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Exploring generic brittleness and the demographic factors for its susceptibility in patients with epilepsy

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ABSTRACT

Purpose: The purpose of this study was to provide an algorithm for generic brittleness and to elucidate the demographic factors that anticipate generic brittleness for patients with epilepsy.
Methods: This exploratory, observational, and nontherapeutic study was conducted in patients with epilepsy who were routinely followed at the University of Maryland epilepsy outpatient clinic in Baltimore, Maryland. Patients were taking at least one antiepileptic drug (AED) for treatment of epilepsy. Based on patient interview and medical history, 12 demographic factors were collected. Each patient was assessed to be either generic brittle (GB) or not GB. Demographic factors were subjected to binary logistical regression and other statistical tests, to elucidate determinants of GB status.
Results: N = 148 patients completed the study. An algorithm to define whether a patient was GB or not GB was devised. The two elements that defined GB status are as follows: patient opinion about generics and (if needed) whether patients were currently taking brand or generic of their most problematic AED. About 40% of patients were GB. From binary logistical regression, two demographic factors that contributed to patients being GB were whether a patient was currently taking a problem AED and total number of current medications for a patient, with odds ratios of 4.06 (95% confidence interval [CI] from 1.53 to 10.81) and 1.10 (95% CI from 1.003 to 1.21), respectively. Of the patients on a problem AED, 46.9% were GB, while only 18.2% of patients not currently on a problem AED were GB. The total number of current medications ranged from 1 to 22, with mode of four medications. From regression, for each additional medication that a patient took, the odds of being GB increased 1.10-fold. Although patient seizure and adverse event history was not employed to define GB status, being GB was associated with less seizure control and greater adverse events.
Conclusions: An algorithm for generic brittleness was derived, and about 40% of patients were GB, usually due to prior history of a switch problem. Two demographic factors favored patients being GB: whether the patient was currently taking a problem AED and the total number of current medications.

1. Introduction

The American Epilepsy Society (AES) rescinded its opposition to generic substitution after two studies in patients with epilepsy under clinical conditions demonstrated that the Food and Drug Administration's (FDA's) bioequivalence standard for antiepileptic drugs (AEDs) yielded similar drug pharmacokinetic profiles in patients with epilepsy [1–3]. Among the two studies, the BioEquivalence in Epilepsy Patients (BEEP) study required patients to be "generic brittle" (GB) [2]. In that study, the GB definition was broad in that patients with any possible history of generic switching concerns were included. While the current AES position statement indicates that FDA standards for bioequivalence are appropriate for patients with epilepsy, some neurologists and patients with epilepsy have concerns that certain individuals are better treated on brand than generic, or on one generic than another generic [4].

A familiar notion is that some patients on certain medications are GB. For example, patients with refractory epilepsy on an AED with a narrow therapeutic index (e.g., phenytoin, carbamazepine, valproic acid) have sometimes been characterized in literature as being poorer patient candidates for generics. Investigations of prescription data provide

Abbreviations: GB, generic brittle; AEDs, antiepileptic drugs; BEEP, BioEquivalence in Epilepsy Patients; FDA, Food and Drug Administration; LAR, legally authorized representative; AES, American Epilepsy Society; CI, confidence interval.

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perhaps the best support for generic brittleness in a population of patients with epilepsy. For example, in evaluating a public-payer pharmacy-claims database from Ontario, Andermann et al. observed a higher switchback rate to brand, reflecting poor acceptance of generic switching of AEDs [5]. Reasons for the higher switchback rate of AEDs compared to non-AED long-term therapies (e.g., antihypertensives, antidepressants) were not identified through the claims analysis. Moreover, factors that anticipate a patient being GB have not been well-studied. The objectives of the present study were to provide an algorithm for GB and to elucidate demographic factors that make individual patients with epilepsy more vulnerable to generic brittleness.

2. Methods

2.1. Patient demographic collection

This exploratory, observational, and nontherapeutic study was conducted in patients with epilepsy who were routinely followed at the University of Maryland epilepsy outpatient clinic in Baltimore, Maryland. Prior to data collection, the study was approved by the University of Maryland Institutional Review Board (IRB) and FDA Research in Human Subjects Committee. Study participants gave their written informed consent.

