Comparative effectiveness of generic versus brand-name antiepileptic medications

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ABSTRACT

Objective: The objective of this study was to compare treatment persistence and rates of seizure-related events in patients who initiate antiepileptic drug (AED) therapy with a generic versus a brand-name product.
Methods: We used linked electronic medical and pharmacy claims data to identify Medicare beneficiaries who initiated one of five AEDs (clonazepam, gabapentin, oxcarbazepine, phenytoin, zonisamide). We matched initiators of generic versus brand-name versions of these drugs using a propensity score that accounted for demographic, clinical, and health service utilization variables. We used a Cox proportional hazards model to compare rates of seizure-related emergency room (ER) visit or hospitalization (primary outcome) and ER visit for bone fracture or head injury (secondary outcome) between the matched generic and brand-name initiators. We also compared treatment persistence, measured as time to first 14-day treatment gap, between generic and brand-name initiators.
Results: We identified 19,760 AED initiators who met study eligibility criteria; 18,306 (93%) initiated a generic AED. In the matched cohort, we observed 47 seizure-related hospitalizations and ER visits among brand-name initiators and 31 events among generic initiators, corresponding to a hazard ratio of 0.53 (95% confidence interval, 0.30 to 0.96). Similar results were observed for the secondary clinical endpoint and across sensitivity analyses. Mean time to first treatment gap was 124.2 days (standard deviation [sd], 125.8) for brand-name initiators and 137.9 (sd, 148.6) for generic initiators.
Significance: Patients who initiated generic AEDs had fewer adverse seizure-related clinical outcomes and longer continuous treatment periods before experiencing a gap than those who initiated brand-name versions.

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1. Introduction

Switching between brand-name and generic versions of antiepileptic drugs (AEDs) is controversial [1,2]. The US Food and Drug Administration (FDA) approves generic drugs based on tests proving their bioequivalence to brand-name counterparts. To demonstrate bioequivalence, the FDA requires similarity in the rate and extent of bioavailability of the active ingredient [3]. Such studies generally evaluate the ratio of the generic product's maximum concentration (C_{max}) to the brand-name product's C_{max}, and the ratio of the generic product's area under the plasma concentration versus time curve (AUC) versus the brand-name product's AUC in healthy volunteers. Two products are deemed bioequivalent if the 90% confidence intervals of the geometric means for these ratios fall within the range of 80% to 125%.

Some have argued that the FDA's standard bioequivalence range of 80–125% can result in clinically meaningful differences in bioavailability between a generic drug and its brand-name reference product [4]. In theory, the difference in bioavailability between two generic products could be even greater. These small potential differences are particularly a concern for narrow therapeutic index drugs, which are drugs with a small range between minimum effective plasma concentrations and minimum toxic concentrations [5]. Certain antiepileptic drugs (AEDs) are well-known narrow therapeutic index drugs. Anecdotal reports and some observational studies have found adverse clinical outcomes among patients switching between brand-name and generic AEDs [6–8].

However, many studies have also shown that patients who use generic drugs display greater adherence to their medication regimens, because generic drugs are often much less expensive than brand-name drugs [9]. Medication adherence is a critical contributor to whether patients achieve and maintain effective plasma concentrations of their narrow therapeutic index drugs [10]. Some have argued that variation in drug use patterns and nonadherence are more likely to explain variability in drug response than are small differences in pharmacokinetics

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[11]. In the case of AEDs, up to 50% of patients with epilepsy report missing more than 20% of their doses [12], and nonadherence to AEDs is associated with an increased risk of seizure [12], emergency room (ER) visits [13,14], hospitalizations [13,14], motor vehicle accidents [14], and fractures [14].

We hypothesized that better adherence to generic AEDs would offset any small fluctuations in plasma concentration resulting from switching among bioequivalent products (e.g., switching between brand-name and generic versions or between multiple generic versions from different manufacturers) [10,15]. To our knowledge, no study has yet examined the comparative effectiveness of generic and brand-name AEDs in a typical care setting in which the clinical consequences of generic drug substitution and nonadherence can play out. Thus, we compared the rates of seizure-related events among patients who initiated AED therapy with a generic product versus those who initiated with a brand-name product.

