Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: **Comparative Effectiveness of Medications in Patients with Epilepsy**

Draft review available for public comment from February 14, 2011 to March 14, 2011.

Research Review Citation: Talati R, Scholle JM, Phung OJ, Baker WL, Baker EL, Ashaye A, Kluger J, Quercia R, Mather J, Giovenale S, Coleman CI, White CM. Comparative Effectiveness of Medications in Patients with Epilepsy. Comparative Effectiveness Review No. 40. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) Rockville, MD: Agency for Healthcare Research and Quality. October 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Executive Summary	"The newer antiepileptic medications compared versus each older agent varied in the comparisons" I don't understand this sentence.	We have made the following change: The newer antiepileptic medications compared versus each older agent varied depending on the endpoint being evaluated.
Peer Reviewer #2	Executive Summary	"Switching from an innovator to a generic antiepileptic medication may increase the risk of hospitalization and hospital stay duration but may not increase outpatient service utilization." Switching from innovator to generic is part of KQ2. Why is it discussed here?	This information is discussed in Key Question 1 because it pertains to the outcome of medical service utilization, which is a part of Key Question 1.
Peer Reviewer #2	Executive Summary	"If generic versions do not meet the FDA guidance for an "A" rate generic, the differences between the innovator and generic group may be greater than when limited to "A" rated versions." This is unlikely to be a valid argument. There are no non-"A-rated" generic medications available in the US. This may be primarily an issue of the use of appropriate technical language.	Remember that many of these trials are done outside the United States where they may or may not be "A" rated. So when we use their data sets and pool them we need to entertain the possibility that the blood concentrations would be more disparate than when innovator and generic "A" rated products were used. It is probable that if "A" rated versions of the drug provide very similar blood concentrations than the differences in response would be less than a scenario where the products were not "A" rated products and had more variations in concentration.
Peer Reviewer #2	Executive Summary	"However, these studies could not control for co-morbidities or changes in other medications and their associated dosages which are known to impact seizure occurrence." These studies "did not" control. They could have attempted to control for many of these co-morbidities using the data they had available.	We have made the suggested change.
Peer Reviewer #2	Executive Summary	"In this study, significant increases in hospitalization of emergency room visits were seen in unadjusted analyses [OR 1.51 (1.29, 1.76)] but no significant difference was found after adjusting for confounders [OR 1.08 (0.91, 1.29)], although the direction of effect was the same." Suggested adding: as the previous studies.	We have made the following change: In this study, significant increases in hospitalization of emergency room visits were seen in unadjusted analyses [OR 1.51 (1.29, 1.76)] but no significant difference was found after adjusting for confounders [OR 1.08 (0.91, 1.29)], although the direction of effect was the same as the unadjusted analyses.

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Peer Reviewer #2	Executive Summary	"In total, the three observational studies suggest that switching from an antipeilpetic medication to an "A" rated version of the product may increase the utilization of a composite of medical services (hospitalization, emergency department visit, with or without utilizing ambulance services for epilepsy)." Suggested adding: two of the three observational studies suggest… The adjusted number from Devine et al were not statistically significant, thus it is inappropriate to conclude that it suggested that switching increased utilization of composite medical services. If included you are disregarding the statistics.	We now say "In total, two of the three observational studies suggest that switching from an antipeilpetic medication to an "A" rated version of the product may increase the utilization of a composite of medical services (hospitalization, emergency department visit, with or without utilizing ambulance services for epilepsy)." The third observational study had the same direction of effect but without significant differences being found.
Peer Reviewer #2	Executive Summary	"What this data does show is that a number of neurologists and patients with epilepsy have concerns about switching between versions of antiepileptic medications." What is the rationale for this statement? This seems to be a very subjective statement. How do the studies sighted directly support this statement.	We have now removed this statement.
Peer Reviewer #2	Executive Summary	"Many trials were excluded from the subgroup analysis because they did not subdivide their populations. In many cases, one subpopulation was evaluated for an outcome but the other subpopulation was not. Therefore, we cannot identify a subpopulation for which differential effects on an outcome might have occurred based on subgroups. The results generally followed those in the base case evaluations although were much less likely to be significantly different." This entire section is difficult to follow. Can you please clarify. Especially the final sentence in the paragraph.	We have made the following change: The results of the subgroup analysis were similar to the base case evaluations. Although, in the subgroup analysis, the results were less likely to show significance.
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Executive Summary	At the end of the first paragraph of the executive summary on page ES19 the word "more" seems to have been transposed with the word "less," based on the preceding comments in the paragraph.	We have made the following change: "So when qualitatively assessing the balance of benefits to harms, carbamazepine offers similar comparative effectiveness versus newer antiepileptic medications with greater benefit but more harms. Newer antiepileptic medications may have some advantages over valproic acid and phenytoin in comparative effectiveness with similar benefits but less harms."

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Peer Reviewer #1	Introduction	Well written and succinct. Authors may wish to consider using the glossary to further describe the FDA classification schema for innovator and generic products (e.g. what is meant by "A" rated generics).	Thank you, we have included a definition of bioequivalent drug products, therapeutic equivalence and what is meant by an “A” rated generic in the glossary.
Peer Reviewer #2	Introduction	Add “to” in front of “suggest” in the sentence, “Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is sufficient evidence suggest a common underlying mechanism.”	Thank you, the change has been made.
Peer Reviewer #3	Introduction	The results of the SANAD study are not appropriately represented in the Background. It is also surprising that the Background does not mention the large VA Coop Study in geriatric patients, which directly compared new and old AEDs. There are errors of omission in the mechanisms of AEDs in Table 3, which suggest either carelessness or lack of expertise in this area.	The background section is supposed to concisely set the need for the review and is not an exhaustive review of mechanisms of action or individual trials. The mechanisms of action were all derived from recent book chapters or reviews from experts in the field. While we might not have included the VA COOP study in the background, we did include all trials meeting our inclusion and exclusion criteria in the report itself, including evaluating this one
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Introduction	While an improved understanding of the comparative merits of different therapeutic options would be useful, recent literature suggests that the old vs. new dimension is not a clinically relevant one when selecting treatments. Current literature recommends that the primary factors to be considered in treatment selection include efficacy, tolerability, toxicity, ease of use, treatment of comorbid conditions and cost. Importantly, for these epilepsy outcomes there is as much variability within the new AED group as there is between the old and new groups	Thank you for your comment.
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Introduction	In the summary table of AEDs on page 6 of the draft report, the listing for "Seizure Types Treated" for LEV is inconsistent with product labeling. Levetiracetam is indicated for the adjunctive treatment of primary generalized tonic clonic seizures (age >6) and myoclonic seizures in JME (age>12).	The table has been updated to reflect the suggested changes.

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Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Introduction	In the summary table of AEDs on page 6 of the draft report, the listing for "Mechanism of Action" for lacosamide is inconsistent with product labeling and current literature. In the summary table, both oxcarbazepine and lacosamide are listed as working via "Na+ channel inhibition." However, the oxcarbazepine labeling states, "Produce blockade of voltage-sensitive sodium channels," while the lacosamide labeling states, "Selectively enhances slow inactivation of voltage-gated sodium channels."	The table has been updated to reflect the suggested changes.
O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	Introduction	With regard to the document as it stands, we advocate the following changes in key summary wording: Line no. 36, "The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services." Please add, "However, extensive quantitative review of the literature shows that we are unable to achieve this goal at this time."	This is standard AHRQ report language. AHRQ reports are intended to be used to inform healthcare decisions. Even when evidence is limited, people still need to make decisions, and EPC reports help to present the evidence that is available to make the best decision that they can.
O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	Introduction	With regard to the document as it stands, we advocate the following changes in key summary wording: Line no.38 "This report is intended as a reference and not as a substitute for clinical judgment." Should be CHANGED TO "This report is intended as a reference to guide future research".	This is standard AHRQ report language. EPC reports are intended to be a reference to help people make decisions. They do not make clinical recommendations, but present the state of the literature so that decision-makers can consider what evidence is available when making their decisions. They are also intended as a reference for identifying research gaps and future research as well.
Peer Reviewer #1	Methods	Search strategy and study selection process appear consistent with other well-designed meta-analyses already in print. Also appears consistent with AHRQ Methods Guide for Comparative Effectiveness Reviews (Feb 2011).	Thank you.
Peer Reviewer #1	Methods	Authors may wish to define the PICOTS typology used in Table 7 on page 52 of 576. The features are spelled out in the table, but the average reader may not make the connection that PICOTS stands for population, intervention, comparator, outcomes, timing and settings). I did not see this defined anywhere else in the document.	The PICOTS typology has now been defined in the methods section.
Peer Reviewer #2	Methods	In the sentence, "The Evidence Based Practice Center (EPC) drafted a topic refinement document with proposed key questions after consult with Key Informants." "TheEvidence" should be The Evidence.	Thank you, the change has been made.

