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Generic antiepileptic drug prescribing: A cross-sectional study

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Abstract

The use of generic antiepileptic drugs (AEDs) in patients with epilepsy is controversial. The purpose of this study is to identify patient characteristics associated with increased odds of receiving a generic AED product. A large commercial database was used to identify patients with a primary diagnosis of epilepsy who were prescribed an AED during a three-month window. Data analysis found that those 65 years old had 15.7% greater odds of receiving a generic AED (OR = 1.157; 95% CI = 1.056–1.268). Patients with Medicaid were found to have 2.44 times the odds of having had a generic AED prescription (OR = 2.44; CI = 2.168–2.754). Patients residing in the Northeast had 12.6% decreased odds of receiving a generic AED (OR = 0.874; CI = 0.821–0.931). These patient characteristics could signify certain health care disparities and may represent potential confounders to future observational studies.

Keywords

Epilepsy; Antiepileptic drugs; Generic drugs; Prescribing; Cross-sectional

1. Introduction

One of the most controversial topics in epilepsy management continues to be the generic substitution of antiepileptic drugs (AEDs) and the switching among A-rated generic AED products [1]. The U.S. Food and Drug Administration (FDA) considers A-rated generic medications to be interchangeable and equivalent to their brand name counterparts in safety and efficacy; therefore, generic substitution of many drug classes is a common health care cost-saving practice [2]. However, some AEDs have a narrow therapeutic index (NTI) which requires very precise dosing due to small changes in serum concentration potentially causing loss of seizure control or toxicity. A 2011 statement by the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology has recommended new guidelines for the therapeutic equivalence for NTI drugs, including some AEDs [3]. This statement recommends that generic products of NTI drugs should have—with 90%

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confidence—ratios of the generic to brand name log-transformed mean values for area under the curve (AUC) and maximum concentration (C_{max}) within an interval of 90% to 105%. This is a smaller interval than the traditional 80% to 125% generic to brand mean values used in bioequivalence testing. While the FDA has not yet come to a consensus as to what guidelines will be used to define a NTI drug, they have also recommended new, more stringent testing procedures for bioequivalence of generic NTI drugs. The new guidelines are being developed in hopes of reducing potential problems that could be associated with the slight variation between generic products [4].

A growing number of observational studies have compared outcomes of patients with epilepsy being treated with brand name AEDs to those patients switched to generic AED counterparts to determine if there is a difference in seizure control or seizure-related adverse events. “The results of these studies are conflicting, with some showing an increased risk of seizures and seizure related injury when generic AED products were switched with brand name products [5–7] and other studies showing no difference in seizure control [8,9].”

“Many studies have examined outcomes for patients wherein A-rated AEDs were switched with generic AEDs, with no consensus as to whether or not generic AEDs are inferior to their brand name counterparts.” One related area, where there is a significant lack of research, is in exploring the differences in patient populations of those that receive brand name products and those that receive generic products of medications. No studies have reviewed patient characteristics associated with receiving brand or generic AEDs, and only one study has examined this issue with all generic medications [10]. The study—conducted in Switzerland—examined several different determinants of generic substitution. This study found decreased use of generics in older patients and major differences depending on the patient's region of residence.

It is hypothesized that certain patient characteristics, such as gender or type of insurance, might be associated with higher odds of generic AED use. This study seeks to explore the patient-specific characteristics of those receiving a generic AED by utilizing a large American commercial database.

2. Methods

2.1. Data source

Health insurance claims from a large commercial insurance data mart (UnitedHealth Group) were utilized for this study. The database contains, largely, commercial insurance information and approximately two percent Medicaid data. Data elements include patient demographics, medical claims data, pharmacy claims data [amount of copayment, date of dispensing, Dispense as Written (DAW) code], and International Classification of Diseases (ICD)-9 diagnosis codes.

2.2. Study population

The study population was identified according to the following criteria: a primary diagnosis of epilepsy [ICD-9: 345.xx excluding 345.3 (status epilepticus) and 345.6 (infantile spasms) and including 780.31, 32, and 39 (febrile and other seizures)] and the dispensing of one of

the brand or generic AEDs listed in Table 1. The included AEDs were chosen based on their Food and Drug Administration (FDA) indication to treat epilepsy and the availability of a generic product. Patients were then classified into two mutually exclusive groups of brand versus generic users of AEDs.

2.3. Time period

The study period was designated from March 1 to May 31, 2009. A three-month period was used in an attempt to capture those patients that might obtain 90-day prescriptions. This period was also chosen to avoid the possibility of traditional insurance plan modifications that occur around January 1st and July 1st.

