Frequency of generic brittleness in epilepsy patients

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Abstract

- Purpose/ Objective: The objective was to determine the frequency of generic brittleness (GB) in epilepsy patients as defined by clinical history and patient opinion about generic medication.
- Methods: Patients were classified as being GB or not GB, based upon a history of reported problems switching between brand and generic medication (or between generic formulations), the presence of intractable seizures or AED adverse events, patient opinion about generic medications, and whether currently taking brand or generic AED. These factors yielded nine types of GB categories, denoted 1-9.
- Results: N=148 patients completed. N=60 subjects were GB (40.5%), with n=88 were not GB (59.5%). The most common scenario to be GB was type 8, where subject had intractable seizures or an adverse event due to an AED, opined generics problematic, and on a current generic AED. Of the n=60 subjects who were GB, n=41 had a prior switch problem (i.e. brand-generic or generic-generic). A vast majority of subjects with a switch problem were type 6 “classic GB” (21 of 24 subjects) or type 8 (19 of 31 subjects). 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.
- Conclusion: About 40% of epilepsy patients 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.

Introduction

- Professional societies have issued position statements against the substitution of AEDs in the treatment of 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 of and patient predictors for GB are not well established.
- The objective was to determine the frequency of generic brittleness (GB) in epilepsy patients.

Methods

- Patients were classified as being GB or not GB, based on patient clinical history and patient opinion about generic medication.
- Nine types of generic brittleness were conceived, depending on three factors (see Table 1).
- 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 by-proxy) associated with lack of seizure control, adverse effects, a switch problem, or a remnant in stool.

Methods: Table 1. Determinants of GB Status.

Factor	Possible Outcome [Description]
Presence of intractable seizures or AED adverse events	Yes or No [Outcome is “yes” if, in the last 12 months before enrollment, subject had a seizure or an adverse event due to a current AED; however, for those subjects with recurring seizures less frequently than every 12 months, intractability was defined as having at least one seizure within the subject's typical period of time. Adverse events were intended to be limited to potentially formulation-specific adverse events.]
Subject opinion about generics (For the n=10 subjects requiring an LAR, the by-proxy opinion was applied.)	Problematic or not problematic [This factor concerns subject overall opinion about generic drugs in patients in general or for the subject him/her-self.]
Currently taking brand or generic AED	Brand or generic on current AED [If a subject was currently taking a problem AED (n=116), that product determined whether brand or generic. A problematic AED was an AED drug product in a specific patient that the patient (or by-proxy) associated with lack of seizure control, adverse effects, a switch problem, or a remnant in stool.]

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. A vast majority were white or African American (about equal distribution).
- 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 class 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 1-3 describe further patient characteristics.

Results: 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 or having remnants in stool	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

Results: Table 3. Counts of Switch and Remnant Problems for GB and Not GB Patients.

Counts of subjects who are GB (n=60).

Problem	Yes	No
Switch problem	41	19
brand-to-generic switch problem	32	28
generic-to-generic switch problem	10	50
Remnant in stool problem	3	57

Counts of subjects who are not GB (n=88).

Problem	Yes	No
Switch problem	3	85
brand-to-generic switch problem	2	86
generic-to-generic switch problem	1	87
Remnant in stool problem	0	88

Results: Table 4. Problem AED Counts.

N=142 subjects had a problem AED. N=6 never had a problem AED and all were not GB. All n=60 GB subjects had a problem AED at some point in time. A vast majority of not GB subjects also had a problem AED at some point in time.