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Peer Reviewer #2	Methods	"Two independent investigators conducted systematic literature search of MEDLINE (from 1950 to the present)." What is "the present" – there should have been a final cut off date of the MEDLINE search. Was it March 2, 2010?	We have specified March 23, 2011 instead of "the present" now that we updated our search as required in the EPC methods guide.
Peer Reviewer #2	Methods	"Controlled clinical trials could be pooled as could controlled observational studies but could not be pooled together." This sentence is unclear. Suggest: Controlled clinical trials could be pooled and controlled observational studies could be pooled, but clinical trials and observational studies could not be pooled together.	We have made the suggested change.
Peer Reviewer #2	Methods	"In the event where there was more than one treatment group versus control, each treatment group was treated as a separate trial of meta-analysis, dividing the control group sample size by the same number of treatment arms." There should be a reference for this approach. I believe this approach is supported in the EPC methods guide.	Thank you, we have now provided the reference for this technique from the Cochrane Handbook of Systematic Reviews.
Peer Reviewer #2	Methods	"Statistical heterogeneity was addressed using I^2 statistic…" the I squared does not "address" statistical heterogeneity. Maybe quantified would be a better word here.	We have replaced "addressed" with "assessed".
Peer Reviewer #2	Methods	Define "present" when discussing search strategy	We have specified March 23, 2011 instead of "the present" now that we updated our search as required in the EPC methods guide.
Peer Reviewer #2	Methods	"Medical service utilization (office/ED visits and hospitalizations)" the Zachry and Rascati oberservational studies both included additional utilization outcomes (ambulance use). These should be included here as well.	Thank you. The information about ambulance service utilization is already included in the report under Key Question 1 composite of medical service utilization for innovator versus generic antiepileptic medications.
Peer Reviewer #2	Methods	"Statistical heterogeneity was addressed…" identified or assessed, but not addressed	We have replaced "addressed" with "assessed".
Peer Reviewer #2	Methods	"Subgroup and Sensitivity Analyses" I would like to know why there were no subgroup / sensitivity analyses done base upon study quality?	Given the large number of outcomes and the large number of subgroup and sensitivity analyses to be performed, subgroup and sensitivity analysis based on study quality was not performed.

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Peer Reviewer #2	Methods	"Because all of the included studies were randomized controlled trials with few limitations, they were considered to have a low risk of bias" I"m not sure what this means. This seems to be a very general statement, but it is not correct for all of your review.	We identified where the studies included had limitations and where downgrades in individual study strength of evidence were needed. However, in the main sections of the paper we needed to use more summarative language to convey the general points.
Peer Reviewer #2	Methods	"We also considered measures of heterogeneity from our meta-analyses in evaluating consistency" Please develop this statement further. How were they "considered"?	Statistical heterogeneity was assessed using the I^2 statistic evaluate the degree of inconsistency not due to chance across studies and ranges from 0 to100 percent with values of >50 percent representing important statistical heterogeneity.
Peer Reviewer #2	Methods	"An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion." I don't agree with this approach. Precision is more directly quantifiable based upon the statistics presented. An estimate can be very precise (i.e. a small confidence interval) while cross the null value and imply superiority or inferiority. It appears that you would call that and "imprecise estimate". Also an estimate can only imply superiority while having a very wide confidence interval (RR of 7.0 95% CI 1.2 - 26.8 for example). The approach that the authors are using should be justified with a reference.	Please see the GRADE Handbook for systematic reviews available at www.who.int/hiv/topics/mtct/grade_handbook.pdf In the help guide under the heading of "About imprecision (random error) for authors of systematic reviews" it shows that a wider confidence interval that is entirely on one side of unity is precise as is a tight (narrow 95% CI) insignificant effect with a pooled effect close to unity. However, other scenarios where the 95% CIs cross unity are imprecise.

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Peer Reviewer #3	Methods	Combining all of the new AEDs together for comparison to individual old AEDs is like comparing apples to oranges. The individual new AEDs have differences in mechanisms, display different side effect profiles, and possess differences in efficacy for types of epilepsy (e.g., partial epilepsy vs. primary generalized epilepsy). Theoretically, half of the new AEDs could be better and half worse than carbamazepine, and this analytical approach would find no differences. Further, different types of epilepsy are lumped together in the analysis. In this case, a drug with superior effectiveness for one type of epilepsy but inferior for another would show no differences (e.g., valproate in primary generalized vs. partial epilepsies). There is a priori plan or justification provided for the group comparisons used in the analyses, so that they appear to simply be a post hoc approach based on convenience of sample size. Why not just compare all old AEDs to new AEDs? This is a rhetorical question. Although the power would be improved, it would increase the problem of noise in the analysis by mixing older AEDs with differences in mechanisms and efficacy in epilepsy subtypes.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions. Clearly, healthcare clinicians need to understand the nature of the literature, the strength of that evidence, and the applicability of the evidence. We were challenged with evaluating the literature that currently exists. We recognized heterogeneity and attempted to explore it via sub group analysis but the data was limited. While there are some important differences between agents within the older and newer groups, we do not believe that the differences between groups are too marked to allow pooling. The drugs in our CER are all used to control or reduce seizure frequency, work in the central nervous system to cause their effect, are all given via the same route of administration, and many share aspects of their mechanism of action (for example sodium channel or glutamate/glutyl-amino-butyric-acid effects) in a broad sense.

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Peer Reviewer #3	Methods	The chosen outcomes for this review are simply listed without any justification for selection. Why was hypotension chosen? This is seldom an issue for antiepileptic drugs unless they are given intraveneously. In contrast, why are bone density, cognition, weight gain, lipid changes, and pregnancy outcomes not chosen, which are clearly concerns for certain antiepileptic drugs. In the Discussion, there is a statement that "Factors such as pregnancy or desire to become pregnant within a specified period of time … can be used to select an optimal therapeutic choice for an individual patient." Women of childbearing potential comprise a sizable portion of patients with epilepsy. To not assess this issue seems out of touch with gender research concerns raised by the US government. This is especially unfortunate given the large amount of new information available on AEDs and pregnancy outcomes; see the recent guideline statement by the American Academy of Neurology, which has concluded that valproate poses an increased risk for both congenital malformations and cognitive impairment in children exposed in utero.	The outcomes chosen for the report come from suggestions provided when the research topic is submitted to the Effective Health Care Program and from the topic refinement phase conducted in conjunction with Key Informants. The team used a process to identify relevant clinical outcomes by engaging stakeholders such as patient payers, providers, and other decision-makers and invited public comment as well. Outcomes were chosen based on the discussion from different stakeholders, and if we all agreed on a particular outcome, it was included. There were many other suggested outcomes but we agreed on the ones that seemed relevant.
Peer Reviewer #4	Methods	The inclusion and exclusion criteria limit the validity of the data because of the inadequate classification scheme currently being used. The authors are very sophisticated statisticians and have done a good job with inadequate information.	Thank you. The current classification scheme used to define the different types of epilepsy and the classification schemes that have been used in the past as well as the inclusion and exclusion criteria used by the studies relevant to the topic make it extraordinarily difficult to identify what type of epilepsy enrolled patients had. We were as precise in analyzing the data based on epilepsy type as the literature base would allow.
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Methods	The epilepsy patient population's needs are also heterogeneous. Type of epilepsy, underlying syndrome, etiology, environmental factors, genetic factors and the patient's history of seizure frequency, density, and clustering all contribute to whether or not a patient will respond favorably to AED therapy.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Methods	While an improved understanding of the comparative merits of different therapeutic options would be useful, recent literature suggests that the old vs. new dimension is not a clinically relevant one when selecting treatments. Current literature recommends that the primary factors to be considered in treatment selection include efficacy, tolerability, toxicity, ease of use, treatment of comorbid conditions and cost (Asconapé J. Neurol Clin. 2010 28(4): 843-52). Importantly, for these epilepsy outcomes there is as much variability within the new AED group as there is between the old and new groups (Stern J. Current Treatment Options in Neurology 2009 11(4): 273-84; Johannessen-Landmark C. Expert Rev Neurother. 2010 10(1):119-40; Morrell M. Semin Neurol. 2002 22(3):247-58)	Thank you for your comment. You are correct that there is likely variability between newer agents in terms of efficacy and safety and there are some limitations with lumping them into a "newer" group. However, when we looked at the newer drugs actually compared, there are only but a few newer drugs which helps with variability in that group but limits applicability to newer agents not studied. We were forthcoming with that applicability weakness in our report.
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Methods	The epilepsy patient population's needs are also heterogeneous. Type of epilepsy, underlying syndrome, etiology, environmental factors, genetic factors and the patient's history of seizure frequency, density, and clustering all contribute to whether or not a patient will respond favorably to AED therapy (French JA. Epilepsia 2007; 48 Suppl 1:3-7; Loddenkemper, T. Epileptic Disord. 7 2005(4), 308-16). Care and treatment selection should reflect this heterogeneity.	Thank you for your comment.
Peer Reviewer #1	Results	Results appear to be complete and appropriately detailed. Each section follows a similar method of data presentation, which I found to be helpful in improving readability of a large amount of data. Study characteristics are well detailed.	Thank you.
Peer Reviewer #1	Results	Major findings in each key question discussion section are clearly stated.	Thank you.
Peer Reviewer #1	Results	Authors may wish to update line 32 on page 94 of 576. The sentence currently states that many of the trials did not use FDA approved "A" rated generics..." I think that a better representation of the facts would be to say that "many of the trials did not specify (or report using) FDA approved A-rated generics..."	Thank you, we made that change as requested.

