

March 14, 2011

Carolyn M. Clancy, M.D., Director
U.S. Department of Health & Human Services
Agency for Healthcare Research and Quality
Effective Health Care Program
VIA ELECTRONIC SUBMISSION

Comments on Draft Comparative Effectiveness Review Topic: Comparative Effectiveness of Medications in Patients with Epilepsy

Dear Dr. Clancy:

The Epilepsy Foundation, American Epilepsy Society, American Academy of Neurology, and the North American Regional Commission of the International League Against Epilepsy are strong supporters of evidence-based medicine and comparative effectiveness research (CER) that incorporates physician, other healthcare professionals, and individual patient needs and concerns in the design, development, evaluation, and use of CER. This type of research can lead to improvements in the quality of care, provide a valuable decision-making resource to healthcare professionals, and increase efficiency in the delivery of healthcare.

With this in mind, we were interested in the CER initiative on epilepsy announced over a year ago. In March 2010, a list of concerns related to the formation and design of the CER initiative in epilepsy was presented to AHRQ. This effort was spearheaded by the Epilepsy Foundation, but had input from members of the other organizations listed in this letter. We appreciated the opportunity to meet with representatives from AHRQ and the dialogue that occurred during that meeting. However, we are greatly disappointed to see that only minimal changes were made to the research plan and evaluation as a result of that discussion.

Appropriate committees and the leadership of the Epilepsy Foundation, the American Epilepsy Society, and the American Academy of Neurology have reviewed the current draft AHRQ Effective Health Care Program on epilepsy that resulted from this research initiative. As a result of this review, we have major concerns with the design, development, evaluation, and use of the proposed Effective Health Care Program on epilepsy. We believe that the outcome of the release of the current document will result in either or both a very negative impact on the care of patients with epilepsy or that healthcare professionals, realizing the major flaws in this research, will determine the AHRQ document to be irrelevant to practice.

Based upon on concerns we shared with AHRQ in March 2010 and our review of the current draft AHRQ Effective Health Care Program on epilepsy, we reiterate issues that were originally raised and highlight other grave concerns from our recent review. Our concerns are briefly summarized here. However, the complexities of these issues require explanations beyond the limitations of this letter, and we welcome ongoing dialogue to provide more complete detail. Briefly stated, our concerns are:

1. Epilepsy is a widely heterogeneous disorder, and not a homogeneous disease state. The underlying pathology for seizures and epilepsy vary greatly (e.g., cortical dysplasia, genetic channelopathies, tuberous sclerosis, traumatic injuries). The latest scientific data clearly demonstrate that seizures are more likely symptoms of vastly different neurologic pathologies and that effective use of antiepileptic drugs (AEDs) differ greatly based on the underlying pathology. For certain types of seizures, the incorrect selection of an AED can result in exacerbation of seizures. Yet, the draft AHRQ document addresses epilepsy and its treatment with AEDs as a monolithic and homogeneous disorder. In our opinion, this is a dangerous approach to the management of epilepsy, and will cause certain patients to have poorer control of seizures.¹
2. There is insufficient published data on all of the underlying pathologies for epilepsy to make accurate comparisons of various AEDs across a wide variety of seizure types. The total number of patients with epilepsy and the broad heterogeneity of the pathology of epilepsy mean that there are insufficient numbers of published studies looking at various types of epilepsy. Based upon a rapidly developing understanding of pathologies for epilepsy, we believe that comparisons of various AEDs are fraught with problems related to statistical power. From our reading of the draft CER document, these issues are inadequately addressed.
3. Teratogenic side effects should be included in an analysis of AEDs. Growing evidence demonstrates that teratogenic side effects differ between AEDs can be severe, and clearly impact therapeutic decision-making.² In this regard, the absence of any consideration of the teratogenic effects of valproate is particularly disconcerting. Current guidelines from the American Academy of Neurology and the American Epilepsy Society recommend, if possible, that valproate be avoided due to the risk of serious congenital malformations and poor cognitive outcomes in the children of women taking valproate during pregnancy.³
4. Outcomes other than seizure control are equally important in the effective use of AEDs. Most people consider seizure control as the primary outcome of importance in treating patients with AEDs. However, numerous studies have shown that many other factors are of equal importance to patients with epilepsy. These factors include, but are not limited to, AED side effects, psychological and psychiatric effects of these drugs, quality of life, ability to work, and the ability to drive a car. In our reading of the draft AHRQ document, only side effects of AEDs were considered in the analysis, and this comparison was poorly done.
5. Different age groups of patients appear to respond differently to AEDs. Multiple studies imply that children and older adults experience different effects when taking AEDs. This difference includes responsiveness to certain treatments and occurrence of adverse effects of AEDs related to age. For example, it is well documented that the risk of hepatotoxicity with valproate in children under 2 years of age is greatly increased, and the occurrence of serious dermatological adverse reactions is increased in children. We did not see any

