepsy Program (CEP) from April to July 2009. This is a tertiary (level four) epilepsy center located in downtown Jacksonville, Florida and is a major referral center in the region. Around 42% of patients seen at the UFHSCJ-CEP are males, 58% are Caucasians, and 31% are African-Americans. A significant portion of patients seen at the UFHSCJ-CEP come from the indigent population and 40% of patients are either uninsured, part of the city's indigent care program, or recipients of Medicaid/Medicaid HMO programs. Around 5% of patients have undergone epilepsy surgery and/or VNS implantation. To date, there are over 3000 patients in our epilepsy database. Physicians from the UFHSCJ serve as both primary neurologists and subspecialists to their patients. This allows the inclusion of a broad variety of epilepsy patients in the study, ranging from those who are easy-to-control to those with refractory seizures.

Only established adult epilepsy patients seen during their out-patient clinic visit were considered for this study. These patients should not have had any history of psychogenic, non-epileptic seizures. They should consider themselves to be their primary caregiver and able to sign the consent form themselves as well as complete the survey without assistance.

We obtained the following information during the survey (See Supplementary Material):

1. Demographic information
   a. age
   b. gender
   c. marital status
   d. race
   e. educational attainment
   f. annual household income
   g. whether they drive
   h. whether they receive disability benefits
   i. employment status
   j. primary insurance status
2. Disease related information
   a. age of seizure onset
   b. duration of seizures
   c. seizure count
   d. whether they experience convulsions
   e. whether they experience seizures while awake
   f. epilepsy classification
   g. number of seizure medications they are currently taking
   h. whether they have side effects on their current AED regimen
3. Psychosocial data
   a. Neurological Institute Disorders Depression Inventory for Epilepsy (NIDDI-E) (Gilliam et al., 2006)
   b. Quality of Life in Epilepsy-10 (QOLIE-10) (Cramer et al., 1996)
   c. Beliefs About Medicines Questionnaire (BMQ) (Horne et al., 1999)
4. Experience with generic AEDs
   a. whether they ever switched from brand name to generic AEDs
   b. whether they experienced increased seizures when switching to generic AEDs