AHRQ Comparative Effectiveness Review Surveillance Program

CER #40:
Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy

Original release date:
December, 2011

Surveillance Report:
November, 2012

Key Findings:

- Contacted experts thought many conclusions for KQ1 to 4 do not make sufficiently clear that they are based on insufficient or low evidence and the broad categorization into newer and older drugs may not be very informative
- There is new evidence available for KQ1 (effectiveness, health outcomes) and KQ3 (adverse events), the conclusions are possibly out of date
- Teratogenic risks are not covered by KQ3 but new research evidence is available and fetal toxicity and adverse event warnings have been communicated by the FDA
- The conclusions for KQ4 (subgroups) do not address women of childbearing potential and could be included in the update

Summary Decision

This CER's priority for updating is **High**

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Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy

1. Introduction

Comparative Effectiveness Review (CER) #40, Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy, was released in December 2011.[1] It was therefore due for a surveillance assessment in June, 2012. At that time, we contacted experts involved in the original CER and subject experts to get their opinions as to whether the conclusions had changed and need to be updated. We also conducted an update electronic literature search. During the assessment, an article expressing dissatisfaction with the report was published.[2] Every month since the CER's original release, we received any FDA updates on the included treatments.

2. Methods

2.1 Literature Searches

We conducted a limited literature search in the database MEDLINE for the years 2011 to August 2012 for articles published in English. The original report employed two search strategies, one for innovator versus generic antiepileptic drug evaluations and one search capturing older versus newer antiepileptic drug evaluations. Our update search for innovator versus generic medications used the original search strategy but we broadened the searches to capture search terms either in the citation or the subject headings to identify newer studies not yet fully indexed and assigned relevant MeSH terms.

Searching for older versus newer antiepileptic drug evaluations we used the search strategy employed for the original report but did not restrict to MeSH-tagged records. Due to the large number of publications we restricted the search to five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Epilepsia, Epilepsy Research, Neurology, Epilepsy Behavior, Seizure European Journal of Epilepsy). The specialty journals were selected according to the search volume of publications on the topic in the last 30 years. Appendix A includes the search methodology for this topic.

2.2 Study selection

We used the same inclusion and exclusion criteria as the original CER. We screened the titles and abstracts and obtained full text copies of publications accordingly.

2.3 Expert Opinion

We shared the conclusions of the original report with 15 experts in the field (including the original project leader, original technical expert panel (TEP) members, peer reviewers, and

professionals responding to the public posting of the draft report) for their assessment of the need to update the report and their recommendations of any relevant new studies. Two subject matter experts provided information for each of the review questions and conclusions while several others referred to a publication outlining perceived shortcomings of the report.[2] Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[3, 4]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 324 titles. After title and abstract review, we further reviewed the full text of 58 journal articles. The remaining titles were rejected because they clearly did not meet inclusion criteria for any of the review questions. In addition to the electronic database searches, we followed up suggestions from the topic experts for studies not already included in the original report. We reference-mined articles that met inclusion criteria as well as systematic reviews identified by the literature searches to identify additional articles that may have been published since the publication of the report.

Thus, 68 articles went on to full text review. Of these, 51 articles were rejected because they did not meet the inclusion criteria of the original report. The remaining studies were abstracted

into evidence tables stratified by key question (Appendix B) for this assessment.[5-21] New pertinent studies were identified for Key Question 1 (effectiveness, health outcomes), Key Question 2 (effectiveness, intermediate outcomes), Key Question 3 (adverse events), and Key Question 4 (subgroups).

3.2 Expert Opinion

When we contacted subject experts in the topic, including some who had served on the TEP for the original report, most expressed dissatisfaction with the original report and did not wish to participate in the process of assessing the potential need for updating. Many subject matter experts referred to a publication outlining perceived shortcomings of the report and a response to the report from the Epilepsy Foundation, American Epilepsy Society, American Academy of Neurology, Finding a Cure for Epilepsy and Seizures, National Association of Epilepsy Centers, and the North American Regional Commission of the International League Against Epilepsy.[2, 22] The publication raised a number of issues and questioned the conclusion that carbamazepine had advantages over newer antiepileptic drugs (AEDs), and that phenytoin and valproate were equivalent to newer AEDs in seizure control. The publication emphasized that the presentation of the results in the report may be misleading, stating that a simplistic reading of the report's conclusions could lead to formulary restrictions that would require the use of carbamazepine, phenytoin, or valproate prior to the use of any newer AED. It highlighted that with few exceptions, the level of evidence for conclusions was consistently judged to be low and of poor quality. Other issues raised by the publication were inadequate data, which prevented careful analysis of important and specific questions; many of the endpoints used in the final analysis not being clinically relevant for individual patients; and incorrect reporting of some of the data in the tables. A further criticism was grouping AEDs into two broad categories based on their date of entry into the market, ignoring major, and more clinically important, differences in pharmacokinetics, adverse effect profiles, and other properties of the individual medications. Furthermore, a large proportion of the effectiveness analysis focused on gabapentin and vigabatrin, drugs that, according to the publication, have either been demonstrated to have lower efficacy or are not used as drugs of choice in treating new-onset epilepsy. Finally, according to the publication, the report placed very little emphasis on the occurrence of adverse effects. The response from the epilepsy organizations highlighted that the report failed to recognize the different types of epilepsy and compared the effectiveness of old-line anticonvulsants to newer epilepsy drugs irrespective of epilepsy type, even though seizures have different pathologies and the use of antiepileptic drugs differs greatly based on the underlying pathology, and the old versus new AED comparison is irrelevant to clinical practice.