2. Methods

The study was designed by the authors and approved by the Institutional Review Board at Brigham and Women's Hospital.

2.1. Data source

We used 2005–2008 prescription drug data from CVS Health, a large national prescription benefit manager and retail pharmacy in the United States. We linked the drug data to enrollment, diagnostic, health care utilization, and demographic data from Medicare Parts A and B, and to US census data. We identified Medicare beneficiaries aged 65 years and older who had prescription drug coverage through either a stand-alone Medicare Part D plan or a retiree drug plan in 2006 and 2007.

2.2. Study drugs and patient population

We focused on initiators of AEDs for which the database contained patients who used both brand-name and generic versions of the drug in the same solid oral dosage form. The specific AEDs we studied were clonazepam, gabapentin, oxcarbazepine, phenytoin, and zonisamide. We did not have data available to study topiramate because the first generic version did not become available in the US until after our study period, and we excluded levetiracetam because the first generic version became available at the very end of our study period in November 2008. We excluded lamotrigine because the first generic versions that were available in the US during the study period were authorized generics, which is the brand-name version sold as a generic. We excluded carbamazepine because the only brand-name use in the database was for an extended-release version and the only generic use was for nonextended release tablets, and we excluded valproic acid because the only use in the database was for generic versions. Phenytoin chewable tablet use was excluded because only brand-name versions of this formulation were documented in the database [15].

We identified all initiators of the five AEDs starting January 1, 2006 and required no use of any AED in the 180 days preceding the date of initiation (the index date). We also excluded patients with fewer than 180 days of continuous enrollment in prescription drug or medical benefit coverage leading up to the index date in order to ensure identification of new users and to allow for sufficient ascertainment of baseline characteristics. Patients were allowed to enter the analysis only once. We excluded patients who initiated more than one AED on the index date.

Patients were classified as exposed to a generic or brand-name AED according to their index prescription. We used the National Drug Code of the index prescription to determine the manufacturer and then used the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") to determine whether the product was a reference brand-name or generic [16].

2.3. Outcomes and follow-up

The primary outcome was a seizure-related ER visit or hospitalization defined using ICD-9 code 345.xx (epilepsy and recurrent seizure) or 780.39 (other convulsions), excluding 345.6x (infantile spasms) [17]. As in other studies [14,18], we examined a secondary outcome of hospitalization or ER visit for bone fracture or head injury defined using ICD-9 codes 800.xx–829.xx (fracture of skull, spine and trunk, upper limb, or lower limb), 850.xx–854.xx (intracranial injury, excluding those with skull fracture), 873.xx (other open wound of the head), and 959.01 (head injury, unspecified), where x represents any single-digit number. We also examined a composite outcome comprising components of both the primary and secondary outcomes.

For the analysis of each outcome, we followed patients beginning after the index date until the first occurrence of an event of interest, a prescription for a different AED (i.e., different active ingredient), death, or the end of the study period (December 31, 2008). We did not censor patients if they switched among brand-name and generic versions of the same drug.

We also examined persistence with the index medication, defined by time to first treatment gap of more than 14 days. We did this by linking serial prescriptions, using the days supply field of each. A treatment gap was defined as a failure to refill a prescription for the index drug within the days supply plus 14 days of a prior dispensing.

2.4. Covariates

We measured potential confounders in the 180-day baseline period preceding each patient's index date. Demographic variables included age, sex, and median household income in the census block group. To determine median household income — a proxy for socioeconomic status — we geocoded patients' street addresses and linked them to US census data at the block group level, which is the smallest level for which census data are publicly available.

Health service utilization variables included number of distinct drugs dispensed, number of physician office visits, number of hospitalizations, number of ER visits, and number of nursing home admissions during the baseline period. In addition to a comorbidity score that captures patients' general health status [19], we determined whether patients had health care encounters with diagnoses for epilepsy, depression, anxiety, mania, attention deficit hyperactivity disorder, alcohol abuse, drug abuse, psychosis, and dementia. We also assessed whether patients had ER visits for falls or hospitalizations for fracture during the baseline period.

