17W1030

Frequency of Generic Brittleness in Epilepsy Patients

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2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
aaps

PURPOSE

Collectively, professional societies currently have mixed position statements about the substitution of antiepileptic drugs (AEDs) to treat epilepsy (1,2). In a Canadian study of more than 1300 patients who underwent compulsory switching to generic lamotrigine,13% of patients switched back to branded Lamictal due to increased toxicity or loss of seizure control (3). “Generic brittleness” (GB) concerns the familiar notion of individual patient sensitivity to generics, although causes and predictors of GB are not well established. In practice, patient and physician perception of a GB problem is based on clinical history, whether a poor outcome was experienced, whether it coincided, conceivably, with a generic switch, and was attributed to the switch. Patient opinion against generic formulation may either result from a perceived GB problem from past experience or may contribute to attributing a poor outcome to a generic switch. The objective was to determine the frequency of generic GB in epilepsy patients at a tertiary care center, as defined by clinical history and patient opinion about generic medication, in order to identify subjects in a subsequent PK study.

METHOD

Patients were classified as being GB or not GB, based on patient clinical history and patient opinion about generic medication. Each epilepsy patient was categorized into one of nine subgroups or types, depending on three factors, leading to each patient being GB or not GB (see Table 1 and 2). Two types represent “classic” subgroups. Type 6 was denoted “classic GB”, where subject had intractable seizure or an adverse event due to an AED, provided opinion or evidence that generics were problematic, and were taking brand AED even though generic was available. Type 3 was denoted “classic not GB”, where subject had no intractable seizures or any adverse events due to an AED, provided opinion or evidence that generics were not problematic, and were taking generic AED. A problematic AED was an AED drug product in a specific patient that the patient (or caregiver) associated with lack of seizure control, adverse effects [including stool remnants(5)], and/or a switch problem.

Methods: Table 1. Determinants of GB Status

Factor	Possible Values
Presence of intractable seizures or AED adverse events	Yes or No
Subject opinion about generics (For the n=10 subjects requiring an LAR, the by-proxy opinion was applied.)	Problematic or not problematic
Currently taking brand or generic AED	Brand or generic on current AED

RESULTS

Table 3. Counts of AED Switch Problems for GB patients.

Problem	Yes	No
Any AED switch problem	41	19
Brand-to-generic AED switch problem	32	28
Generic-to-generic AED switch problem	10	50

RESULTS

N=148 patients completed. N=60 subjects were GB (40.5%), with n=88 were not GB (59.5%). A vast majority had focal epilepsy. There were about equal numbers of men and women and about equal racial distribution between white and African American subjects. Table 2 characterizes the types and numbers of GB and not GB subjects. The most common scenario to be GB was type 8. The most common scenario to be not GB was type 7. Table 3 characterizes differences between GB and not GB patients. Of the n=60 subjects who were GB, n=41 had a prior switch problem (i.e. brand-generic or generic-generic switch problem) and were almost always type 6 and 8. Also, almost all type 6 GB subjects had a switch problem. Of the n=41 subjects with a prior switch problem, the problems involved n=32 brand-generic switch problems and n=10 generic-generic switch problems. Table 4-5 and Figure 1-2 describe further patient characteristics. Demographic information was examined to assess what demographic factors, if any, favored GB. Chi squared analysis was employed, using critical p-value of 0.0038, since multiple comparisons were performs using 13 factors: sex, age, race, type of epilepsy, number of current AEDs, number of problem AEDs, currently on a problem AED, presence of an AED allergy, previous epilepsy surgery, number of co-morbidities, number of auto-immune co-morbidities, number of total current medications, and currently taking brand or generic. From Chi square, the following factors did not anticipate GB: sex (p>0.5), age (p>0.5); race (specifically, white versus African American or black; p>0.9), type of epilepsy (specifically, focal versus primary generalized, p=0.46), number of current AEDs (p>0.6), number of problem AEDs (p>0.1), currently on a problem AED (p=0.009), presence of an AED allergy (p=0.8), previous epilepsy surgery (p=0.2, although 5 GB subjects had surgery and only 1 not GB subject had surgery), number of co-morbidities (p>0.3), and number of auto-immune co-morbidities (p>0.7). Figure 2 plots the percentages of GB and not GB subjects versus their number of medications (i.e. prescription, OTC, and dietary supplements). While there was some propensity for patients who took 6 or more medications to be GB more frequently than patients who took only 1-5 medications (Chi square p=0.02), number of medications was not a factor for GB (other statistical results not shown). The best predictor of GB status was whether subject was taking brand or generic, with respect to the selected AED. Taking brand for the selected AED was associated with being GB (p<<0.001). Of the 60 GB subjects, 29 were taking brand. Among the 88 not GB subjects, only two were taking brand. This association in part reflects the taking brand or generic is one of three determinates of GB status (Table 1 and 2).

Table 2. GB status of subjects.