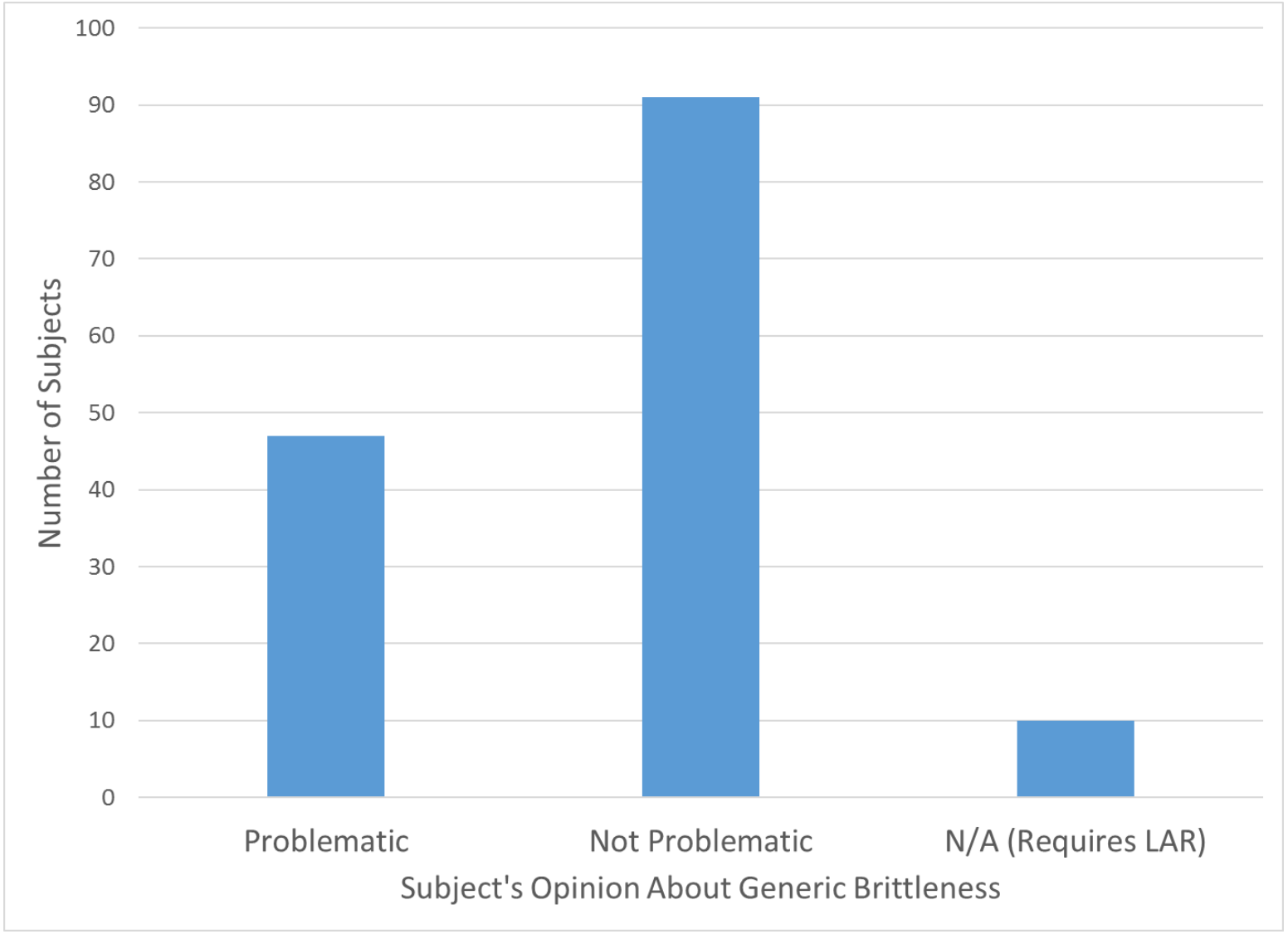
GB Status	Problem AED is a Current Medication	Problem AED is Not a Current Medication
GB	55	5
Not GB	61	21

Results: Table 5. Subject counts by number of AED medications.