2.5. Statistical analysis

We used propensity score (PS) matching to account for potential differences in baseline characteristics between generic and brand-name AED initiators [20]. Patients' PSs were defined as their probabilities of receiving generic versus brand-name AEDs, conditional on measured baseline covariates, and estimated using a logistic regression model. We included all covariates listed above as independent variables in the model.

In primary analyses, we matched generic and brand-name initiators in a 1:1 ratio using a nearest neighbor algorithm and within a caliper of 0.025 units on the PS scale. We allowed brand-name initiators to match only generic initiators of the same product to compare patients who had initiated brand-name drugs and their bioequivalent generic versions (e.g., brand-name Trileptal to generic oxcarbazepine initiators). This ensured that differences in outcome rates between treatment groups could be attributed to the generic versus brand-name status rather than to differences among the AEDs.

We plotted Kaplan–Meier event-free probabilities based on the primary matched cohort. We used Cox proportional hazards models,

stratified by matched pair, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We also estimated rate differences.

2.6. Sensitivity analyses

We conducted several sensitivity analyses to assess the robustness of our results. First, we repeated the primary analysis but truncated follow-up at a maximum of one year. Second, we performed n:1 variable ratio matching to increase the number of patients included in the matched analysis. To maximize the number of matched sets for each molecular entity, n:1 matching was done such that the larger treatment group (i.e., brand-name or generic initiators) was matched in the variable ratio to the smaller treatment group. For example, we identified more generic than brand-name initiators of clonazepam, so generic initiators were matched n:1 to brand-name initiators; whereas we identified more brand-name initiators of oxcarbazepine, so they were matched in an n:1 ratio to the generic initiators. Next, we repeated the n:1 ratio matched analysis omitting each drug separately to examine the influence of each drug on the results. Finally, we repeated the n:1 ratio matched analysis restricted to patients with a code for an epilepsy diagnosis in the baseline period. These latter two sensitivity analyses were conducted as variants of the n:1 matched, rather than the 1:1 matched cohort, to maximize power in the smaller subgroups.

3. Results

3.1. Cohort characteristics

We identified 19,760 initiators of AEDs who met eligibility criteria during the study period (Table 1). Of these, 18,306 (93%) initiated generic AEDs. The majority of patients initiated gabapentin (16,654 [84%]; 16,325 generic, 329 brand-name), while 1647 (8%) initiated clonazepam (1549 generic, 98 brand-name), and 813 (4%) initiated phenytoin (339 generic, 474 brand-name). The mean age of the cohort was 75 years, and 7861 (40%) were female. Brand-name initiators lived in census blocks with higher median household incomes ($64,602 versus $58,210) and were more likely to have had a diagnosis code for epilepsy in the baseline period (15% versus 1%), likely because AEDs for which more patients initiated generic versions (e.g., clonazepam, gabapentin) are commonly used to treat other conditions. After PS matching, differences in median income in the census block ($67,325 for brand-name initiators and $64,056 for generic initiators) and record of an epilepsy diagnosis in the preceding 180 days (9% for both groups) were less apparent.

3.2. Primary analyses

In the primary 1:1 matched cohort, we found adequate matches for 754 of 799 (94%) potential matches. The number of potential matches corresponds to the total number of patients in the smaller treatment group (i.e., brand-name or generic) across the five drugs. We observed 47 seizure-related hospitalizations and ER visits among brand-name initiators and 31 events among generic initiators, corresponding to an HR of 0.53 (95% CI, 0.30 to 0.96; Table 2) and an incidence rate difference of −34.32 (95% CI, −62.36 to −6.28) per 1000 person–years. Fig. 1 displays the Kaplan–Meier plot for the primary outcome.

3.3. Analyses of secondary endpoints

Few patients (a total of 11 between both brand-name and generic AED initiators) had a hospitalization or ER visit for bone fracture or head injury during follow-up. The resulting HR was 0.67 with wide 95% CIs (0.19, 2.36). In the analysis that combined this secondary outcome into a composite endpoint with the primary outcome, the HR was 0.51 (95% CI, 0.30 to 0.89).