Patients had to be a male or female between the ages of 18 and 76 years inclusive, have a diagnosis of either focal or generalized epilepsy, and currently taking at least one AED for treatment of epilepsy. Informed consent was obtained. Patients who needed a legally authorized representative (LAR) for informed consent were not excluded. No patient could be pregnant or lactating. Based on patient interview and medical chart reviews, the following 12 demographic factors were collected: sex, age, race, type of epilepsy (focal or generalized), number of current AEDs, number of problem AEDs, whether the patient was currently taking a problem AED, presence of an AED allergy, previous epilepsy surgery, number of comorbidities, number of autoimmune comorbidities, and total number of current medications (i.e., AED and non-AED prescription, over-the-counter [OTC], and dietary supplements).

2.2. Algorithm for GB status and patient assignment

Each patient with epilepsy was categorized as GB or not GB, depending on two elements (Table 1 and Fig. 1). In Table 1, the two elements were patient opinion about generics, and whether the patient was currently taking brand or generic AED of their most problematic AED. In Fig. 1, either element could cause a patient to be GB (i.e., negative opinion about generics or patient taking brand of most problematic AED when generic available). In Fig. 1 and Table 2, there are three subtypes of GB, and two subtypes of not GB. Patients who opined that generics are unacceptable and take brand AED even though generic is available are denoted as classic GB (i.e., GB subtype 1). Patients who opined that generics are acceptable and take generic AED are denoted classic not GB (i.e., not GB subtype 1).

Table 1
Defining elements of GB status. Two elements defined if a patient was GB or not GB. The primary element was patient opinion about generics, which could be either "negative" or "acceptable". Patients with a negative opinion of generics are categorized as GB. A secondary and less impactful element in identifying GB patients concerned whether the patient was currently taking the brand or generic of their most problematic AED. Here, only three patients were defined to be GB after they opined that generics were acceptable, since they were taking brand of their most problematic drug, although generic was available (Fig. 1).

Element	Possible values. Additional comments.
Patient opinion about generics	Negative or acceptable. A patient that has had a switch problem was classified as opining negatively about generics.
Currently taking brand or generic AED of most problematic AED[a]	Brand or generic. A problem AED was a current or prior AED that the patient (or caregiver) associated with lack of seizure control, adverse events, and/or a switch problem. The most problematic AED was the problem AED with the greatest lack of seizure control, adverse events, and/or a switch problem, as reported by the patient (or caregiver).

[a] The most problematic AED was available as both brand and generic in all but two of 148 patients. The two patients whose most problematic AED was not available as generic were taking brand, and found to be not GB.

A problem AED was a current or prior AED that the patient (or caregiver) associated with lack of seizure control, adverse events, and/or a switch problem. A problem AED could be either brand or generic. As results show, a vast majority of patients have taken a problem AED, and usually more than one problem AED. Since most patients had more than one problem AED, GB assignment may require the identification of the most problematic AED, among the patient's several problem AEDs. The most problematic AED was the problem AED with the greatest lack of seizure control, adverse events, and/or a switch problem, as reported by the patient (or caregiver).

Of note, a patient taking a problem AED does not mean that the patient is GB. A problem AED and a patient being GB are separate concepts. As results show, a majority of patients that are not GB identified at least one of their AED medications as a problem AED, and experienced seizures or adverse events while taking the problem AED.

2.2.1. Patient opinion about generics

Patient opinion about generics was assigned to be either negative or acceptable. In Fig. 1, a patient is immediately denoted to be GB if they have a negative opinion of generics. This perspective to rely on patient opinion considers that a) epilepsy is a chronic condition, for which patients often have significant awareness, and b) patients drawn on this awareness to yield an opinion that reflects their medical history. In practice, patient opinion about generics was the primary element defining GB status. Of the two determinants of GB status, results indicate patient opinion was the more important element.

Patient opinion concerns patient overall opinion about generic drugs in patients in general, or for that patient. A negative opinion about generics resulted from reporting a switch problem, expressing that brands are better than generics, or indicating that they would use brand if they could afford brand. A switch problem was a brand–generic or generic–generic switch of pharmaceutical equivalents that was considered by the patient to result in seizure worsening or adverse events. A switch was limited to pharmaceutical equivalents (e.g., excludes changes from immediate-release to extended-release).