Brittleness type	GB status	Intractable seizures or AED adverse events?	Subject’s opinion about being GB; Subject’s experience with switching problem	Currently taking brand or generic	Number of subjects (n=148 total)
Type 1	GB	No	No and No	Brand	0
Type 2	GB	No	Yes or Yes	Brand	2
Type 3 (classic not GB)	Not GB	No	No and No	Generic	39
Type 4	GB	No	Yes or Yes	Generic	0
Type 5	GB	Yes	No and No	Brand	3
Type 6 (classic GB)	GB	Yes	Yes or Yes	Brand	24
Type 7	Not GB	Yes	No and No	Generic	47
Type 8	GB	Yes	Yes or Yes	Generic*	31
Type 9	Not GB	Yes	No and No	Brand since no generic available	2

Table 5. Subject counts by number of AED medications for GB and and Not GB Subjects.

Number of Current Antiepileptic Drugs for Not GB Subjects	Count (of n = 148 total)
1	31 (35.2%)
2	45 (51.1%)
3	12 (13.6%)
Number of Current Antiepileptic Drugs for GB Subjects.	**Count (of n = 148 total)**
1	15 (25%)
2	28 (46.7%)
3	17 (28.3%)

Table 4. Problem AED Counts.

GB Status	Problem AED is a Current Medication	Problem AED is a Past Medication
GB	55 (91.7%)	5 (8.3%)
Not GB	61 (69.3%)	21 (23.9%)

Figure 1. Subject percentage by subject opinion about generic brittleness for GB and Not GB Subjects.

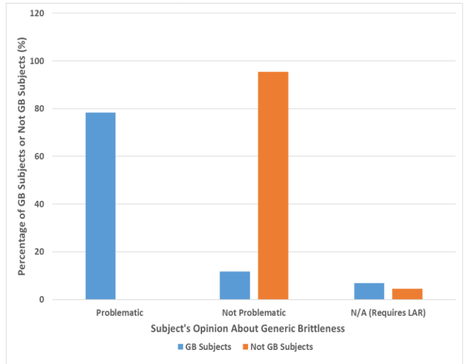
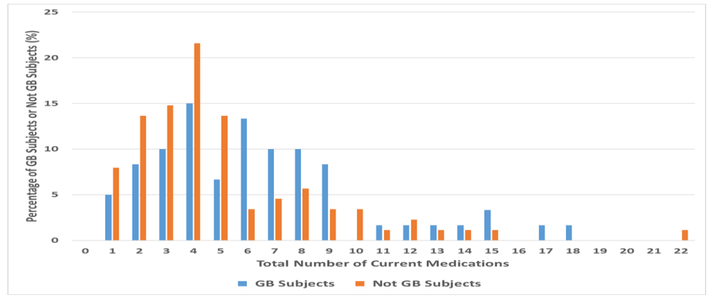


Figure 2. Percentages of GB and not GB subjects versus their number of medications.



CONCLUSION

About 40% of epilepsy patients in this sample at a tertiary care center were found to be generic brittle. A majority of these subjects had reported a history of brand-generic or generic-generic AED switch problems in the past and/or had an opinion against generic formulations. A vast majority of subjects (N=142), whether GB or not GB, had a problem AED, either as a past or current medication. All n=60 GB subjects had a problem AED. A vast majority of not GB subjects (N=88) also had a problem AED. Only N=6 never had a problem AED, and all were not GB. None of the following factors explained which subjects were GB or not GB: sex, age, race (specifically, white versus African American or black, type of epilepsy (specifically, focal versus primary generalized), number of AEDs, number of problem AEDs, presence of an AED allergy, previous epilepsy surgery, number of co-morbidities, and number of auto-immune co-morbidities. While there was some propensity for patients who took 6 or more medications to be GB more frequently than patients who took only 1-5 medications, we conclude that number of medications was not a factor for GB.

FUNDING / GRANTS / ENCORE / REFERENCE or other use

Funding: Supported by FDA contract HHSF223201400188C.

References:

1. Liow K, Barkley GL, Pollard JR, Harden CL, Bazil CW. (2007): Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. Neurology 68:1249–1250.
2. Vossler DG, Anderson GD, Bainbridge J. (2016): AES Position Statement on Generic Substitution of Antiepileptic Drugs. Epilepsy Currents 16:209–211.
3. Andermann F. Duh MS. Gosselin A. Paradis PE. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. Epilepsia. 48:464-9, 2007.
4. Ting, T.Y., Jiang, W., Lionberger, R., Wong, J., Jones, J.W., Kane, M.A., Krumholz, A., Temple, R., and Polli, J.E. (2015): Generic lamotrigine versus brand-name LAMICTAL bioequivalence in epilepsy patients: a field test of the FDA bioequivalence standard. DOI: 10.1111/epi.13095. Epilepsia 56:1415-24.
5. Vaithianathan S, Ting TY, Jiang W, Polli JE (2016): Release of levetiracetam from extended-release tablets that appear intact in patient stool. DOI: 10.1016/j.seizure.2016.05.011. Seizure-Eur. J. Epilep. 40:7-9.