Mean time to first treatment gap was 124.2 days (standard deviation [sd], 125.8) for brand-name initiators and 137.9 (sd, 148.6) for generic initiators ($p = 0.01$).

3.4. Sensitivity analyses

In the n:1 matched sensitivity analysis, we found adequate matches for 97% of the entire cohort. Analysis of these patients led to an estimate (HR, 0.52; 95% CI, 0.32 to 0.83) very similar but slightly more precise than the estimate from the primary analysis (Fig. 2). Although based on a much smaller subset of the cohort, the analysis among only patients with a diagnosis code for epilepsy in the baseline period resulted in a qualitatively similar HR (0.62; 95% CI, 0.38 to 1.04). Estimates were highly consistent across analyses omitting each drug one at a time,

Table 1
Characteristics of generic and brand-name AED initiators in full and propensity score-matched cohorts.

	Full cohort		1:1 matched cohort	
	Generic (n = 18,306)	Brand-name (n = 1454)	Generic (n = 754)	Brand-name (n = 754)
Demographic characteristics				
Age, mean (sd)	75.3 (7.6)	74.9 (7.6)	75.0 (7.5)	75.0 (7.4)
Female, n (%)	7266 (39.7)	595 (40.9)	334 (44.3)	302 (40.1)
Median household income in census block	58,210.2 (29,807.6)	64,601.8 (36,538.5)	64,056.0 (32,470.6)	67,325.4 (39,457.0)
Health service utilization measures, mean (sd)				
No. unique drugs dispensed	11.0 (5.7)	10.1 (5.7)	10.3 (5.3)	10.2 (5.8)
Physician visits	5.3 (4.9)	5.3 (4.9)	5.4 (4.8)	5.4 (5.0)
Hospitalizations	0.4 (0.8)	0.4 (0.8)	0.4 (0.9)	0.3 (0.7)
Emergency room visits	0.5 (1.1)	0.5 (1.3)	0.6 (1.1)	0.4 (0.8)
Nursing home admissions	0.2 (0.8)	0.1 (0.7)	0.2 (0.7)	0.1 (0.6)
Clinical characteristics				
Combined comorbidity score, mean (sd)	1.5 (2.5)	1.3 (2.3)	1.7 (2.6)	1.1 (2.1)
Epilepsy diagnosis, n (%)	203 (1.1)	219 (15.1)	70 (9.3)	68 (9.0)
Hospitalization for fracture, n (%)	181 (1.0)	11 (0.8)	*	*
Emergency room visit for fall, n (%)	21 (0.1)	1 (0.1)	*	*
Depression diagnosis, n (%)	1329 (7.3)	126 (8.7)	69 (9.2)	53 (7.0)
Anxiety diagnosis, n (%)	2217 (12.1)	184 (12.7)	95 (12.6)	96 (12.7)
Mania diagnosis, n (%)	123 (0.7)	32 (2.2)	*	*
ADHD diagnosis, n (%)	38 (0.2)	18 (1.2)	*	*
Alcohol abuse diagnosis, n (%)	73 (0.4)	15 (1.0)	*	*
Drug abuse diagnosis, n (%)	119 (0.7)	14 (1.0)	*	*
Psychosis diagnosis, n (%)	452 (2.5)	68 (4.7)	26 (3.5)	16 (2.1)
Dementia diagnosis, n (%)	488 (2.7)	71 (4.9)	36 (4.8)	17 (2.3)

AED, antiepileptic drug; sd, standard deviation.
  * Cell sizes suppressed in accordance with the Centers for Medicare & Medicaid Services Data Use Agreement, which requires that no cell with fewer than 11 patients be displayed.

Table 2
Hazard ratios for outcomes in patients starting generic versus brand-name AEDs: primary analyses.