2.2.2. Brand or generic of most problematic AED

Currently taking brand or generic AED of their most problematic AED was a secondary element defining GB status. Assignment was either brand or generic. In Fig. 1, when a patient opined that generics were acceptable, it was still possible for the patient to be categorized as GB, if they took brand when generic was available for their most problematic AED. This inclusive effort was to guard against patients who may be GB, and thus on brand, but do not consider themselves GB. Results indicate that this second element of GB status was of modest impact. Here, only three patients without negative opinion of generics were classified as GB because they were taking brand of their most problematic drug, although generic was available (Fig. 1; GB subtype 3). The vast majority of patients were taking either only brand AEDs or only generic AEDs. There were six patients who never had a problem AED, but all six were only on generics, such that generic assignment was applied.

2.3. Statistical analysis

Three analyses were performed: Chi square, independent samples *t*-test, and binary logistical regression (SPSS; IBM, Armonk, NY) [6]. Six of the 12 independent demographic variables were continuous variables.

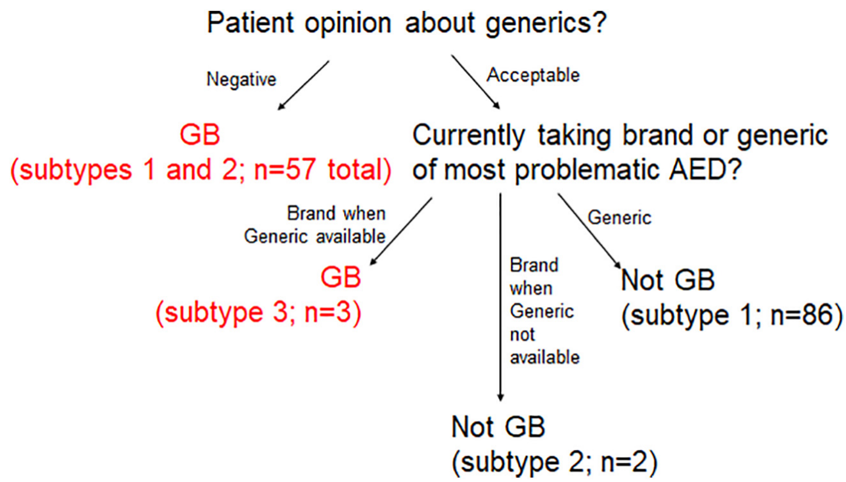

Fig. 1. Flow diagram to assess GB status. Patients were categorized as GB or not GB. There are three subtypes of GB, and two subtypes of not GB. Patient numbers in each subtype are noted. Opinion about generics was the primary element that defined GB status. Fifty-seven of the 60 GB patients had a negative opinion about generics (i.e., GB subtypes 1 or 2). Only three patients were categorized to be GB subtype 3 (i.e., opined that generics were acceptable but still took brand of most problematic AED when generic was available). GB status reflected the current status of the patient.

Student's *t*-test (for continuous variables) and Chi square analysis (for categorical variables) were performed to examine for differences between the demographic variables between the GB and not GB patients. To control for multiple comparisons, Bonferroni correction was applied with a critical p-value of 0.0042 [7,8]. All reported p-values were two-sided. The Fisher's Exact test was used in place of Chi square analysis when any expected value was less than five from Chi square analysis [9].

In addition to Chi square and independent samples *t*-test analysis of individual demographic variables, binary logistical regression was performed [10]. Collinearity among independent variables was assessed, prior to binary logistical regression. A variable was eliminated from the dataset if tolerance <0.1 (where tolerance $= 1 - r^2$); tolerance was always greater than 0.4, such that none of the 12 independent variables was excluded. Both forward and backward elimination binary logistical regressions were performed. The likelihood ratio χ^2 test (a/k/a Omnibus Chi square test) was applied to assess the null hypothesis that all slopes were zero. If rejected, the Wald statistic was then applied to assess if each parameter slope was zero. Both the Omnibus Chi-squared test and Wald statistic p-values were used to identify the best model; in all cases for each forward and backward regression, both approaches agreed upon the best model. Forward selection required Wald statistic p-value ≤0.05. Backward elimination required Wald statistic p-value ≥0.1.