2.4. Study design

A cross-sectional design was used to identify patients with epilepsy with at least one prescription of an AED during the specified time period. Only the first prescription event during the time period was taken into account to capture the point prevalence of generic AED use. Selected patient characteristics were compared between the two groups of brand and generic users. Patient age, gender, copayment per 30-day amount, insurance plan type and state of residence were collected.

2.5. Standard protocol approvals, registrations, and patient consents

This study was exempted by the institutional review board. All data were collected without identifiers, and records were maintained confidentially.

2.6. Statistical methods

Statistical analyses were conducted using SAS version 9.2 (Cary, NC, USA). For the univariate analysis of characteristics for generic versus brand cohort, the median was compared using the Wilcoxon rank-sum test for the continuous variable of copayment per 30-day amount. For categorical and binary variables, chi-square tests were used to determine significant differences. The patient characteristic of age was placed into the following age categories: 0 to <18; 18 to 29; 30 to 39; 40 to 49; 50 to 64; and 65 and older, as seen in Table 3. Age zero to 18 years was used as the youngest category of patients to capture the pediatric population before the possibility of minors losing Medicaid coverage at age 18. Likewise, 65 years of age and older was chosen as the oldest category because at this age people become eligible for Medicare insurance coverage. Other than the previously mentioned categories, age was divided by decade of life. Patient state of residence was converted into region based on standard divisions from the U.S. Census Bureau (see Fig. 1). Logistic regression was used to examine the relationships between the following patient characteristics and the odds of being prescribed a generic AED: age category, Medicaid insurance, insurance plan type, gender and region of residence. A summary of these findings can be found in Table 3.

3. Results

3.1. Study population

A total of 47,833 patients were identified as having a primary diagnosis of epilepsy with at least one AED prescription filled during the study period of March 1st, 2009–May 31st, 2009. Three hundred ten patients were found to have a negative copayment, possibly due to a reimbursement from a previous copayment. Because the original copayment was not known, these 310 patients were excluded, leaving a total of 47,523 eligible patients. Of these patients, 28,367 (59.7%) received a generic prescription and 19,156 (40.3%) received a brand name product. Table 3 presents the univariate analysis of characteristics of the patients, and Fig. 2 shows the number of patients receiving the most commonly used AEDs. The median copayment per 30 days for the generic and brand users was \$9.90 and \$30.00, respectively. Table 4 contains the variables included in the logistic analysis along with corresponding parameter estimates, odds ratios and 95% confidence intervals.

3.2. Age

The number of patients in each age category with relative percentages can be seen in Table 3. After adjusting for covariates, an increase in age was found to be associated with increased odds of receiving a generic AED prescription. Table 4 presents each age group and their relative odds ratios of receiving a generic AED with 95% confidence intervals. The age group of 50–64 had the most patients (13,005 [27.36%]) and was used as the referent variable. All age categories had decreased odds of receiving a generic AED compared to the 50–64 age group with the exception of the 65 and older category which was found to have 15.7% greater odds of receiving a generic AED prescription (CI = 1.056–1.268).

3.3. Medicaid status

There were a total of 2087 Medicaid patients in the study group. Of these, 1594 received a generic prescription, and 493 received a brand name prescription. After adjusting for covariates, it was found that the Medicaid patients had 2.44 times the odds of receiving a generic AED compared to those with commercial insurance (CI = 2.150–2.720).

3.4. Insurance plan type

The commercial insurance plans included in the dataset were the following: Exclusive Provider Organization (EPO); Health Maintenance Organization (HMO); Indemnity (IND); Other (OTH); Point of Service (POS); and Preferred Provider Organization (PPO). Table 2 provides a brief comparison of the characteristics of the different plan types. Table 4 presents each insurance plan and their relative parameter estimates, odds ratios of receiving a generic AED and 95% confidence intervals. POS was chosen as the referent category because it represented more than half of the patients with commercial insurance (29,373 [61.8%]). After adjusting for covariates, it was found that, compared to POS patients, EPO, IND, OTH and PPO members had statistically increased odds of receiving a generic AED.

3.5. Region

The patient's state of residence was placed into geographical regions based on the map in Fig. 1. Table 4 presents each region and their relative parameter estimates and odds ratios of receiving a generic AED with 95% confidence intervals. The South contained the most patients ($n=23,837$ [49%]) and was, thus, treated as the referent category. After adjusting for covariates, it was found that, compared to those living in the South, patients residing in the West had statistically increased odds of receiving a generic AED prescription. Those residing in the Northeast had decreased odds of receiving a generic AED prescription compared to those in the South.