Outcome	Hazard ratio (95% CI)
Seizure-related hospitalization or emergency room visit	0.53 (0.30, 0.96)
Hospitalization or emergency room visit for bone fracture or head injury	0.67 (0.19, 2.36)
Composite hospitalization or emergency room visit for seizure, bone fracture, or head injury	0.51 (0.30, 0.89)

AED, antiepileptic drug; CI, confidence interval.

except for the analysis that omitted phenytoin, which resulted in an HR of 0.79 with wide 95% CIs (0.26, 2.34). A post hoc analysis limited to phenytoin initiators produced an HR of 0.45 (95% CI, 0.24, 0.85).

4. Discussion

This study, the first to our knowledge directly comparing seizure-related outcomes between brand-name and generic AED initiators in typical care, found that patients who initiated generic versions of five AEDs had better treatment persistence and were less likely to experience hospitalizations or ER visits for seizures. While the primary analysis included all patients initiating these medications, regardless of indication, the results persisted when we controlled for underlying diagnoses (including epilepsy) and when we limited the analysis only to patients with a documented seizure disorder. Our results suggest that for every 1000 person-years of treatment for patients who begin treatment with a generic AED, there would have been 34 fewer seizure-related hospitalizations and ER visits, and an additional 110 gap-free treatment days than if they had begun treatment with a brand-name version instead.

These findings, if replicated in other settings, may have important clinical implications. In considering the comparative effectiveness of brand-name and generic AEDs, it is necessary to consider both potential small differences in plasma concentrations that may arise from switching among bioequivalent AEDs from different manufacturers as well as differences in affordability and adherence that may result from the use of brand-name versus generic medications. A number of observational studies have examined associations between switching — either between brand-name and generic products or between generics produced by different manufacturers — and seizure-related events with mixed results [6–8,17,21]. This study compared outcomes of brand-name and generic AEDs in a way that simultaneously considered both the effect of switching (i.e., patients were allowed to switch among brand-name and generic versions from multiple different manufacturers) and the effect of nonadherence as manifested in typical care settings. It is important to note, however, that our study does not specifically address the safety of switching among versions of the same

antiepileptic medications manufactured by different companies in highly adherent patients with medically refractory epilepsy.

Our study has several limitations. Administrative claims databases lack information on some potentially important confounding variables, such as sleep deprivation, illicit drug use, and alcohol consumption that may affect seizure rates. While we restricted our study to initiators of AEDs and further adjusted for confounding using PS matching, our results may be affected by unmeasured confounding. Before matching, generic AED initiators lived in census block groups with higher median household incomes, were less likely to have an epilepsy diagnosis, and had lower prevalence of certain comorbid conditions, such as psychosis and dementia. It is possible that after matching patients on measured variables, differences in important unmeasured factors remained that could partly explain our findings. Also, AEDs are used to treat many conditions, but the indications for use are not included in the database. If generic initiators in the matched cohort were less likely to have seizure disorders as compared to brand-name initiators, then we would expect our results to be biased downward since generic initiators would be at lower risk of seizure-related events. Prior to PS matching, brand-name initiators were more likely to have a recorded diagnosis of epilepsy, suggesting preferential prescribing of brand-name versus generic versions of AEDs in epilepsy. However, recorded epilepsy diagnosis was well balanced in the matched cohort, and restricting the analysis to those patients with a recorded epilepsy diagnosis resulted in materially similar results. Furthermore, our results were driven in large part by initiators of phenytoin, which is used only to treat epilepsy. This bolsters our findings as we would not expect AEDs to prevent seizures in patients who do not have epilepsy.

Another limitation is that we could not assess patients' AED plasma concentrations, and seizure events that did not result in an ER visit or hospitalization are not reliably captured in administrative claims databases. While our hospital- and ER-based seizure outcome has not been validated in older patients, such outcomes tend to have high positive predictive values across other patient populations [22].

The generalizability of our findings may also be limited because we focused on older patients because of the availability of Medicare data from Parts A and B linked to census data, and because the incidence of epilepsy and the outcomes we studied are highest in people over the age of 65 years [23]. However, the mean age of the cohort (75 years) is higher than the average age of patients experiencing new onset seizures and likely higher than the average age of most patients in neurology practices. Subsequent studies should investigate whether our findings are generalizable to younger patients. Furthermore, 93% of patients in our study initiated generic versions, which is higher than estimates from other populations. However, among patients in our cohort with a diagnosis of epilepsy, 48% initiated a generic, which is more similar to previous estimates [24]. Finally, we were unable to ascertain in the claims data how many patients had supervised medication administration. This could create bias if these patients are more likely to receive generic medications and if supervised medication administration improves adherence.