Data are reported as mean (±standard error of the mean). A posterior predictive simulation was performed to assess model validation (see Supplementary Material for description of methodology).

3. Results

3.1. Description of patients and GB categorization

A total of 152 patients enrolled with 148 patients completing patient interviews. Tables 3 and S1 (in Supplementary Material) characterize the 148 completed patients. Sixty patients were GB (40.5%), and 88 were not GB (59.5%). A vast majority had focal epilepsy (78.4%). There were approximately equal numbers of men and women and approximately equal racial distribution between whites and blacks or African Americans. A vast majority had at least one comorbidity (Fig. S1 in Supplementary Material); with 10.1% having at least one autoimmune comorbidity, and 20.9% having an allergy to an AED. The vast majority were taking one or two AEDs. In Table S1, the total number of medications being taken by the patients was wide, ranging from 1 to 22; the largest group was taking four total medications (18.9% of patients). In Table 3, 14 (9.5%) required a LAR. In Table 3, 35.1% of non-LAR patients held negative opinion of generics, and 60.7% of caregivers opined negatively about generics, including 10 of the 14 LARs.

Table 2 counts the number of GB and not GB patients, including their subtypes. There are three subtypes of GB, and two subtypes of not GB, reflecting that a patient could be GB for any of three different scenarios, or not GB for two different scenarios. The most common scenario to be GB was GB subtype 2, where patients held a negative opinion about generics, yet were taking a generic AED. The most common scenario to be not GB was not GB type 1, by far, where patients opined that generics were acceptable, and were taking generic AED (classic not GB).

Table 2
Subtypes of GB and of not GB. There are three subtypes of GB, and two subtypes of not GB. Patients who opined that generics are unacceptable and take brand even though generic is available are denoted classic GB (i.e., GB subtype 1). Patients who opined that generics are acceptable and take generic are denoted classic not GB (i.e., not GB subtype 1). The 41 patients with a switch problem were classic GB (n = 22, with all but one had intractable seizures or AED adverse events) or GB subtype 2 (n = 19, all who had intractable seizures or AED adverse events). Almost all classic GB patients had a switch problem.

GB status	Subtype	Patient's opinion about generics[a]	Currently taking brand or generic for most problematic AED	Number of patients (n = 148 total)[b]
GB	Subtype 1 (classic GB)	Negative	Brand even though generic is available	26
	Subtype 2	Negative	Generic	31
	Subtype 3	Acceptable	Brand even though generic is available	3
Not GB	Subtype 1 (classic not GB)	Acceptable	Generic	86
	Subtype 2	Acceptable	Brand since no generic available	2

[a] Any patient that has had a switch problem is denoted to opine negatively about generics.
[b] 24 of 26 classic GB patients had uncontrolled seizures or formulation-specific AED adverse events. All 31 GB subtype 2 patients had uncontrolled seizures or formulation-specific AED adverse events. All 3 GB subtype 3 patients had uncontrolled seizures or formulation-specific AED adverse events. Forty-seven of 86 classic not GB patients had uncontrolled seizures or formulation-specific AED adverse events.

Table 3
Patient counts of patient opinion about generics.

Patient's opinion about generics	Number of patients
Negative	47[a]
Acceptable	87[b]
Needed a Legally Authorized Representative	14[c]

[a] All 47 were GB.
[b] Three of 87 were GB.
[c] Ten of 14 were GB. Of the four patients needing a LAR but able to provide an opinion, both the patient and their LAR opined negatively about generics.

3.2. Demographic factors associated with GB: Chi square analysis and t-test analysis

Demographic information was examined to assess which of the six categorical demographic factors, if any, favored GB. From Chi square, one factor was statistically significant: whether currently on a problem AED or not ($p = 0.003$). A *t*-test was performed for the six continuous variables (Table S1). None was associated with GB status.

Fig. 2 plots the distribution of total number of current medications for each GB and not GB patient populations (i.e., AED and non-AED prescription, OTC, and dietary supplements). There was propensity for patients who took six or more medications to be GB more frequently than patients who took only 1–5 medications (Chi square $p = 0.001$).