¹ For an example of the importance of mood and cognition issues in a study that was narrow in its scope, objective and analysis, see: Glauser, T.A. et al. Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy. *N Engl J Med* 2010 362: 790-799.

² Meador, K.J., et al. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. *N Engl J Med* 2009 360: 1597-1605.

³ See also, Jentik, J. et al. Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations. *N Engl J Med* 2010; 362:2185-2193

consideration in the draft document of the differences that a patient's age makes on selection and use of AEDs.

6. The complex pharmacokinetic profiles of many AEDs complicate the effective use of these agents. Several AEDs demonstrate unique pharmacokinetic properties; for example Michaelis-Menten pharmacokinetics for phenytoin and autoinduction for carbamazepine. Additionally, nearly all of the AEDs have important, documented interactions with a variety of other medications. Each of these properties clearly impacts the effective selection and use of these drugs. Once again, our review of the draft AHRQ document did not reveal any serious consideration of this aspect of the effective use of AEDs. A major underlying assumption to this study is that the underlying pathophysiology for seizures is identical or similar for all patients. Seizures – and in essence epilepsy – are now considered to be symptoms of an underlying neurologic pathology. Because that pathology is different between patients who present with similar seizures, it is difficult, if not impossible, to make broad sweeping statements about treatments for epilepsy. One example of this concept is patients who have epilepsy due to tuberous sclerosis compared to patients who have idiopathic partial seizures and epilepsy. Both patients may present with similar clinical symptoms, but the underlying pathology is vastly different and results in very different treatment approaches.⁴
7. The current study does not consider how pharmacokinetic differences between AEDs and between various types of patients relate to the clinical outcomes used in this study. Efficacy and effectiveness of AEDs are very separate issues from the consideration of generic substitution of AEDs. The issue of generic substitution of AEDs revolves around the standards for determining bioequivalence of various products and the clinical implications of these standards. These are very different considerations from determining if a particular AED is efficacious and effective in treating certain seizures. Published data on generic substitution are conflicting and prospective study data are very limited. We believe that including the issue of generic substitution in this document confuses the important consideration of two very different concerns in the treatment of epilepsy.
8. The major reason for the report's weakness is reliance on published studies designed only to answer specific questions in a regulatory context. Thus, these studies are inappropriate to address the 'key questions' posed in the AHRQ report.

Recommendations:

We strongly recommend that AHRQ not publish this report and collaborate with our organizations to define a more appropriate research proposal. AES and AAN have co-developed guidelines for a number of years and invite the collaboration of AHRQ to develop a more meaningful report using the American Academy of Neurology classification scheme for controlled equivalence trials.⁵ In addition, we urge AHRQ to revise its disclaimer language for

⁴ Glauser, Ibid. Study that included 10 years of work and a cost of over \$20 million and could not completely distinguish between absence seizure patients who respond to various AED and those who did not respond, even though there were clinical similarities in the presentation of their seizures.⁵ Similarly, we have learned that structural differences (e.g., mesial temporal sclerosis, cortical dysplasia, no lesions) exist for patients who all present clinically with partial seizures. Little work has been done to explore the differences in response to AED based upon these obvious differences. It is unlikely that patient databases typically used for CER studies will be able to identify known pathophysiological differences in patients with epilepsy.

⁵ See attached AAN classification.

this report, and potentially for all such reports, so that individual patient needs and physician directed care are not overlooked by the reimbursement community's reliance on such reports to make broad coverage decisions.