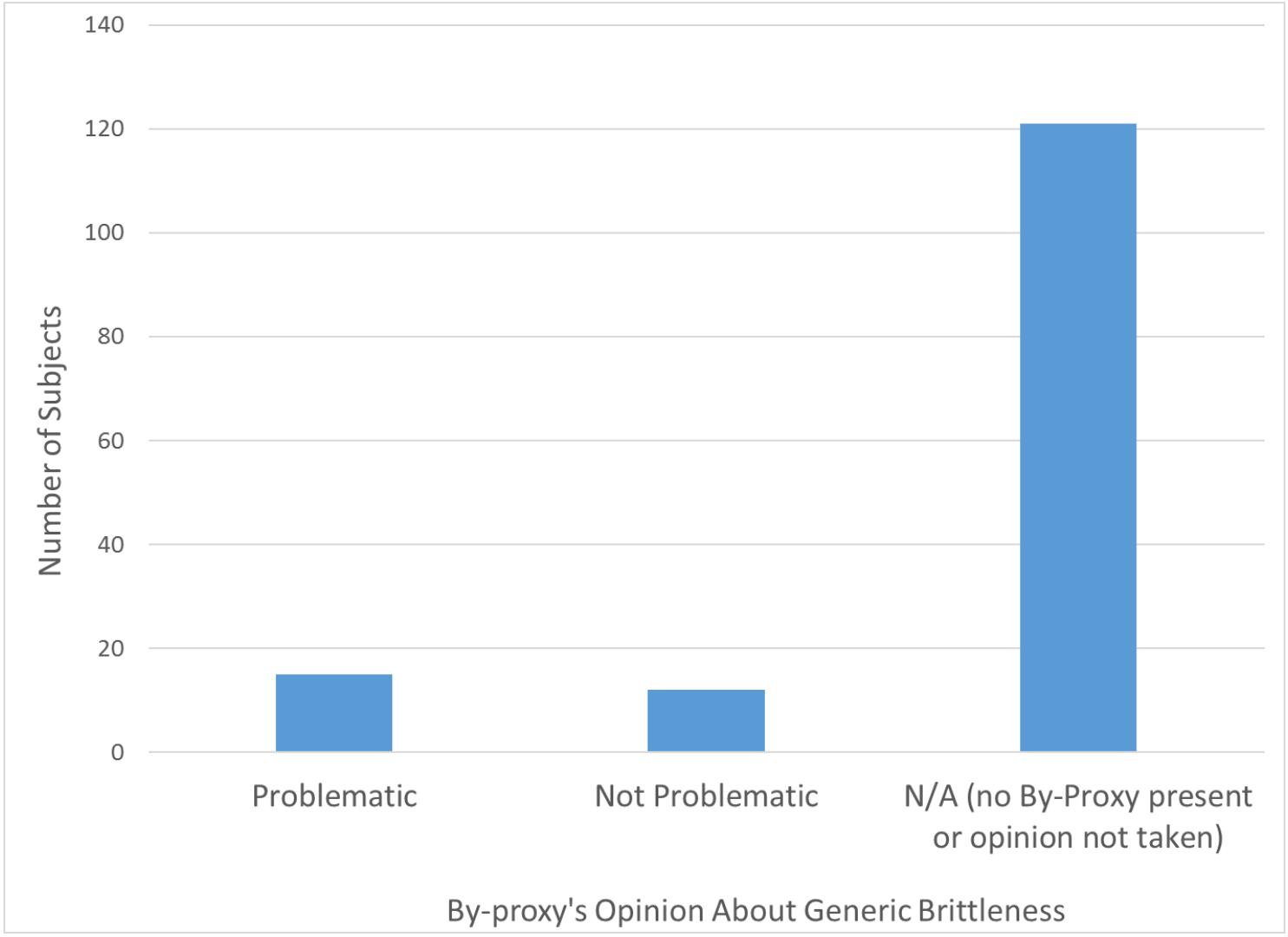
All subjects were taking at least one AED.