3.3. Demographic factors associated with GB: best model from logistical regression analysis

Forward and backward elimination regressions yielded the same best model to anticipate which patients were GB. Eq. (1) shows the fitted model. The two factors were whether the patient was currently on a problem AED and total number of current medications for a patient. Table S2 shows regression parameters and odds ratios.

$$\ln \frac{\hat{p}}{1-\hat{p}} = 1.40X_1 + 0.095X_2 - 2.064 \quad (1)$$

where $\ln \frac{\hat{p}}{1-\hat{p}}$ is the logit (and $\hat{p}$ is the estimated/predicted probability of being GB); X_1 is the binary variable for whether the patient was currently on a problem AED, and X_2 is total number of current medications. Table 4 tabulates the numbers of GB and not GB patients that were currently taking (and currently not taking) a problem AED. Subjects took 1–22 total numbers of medications.

This model can be interpreted in terms of odds, where $odds = \frac{\hat{p}}{1-\hat{p}}$. An odds value of 1 indicates an equal probability of being GB or not GB (i.e., 50% probability). Fig. 3 plots the estimated odds for being GB as a function of currently taking a problem AED or not, as well as a function of total number of current medications, over a range of 2–5 medications. The higher curve plots odds of being GB when currently taking a problem AED. The lower curve plots odds of being GB when not currently taking a problem AED.

In Fig. 3, for a patient currently taking two total medications, the estimated odds of being GB was about 0.6 if currently taking a problem AED and 0.15 if not currently taking a problem AED, such that the odds ratio for a patient who is currently on a problem AED than not currently on a problem AED was 4.061. From the model, a patient who is currently on a problem AED had 4.061 times the odds of being GB than a patient who is not currently on a problem AED, controlling for other factors. The observed odds of being GB was 0.883 for patients who were currently on a problem AED and 0.222 for patients who were not currently on a problem AED. Hence, the observed odds ratio of being GB was 3.98.

Also, from the model, for each additional medication that a patient took, the odds of being GB increased by 1.099-fold. The total number of current medications ranged from 1 to 22. The most common total number of medications being taken were 2, 3, 4, and 5 (i.e., $n = 17$, 19, 28, and 16 patients, respectively).

Currently taking a problem AED had higher impact than number of medications on the odds of being GB, reflecting its larger odds ratio (i.e., 4.061 versus 1.099 in Table S2). Comparing the effects of these two variables is complicated by currently taking a problem AED being binary, while total number of current medications being continuous.

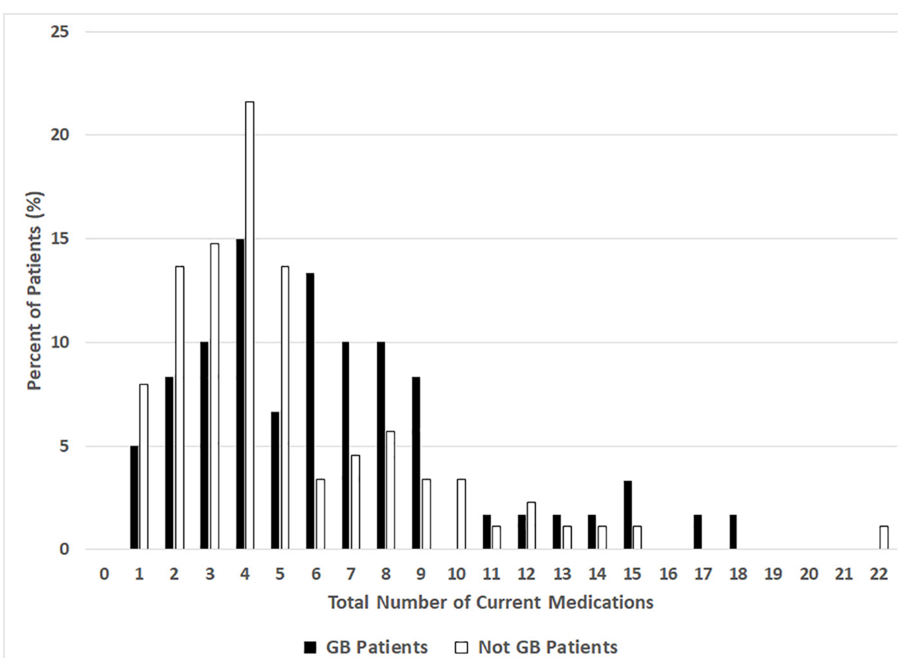

Fig. 2. Distribution of total number of current medications for each GB and not GB patient populations. Black bars indicate number of GB patients, and unfilled bars indicate the number of not GB patients. In both GB and not GB patients, the most common total number of current medications was four. There was some tendency for patients with six or more medications to be GB, compared to patients with less than six medications.