The report presents the questions that have global scope to the treatment of epilepsy, yet the results are presented with "insufficient" "low strength of evidence" or as "not very informative." We believe that the scientific credibility and usefulness for individuals with epilepsy and their healthcare providers is nonexistent. It would be a disservice to patients, physicians, and researchers to publish this report. We recommend the following issues be addressed before publication:

1. The comparison of CBZ vs new AEDs is weakened by the grouping of all new AEDs in one category. These new AEDs are totally different medications with different mechanisms of action, different efficacy (including broad spectrum efficacy--i.e., effective in both partial and generalized onset seizures), and with dramatic differences in adverse effect profiles.
2. 'New' versus 'old' AED comparisons should be grouped by epilepsy syndrome, with particular attention to the difference between partial and primary generalized seizure syndromes.
3. Issues concerning AED risks and tolerability in special populations, such as small children, women, the elderly, and patients with other chronic diseases should be addressed explicitly.
4. The problem of pharmacokinetic interactions in patients taking other medications should be considered.
5. The comparison of generic to brand name AEDs requires more data to make any conclusions. The published literature on direct comparisons is based on studies that are small and were not adequately powered to detect a difference between treatments. The data is conflicting and well-designed prospective trials are lacking. Therefore, it is not possible to draw definitive conclusions. Generic equivalence studies submitted to FDA are single dose studies on normal volunteers. Future studies should include multiple dose studies on people with epilepsy (preferably those taking concomitant medications); additional studies are indicated examining pharmacokinetic measures in an enriched population of people with epilepsy who believe, or whose physicians believe, there was clinical evidence of non-equivalence between generic and brand products. Future studies should also examine the pharmacokinetic and clinical impact of switching from one generic product to another at the extremes of FDA allowed bioequivalence.

Additionally, there are concerns with the current disclaimer language: "This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied." This report acknowledges that in many areas there are insufficient published data. Given this limitation, a statement that implies this study is adequate to make decisions regarding practice guidelines, drug formularies, or other management tools seems imprudent. We believe a disclaimer that acknowledges the inadequacies in this study and recommends caution in broad application of these results is far more advisable.

At minimum, AHRQ should develop language that includes a warning or caution about the use of the report for coverage or reimbursement decisions for a broad class of patients; and include a statement that the report may have limitations in its application to individual patient needs and physician recommendations. Such a disclaimer may be useful for all such reports, lest they risk being overly broad and discounted by the medical community.

For all of the above reasons, the Epilepsy Foundation, American Epilepsy Society, American Academy of Neurology, and the North American Regional Commission of the International League Against Epilepsy strongly urge AHRQ and the Effective Health Care Program to delay or pull the report from publication and work with key epilepsy experts to revise the proposed research topic and key questions. Our groups and community of experts in the treatment and care of the epilepsies stand ready to assist AHRQ in the development and design of meaningful and useful research. We urge the agency to bring these topics back to epilepsy experts and convene a working group that provides true input and collaboration in developing research questions and study protocols. We continue to encourage you and AHRQ leadership to provide not only an outlet for receiving research topics, but also take a leadership role in convening a collaborative dialogue with epilepsy experts to ensure that research protocols reflect an accurate understanding of epilepsy and its treatment, as well as the areas of critical need for research and how to best design that research.

Our organizations would be interested in setting up a meeting with you to further discuss this epilepsy research to ensure that the project better reflect the current understanding of epilepsy and the areas for needed research to improve patient outcomes and quality of life. Please feel free to contact Angela Ostrom, Epilepsy Foundation Director Federal Relations at (301) 918-3766 or aostrom@efa.org.

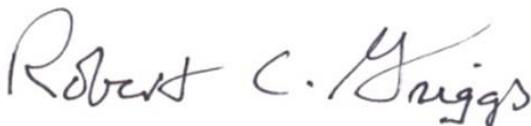
Sincerely,



Rich Denness
President & CEO, Epilepsy Foundation



John M. Pellock, M.D.
American Epilepsy Society President 2011



Robert C. Griggs, MD, FAAN
President, American Academy of Neurology



Sheryl Häut, M.D.
Associate Professor of Clinical Neurology
North American Regional Commission
International League Against Epilepsy

cc: Jeffrey Crowley, Senior Advisor on Disability Policy, White House

Attachment – American Academy of Neurology

Proposed Classification Scheme for Active Control Equivalence Trials

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

The following are also required:

- a. concealed allocation
- b. primary outcome(s) clearly defined
- c. exclusion/inclusion criteria clearly defined
- d. adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.
- e. For non inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment. (e.g. for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II. A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class III. All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.

Class IV. Studies not meeting Class I, II or III criteria including consensus or expert opinion.

* Note that numbers 1-3 in Class I, e, are required for class II in equivalence trials. If any one of the three are missing, the class is automatically downgraded to a Class III.