Number of Current Anti-Epileptic Drugs	Count (of n = 148 total)
1	46 (31.1%)
2	73 (49.3%)
3	29

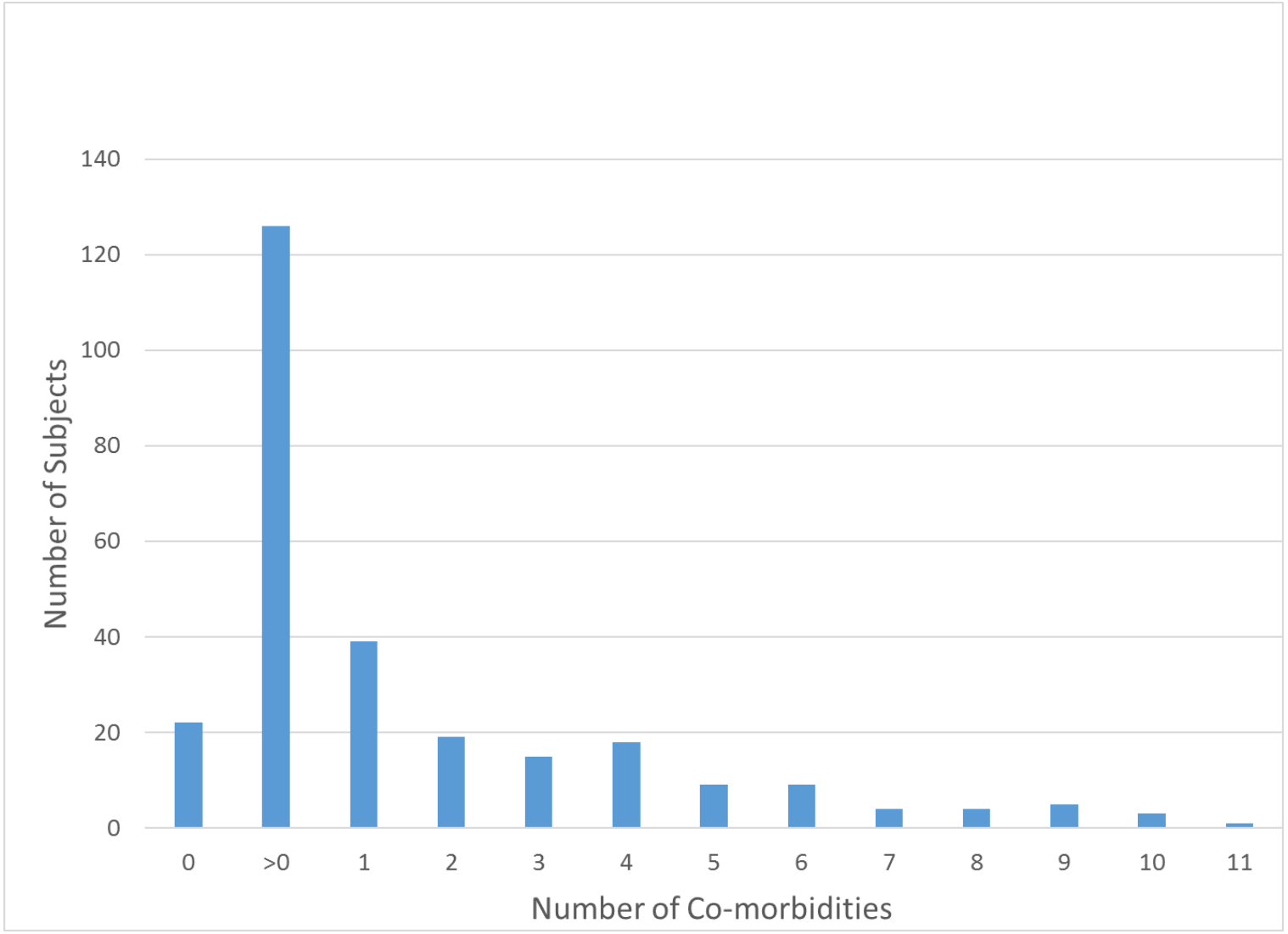
Results: Figure 1. Subject counts by subject opinion about generic brittleness.



Results: Figure 2. Counts of by-proxy opinion about generic brittleness.



Results: Figure 3. Subject count by number of comorbidities.



Conclusion

- About 40% of epilepsy patients 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.

Acknowledgement and References

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- 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. American Epilepsy Society (AES). Position statement on the substitution of different formulations of antiepileptic drugs for the treatment of epilepsy. http://www.AESNET.org
  - 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.