Table 4
Association table between currently taking a problem AED and GB status.

GB status	Number of patients currently on a problem AED[a]	Number of patients not currently on a problem AED[b]
GB[c]	54	6
Not GB	61	27[d]

[a] N = 115 patients were currently on a problem AED. About equal numbers were GB and not GB. For patients who were currently on a problem AED, the observed probability of being GB was 0.469 (54 of 115 total patients).

[b] N = 33 patients were not currently on a problem AED. A vast majority were not GB. Of these 27 not GB patients, 6 never had a problem AED. For patients who were not currently on a problem AED, the observed probability of being GB was 0.182 (6 of 33).

[c] All 60 GB patients had a problem AED at some time. A vast majority of 88 not GB patients (82) also had a problem AED at some time. Only 6 never had a problem AED, and all were not GB. A vast majority of all patients had multiple problem AEDs, collectively over time.

[d] Of these 27 patients, 18 patients were assigned taking a generic AED currently because they were only taking generic AEDs currently; the other nine were assigned brand.

The model can also be interpreted in terms of estimated probabilities of being GB (i.e., $\hat{p}$, where $\hat{p} = \frac{odds}{1+odds}$). Fig. S2 plots the estimated probabilities of being GB as a function of currently taking a problem AED or not, as well as a function of total number of current medications. Overall, the plot is similar to the plot for estimated odds (i.e., Fig. 3).

Model validation of Eq. (1) showed good agreement between predicted and observed probabilities for being GB (see Supplementary Material).

3.4. Data reflecting definition of GB

As expected, the two elements that contribute to the algorithm for GB status (Tables 1 and 2; Fig. 1) were associated with GB status, based on Chi square analysis. Being GB was associated with patient (or LAR) opinion against generics ($p << 0.001$), and currently taking brand AED ($p << 0.001$).

Fig. S3 plots the distribution of patient opinions about generics for each GB and not GB patient populations. A vast majority of GB patients opined negatively about generics. Among the 60 GB patients, 57 were associated with having a negative opinion of generics (i.e., 47 patients and 10 patients with a LAR). By definition, all not GB patients opined that generics were acceptable (Fig. 1). None of the 88 not GB patients were associated with having a negative opinion of generics, although four non-LAR caregivers opined against generics.

Regarding taking brand or generic of the most problematic AED, 29 of the 60 GB patients were taking brand. Among the 88 not GB patients, only two were taking brand, and only nine were taking any brand AED at all. A majority (41) of GB patients experienced a switch problem; about half (22) of such patients were taking brand.

3.5. Concordance of GB algorithm with patient history

Although patient seizure and adverse event history was not employed to define GB status, being GB was associated with the patient having uncontrolled seizures ($p << 0.001$), formulation-specific AED adverse events ($p << 0.001$), and uncontrolled seizures and/or formulation-specific AED adverse events ($p << 0.001$). Table S3 defines uncontrolled seizures and formulation-specific AED adverse events, which are more narrowly defined than intractable seizures and AED adverse events, respectively. Among the 60 GB patients, 54 had uncontrolled seizures; meanwhile, only half of the 88 not GB patients had uncontrolled seizures. Of the 60 GB patients, 51 had formulation-specific AED adverse events; meanwhile, only 45 of the not GB patients had such adverse events. Among the 60 GB patients, 58 had uncontrolled seizures and/or formulation-specific AED adverse events; meanwhile, only 49 of the 88 not GB patients had uncontrolled seizures and/or formulation-specific AED adverse events.

3.6. Problem AEDs and switch problems

A vast majority of the 148 patients (n = 142), whether GB or not GB, had a problem AED, either as a past or current medication. All 60 GB patients had a problem AED at some time. A vast majority (82) of 88 not GB patients also had a problem AED at some time. Only six never had a problem AED, and all were not GB.