Despite these limitations, this study adds to the growing body of evidence that generic drugs — even narrow therapeutic index drugs — are as effective as their brand-name counterparts [25]. It also provides more evidence that adherence is better for generic medications than corresponding brand-name versions [9,26] and that better medication adherence is associated with better patient outcomes [12–14,26–28]. Although concerns have been raised about the safety and effectiveness of switching between brand-name and bioequivalent generic versions of AEDs, these findings suggest that, overall, patients who begin treatment with generic AEDs have better clinical outcomes than those who begin brand-name versions of these same drugs.
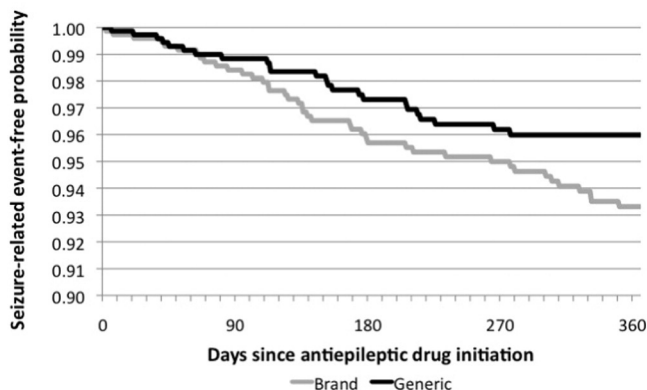
Acknowledgments

Fig. 1. Cumulative seizure-related event-free probability following initiation of a generic versus brand-name antiepileptic drug.
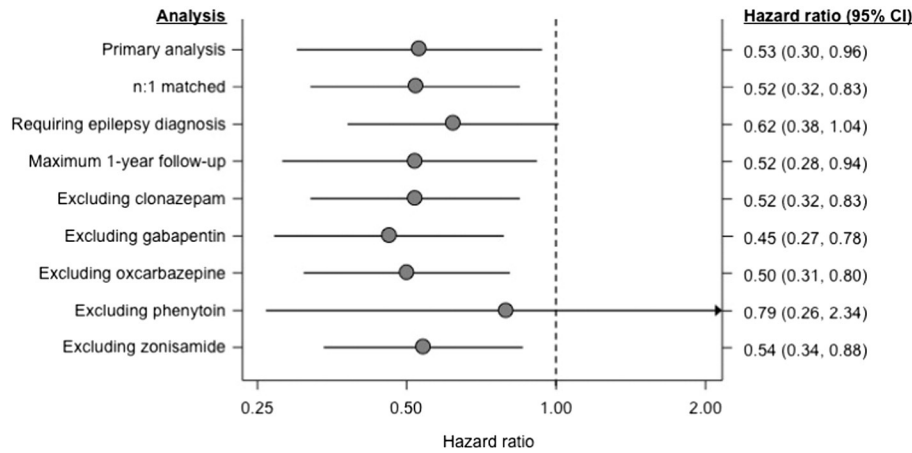
Fig. 2. Forest plot of hazard ratios from sensitivity analyses.

role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation of the manuscript. The sponsor was given the opportunity to review the manuscript but had no role in approval or the decision to submit the manuscript for publication.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of conflicts of interest

Drs. Polinski, Matlin, Brennan, and Shrank and Mr. Hutchins are employees of CVS Health. At the time of the study, Drs. Polinski and Shrank were employees of the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School. Drs. Gagne and Kesselheim are principal investigators on grants from the US Food and Drug Administration's Office of Generic Drugs for projects unrelated to this study. Dr. Kesselheim's work is supported by a career development award from the Agency for Healthcare Research & Quality (K08HS18465-01), the Greenwall Faculty Scholars in Bioethics, and a Robert Wood Johnson Foundation Investigator Award in Health Policy Research. Dr. Gagne had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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