Are neurologists really data driven in selecting epilepsy treatment?

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EDITORIAL

Are neurologists really data driven in selecting epilepsy treatment?

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Neurology is considered a cognitive field, with thoughtful practitioners who are driven by empiric data. With the development of guidelines, practice parameters, and now a review of how physicians practice, this notion could be called into question.

There is no doubt that evidence-based medicine (EBM) should be and is the basis for the practice of modern medicine. Medical school curricula worldwide have recognized the importance of EBM, incorporating it into standard medical student education. The American Academy of Neurology (AAN), recognizing the need to supplement this type of thinking, developed a resident education program covering the basics of EBM.[1] So how do we as neurologists fare in the practice of EBM? Our track record is mixed.

We hear our colleagues utter, "there is no evidence to support that." That statement is more an editorial comment than a valid conclusion. EBM is built on the principle that there exists a hierarchy of evidence, some of which is strong and other weak, with the rest falling somewhere in between. Data, properly collected, should not be considered valid or invalid, but rather strong or weak. Similarly, an individual's opinion should not be thought of as valid or invalid but rather as a type of evidence, albeit weak.

An example can be found in fosphenytoin: when introduced, there was much controversy about its use, not based on evidence but rather on its cost. Many thought it was superior to phenytoin, on a safety basis, although with similar efficacy. Many advocated its use in seizure emergencies. An article described a protocol for its use in nonemergency situations,[2] developed through a consensus process involving epilepsy experts and those who treated seizures. Some of the independent reviewers robustly criticized the article because "it was not data driven." In an accompanying editorial,[3] it was argued that in the absence of double-blind, placebo-controlled studies, we sometimes have to accept experience of clinicians as one level of evidence to support our practices.

The AAN utilizes a well-structured model, classifying studies using a ranking system and translating these into recommendations (tables 1 and 2).[4] It also has a well-developed process for developing evidence-based guidelines and reviews. There are now multiple guidelines for the use of antiepileptic medications.[5–7] Both the AAN and the International League Against Epilepsy have identified that phenytoin and carbamazepine have the highest level of evidence for the treatment of partial onset seizures, with or without secondary generalization. Yet expert consensus, a proxy for real practice, showed that carbamazepine and oxcarbazepine were the first choices for monotherapy, along with lamotrigine and levetiracetam.[8] The problem with this practice, from an evidence standpoint, is that both oxcarbazepine and lamotrigine have only class C evidence supporting their use in this setting while levetiracetam is not rated. Phenytoin, which has class A evidence to support its use, is not among the consensus choices for treatment. It could be argued that the problem lies, in part, with the guidelines themselves, which are of necessity narrowly focused on particular issues. Some guidelines are

Table 1 American Academy of Neurology evidence classification scheme for therapeutics

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:
a) Primary outcome(s) clearly defined
b) Exclusion/inclusion criteria clearly defined
c) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
d) Relevant baseline characteristics presented and substantially equivalent among treatment groups or appropriate statistical adjustment for differences
Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a randomized, controlled trial in a representative population that lacks one criteria a–d
Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

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Table 2 American Academy of Neurology System for translation of evidence to recommendations

Translating evidence to recommendations	Rating of recommendations
Level A rating requires at least one convincing Class I study or at least 2 consistent, convincing Class II studies	A: Established as useful/predictive or not useful/predictive for the given condition in the specified population
Level B rating requires at least one convincing Class II study or overwhelming Class III evidence	B: Probably useful/predictive or not useful/predictive for the given condition in the specified population
Level C rating requires at least 2 convincing Class III studies	C: Possibly useful/predictive or not useful/predictive for the given condition in the specified population
	U: Data inadequate or conflicting. Given current knowledge, test, predictor is unproven

contradictory; many are difficult to interpret and often are not applicable to clinical settings. They often do not take patient-specific variables into account. Guidelines, by definition, will lag behind the development of new evidence. Finally, they tell us what works but not how to use medications, devices, or tests.

Another AAN guideline for temporal lobectomy in the treatment of epilepsy, along with a well-designed clinical trial,[9,10] does not suffer from these criticisms. The evidence is so clear that the presence of this information in highly regarded, and well-read, journals should change behavior. Englot and colleagues,[11] in this issue of *Neurology*®, look at the trends for epilepsy surgery in the United States over the past 20 years, a time when the AAN guideline became public as did the results of the clinical trial for surgery. While one must always be careful when interpreting data from a database (in this case the Nationwide Inpatient Sample hospital discharge database), the data from this study are compelling and tell a somewhat troubling story. Despite an increase in hospitalizations over time for an epilepsy diagnosis, there was no increase in overall surgical rates. In fact, while the total number of hospitals in which surgical epilepsy services increased, the number of procedures decreased. Further, surgery rates were lower in minority patients as well as those insured by Medicaid or Medicare. These trends did not change over the time in this study. There are many reasons that could explain these findings: more antiseizure medications, leading to longer trials and combination of trials of medication; and vagus nerve stimulation, which also became available during the study period. These treatments might delay surgical intervention. Given the widely disseminated data that medically refractoriness can be defined early in the course of medical treatment for epilepsy,[12] the delay or reduction in epilepsy surgery is hard to understand or defend.

So the question posed in the title remains, are neurologists data driven? At best, the evidence appears weak, at least in regard to epilepsy treatments and appropriate referral for surgical intervention. We can, and should, do better.

DISCLOSURE

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REFERENCES

1. The Evidence-based Medicine Toolkit. Available at: www.aan.com/education/ebm/. Accessed on February 27, 2012.
2. Meek PD, Davis SN, Collins DM, et al. Guidelines for the nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. Arch Intern Med 1999;159:2639–2644.
3. Labiner DM. Data vs opinion, phenytoin vs fosphenytoin: the saga continues. Arch Intern Med 1999;159:2631–2632.
4. American Academy of Neurology. Clinical Practice Guideline Process Manual, 2011 ed. St. Paul, MN: The American Academy of Neurology. Available at: http://www.aan.com/globals/axon/assets/9023.pdf. Accessed on February 27, 2012.
5. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004;62:1252–1260.
6. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004;62:1261–1273.
7. Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094–1120.
8. Karceski S, Morrell MJ, Carpenter D. Treatment of epilepsy in adults: expert opinion, 2005. Epilepsy Behav 2005;7:S1–S64.
9. Weibe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345:311–318.
10. Engel J, Weibe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in Association with the American Epilepsy Society and the American Association of Neurological Surgeons. Neurology 2003;60:538–547.
11. Englot DJ, Ouyang D, Garcia PA, Barbaro NM, Chang EF. Epilepsy surgery trends in the United States, 1990–2008. Neurology 2012;78:XXX–XXX.
12. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–319.