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Peer Reviewer #2	Results	"The risk of being seizure free for either 12 or 24 months was significantly lower for newer antiepileptic agents versus carbamazepine. In individual newer antiepileptic medication versus carbamazepine analyses, the risk of being seizure free was significantly reduced by gabapentin or oxcarbazepine versus carbamazepine at 12 and 24 months and for topiramate versus carbamazepine at 12 months. No differences in 12- or 24-month seizure freedom were seen for newer antiepleptic medications versus valproic acid although this was based on a single controlled clinical trial. No trials were available evaluating newer antiepileptic medications versus controlled/sustained release carbamazepine or phenytoin." This is poorly worded. I really can't tell after several readings if being on carbamazepine improves your seizure free time or makes it worse. Consider revising this to clearly describe direction of effect.	We have made the following change: The risk of seizure freedom at 12 or 24 months was significantly lower for newer antiepileptic agents versus carbamazepine, therefore patients were more likely to be seizure free at 12 or 24 months when receiving carbamazepine compared to newer agents. When either gabapentin or oxcarbazepine were compared to carbamazepine individually, the risk of seizure freedom was significantly reduced at 12 and 24 months, therefore patients were more likely to be seizure free at 12 and 24 months when receiving carbamazepine compared to gabapentin or oxcarbazepine. When topiramate was compared to carbamazepine the risk of seizure freedom at 12 months was significantly reduced, therefore patients were more likely to be seizure free at 12 months when receiving carbamazepine.
Peer Reviewer #2	Results	"Four instruments were used to assess for health-related quality of life in the newer versus older antiepileptic medication evaluation and the instruments have differences in the importance of subscales or which areas are evaluated." Change to: ". The instruments..." Change to: "as well as"	We have made the following change: Four instruments were used to assess for health-related quality of life in the newer versus older antiepileptic medication evaluation. The instruments have differences in the importance of subscales as well as the areas that are evaluated

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Peer Reviewer #2	Results	Thirteen reports were conducted in the United States;[50,51,66,68,69,71,72,76,78,84,89,90,93] two reports were conducted in China;[92,94] two reports were conducted in Finland;[47,53] one report was conducted in Germany;[80] three reports were conducted in the United Kingdom;[61,85,87] three reports were conducted in Italy;[56,75,91] one report was conducted in Korea;[83] one report was conducted in the Netherlands;[65] eight multinational report conducted in Europe[49,52,63,64,67,70,82,86] one multinational report was conducted in Asia, Europe, North America, and South America;[88] one multinational report was conduced in Australia and Europe;[55] one multinational report was conducted Australia, Europe, and South Africa;[62] one multinational report was conducted in Australia, Europe, South Africa, the United States, and South America;[74] and one multinational report was conducted in Europe and South Africa.[81]" Insert "were" Insert "reports" Insert "was" Insert "in" Insert ","	We have made the suggested changes.
Peer Reviewer #2	Results	"Three reports did report any country." Insert "not"	We have made the suggested change.
Peer Reviewer #2	Results	"All of the reports were funded by the pharmaceutical industry" Reference 35 was not funded by the pharmaceutical industry; it was funded by Express Scripts, a prescription benefit manager. PBM's such as express scripts have very different motivations, and could be considered biased towards generics rather than biased towards brands. Please double check all of these statements for accuracy.	We have changed the statement to the following: Eight of the reports were funded by the pharmaceutical industry, and one was funded by industry.

