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Bioequivalent antiepileptic drug switching and the risk of seizure-related events

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KEYWORDS
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Summary
Background: Older antiepileptic drugs (AEDs) are known to have a narrow therapeutic index. As a consequence, switching between bioequivalent AEDs remains controversial in the management of epilepsy. We investigated the association between A-rated switching of each class of currently available AED and emergent treatment for a seizure-related event.
Methods: We used a case—control method and claims data from the 2010 to 2011 Truven Health MarketScan® Commercial Claims Database to estimate the risk of seizure following a medication switch. Cases and controls with an epilepsy diagnosis were identified by emergency/inpatient or outpatient visit claims, respectively. Cases and controls ($N = 9110$) were matched 1:1 by age, epilepsy diagnosis category and seizure medication. The exposure was defined as a switch between A-rated AEDs during the 90 days prior to index date. Conditional logistic regression was used to estimate the association, adjusting for gender, baseline Deyo—Charlson Comorbidity Index (0, 1, 2, or 3+), region (Northeast, Central, South, and West), and total AED medications.
Results: A switch between A-rated AEDs occurred in 1053 (23.2%) cases and 827 (18.1%) matched controls. The unadjusted and adjusted odds ratios of a seizure-related event for switching were 1.38 (95% CI: 1.25—1.52) and 1.27 (95% CI: 1.14—1.41), respectively. The independent risk of an event also increased with each category increase in the Charlson score (CCI = 1: 1.17, 95% CI: 1.02—1.33; CCI = 2: 1.33, 95% CI: 1.09—1.62; CCI = 3+: 1.99, 95% CI: 1.64—2.41). Older AEDs had infrequent switches compared to newer agents and were not associated with events.
Discussion: We found a modest association between AED switching and seizure-related events. Our analysis suggests that the behavior of switching alone may lead to seizure-related events regardless of the medication or type of switch. Other disease or environmental characteristics may contribute to this association. Based on these and other findings, health care professionals and patients should be cautious about switching bioequivalent AEDs.

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Background

Epilepsy is a common and chronic disease that affects 3% of people in the United States (US) during the course of their lifetime (Epilepsy at a Glance, 2011). Approximately 200,000 new cases are diagnosed each year and incidence is highest among children younger than age 2 and adults older than age 65 years (Epilepsy Foundation of America). Because of its prevalence, early age of onset, and effects on health and well being, epilepsy is associated with considerable direct and indirect costs. Epilepsy imposes an annual economic burden of $15.5 billion in the US in associated healthcare costs and losses in employment, wages, and productivity (Epilepsy at a Glance, 2011).

The goal of epilepsy treatment is to achieve a seizure-free status without adverse effects from medications or surgical interventions (Liow et al., 2007). Lifelong treatment with mono- or poly-therapy antiepileptic drugs (AEDs) is often required. The early-generation AEDs, such as phenytoin, valproic acid, ethosuximide, and carbamazepine, continue to be commonly prescribed treatment options (DiPiro et al., 2011). Since 1993, FDA-approval of newer, second-generation AEDs (e.g., gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate and zonisamide) considerably expanded the therapeutic options for the treatment of epilepsy (Sirven et al., 2012). Some newer AEDs have less toxicity and fewer side effects compared with older AEDs (Vazquez, 2004; Marson et al., 1997). Despite a better drug profile, both newer and older AEDs are considered to be treatments with a narrow therapeutic index (NTI) (Makus and McCormick, 2007; Andermann et al., 2006; Benet and Goyan, 1995; Crawford et al., 2006). Drugs with a NTI have a narrow range between drug levels that are therapeutic and those that may cause an adverse event, thus requiring scrutiny in the dosing and monitoring during each treatment. A NTI implies that slight variations in drug absorption could result in significant negative health outcomes, seizures in the case of epilepsy (Crawford et al., 2006).