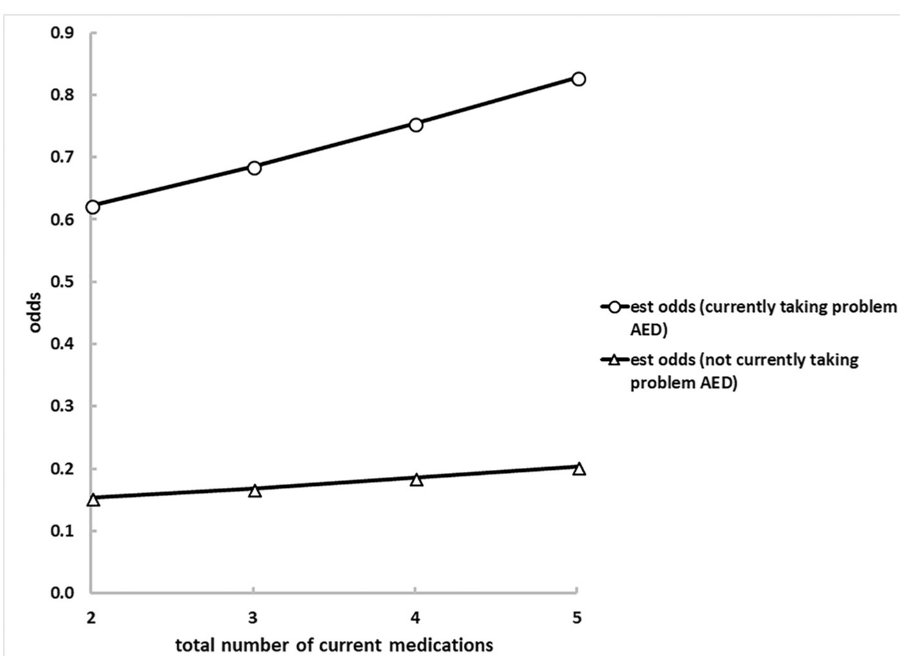

Fig. 3. Plot of estimated odds of being GB as a function of currently taking a problem AED or not, as well as a function of total number of current medications. Open circles are the estimated odds of currently taking a problem AED, and open triangles are the estimated odds of not currently taking a problem AED, each as a function of total number of current medications.

A vast majority of all patients had multiple problem AEDs, collectively over time. Each patient had 0 to 12 different problem AEDs, either currently or previously. The number of patients taking 0 to 12 problem AEDs were 6, 17, 34, 31, 26, 11, 13, 2, 1, 3, 3, 0, and 1, respectively. The number of problem AEDs did not anticipate GB status ($p > 0.1$).

Table 4 indicates that the majority of patients, both GB and not GB, were currently taking a problem AED. A patient currently on a problem AED anticipated GB status ($p = 0.003$). For the 115 patients who are currently on a problem AED, the observed probability of being GB was 0.469 (54 of 115 total patients). Meanwhile, for patients who were not currently on a problem AED, the observed probability of being GB was 0.182 (6 of 33).

Of the 60 GB patients, 41 had a switch problem and were always GB subtype 1 or 2. Almost all GB subtype 1 patients with intractable seizures or AED adverse events had a switch problem. Of the 41 switch problem patients, their problems involved 32 brand–generic switch problems and 10 generic–generic switch problems. One patient experienced both a brand–generic switch problem and a generic–generic switch problem. The remaining 19 GB patients did not have a switch problem, but did have uncontrolled seizures and/or formulation-specific AED adverse events.

4. Discussion

4.1. Algorithm to determine GB status

The interchangeability of generic and brand AEDs has been a long standing question [11–15]. Recent studies indicate some continued questions about the suitability of AED generics [16–21].

This study assumes that generic brittleness is a contributor in some patients with epilepsy to suboptimal therapeutic outcomes. Two potential considerations for patients with epilepsy being GB are pharmacologic and psychological. Pharmacologic considerations include allowable differences between various formulations (e.g., assay, impurities, excipients) [22]. Also, several AEDs are classified as narrow therapeutic index drugs, such that small differences in dose can be thought to potentially have clinically significant effect, although actual examples have not been documented [23–26]. Psychological consideration includes the nocebo effect [27–29]. An algorithm to determine whether a patient is GB or not GB is needed.