3.6. Gender

More than half of the eligible patients were females ($n = 25,654$ [53.9%]). Table 4 presents the female gender and its relative parameter estimate and odds ratio of receiving a generic AED with 95% confidence limits. After adjusting for covariates, it was found that females were at 5% increased odds of receiving a generic AED prescription as compared to males ($CI = 1.01-1.09$).

4. Discussion

Despite the controversy surrounding generic AED substitution, the data from this cross-sectional study estimate the point prevalence of patients with epilepsy receiving generic AEDs during March 1, 2009–May 31, 2009, to be 59.7%. This is a much larger percentage than Decollogny et al. found in their 2003 study looking at factors influencing generic substitution rates. These authors found that generics made up only 20% of the prescription volume; however, according to the authors, Switzerland, historically, has a lower-than-average generic substitution rate. The findings from this study are more in accord with other generic substitution rate estimates which are anywhere from 40 to 60% [11]. Also, despite the findings of multiple surveys which suggest mistrust by patients and prescribers of generic AEDs, the majority of the patients with epilepsy in this study were receiving generic AEDs [12,13].

After multivariable analysis, the patient's age category was found to be associated with the odds of a patient with epilepsy being prescribed a generic AED. In this study population, the lowest odds of being prescribed a generic were found in the youngest age group of 0–<18 years (this category had 51% lower odds of receiving a generic AED compared to the 50–64 age group). The odds of being prescribed a generic AED rose steadily with each age group, with the highest odds being found in the 65 and older group (18% greater odds of receiving a generic AED prescription compared to those in the 50–64 age group). The relationship between older patients and higher odds of receiving a generic AED could be due to several factors, including medication cost-cutting behaviors associated with the rising costs of multiple medications and health problems associated with being elderly [14].

We also found that Medicaid patients had 2.44 times the odds of receiving a generic AED, which appears to be an insurance-related disparity. A 2010 study reviewing prescribing patterns for patients with coronary heart disease found similar insurance-related disparities

in those receiving prescriptions for statins—54.8% of those with private insurance received a statin versus 38.3% of those with Medicaid [15].

For those with commercial insurance, the plan type was also associated with the odds of receiving a generic AED. In this study, those enrolled in an indemnity (IND) plan had 79% greater odds of receiving a generic AED compared to those enrolled in Point of Service (POS) plans. Indemnity plans are traditionally known as having higher out-of-pocket costs for the patient, which could influence the choice of the typically less expensive, generic prescriptions. In one study examining chronic disease medication use between managed care and indemnity insurance members, it was found that there were a disproportionate number of elderly patients with indemnity insurance [16].

The US region of residence was associated with the odds of receiving a generic prescription. This study found that patients residing in the West have increased odds of receiving a generic AED prescription compared to those living in the South. Also, those residing in the Northeast had lower odds of receiving a generic AED prescription compared to those residing in the South. These findings are similar to those in Decollogny's study which found that patients residing in different regions of Switzerland had very different rates of generic prescribing. It is thought that prescriber beliefs and practices may vary from region to region and are an important factor in prescribing patterns [10]. It is interesting to note that as of 2005, the Northeast region of the United States had the highest rate of commercially insured residents, which may contribute to the lower odds of receiving a generic AED [17].

The Agency for Healthcare Research and Quality conducted a Comparative Effectiveness Review in December 2011 which evaluated the effectiveness and safety of AEDs in patients with epilepsy. The review states that in a patient who needs to initiate an AED, there are “no substantive differences in terms of benefits or harms associated with the use of a generic version versus an innovator [brand name] product”. The review also acknowledges that switching from a brand name AED to a generic AED may increase health care utilization but recognizes that “this is based on controlled observational study data, which has inherent limitations substantially reducing the strength of evidence” [18].

Similarly, a 2011 systematic review of the current evidence on generic substitution of AEDs was conducted by Yamada et al., including retrospective and prospective controlled studies of generic substitution of AEDs [19]. The review found that “most retrospective studies have indicated that generic AED substitution resulted in higher use of medical services in patients with epilepsy.” The review also found that “most prospective studies, classified with higher levels of evidence, showed no significant differences in clinical outcomes or in pharmacokinetic parameters.” Finally, the review points out that numerous other factors—factors which were not routinely evaluated in these studies—such as age or severity of disease, could predispose certain patient populations to complications. Complications include increased seizure activity or side effects. According to Yamada, accounting for these patient-specific factors has the potential to impact generic substitution studies.