Despite the many treatment options, management of epilepsy remains controversial with regard to bioequivalent medication switching. The FDA supports bioequivalence of approved brand-name and generic AEDs, suggesting that generic drugs can be safely interchanged with brand-name or other generic products (FDA, 1998). However, physicians and patients remain concerned about potentially increasing seizure events when switching between A-rated (bioequivalent) brand name and generic AED products, since AEDs possess a NTI (McAuley et al., 2009; Papsdorf et al., 2009; Andermann et al., 2007; Berg, 2007; Berg et al., 2008). The American Academy of Neurology also opposes antiepileptic generic substitution without physician approval (Liow et al., 2007). However, the current evidence supporting the policy and clinical assertions is wrought with conflict (Fitzgerald and Jacobson, 2011; Kesselheim et al., 2010; Yamada and Welty, 2011).

We sought to investigate the association between A-rated switching and the odds of emergent treatment for a seizure-related event over a 1-year period using recent data from a large pooled commercial health plan database, controlling for differences in risk between older and newer generation AEDs.

Methods

Data source

This case–control study utilized data from the Truven Health MarketScan® Commercial Claims and Encounters Database. MarketScan® data include the inpatient, outpatient, and prescription drug claims data for 52 million lives covered by a variety of US commercial health plans. Detailed longitudinal claims data are linked together within MarketScan® including outpatient, inpatient and pharmacy records, matched to administrative data regarding coverage status and demographics. The MarketScan® database is comprised of de-identified data in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations, thus making the study exempt from institutional review board review.

Study design

Cases and controls with a diagnosis of epilepsy (International Classification of Disease, Version 9 (ICD-9) 345.xx) were identified in the database between January 1, 2011 and December 31, 2011. The index date was defined as the visit date for the first claim during the identification period that corresponds with the case and control definition. Cases were defined as subjects with a claim for an ambulance encounter, emergency department (ED) visit, or inpatient hospitalization and a primary or secondary diagnosis of epilepsy during the identification period. Controls were non-cases with a claim for an outpatient office visit during the identification period and a primary or secondary epilepsy diagnosis. Cases and controls were matched using a 1:1 ratio for age within 5 years of the case's age, epilepsy diagnosis category, and AED. One control was randomly selected and matched to each case using a previously reported computer algorithm to assign the best matched control to each case (Bergstralh and Kosanke, 1995).

Subjects were included if they were continuously enrolled with coverage for at least the most recent 6 months preceding the index date (pre-index period), were between age 12–64 years, and had an AED filled for at least 145 days during the 6 months preceding the index date. Subjects were excluded if they had a diagnosis of infantile spasms (ICD-9 345.6x) or an ambulance encounter, ED visit, or inpatient hospitalization with a diagnosis of epilepsy in the 6 months prior to the index date. Age exclusion was based on selection of a stable, prevalent cohort rather than incident cases and access to claims data (commercial only).

The exposure of interest was an A-rated switch of an AED (brand to generic, generic to brand, generic to generic) during the 90 days prior to the index date. A switch was defined by a change in the manufacturer within the same generic code number (unique identifier of individual chemical and dosage form). If multiple switches occurred, only the closest switch to the index date (the switch that was most likely associated with the outcome) was evaluated. Independent variables included the following demographic characteristics: patient age during the index year, gender, and U.S. region. We controlled for comorbidity burden using the Deyo version of the Charlson Comorbidity Index (CCI) score, developed specifically for use with administrative claims databases (Deyo et al., 1992; Charlson et al., 1987). The Deyo version is based on 17 diagnostic indicators, each assigned a weight depending on its relative risk of mortality. Diagnostic values from all pre-index visits back to January 2010 were included in the calculation of each patient's CCI (Deyo et al., 1992). The scores were summed to a total comorbidity index score; the higher the score, the more severe the burden of comorbidity. Epilepsy diagnoses were grouped into categories based on seizure type and history of intractability. The six categories were ''generalized'' (345.0x–345.3x), ''partial'' (345.4x, 345.5x, 245.7x), and ''other'' (345.8x, 345.9x) with each subdivided into intractable (xxx.x1) and non-intractable (xxx.x0) designations.