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Peer Reviewer #2	Results	"The use of combination therapy was reported in four of the eight trials and the percent of patients on combination treatment ranged between 52 and 94 percent." Reference 35 also reported use of multiple AEDs.	We have changed the statement to the following: "The use of combination therapy was reported in five of the eight trials and the percent of patients on combination treatment ranged between 52 and 94 percent." We have also changed the percentage of patients on combination therapy in the evidence tables in the appendix of the report.
Peer Reviewer #2	Results	"The cases were more likely to have undergone a switch from one "A" rated antiepileptic medication to another "A" rated version of the medication in the base case analysis [OR 1.81 (1.25, 2.63), 11.3 percent versus 6.5 percent], the analysis excluding patients with a concurrent change in dosage [OR 2.01 (1.19, 3.40), 9.7 percent versus 5.1 percent], and the analysis excluding patients with Medicaid coverage [OR 1.86 (1.26, 2.73), 11.3 percent versus 6.4 percent]." It is important to emphasize that this was essentially an unadjusted result. They did not conduct a multivariate analysis in this study. This needs to be emphasized as it is a VERY biased result because of the failure to conduct an adjusted analysis.	We have added the following statement: However, these results are unadjusted and therefore may be biased.
Peer Reviewer #2	Results	"After adjusting for potential confounders, the odds ratio was 1.08 (0.91–1.29)." Please note that this was not statistically significant. You note the statistical significance in previous studies in prior sections. You should note it here.	We have made the following change: After adjusting for potential confounders, the odds ratio was non-significant.
Peer Reviewer #2	Results	"Upon reanalysis, the adjusted odds ratio of acute epilepsy exacerbations were increased to 1.14 (0.99–1.31)." As above, not statistically significant.	We have made the following change: Upon reanalysis, the adjusted odds ratio of acute epilepsy exacerbations were non-significantly increased to 1.14 (0.99–1.31).
Peer Reviewer #2	Results	"The risk of remaining seizure free for duration of study is nonsignificantly increased by 8 percent when topiramate is used versus carbamazepine [RR 1.08 (0.91 to 1.27)] (Appendix J Figure 26)." insert "the" before duration	We have made the suggested change: The risk of remaining seizure free for the duration of study is non-significantly increased by 8 percent when topiramate is used versus carbamazepine [RR 1.08 (0.91 to 1.27)] (Appendix J Figure 26).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	"The risk of remaining seizure free for duration of study is nonsignificantly decreased by 30 percent when vigabatrin is used versus carbamazepine [RR 0.70 (0.49 to 1.01)] (Appendix J Figure 26)." for "the" duration	We have made the suggested change: The risk of remaining seizure free for the duration of study is non-significantly decreased by 30 percent when vigabatrin is used versus carbamazepine [RR 0.70 (0.49 to 1.01)] (Appendix J Figure 26).
Peer Reviewer #2	Results	"Fifteen randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration." for "the" study	We have made the suggested change: Fifteen randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for the study duration.
Peer Reviewer #2	Results	"No significant statistical heterogeneity (I2: 0 percent) or publication bias was detected (Egger's p=0.997) was detected." remove "was detected"	We have made the suggested change: No significant statistical heterogeneity (I2: 0 percent) or publication bias was detected (Egger's p=0.997).
Peer Reviewer #2	Results	The risk of remaining seizure free for study duration is nonsignificantly decreased by 3 percent when newer antiepileptic medications are used versus valproic acid [RR 0.97 (0.87 to 1.08)] (Appendix J Figure 30) change to "was"	We have made the suggested change: The risk of remaining seizure free for study duration was nonsignificantly decreased by 3 percent when newer antiepileptic medications are used versus valproic acid [RR 0.97 (0.87 to 1.08)] (Appendix J Figure 30).
Peer Reviewer #2	Results	"A high level of statistical heterogeneity was detected (I2: 70.3 percent), but tests for publication bias was could not be performed." Remove "was"	We have made the suggested change: A high level of statistical heterogeneity was detected (I2: 70.3 percent), but tests for publication bias could not be performed.
Peer Reviewer #2	Results	"No statistical heterogeneity was detected (I2: 0 percent), but tests for publication bias was could not be performed." Remove "was"	We have made the suggested change: No statistical heterogeneity was detected (I2: 0 percent), but tests for publication bias could not be performed.
Peer Reviewer #2	Results	"No statistical heterogeneity was detected (I2: 0 percent), but tests for publication bias was could not be performed." Remove "was"	We have made the suggested change: No statistical heterogeneity was detected (I2: 0 percent), but tests for publication bias could not be performed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	"No statistical heterogeneity was detected (I2: 0 percent), and tests for publication bias was could not be performed." Remove "was"	We have made the suggested change: No statistical heterogeneity was detected (I2: 0 percent), and tests for publication bias could not be performed.
Peer Reviewer #2	Results	"No statistical heterogeneity was detected (I2: 0 percent), and tests for publication bias was could not be performed." Remove "was"	We have made the suggested change: No statistical heterogeneity was detected (I2: 0 percent), and tests for publication bias could not be performed.
Peer Reviewer #2	Results	Two observational study comparing newer antiepileptic medications to valproic acid reported data on skin rash. Change to "studies"	We have made the suggested change: Two observational studies comparing newer antiepileptic medications to valproic acid reported data on skin rash.
Peer Reviewer #2	Results	No statistical heterogeneity (I2: 0 percent) or publication bias (Egger's p=0.540) was not detected. Remove "was"	We have made the suggested change: No statistical heterogeneity (I2: 0 percent) or publication bias (Egger's p=0.540) was detected.
Peer Reviewer #2	Results	"However, even with adjusting for confounders, the study by Devine and colleagues still had the same direction of effect as those of Zachry and colleagues and Rascati and colleagues." Above crossed out and added: The adjusted number resulted in a non-significant finding. It could have been the opposite direction per the 95% CI. I find this statement misleading and false. It appears that the authors are disregarding the statistics in this part of the key question, while emphasizing it in other parts. This should be justified or revised to be consistent with the rest of the document.	This is what we found in our report. I understand that your observational study did not find a significant effect and we do not say that it does. But the direction of effect is similar to the others and we feel that this is important for our stakeholders to know. We are generating these reports for a broad number of stakeholders, not just methodologists or not just clinicians.
Peer Reviewer #2	Results	"Unfortunately, these observational studies, while well conducted, have inherent biases and limitations which reduce their internal validity." "Internal" not necessary	We need to differentiate between internal validity and external validity (applicability) here.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	"Future research should not be directed at evaluating whether "A" rated versions of innovator and generic medications provide similar seizure control, pharmacokinetics, and tolerability in a large population. Instead, randomized, controlled trials should be directed at determining whether patients switched from one "A" rated version of a medication to another "A" rated version have alterations in intermediate and final health outcomes versus continuing on their original antiepileptic medication." The author's recommendation that future RCT research should NOT be directed at assessing "A" rated generics versus branded agents for seizure control and tolerability, may be premature. It may be difficult to justify a switching study (which will be very difficult to implement) before it is 100% agreed that they have equivalent efficacy.	Thank you, we have changed the statement to address this comment. We now say "Whether "A" rated versions of innovator and generic medications provide similar seizure control, pharmacokinetics, and tolerability in a large population is not as important as conducting randomized, controlled trials directed at determining whether patients switched from one "A" rated version of a medication to another "A" rated version have alterations in intermediate and final health outcomes versus continuing on their original antiepileptic medication." You may be correct except the preliminary data from controlled trials suggests that when an innovator or a generic is started in a population at the same time that the results are similar whereas when people are being switched in observational studies, there is an indication of potential harm. It seems that the most pressing patient safety evaluation would be in this group even though it may be harder to do. This seems to be supported by some epilepsy position statements where their biggest concern is that of switching and not the risk of starting someone on a generic versus an innovator product.
Peer Reviewer #3	Results	Given the flaws in methodology, the results are meaningless.	This comment needs to be more specific in order for us to respond.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	"In patients with epilepsy…" Epilepsy is not a unitary disease. Epilepsy, epidemiologically defined, means only that a patient has had more than one seizure on more than one occasion. Seizures have a multitude of "causes". The basic seizure threshold in all humans is polygenetically determined. Anyone can have a seizure under certain circumstances, though some are more resistant than others. The current classification dates back to the 1960s and in the minds of many experts is seriously flawed. There is currently a good deal of controversy taking place. Seizure syndromes are being increasingly defined and maybe more relevant to the choice of antiepileptic drugs than are seizure types alone. The task of obtaining a precise and accurate diagnosis of seizure type is not trivial. Thus many of the patients included in the literature were not properly classified.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions. Clearly, healthcare clinicians need to understand the nature of the literature, the strength of that evidence, and the applicability of the evidence. We were challenged with evaluating the literature that currently exists. As you saw in the extensive report we tried to conduct numerous subgroup analyses and analyzed data in a number of ways to account for heterogeneity when such heterogeneity was anticipated or found. But the data on subgroups was either sparse or of poor quality.
Peer Reviewer #4	Results	We know that the disorder is not "unitary" and that the heterogeneities are too great to permit aggregation of cases in many situations. After all, not all patients respond to any one drug or any one class of drugs (except in anesthetic doses). The differences in pharmacodynamics, pharmacokinetics, and pharmacogenetics are vast.	In the subgroup analyses of our review, we were careful to aggregate only studies that reported enrolling a single type of epilepsy. Studies that included multiple types of epilepsy were not pooled. Therefore we are limited by the data that is available and we agree that with advances in detection of epilepsy subtypes, especially genetic testing, there may be some level of inaccurate diagnosis in these trials. However, we can only summarize the literature as it currently exists.
Peer Reviewer #4	Results	Therefore, Question 1 is unanswerable. All that can be said is that a particular drug or class of drug is effective in some patients and not all patients of the group studied. The group is so variable that broad generalizations are limited.	In the report, individual drug comparisons were made that you may find more relevant. We could not, given the space available, address individual comparisons in the executive summary. We think you will find the information you desire in the body of the report though. Please also see our response to your comment above which will help to answer this comment as well.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	The studies included in the report, indeed nearly all the studies in the literature, were not designed to answer the question of comparative efficacy. FDA rules force the studies of new antiepileptic drugs into (largely) a "not less effective than" design. Although not part of the experimental design/objectives, all the studies demonstrate that new drugs are more effective in some patients because almost no pure placebo control groups have been used. The studies use an add-on design.	Our review sought to answer questions about the efficacy of newer antiepileptic medications as compared to older antiepileptic medications. We included studies in our review that met the inclusion criteria that were specified a priori. You are correct that many of the studies included in the report were not designed to answer questions of efficacy but were included because they met the inclusion criteria for the report. In addition to summarizing the results of each study included in the report, we rated the applicability of the individual studies and the applicability of the studies that were pooled to evaluate different endpoints to illustrate what studies were efficacy studies as compared to those that were effectiveness studies.
Peer Reviewer #4	Results	It must be emphasized that the clinical goal is not a reduction in seizure rate. The clinical aim is NO seizures and NO side effects. Even to approach this goal requires a balancing act because of the narrow therapeutic window (and side effect window) of nearly all antiepileptic drugs.	While we recognize that the absence of seizures and side effects are important therapeutic goals, our key informants, including content experts, felt this endpoint was relevant because in some patients, the best you can do is reduce the number of events. In a very sick population with refractory disease doing a dichotomous outcome would be meaningless because everyone would have a seizure although the reality is that one group may have had significantly fewer. We did use other seizure endpoints such as time to first seizure and seizure freedom during study duration which are closer to the outcomes you noted.
Peer Reviewer #4	Results	The question is clinically meaningless. It lumps diverse issues. Dose per se is basically irrelevant (side effects and costs are), and switchback is not a standard of practice. If the drug was working in the first place, why would the patient be put back on the old drug rather than a new one be tried? Experts change one drug at a time, bearing in mind what is known about the mechanism of action of that class of drug on the epilepsy syndrome.	Switchback rates are surrogates for either efficacy or tolerability that some content experts felt relevant. We agree with the comment but there were other stakeholders who did consider it to be an important outcome and therefore we have included it. This report is meant to summarize information for a broad range of stakeholders.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	This is an important question that can only be answered by looking at individual drugs. "Older" vs. "innovative" is meaningless here.	Thank you for your response, but the none of the evaluations in Key Question #3 compare older antiepileptics to innovator antiepileptics. The comparisons made in the report were older versus newer agents and innovator versus generic agents.
Peer Reviewer #4	Results	This is an important question that can only be answered by looking at individual drugs. "Older" vs. "innovative" is meaningless here. See response to Question 3. I assume that the reason this question was not answered in the abstract is that the authors could not find any reasonable data.	Thank you for your response, but the none of the evaluations in Key Question #3 compare older antiepileptics to innovator antiepileptics. The comparisons made in the report were older versus newer agents and innovator versus generic agents. Key Question #3 is answered in the abstract.
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	Pooling data from Brodie 2007 (LEV vs. CBZ-CR) and Saetre 2007 (LTG vs. CBZ-SR) should include a caveat that this analysis combined populations with markedly different age ranges (mean age in Saetre: 73-74; mean age in Brodie: 39). Age may affect responsiveness to AEDs with respect to both seizure response and tolerability; as a result, therapeutic drug trials in younger patients with epilepsy may not be readily extrapolated to an elderly population. Pooling Saetre 2007 with Brodie (1999) rather than Brodie (2007) might yield more consistent results as both of the former studies examined LTG vs. CBZ in new onset epilepsy in the elderly.	Thank you. In the discussion section right after that key question, we now note that the Brodie 2007 and Saetre 2007 studies utilized patients with different age ranges. We followed a systematic and a priori format in our data analysis that we not like to alter. Here we have the sustained release evaluation where in another key question the impact of age is explored.
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The results for the Brodie 2007 (LEV vs CBZ-CR) reference are mistakenly attributed to LTG in several sections of the draft report (pg 76 and 79). Conversely, the results of Brodie et al. (1999) (LTG vs CBZ) is mistakenly reported as LEV vs CBZ-CR in several places (p84, 90). We have provided specific citations in appendix 1 included below. Study one: Brodie et al. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology (2007) 68;402-408. Study two: Brodie et al. Multicentre, double-blind, randomized comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. Epilepsy Research (1999) 37:81-87.	On page 76 of the draft report, the references are correctly attributed. On page 79 of the draft report, the references are correctly attributed. The references for 84-90 were checked and appropriately cited.

Commentator & Affiliation	Section	Comment	Response
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The dizziness data for Brodie (2007) is incorrectly cited (p87, p117): an increased risk of dizziness with LEV is cited, but the study reported a reduction in dizziness for LEV vs CBZ. The conclusions regarding this side effect for new versus old from this single study and then once combined with the Saetre 2007 (LTG- vs CBZ-SR) reference are, as a result, inaccurate. The data from Brodie (1999) regarding dizziness and other adverse events are also either inverted from or inconsistent with the original paper. Specific details of the relevant sections from cited literature are provided in appendix 2. AHRQ Report Reference: AHRQ Report Page 87: "One randomized trial reported data on dizziness when levetiracetam was compared to controlled release CBZ. The risk of dizziness was significantly increased by 7.9 fold when levetiracetam is used vs. CBZ. [RR 7.91 (2.97 to 21.31)]." Recommended Correction: Per Brodie (2007) table 2, the risk of dizziness was decreased by 21% when LEV was used versus CBZ: 10.9% of LEV vs. 13.7% CBZ patients reported dizziness [RR 0.79 (.51-1.23)]. It appears that the decimal place for RR has been moved, which greatly impacts direction and magnitude of risk of dizziness with LEV vs. CBZ.	We have made the following change: One randomized controlled trial reported data on dizziness when levetiracetam was compared with controlled-release carbamazepine. The risk of dizziness was non-significantly decreased by 21% when levetiracetam is used versus carbamazepine-CR [RR 0.79 (0.51 to 1.22)] (Appendix J Figure 59).
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The dizziness data for Brodie (2007) is incorrectly cited (p87, p117): an increased risk of dizziness with LEV is cited, but the study reported a reduction in dizziness for LEV vs CBZ. The conclusions regarding this side effect for new versus old from this single study and then once combined with the Saetre 2007 (LTG- vs CBZ-SR) reference are, as a result, inaccurate. The data from Brodie (1999) regarding dizziness and other adverse events are also either inverted from or inconsistent with the original paper. Specific details of the relevant sections from cited literature are provided in appendix 2. AHRQ Report Page 87: "Two randomized controlled trials reported data on dizziness when lamotrigine or levetiracetam were compared to controlled or sustained release carbamazepine and both were amenable for pooling. The risk of dizziness was non-significantly increased by 3.3 fold when either newer agent was compared to controlled or sustained release CBZ [RR 3.26 (.58 to 18;52)]." Recommended Correction: The numbers reported for Brodie (2007) are incorrect and therefore, the risk for dizziness in the pooled analysis needs to be recalculated.	We have made the following change to the text, figures and tables: Two randomized controlled trials reported data on dizziness when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling. The risk of dizziness was nonsignificantly decreased by 4% when either newer agent was compared with controlled- or sustained-release carbamazepine [RR 0.96 (0.56 to 1.66)] (Appendix J Figure 59).