The American Epilepsy Society and the American Academy of Neurology recommend against switching from brand to generic AEDs without prescriber and patient permission

[20]. Several states have laws which require a pharmacist to contact both the prescriber and patient before substituting a brand name AED for its generic. Many other states have discussed, or are considering, similar legislation which will prevent generic AED substitution by pharmacists until patients and/or prescribers are contacted [18].

“The controversy surrounding AED substitution is not limited to brand name to generic product substitution—switching patient medication from one generic product to another generic product has also been scrutinized.” As most generic AEDs have multiple manufacturers, a patient could potentially receive a different generic product from month to month. One recent study assessing the bioequivalence of generic AEDs by Krauss et al. found that “Switches between generic AED products may cause greater changes in plasma drug concentrations than generic substitutions of reference products” [21]. More prospective studies analyzing the pharmacokinetics of brand-to-generic substitution, as well as generic-to-generic substitution, are needed to assess the true variability of generic products.

This study finds that certain patient groups, namely, the elderly and those with Medicaid insurance, have higher odds of receiving a generic AED. These findings could be associated with certain disparities in health care, such as decreased access to a prescriber who is willing to advocate for a patient to have brand name AED prescriptions. Pricing may also be an issue, and the prescribing trends suggest that those patients traditionally less likely to be able to afford brand name are less likely to receive one. A 2010 study by Mattsson et al. found that certain sociodemographic factors of patients with epilepsy were linked to access to a specialist—these factors included being young and having a higher income [22]. This suggests that patients with epilepsy who are elderly and have lower incomes are less likely to have access to a specialist and, possibly, brand name AEDs. No previous studies have specifically examined the characteristics of patients with epilepsy receiving generic AEDs. This study revealed patient-specific factors that should be considered when conducting future studies on the use and outcomes of generic AEDs.

5. Limitations

This cross-sectional study design provides a survey of the prevalence of generic use at a single point in time (the three-month window of March 1, 2009–May 31, 2009). Due to the nature of the survey, prevalence of generic AED prescriptions could be over- or underestimated. In general, logistic regression analysis and the resultant odds ratios of cross-sectional studies can overestimate the prevalence ratio [23]. Also, the possibility of coding errors within the database poses a limitation.

Finally, while the cross-sectional study design shows association, it does not show causality. The study describes the use of generic AEDs at one point in time, but it cannot be used to explain why the patients are using generics because it does not take into account potential confounders such as length of AED therapy or severity of disease (number of seizures, emergent visits, etc.). Further, only the first prescription event of the three-month window was analyzed, which does not take into account those patients receiving multiple AEDs which may have more refractory forms of epilepsy.

Amount of copayment per 30 days was not included in the logistic regression analysis. This is because price difference between brand and generic AEDs was not available for each insurance plan. This unknown factor may have influenced the patient's choice in brand or generic AED which would have affected the amount of copayment on the prescription. Another limitation to this study is the lack of socioeconomic status (SES) data in the database. One could hypothesize that numerous SES characteristics might be associated with the rate of generic prescribing, but the authors did not have access to these factors. Also, because the database only contained a small amount of Medicaid claims compared to private insurance—about two percent—it is not a true representation of the US population, which is estimated to have 20% of the population receiving Medicaid [24]. Finally, slight differences in patient characteristics that may not necessarily be clinically significant are found to be statistically significant due in part to the very large number of subjects in this study.

6. Conclusions

The findings of this cross-sectional study suggest that certain characteristics of patients with epilepsy—such as age, gender, type of insurance and region of residence—are associated with increased odds of receiving a generic AED. It is thought that these same patient groups—namely, the elderly and those with Medicaid insurance—may also be subject to certain disparities, such as decreased access to specialized care and the inability to pay for brand name prescriptions. Further studies including SES data as factors for generic AED substitution would be a logical next step in this field of research. To ensure that every patient with epilepsy is receiving the best health care possible, prescribers and policy makers should be aware of the current state of disease management—including prescribing patterns of generic AEDs.

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Fig. 1.
Map of the United States divided into South, Northeast, Midwest, West and Pacific regions [25].

Fig. 2.

Distribution of antiepileptic prescriptions by brand and generic formulation*. *Those AEDs comprising less than 1% of the collective prescriptions were not included on the graph.

Table 1

Included generic and corresponding brand name antiepileptic drugs.