In the BEEP study, GB was broadly defined as patients with any possible history of generic switching concerns were included [2]; GB meant having a potential problem with generic switching by virtue of (a) a history of reported prior exacerbation of seizures or side effects following AED formulation changes; (b) intolerable AED side effects within the last year prior to study; or (c) refractory seizures within the last year prior to study, which could reflect clinical sensitivity to slightly higher AED peak plasma concentration or slightly lower drug exposure, respectively.

In the present study, we aimed to narrow the working definition of GB, with the intent to only identify patients with less seizure control or greater adverse events, because of real or perceived formulation differences between pharmaceutical equivalents that FDA has designated as bioequivalent. Hence, seizure and AED adverse event histories were not part of GB status definition (Fig. 1 and Table 1).

4.2. GB status provided concordance with seizure and adverse event history

Nevertheless, GB status was statistically associated with less seizure control and greater adverse events; GB was associated with the patient having uncontrolled seizures ($p << 0.001$), as well as associated with intractable seizures ($p = 0.0013$). It also was associated with the patient having formulation-specific AED adverse events ($p << 0.001$), but not with AED adverse events ($p = 0.3$), such that formulation-specific AED adverse events is preferred over AED adverse events as a potential correlate with generic brittleness.

4.3. GB status, patient opinion, and switch problems

Two elements defined GB status in this study at our tertiary care center: patient opinion about generics and whether the patient was currently taking brand or generic AED of their most problematic AED. Either element could cause a patient to be GB, although opinion about generics was practically the primary element. Fifty-seven of the 60 GB patients had a negative opinion about generics. Only three patients were categorized to be GB, after opining that generics were acceptable but still took brand of most problematic AED when generic was available.

A majority of GB patients had reported a history of brand–generic or generic–generic AED switch problems in the past, as well as had an opinion against generics. A limitation of the present study was the reliance on patient interviews (e.g., patient opinion about generics), rather than objective assessment of brand–generic or generic–generic switching effects. An additional limitation is that this study was performed at a single site tertiary care center that includes patients with refractory seizures. Other sites may have a different patient population.

4.4. Demographic factors associated with GB

Twelve demographic factors were assessed. Overall, the following 10 were not predictors of GB status: sex, age, race, type of epilepsy, number of current AEDs, number of problem AEDs, presence of an AED allergy, previous epilepsy surgery, number of comorbidities, and number of autoimmune comorbidities.

Two predictors of GB status were whether the patient was currently taking a problem AED, and total number of current medications. Total number of current medications may reflect compromised health or psychological status. Interestingly, neither number of current AEDs nor number of problem AEDs was a factor. The most common total number of current medications was four (range 1 to 22). For each additional medication that a patient takes, the odds of being GB increased by 1.10-fold.

Currently taking a problem AED was the most impactful demographic factor in anticipating GB status. For patients who were currently on a problem AED, 46.9% were GB. Meanwhile, only 18.2% of patients who were not currently on a problem AED were GB. It is interesting that this factor held the greatest impact, since a vast majority (142 of all 148 patients) had a problem AED, either as a past or current medication. All 60 GB patients had a problem AED at some time. A vast majority (82 of 88) not GB patients also had a problem AED at some time. Regardless of prior problem AEDs that are no longer taken, currently taking a problem AED may impact a patient's outlook to be more susceptible to nocebo effect with a greater tendency to attribute breakthrough seizures or side effects to generic AED formulation.

5. Conclusions

An algorithm for generic brittleness was derived, and about 40% of patients were GB, usually due to prior history of a switch problem. The algorithm did not rely on a history of seizures or AED adverse events (e.g., having refractory seizures) to assign patients as being GB or not GB. However, results indicate that being GB was associated with the patient having uncontrolled seizures and formulation-specific AED adverse events. Results also indicate two demographic factors that contributed to patients being GB were whether a patient was taking a problem AED and the total number of medications for a patient, though neither number of current AEDs nor number of problem AEDs were associated with generic brittleness.

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Disclosures

None of the authors have any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.11.039.

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