Commentator & Affiliation	Section	Comment	Response
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The dizziness data for Brodie (2007) is incorrectly cited (p87, p117): an increased risk of dizziness with LEV is cited, but the study reported a reduction in dizziness for LEV vs CBZ. The conclusions regarding this side effect for new versus old from this single study and then once combined with the Saetre 2007 (LTG- vs CBZ-SR) reference are, as a result, inaccurate. The data from Brodie (1999) regarding dizziness and other adverse events are also either inverted from or inconsistent with the original paper. Specific details of the relevant sections from cited literature are provided in appendix 2. AHRQ Report Page 117: "Two randomized controlled trials reported data on dizziness when lamotrigine or levetiracetam were compared to controlled or sustained release carbamazepine and both were amenable for pooling in patients with new onset epilepsy. The risk of dizziness was nonsignificantly increased by 3.3 fold when either newer agent was compared to controlled or sustained release CBZ [RR 3.26 (.58 to 18;52)]." Recommended Correction: The numbers reported for Brodie (2007) are incorrect and therefore, the risk for dizziness in the pooled analysis needs to be recalculated.	We have made the following change to the text, figures and tables: Two randomized controlled trials reported data on dizziness when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling. The risk of dizziness was nonsignificantly decreased by 4% when either newer agent was compared with controlled- or sustained-release carbamazepine [RR 0.96 (0.56 to 1.66)] (Appendix J Figure 59).

Commentator & Affiliation	Section	Comment	Response
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The dizziness data for Brodie (2007) is incorrectly cited (p87, p117): an increased risk of dizziness with LEV is cited, but the study reported a reduction in dizziness for LEV vs CBZ. The conclusions regarding this side effect for new versus old from this single study and then once combined with the Saetre 2007 (LTG- vs CBZ-SR) reference are, as a result, inaccurate. The data from Brodie (1999) regarding dizziness and other adverse events are also either inverted from or inconsistent with the original paper. Specific details of the relevant sections from cited literature are provided in appendix 2. AHRQ Report Page 84: "One randomized controlled trial reported data on somnolence while patients were receiving levetiracetam compared to controlled release CBZ. Risk of somnolence is nonsignificantly increased by 21 percent when levetiracetam is used versus carbamazepine-CR [RR 1.21 (0.75-1.960]". Recommended Correction:Lamotrigine was the comparator in this study not LEV. Per Brodie (1999) Table 4, lamotrigine was significantly less likely than CBZ-CR to produce somnolence (LTG=12%, CBZ=29%, 95% CI 4- 30%). The percent with somnolence with CBZ was more than double that with LTG, per Brodie.	The data reported is correct. There was an error in referencing. The report has been fixed to reflect reference to Brodie MJ, Perucca E, Ryvlin P, et al. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology 2007;68:402-8. PMID: 17283312

Commentator & Affiliation	Section	Comment	Response
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The dizziness data for Brodie (2007) is incorrectly cited (p87, p117): an increased risk of dizziness with LEV is cited, but the study reported a reduction in dizziness for LEV vs CBZ. The conclusions regarding this side effect for new versus old from this single study and then once combined with the Saetre 2007 (LTG- vs CBZ-SR) reference are, as a result, inaccurate. The data from Brodie (1999) regarding dizziness and other adverse events are also either inverted from or inconsistent with the original paper. Specific details of the relevant sections from cited literature are provided in appendix 2. AHRQ Report Page 84: "One randomized controlled trial reported data on nausea while patients were receiving LEV compared to CBZ-CR. Risk of nausea is nonsignificantly decreased by 34 percent when LEV is used versus CBZ-CR". Recommended Correction: Lamotrigine was the comparator in this study not LEV. Nausea risk is not specifically reported in the adverse event section or tables of Brodie (1999). Rates for vomiting are reported and demonstrate non-significance between LTG and CBZ-CR. Withdrawal due to nausea was reported and this data shows 3% for LTG vs. 2% for CBZ-CR.	The data reported is correct. There was an error in referencing. The report has been fixed to reflect reference to Brodie MJ, Perucca E, Ryvlin P, et al. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology 2007;68:402-8. PMID: 17283312

Commentator & Affiliation	Section	Comment	Response
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The results for cognition and mood for PHB vs. LTG and LEV (Cumbo 2010) under represent the cognitive worsening with PHB reported in the original paper. In some instances the order in which the performance of PB, LEV and LTG are listed on various cognitive measures has been inverted relative to the original paper. For example, the report states (p72): "Phenobarbital had better effects on the MMSE than LTG." yet the study showed that patients taking PHB had a -1.57 worsening in MMSE score at 12 months relative to baseline compared to -0.64 worsening for LTG and a +0.23 clinical improvement with LEV. We have provided a full listing of inconsistencies between the draft report and included citations that we have observed in the appendix 3 listed below. AHRQ Report Reference: AHRQ Report Page 72: "Phenobarbital had better effects on the MMSE than LTG while exhibiting similar effects on the ADAS-Cog test to lamotrigine and inferior effects versus levetiracetam." Recommended Correction: MMSE: LEV produced improvement on MMSE while LTG and PHB produced worsening. LEV produced significantly better effects than both PHB and LTG on the MMSE (p's<.05). PHB produced greater clinical worsening on the MMSE compared to LTG (p<.05). ADAS-COG: LEV produced clinical improvement over 12 months while there was a worsening with PHB and LTG on the ADAS-COG. LEV was significantly superior to LTG (p<.05). PHB was inferior to LEV but superior to LTG on ADAS-Cog (non-significant for both).	We have made the following change: They found that phenobarbital and lamotrigine produced a worsening on the Mini Mental State Exam (MMSE) from baseline to 12 months ($p<0.05$), whereas levetiracetam produced significantly better effects on the MMSE than both phenobarbital and lamotrigine ($p<0.05$). There was a worsening in the Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog) score from baseline with phenobarbital and lamotrigine (p=NS). Levetiracetam was significantly superior to lamotrigine ($P<0.05$).

Commentator & Affiliation	Section	Comment	Response
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	The results for cognition and mood for PHB vs. LTG and LEV (Cumbo 2010) under represent the cognitive worsening with PHB reported in the original paper. In some instances the order in which the performance of PB, LEV and LTG are listed on various cognitive measures has been inverted relative to the original paper. For example, the report states (p72): “Phenobarbital had better effects on the MMSE than LTG." yet the study showed that patients taking PHB had a -1.57 worsening in MMSE score at 12 months relative to baseline compared to -0.64 worsening for LTG and a +0.23 clinical improvement with LEV. We have provided a full listing of inconsistencies between the draft report and included citations that we have observed in the appendix 3 listed below. AHRQ Report Reference: AHRQ Report Page 73: “Phenobarbital had inferior effects on mood as compared to lamotrigine but may be similar to levetiracetam.” Recommended Correction: Lamotrigine produced a superior effect on mood, i.e. depression compared to LEV and PHB (p's<.05). However, patients treated with LEV experienced significantly less depression than patients treated with PB (p<.05).	We have added the suggested comment: Lamotrigine produced a superior effect on mood, i.e. depression compared to LEV and PHB (p's<.05). However, patients treated with LEV experienced significantly less depression than patients treated with PB (p<.05).
Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	Results	There are useful summary data in this report, including the high risk of gingival hyperplasia with phenytoin, that are of value in that, in this report, the literature was assessed systematically.	Thank you.

Commentator & Affiliation	Section	Comment	Response
O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	Results	With regard to the document as it stands, we advocate the following changes in key summary wording: Line no.41-45, "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." should be CHANGED TO, "The results of this report show that we do not currently have sufficiently rigorous evidence to make broad recommendations, in whole or in part, 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. Rather, AHRQ recommends further research which takes into account more specific features of the many forms of epilepsy that afflict children and incorporates more specific information which can be used for individualized risk benefit analyses."	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions. Clearly, healthcare clinicians need to understand the nature of the literature, the strength of that evidence, and the applicability of the evidence. As you saw in the extensive report we tried to conduct numerous subgroup analyses and analyzed data in a number of ways to account for heterogeneity when such heterogeneity was anticipated or found. But the data on subgroups was either sparse or of poor quality.