Generic name(s)	Brand name(s)
Acetazolamide	Diamox Sequels
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol
Clonazepam	Klonopin
Clorazepate	Tranxene
Diazepam	Diastat, Valium
Divalproex, valproic acid	Depakene, Depakote, Stavzor
Ethosuximide	Zarontin
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Lorazepam	Ativan
Mephobarbital	Mebaral
Methsuximide	Celontin
Oxcarbazepine	Trileptal
Phenobarbital	Solfoton
Phenytoin	Dilantin, Phenytek
Tigabine	Gabitril
Topiramate	Topamax
Zonisamide	Zonegran

Table 2

Brief description of included insurance plans.

Exclusive Provider Organization (EPO)	Offers a very limited number of providers who offer large discounts on rates.
Health Maintenance Organization (HMO)	Arranges for health care either directly in its own group practice or through health professionals under contract. Usually requires a small copayment.
Indemnity (IND)	Also called “fee-for-service” plans. Reimburses medical providers for each service on a case-by-case basis. Offers the most freedom to choose a provider but, typically, have the highest out-of-pocket costs.
Other (OTH)	Could include any other purchased health care plan, including but not limited to the following: high-deductible health plan; tax-preferenced health care spending accounts; and limited benefit plans.
Point of Service (POS)	Combines characteristics of the HMO and PPO. Patient chooses a primary care physician from within the health care network who can make referrals to providers outside the network. Offers more flexibility but is more expensive.
Preferred Provider Organization (PPO)	A managed care organization of health care providers who are in contract with the insurer to provide health care at reduced rates to the insurer's clients. Tends to be more expensive but offers more flexibility when choosing a primary care provider.

Table 3

Patient characteristics of brand and generic antiepileptic drug users.

	Brand (n = 19,157; 40.3%)	Generic (n = 28,367; 59.7%)	p-Value
<i>Demographic characteristics</i>			
Age category (n, %)			<0.0001
0–<18	4196 (21.9%)	3620 (12.76%)	
18–<30	3013 (15.73%)	3999 (14.1%)	
30–<40	2874 (15.0%)	4306 (15.18%)	
40–<50	3484 (18.9%)	5487 (19.34%)	
50–<65	4538 (23.69%)	8467 (29.85%)	
65 and over	1051 (5.49%)	2489 (8.77%)	
Female (n, %)	10,090 (52.67%)	15,564 (54.87%)	<0.01
Regions			<0.0001
Midwest	4966 (25.93%)	7603 (26.81%)	
Northeast	2186 (11.41%)	2861 (10.09%)	
South	9509 (49.65%)	13,792 (48.63%)	
West	2492 (13.01%)	4102 (14.47%)	
<i>Insurance information</i>			
Copayment—30 day (median, IQR)	\$9.90 (5.70–9.90)	\$30.00 (16.80–50.10)	<0.001
Insurance type			<0.001
Medicaid	493 (2.57%)	1594 (6.52%)	
Commercial	18,663 (97.43%)	26,773 (94.38%)	
Plan type (n, %) ^a			<0.001
EPO	2548 (13.3%)	3724 (13.13%)	
HMO	2246 (11.72%)	4103 (14.46%)	
IND	300 (1.57%)	861 (3.04%)	
OTH	16 (0.08%)	83 (0.29%)	
POS	12,412 (64.79%)	16,961 (59.79%)	
PPO	1634 (8.53%)	2635 (9.29%)	

^aEPO = Exclusive Provider Organization; HMO = Health Maintenance Organization; IND = Indemnity; OTH = Other; POS = Point of Service; PPO = Preferred Provider Organization.

Table 4

Adjusted odds ratio estimates of receiving a generic antiepileptic drug.

Patient characteristic	Parameter estimate (β)	Odds ratio estimate	95% confidence limits
Age category (vs. 50–64)			
0–<18	–0.7853	0.456	0.430–0.483
18–<30	–0.3547	0.701	0.661–0.745
30–<40	–0.2292	0.795	0.749–0.844
40–<50	–0.1763	0.838	0.793–0.887
65 and older	0.1460	1.157	1.056–1.268
Medicaid patients	0.8935	2.444	2.168–2.754
Type of commercial insurance plan (vs. POS)			
EPO	0.0842	1.088	1.028–1.151
HMO	0.0398	1.041	0.974–1.112
IND	0.3479	1.416	1.215–1.651
OTH	0.5669	1.763	1.017–3.055
PPO	0.0794	1.083	1.011–1.159
Region of the US (vs. South)			
Midwest	0.0424	1.043	0.997–1.092
Northeast	–0.1348	0.874	0.821–0.931
West	0.1348	1.144	1.080–1.212
Gender			
Female	0.0443	1.045	1.007–1.085