Commentator & Affiliation	Section	Comment	Response
Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	Results	'New' versus 'old' AED comparisons should be grouped by epilepsy syndrome, with particular attention to the difference between partial and primary generalized seizure syndromes.	We attempted to look at seizure subtype in KQ4 and where possible looked at partial vs. generalized seizures. We tried to conduct numerous subgroup analyses and analyzed data in a number of ways to account for heterogeneity when such heterogeneity was anticipated or found. But the data on subgroups was either sparse or of poor quality.

Commentator & Affiliation	Section	Comment	Response
Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	Results	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.	We agree and state that as a limitation. Where possible we showed where individual agents' differences occurred but in the executive summary had to eliminate that due to brevity. While there are some important differences between agents within the older and newer groups, we do not believe that the differences between groups are too marked to allow pooling. The drugs in our CER are all used to control or reduce seizure frequency, work in the central nervous system to cause their effect, are all given via the same route of administration, and many share aspects of their mechanism of action (for example sodium channel or glutamate/glutyl-amino-butyric-acid effects) in a broad sense. We look at seizure etiology where possible and other subgroups separately in KQ4 but were limited by the paucity of data since studied did not report or stratify results by seizure subtype or other prespecified factors.

Commentator & Affiliation	Section	Comment	Response
Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	Results	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.	Even when small trials are underpowered to draw conclusions, where many such trials exist, the pooling of this data helps alleviate that limitation. The heterogeneity between the trials can be assessed as well and we did so. So it may not be the conclusion but the strength of evidence that may be impacted. We believe that one needs to look at the conclusion, the strength of evidence, and the applicability of evidence. Only looking at the conclusion without these other factors that we clearly laid out does not give the reader an accurate picture of the data. We agree with your recommendations for future research although doing studies that are centered around kinetics would not have the same strength of evidence as studies looking at final health outcomes.

Commentator & Affiliation	Section	Comment	Response
Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	Results	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.	Thank you for your suggestion, these subgroups are addressed by the report.

Commentator & Affiliation	Section	Comment	Response
Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	Results	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.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions We summarized the literature that was available regarding efficacy for seizure subtypes but the evidence was scant. Where scant data exists, this negatively impacts the strength of evidence and the conclusions and the strength of evidence need to be viewed together. Problems with statistical power translate to reduced precision and thus reduce strength of evidence.
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	Results	We do agree with the conclusion that none of the newer medications have ever been proven to be more efficacious than carbamazepine. It is important to recognize, however, that all innovator drugs have been approved based on their ability to reduce seizure frequency in patients who are already on existing medications (add-on study design). Unfortunately, there are no head-to-head, well-controlled, comparative effectiveness studies of AEDs in common use and as such the existing data are not sufficient to distinguish a difference between these treatments. In the absence of such comparative data we caution against concluding there is no difference between old and new AEDs in regard to efficacy.	Thank you for your thoughts We already include this as a research need.

Commentator & Affiliation	Section	Comment	Response
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	Results	We would emphasize that as a group, as was mentioned in the report, the newer medications seem to have a more favorable safety profile. As with all evidence-based reviews, we realize that practical real world concerns of how best to use different medications in different groups of patients (Key Question 4) is presently not answerable due to lack of evidence.	We agree, thank you for understanding the limitations of systematic reviews, especially those with such a broad set of objectives. We were not charged with finding a certain outcome but to independently and transparently review the literature that existed and to lay it out for stakeholders to see. In the case of key question 4, it would be great if the literature base was more extensive, but it is not.
Peer Reviewer #2	Discussion	"For the innovator versus generic evaluations, the lack of specification that the products were "A" rated generics and the multitude of studies conducted outside the United States limited applicability" As mentioned before, I'm not sure this is an accurate argument as I do not believe there are nor have there been in many many years any non "A-rated" generics available in the US. Please verify that they are if you are going to make this claim. This may be a simple issue of using terminology that may only be used to pharmacists.	There are definitely non-"A" rated generics available in the United States but there is no automatic substitution of non-"A" rated products. It is less likely though that non-"A" rated products would be compared to each other in the United States than in international studies where the concept of "A" rated products might not be as prevalent. We just want to be explicit and transparent about the potential weakness.
Peer Reviewer #2	Discussion	"Switching from and innovator to a generic, generic to generic, or generic to innovator version of the same medication may increase the short term risk of hospitalization and hospital stay duration and may increase the short term risk of a composite of having an emergency department and hospitalization visit with or without ambulance service utilization. We had insufficient to low strength of evidence for these conclusions" This comment is incongruent with the last sentence. I'm unsure as to how something "may increase..." while having "insuffiient to low SOE for these conclusions. It seems that a more apporpriate statement would be that there was insuffient to low SOE for switching to increase short term risks of hospitilization...	Thank you for this suggestion, we now make your suggested wording change. We believe that people who understand the systematic review process would understand that there is a conclusion that may or may not have a strong strength or applicability of evidence. However, your revised sentence is more compacted and we need to reduce verbiage wherever we can. We now say: "There was insufficient to low strength of evidence suggesting that switching from an innovator to a generic, generic to generic, or generic to innovator version of the same medication may increase the short term risk of hospitalization and hospital stay duration and may increase the short term risk of a composite of having an emergency department and hospitalization visit with or without ambulance service utilization."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion	In the Discussion, the authors conclude based on the current literature that it cannot be determined "whether a switch from one antiepileptic medication to another … whether an innovator or generic, would increase the loss of seizure control or adverse events versus maintaining therapy with the same version." This actually the most critical clinical issue related to generic antiepileptic drugs, and thus should be noted in the Abstract in some fashion.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions. We structured the abstract so that most critical points from our review were addressed.
Peer Reviewer #3	Discussion	Another major conclusion from the review is that there are numerous areas with inadequate data and that future research is critically needed to better define the comparative effectiveness of AEDs. This should be emphasized in the Abstract.	We structured the abstract so that most critical points from our review were addressed. We did provide that information in the report.
Peer Reviewer #3	Discussion	The review compared benefits or harms for AEDs in subgroups of patients differentiated by seizure etiology, seizure type, … and by AED types. The authors note that these subgroup analyses were not very informative. They should at least comment on there are differences across AEDs for localization related (partial) epilepsy vs. generalized epilepsy (e.g., FDA indications).	We tried to limit our discussion in this area to where we had literature from our search.
Peer Reviewer #3	Discussion	It is inappropriate to state that this is only a concern for AED selection in pregnancy or when there is a desire to become pregnant within a specified period of time. Half of the pregnancies in the USA are unplanned, and one cannot wait until pregnancy because by the time a woman finds out that she is pregnant, congenital malformations have already occurred.	What we said was the following "Factors such as pregnancy or desire or possibility to become pregnant within a specified period of time, concomitant drugs and risk of serious drug interactions, and genetic polymorphisms or the ethnicities most likely to harbor polymorphisms that increase the risk of severe skin rashes can be used to select an optimal therapeutic choice for an individual patient." We did not say it was only a concern for this group but this group should be especially concerned. Women on hormonal/IUD hormonal birth control with reasonable compliance should not be denied an effective treatment option for her epilepsy simply because she is a woman of childbearing potential. We are simply alerting stakeholders that factors not evaluated in the report can impact agent selection decisions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Conclusion	"This suggests that the difference in magnitude between these three studies may be due to inadequate confounder adjustment. Alternatively, since the first two controlled observational studies used a composite endpoint that included ambulance service utilization while the third study did not, this may also explain differences in magnitude between the three studies." This is much better than the previous explinations. I would suggest this be used throughout.	Thank you. We now have a statement like this in the executive summary. We need to be concise above and then expand it here. We would like to specify it more broadly each time but are limited by words.
Peer Reviewer #3	Conclusion	The authors conclude that they could not find any significant difference in the risk of withdrawing for any reason when newer AEDs were compared to carbamazepine. However, there are studies in which specific newer AEDs have demonstrated better effectiveness than carbamazepine due to fewer withdrawals from side effects (e.g., SANAD and the geriatric VA Coop study).	Thank you for your comment. In our report, we evaluated overall withdrawal, withdrawal due to lack of efficacy and withdrawal due to adverse events and when newer antiepileptics were compared to carbamazepine in randomized controlled trials and observational studies based on an a priori determination of inclusion criteria and endpoints. Both the SANAD study and the VA Coop Study met the inclusion criteria for our report and evaluated all three withdrawal endpoints we sought to collect. Individually, the SANAD study and the VA Coop study demonstrate better efficacy and fewer withdrawals from side effects when newer antiepileptcs are compared with carbamazepine. However, when the results of the SANAD and VA Coop studies are combined via meta-analysis with the results of the other studies that met our inclusion criteria and evaluate withdrawal for any reason, there is no significant difference in risk when newer antiepileptics are compared to carbamazepine.

Commentator & Affiliation	Section	Comment	Response
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	Conclusion	Conclusion - We at the NAEC applaud the AHRQ for funding a review of such importance to epilepsy patients. We ask the report more clearly emphasizes that absence of comparative effectiveness data (old versus new AEDs) does not prove an absence of difference. Further, we believe that the clinically relevant question regarding innovator versus generic questions, that of formulation substitution, was not addressed in the report and in fact couldn't be due to lack of data. We caution against the use of this report for the development of clinical practice guidelines or quality standards. Well-designed comparative effectiveness studies of the AEDs in common use are needed to answer the questions raised in this research review. Until such studies are undertaken policy decisions should not be made based on inadequate data as they may result in harm to patients.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions. We rated the strength of evidence for all of our outcomes and agree that future well done trials are needed.
Peer Reviewer #2	Figures	"Not in English Language (n=5)" I thought there were no language restrictions. It would appear that only english language articles were actually reviewed.	No English language restrictions were imposed on the literature search. The seven articles were excluded at the full text review stage.
Peer Reviewer #1	General	Providers who treat epilepsy will now have access to an enriched view of the available scientific evidence when prescribing AEDs for their patients. The key questions are on target with the current controversial issues related to AED prescribing in this country. The findings of this report should be a resource to those conducting future research into AED safety and effectiveness. I also feel that the authors have been mindful in the wording of the conclusion in keeping with a patient-centric philosophy (for examples the data points to this conclusion, however the authors indicate that individual patient characteristics also need to be considered in choosing the optimal agent).	Thank you.
Peer Reviewer #1	General	I feel that Chapter 4, in particular, will be very helpful in informing evidence-based practice decisions. For me, Chapter 4 tied together large groups of data and summarized it succinctly.	Thank you.
Peer Reviewer #1	General	Overall, the report is organized and flows well. There is some repetition of information in the various sections, but I think that this amount of repetition is necessary given the large body of data reviewed and the complexity of the questions being answered.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	The main conclusions from this comparative effectiveness review are carbamazepine is more efficacious in maintaining seizure freedom than newer antiepileptic drugs (AEDs) as a class, but that carbamazepine produces greater adverse effects. Valproate and phenytoin did not differ in seizure control from new AEDs, but both had greater adverse effects. The authors state that theses adverse events did not lead to greater withdrawals. Initial innovator vs. generic AED did not differ, but switching may increase ER visit, and hospital visit, stay or duration (based on insufficient to low strength of evidence).	Thank you for your comment.
Peer Reviewer #3	General	The statement on page 3 of the report notes that "The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. … 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." Due to the issues discussed below, this report will be of no help to clinicians, and it would be most unfortunate if the flawed overall conclusions were used to direct heath care policy or to determine reimbursement or coverage policies.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions.
Peer Reviewer #3	General	Many components of the report are redundant. The paginations noted in the Table of Contents are incorrect, which reflects carelessness in preparation of the report.	The pagination has been updated.
Peer Reviewer #4	General	The report is not clinically meaningful. The target population is ill-defined. The key questions are poorly worded.	Thank you for your comment The questions we sought to address through our literature review were posed and reviewed by clinical decision makers.
Peer Reviewer #4	General	The detail presented in the results is overwhelming and the abstract is indecipherable to anyone who is not truly comfortable with risk calculation statistics.	The abstract is highly complex due to space limitations requiring that a large volume of information be condensed into a small space. We now simplify it by leaving out the data that is available in the executive summary.

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Peer Reviewer #4	General	The implications are not clearly stated. The limitations of the review are not described adequately. The conclusions omit important considerations. Future research is clearly needed but will not necessarily be achieved by further literature review.	It is difficult to address this comment without additional specificity. The limitations of the current research are clearly outlined in the Future Research section of the report. We agree that further research is needed to fully answer all of the questions posed by the report, but that further literature review would not address the research gaps.
Peer Reviewer #4	General	This paper is not ready for publication. It may not be publishable even with further revisions as it is currently structured. The authors have done excellent statistical work but the literature is inadequate and hence the results are not valid in many cases. This situation is the result of poorly defined questions, the nature of the disorder, and the absence of relevant literature.	The questions we sought to address through our literature review were posed and reviewed by clinical decision makers but could not be adequately answered through the review due to the limitations of the literature base.
Peer Reviewer #4	General	The issue of brand vs. generic is important. The authors note that switching from brand to generic caused short-term problems including hospitalizations. Here again, the literature is just beginning to be formed. We know that the broad range of active drug blood concentration allowed by the FDA for generic drugs adversely affects many patients. Therefore, when exploring this topic, concentration, drug-drug interactions, and the fact that phenytoin has zero order kinetics must be taken into account. The issue to be addressed is what is the mean and standard deviation of the blood concentration for the administered drug and the nature of incipients in the various generics. A few papers have approached this problem. It appears that many of the generics cluster closely around the value of the original brand, but a significant number are outliers (although still within the FDA guidelines). Since the generics are not uniform, not "branded" in the sense of identifying the manufacturer, the product packaged by the distributor can very from lot to lot and among distributors. This diversity accounts for the increase in seizures, hospitalizations, and cost. It would be useful to discuss the problem in the report. The authors are comparing uniform product from a single source (the original manufacturer) with a population of generic products producing different concentrations of active drug in the blood. For the clinician and the patient, achieving seizure control requires a consistent product consistently available.	Thank you for this insight. We were interested in evaluating the kinetics of innovator and generic products in total. When we do that there is the possibility of variability due to the origin of the innovator and the generic but it did allow us to discern if the results were congruent with the impact on final health outcomes. It was. So while we cannot say that switching is a safe and effective strategy, we can say that when starting an innovator versus starting a generic that you likely have similar results. This is an important finding, we believe.

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Kathleen Bos, MD, FACP, FACR VP, US Medical Affairs UCB, Inc.	General	We applaud AHRQ for its inclusiveness in the vast amount of literature considered in the draft report. We note that while retaining a predominant focus on old versus new molecules may be a statistically valid approach to an analysis of Anti-Epilepsy Drugs (AEDs), the clinical utility of such a comparison is limited	Thank you for your comment.
O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	General	The Academy believes that medical decisions about children require different sets of priorities and considerations. ("Children are not small adults."). For example, issues related to side effects such as school performance, cognition, and mood in children and adolescence require special scrutiny. For adults there are issues related to driving, employment, and disability. Moreover, as the document points out, there are more genetic epilepsies in children and more acquired epilepsies in adults. A combined CER risks obscuring these vital differences and diluting clinical points of special relevance to children. Therefore, we advise that the AHRQ CER should be split into two parts, one for children and adolescents, and one for adults.	Thank you for your suggestion. We agree that children are not small adults. We clearly were aware of this given Key Question 4 which specifically evaluated the impact of patient age and many other factors. In order to fully appreciate the nuances in subpopulations, it is important to read the full body of the report.
O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	General	A seizure is an event with diverse etiologies. There are many chronic conditions in which seizures are a symptom which for convenience we classify as all being epilepsies. However, lumping epilepsies together to understand evidence based treatment, while consistent with many approaches in the treatment literature, has severe limits when making policy recommendations. The CER as written addresses this, however, the main issue is that for many important etiologies, the numbers of studies are too few to detect clinically important outcomes. Moreover, we anticipate, over the next few years, the understanding of specific genetic forms of epilepsy will increase, such that a global guideline policy statement will have even less relevance than it does currently.	Thank you, we believe that personalized medicine is an important research area and that in the future will further differentiate subpopulations that will or will not benefit from a particular treatment. The impact of HLA polymorphisms in skin rash is an example of that. Since evidence reports can be updated, in the next 5-10 years an update accounting for new evidence coming out I the intervening years may be required.
O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	General	The level of evidence identified in this report, based on only about 70 studies, is too weak for any policy recommendations. Suggesting that this should be used for policy recommendations risks harming children by restricting the treatment options available to good clinicians.	Thank you for your suggestion. The CER illustrates the available evidence, but is not meant as a substitute for clinical decision making. Our report is not a clinical guideline but does help to inform stakeholders of the available literature, the strength of the evidence, and its applicability.

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O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	General	Therefore, we propose that after splitting this into two parts, publication of this report be considered as a guideline for future research studies but not for any policies about treatment. A number of additional areas for future research, including cognitive effects in children and adherence in various family settings, should be included in the pediatric report.	Thank you for your suggestion. We feel that the report in its current form is sufficient and uses Key Question 4 to alleviate your concerns.
O. Marion Burton, M.D., FAAP President, American Academy of Pediatrics	General	Also issues regarding typos and grammatical errors were noted (misspellings of vigabtrin and carbamazepine, were noted).	Thank you, we have corrected these misspellings.
Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	Our charge was to work with a panel of content experts and key stakeholders to devise and answer the key questions. We were asked to, in an unbiased manner, assess, evaluate, and summarize the available data. We needed to then rate the strength of the evidence and the applicability of the evidence. This is not a clinical guideline, this is an evidence report. If a pooled effect or direction of effect is provided, but the strength of evidence is low, there is low confidence that future studies would not change the results. In cases of poorer strength or applicability of evidence, we recognize that practice may not be changed by such findings.

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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 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 purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions.

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions. This project was not intended to generate new data or to conduct a new study. Rather, we were challenged with evaluating the literature that currently exists. As you saw in the extensive report we tried to conduct numerous subgroup analyses and analyzed data in a number of ways to account for heterogeneity when such heterogeneity was anticipated or found. But the data on subgroups was either sparse or of poor quality.

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Profesor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	We agree that published literature is often unable to fully answer questions of importance to all stakeholders, but the role of systematic review is not to conduct new studies or to answer the questions, but to summarize what evidence is available to answering the questions for decision-makers to consider.

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	We agree that teratogenicity is an important issue. We talk about adverse effects in the introduction and discussion section. We devote a sizeable space to discussing teratogenic effects in the discussion. However, if the available studies included in our review (trials comparing older or newer antiepileptics or innovator versus generic medications) did not assess the adverse event, then it cannot be evaluated

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	Thank you for your comment. Using the available literature, data on psychological and psychiatric effects of antiepileptic drugs as well as health-related quality of life, and loss of driver's license were collected. However, the data was too heterogeneous to be amenable to pooling. Data on the most common side effects of antiepileptic drugs including nausea, vomiting, somnolence, dizziness, headache, diplopia were collected and were amenable for pooling.

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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 consideration in the draft document of the differences that a patient's age makes on selection and use of AEDs.	Subgroup analysis was performed based on patient age including children less than 18 years of age, adults from 18 to 65 years of age and adults greater than 65 years of age. We evaluated direct comparative trials of older versus newer medications. We reported the reported final health outcomes and the harms from those studies. If there are data from placebo controlled trials or the use of the same drug in two populations, they would not be included in our review. Our review was looking specifically at direct comparative trials

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	We specifically say in the limitations section that factors such as pregnancy, genetics, and drug interactions can lead people to make individual treatment choices. In KQ2 for the innovator vs generic comparison we looked specifically at the pharmacokinetic outcomes and did not find significant differences. Kinetic parameters are intermediate and not final health outcomes. The available literature for this topic area assesses the patients in a more aggregate manner. We suggest that future research could be very important

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	Our report and subsequent translational products are designed to be viewed by many key stakeholders including clinicians, policymakers, payers, and patients. During the topic refinement phase we engaged a variety of stakeholders to determine the questions and PICOTS needed to help inform clinical decision-making. As such, we received very disparate feedback on the types of outcomes that would most appeal to them. We were very agreeable to evaluating outcomes even though we included far more endpoints and analyses than traditional reviews. As such, for completeness sake we evaluated both the innate use of a brand versus a generic and the switching from one type to another. Our main charge was not to evaluate how kinetics drove dynamics. We were evaluating the impact of older versus newer antiepileptic medications and then innovator versus generic medications on health outcomes. We do not believe that the stakeholders of this report would have thought a limited review of the link between kinetics and dynamics would be informative. We believe that a review of the outcomes, a rating of the strength of the evidence, and the applicability of the evidence provides more important information.

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	The problem of pharmacokinetic interactions in patients taking other medications should be considered.	Thank you for your suggestion. The problem of pharmacokinetic interactions of other drugs with antiepileptic drugs is important to clinicians, patients and policy makers. We note that under the limitations section.

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Richard Denness, President and CEO, Epilepsy Foundation Robert C. Griggs, M.D. FAAN, President, American Academy of Neurology Sheryl Haut, M.D., Associate Professor of Clinical Neurology, North American Regional Commission of the International League Against Epilepsy John M. Pellock, M.D., American Epilepsy Society President 2011	General	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.	The purpose of this report is to systematically identify and synthesize the available evidence. We hope that decision-makers, such as patients, providers, and policy-makers, will then consider the available evidence along with other factors in making their clinical decisions.
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	General	The NAEC is pleased that AHRQ funded this literature review as questions are frequently raised about the comparative effectiveness and safety of the various antiepileptic drugs (AEDs). At the same time our Association believes that it is important to recognize and understand the limitations of the evidence collected. In reviewing the report we also feel that some clarifications need to be made in the report.	Thank you.
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	General	Our greater concern with the review relates to the issue of innovator versus generic medications and the practical ramifications of the report's conclusions when considering potential public policies that may be derived, from this report. For this reason, we felt that it was important to provide a general view of pharmacological treatment of patients with epilepsy.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	General	Epilepsy Drug Treatment - Epilepsy is a life-long chronic disease. Effective treatment is essential to the health and quality of life of individuals living with this disorder. The major issue in treating patients with epilepsy is to determine the AED that is most effective in controlling a patient's seizures without causing medical, psychological or cognitive side-effects. Most individuals living with epilepsy can be effectively treated with a single drug, which is often the first drug prescribed for the patient. Unfortunately, for 0.3% of the general population, or about 30% of epilepsy patients their seizures are difficult to control and are considered to have intractable epilepsy. These patients typically go on multiple drug trials and are often treated with more than one medication. Once the optimal medication is determined for a patient with epilepsy, it is critical that the drug's pharmacokinetic behavior, especially absorption, is consistently maintained. To a high degree of probability, this will be the case when a brand drug is prescribed or if the patient is given the same manufacturer's generic version of the drug. Problems arise when patients are given variable and/or multiple generic formulations of the same drug. This is due to manufacturers' variations in product formulation which alter dissolution and can impact absorption. We do not believe that brand drugs are superior to their bioequivalent versions, but they provide the prescribing physician the assurance that the drug's absorption rate will be consistent This is typically not the case when a generic is provided to patients since the pharmacy will dispense whatever generic version of the drug is on hand.	Thank you. Your feeling is in line with our reports findings, that the available literature suggests that initiating innovator and "A" rated products provide inherently similar efficacy and harms but we cannot say that the switching from one to the other would be safe. We reviewed the literature on switching very carefully and present it transparently with its weaknesses. That in essence is what we are saying and it is important that people know that in an unbiased review with explicit a priori defined methodology, that these are the results so the results cannot be underplayed or overplayed.

Commentator & Affiliation	Section	Comment	Response
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	General	The FDA Definition of Bioequivalence - Innovator vs Generic AEDs - For a generic product to be considered bioequivalent to a brand drug, FDA requires that the drug's absorption rate (the log-transformed ratios of AUC and Cmax between brand and generic products) fall within the range of 80% to 125%. Each generic is tested against the branded equivalent to make this determination, but not against other generic preparations. This can result in significant differences in absorption rates between two generics. For example, a given generic can have a high but acceptable bioequivalence, while a second generic can have a low but also acceptable bioequivalence, potentially resulting in a 45% difference in the drug's absorption, as recently demonstrated by Krauss and colleagues1D at a presentation at the American Academy of Neurology meeting (data not yet published). In this case, if the patient was started on the first generic and then switched to the second, the total decrease in delivered dose could be enough to result in seizure breakthrough and, of course, potentially devastating consequences. The opposite can also occur if the first generic given has low but acceptable bioequivalence and the second generic given has a high but also acceptable bioequivalence, resulting in an increase in delivered dose that could result in toxic symptoms. This problem is further amplified for patients with intractable epilepsy that require polypharmacy of two, three, four, or five antiepileptic drugs, often together with other classes of drugs such as antihypertensives, psychotropics, and oral hormones. In this case, the generic to generic drug changes combined with the interaction with these other medications (inducers and inhibitors) can have a dangerous impact.	Thank you. This report was not charged with looking at how two drugs may theoretically differ but to look at direct comparative studies that provided data on kinetics and final health outcomes, how innovator and generic products impacted these outcomes. We do believe that the literature has an extensive number of position statements, reviews, and commentary on theoretical findings and dissolution.
Robert Labiner, M.D., Vice President National Association of Epilepsy Centers	General	Potential Results of Generic Substitution - Many patients with epilepsy can safely use generic medications, with accompanied financial savings. Unfortunately, there is little information available to determine which specific individuals might have problems with the switching of generic AEDs. There is a growing body of peer-reviewed data that suggests there might be problems associated with generic AED utilization. Retrospective studies such as the Claims Database Analysis done by Zachry et al.D2D studied the association between a recent substitution of an A-rated generic product and emergency care for a seizure-related event. In this analysis, patients requiring emergency care had 81% greater odds of having a generic AED formulation	You make very good points. These are things that we found in our review. We include data from Zachry, Andermann, and all other studies meeting our inclusion and exclusion criteria. One type of product is not inherently different than another but switching from one to the other may be associated with problems, although the literature for this latter point is observational in nature and does not constitute a high strength of evidence. We agree with your assessments of the studies you identified but also need to evaluate the study by Devine (what you refer to

Commentator & Affiliation	Section	Comment	Response
		switched in the previous six months than controls (11.3% versus 6.2%). In another retrospective analysis of data from Ontario, Canada, Andermann et al.D3D evaluated switchback rates of several classes of drugs including antiepileptic drugs (lamotrigine, Depakote) as well as several antidepressant and cholesterol-lowering drugs. Please be aware that in Canada, the physician has to write a letter of medical necessity before the patient can be switched back from a generic to an original product. In this analysis, a high switchback from generic to brand (12.9%-20.9%) was seen for AEDs as compared for non-AED classes of drugs (1.5%-2.9%). Other more recent studies have shown that use of generic medications (compared with brand) lead to increased downstream healthcare utilization4D as well as related increased costs5D. One study cited in the report was the so called Express Scripts study6. This study has been widely used to refute the other observational studies. What is routinely ignored in these analyses and discussions is that the data in this study actually supports the concerns raised in the preceding paragraphs. There was in fact an increased hospitalization and emergency department utilization noted in the raw data that disappeared with adjustment for confounders. However there was significant increase in risk when the patient was on two or greater than three AEDs. This latter point was not addressed in the report. The key issue, in our assessment, is not whether innovators are more efficacious that generics but rather the risk of formulation substitution (brand to generic, generic to generic, and generic to brand). It is assumed in the observational studies that individuals in the generic groups are likely receiving generics from different manufacturers. It is also very possible that these formulation substitutions are irrelevant in many patients. That said, we have no ability to determine *a priori* which patients would be negatively affected by such switching.	as the Express Scripts Study) as well. We feel we adequately describe the similarities and differences between these studies evaluating switching of epilepsy medications and we do show how even with correcting for confounding the direction of effect is the same for the different studies. However, these studies are observational and have inherent limitations. This reduces the strength of evidence and cannot be considered proof of effect. That is why we wrote the future research needs section the way we did and highlighted the type of trial that needs to be conducted to truly answer this important question.