Other subject matter experts and representatives of epilepsy organizations that we contacted specified that they did not want to contribute to a report update assessment because of a host of concerns related to the formulation and design of the CER initiative in epilepsy, their belief that AHRQ should have waited for more research studies before undertaking such an assessment of antiepileptic medications, and a strong belief that published data on the various underlying pathologies for epilepsy are insufficient to make accurate comparisons of various antiepileptic drugs across a wide variety of seizure types. They further pointed out that they had heard from some patients and providers who claim that as a result of the report, patients are being asked to fail first on carbamazepine regardless of patient history or physician directed care, and urged AHRQ to withdraw the report. Other stated reasons for not being willing to participate were the

perception that the questions the review was designed to address were poorly formulated and irrelevant to questions clinicians and people with epilepsy face on a daily basis. They also echoed the criticisms of the publication that the combination of new antiepileptic drugs into a single category introduces a large degree of heterogeneity as does combining seizure types and epilepsy syndromes and shared the perception that the report did not adequately address concerns about cognitive and mood adverse effects or issues in women's health, including teratogenic effects. Still other subject matter experts acknowledged that the review's task was made more difficult by the limited data. Yet they added that evaluating the data without differentiating epilepsy or seizure-type, appropriately assessing adverse side-effects, or recognizing the specific needs of women, and evaluating all of the newer medications as a single group limits the applicability of the review's conclusions and could negatively impact patient care. Finally, a number of experts stated that any new review should involve epilepsy specialists, especially in developing the key questions.

In the end, only two subject matter experts were willing to comment directly on the availability of new evidence for the key questions.

Key Question 1: One expert indicated that most conclusions regarding the effectiveness of health outcomes were still supported by the evidence except the comparison between newer medications and carbamazepine (the expert did not agree with the conclusion but was not aware of additional evidence) and thought there is new evidence regarding switching from innovator to generic medications. The second expert emphasized that most conclusions are based on low strength of evidence and therefore suspect and outlined flaws in the analysis. In particular, combining all new AEDs and comparing these to a group of old medications despite differences in mechanisms, side effect profiles, and efficacy based on the type of epilepsy was pointed out as problematic. In addition, this reviewer noted that theoretically, half of the new AEDs could be better and half worse than carbamazepine, and the analysis would find no differences. Furthermore, lumping different types of epilepsy in the analysis is also problematic given that a drug with superior effectiveness for one type of epilepsy but inferior for another would show no differences, citing the example of valproate in primary generalized versus partial epilepsies. Regarding the evidence from innovator to generic comparisons, the expert cited the subsequent journal article[23] based on the report because it emphasized the low or insufficient strength of evidence, whereas the AHRQ report did not make this lack of evidence sufficiently clear. Exceptions to this limitation, the reviewer noted, may be the comparison between phenytoin and valproate (moderate strength of evidence) and the report's conclusion that the results are similar to a 2010 published meta-analysis, these may possibly still supported. However, the expert mentioned that the most critical question— the risk of switching from innovator to generic or from generic to generic drug—was not addressed. Both experts agreed that data regarding quality of life, loss of driver's license or employment, secondary seizure injury, and status epilepticus endpoints are still inadequate.

Key Question 2: One expert agreed that the data on intermediate outcomes are still too limited to draw conclusions, as stated in some of the conclusions, but referred again to the journal article,[23] which mentioned low or insufficient strength of evidence 11 times in the abstract compared to only once in the CER report. The other expert thought there was new evidence regarding the comparison of innovator versus generic AEDs, concerning two of the three conclusions.

Key Question 3: One expert thought the conclusions regarding adverse events are almost certainly still supported by the evidence. The other expert agreed that the evidence on adverse events is still insufficient, as stated in the report's conclusion, but noted that considerable additional data are available. This expert did not agree with the prioritization of adverse events in the key question, indicating that hypotension is an unusual side effect for oral antiepileptic drugs, whereas teratogenic risks should have been investigated in the evidence report. The expert emphasized that the large amount of new information on pregnancy outcome risks in women taking antiepileptic drugs should have been addressed; furthermore, the practice of waiting to make drug choices until "the desire or possibility to become pregnant within a specified period of time" is known, as stated in the report, ignores that almost half of the pregnancies in the US are unplanned, so conclusions should address women of childbearing potential. The FDA warning regarding children exposed to valproate in utero having lower cognitive test scores is a serious omission according to this expert. This expert also noted again that all comparisons, apart from greater withdrawals due to adverse events for carbamazepine compared to newer antiepileptic drugs, are based on low strength of evidence and thus conclusions are not justified. The expert summarized the evidence for newer antiepileptic medications somewhat differently and pointed out that several comparisons are based on low or insufficient strength of evidence and thus cannot provide definitive conclusions. Finally, the expert stated that comparisons between innovator and generic antiepileptic medications are based on low to insufficient strength of evidence, and no conclusions are warranted.

Key Question 4: One expert thought the conclusions regarding subgroups are almost certainly still supported by the evidence. The second expert agreed with the conclusion that the analyses are not very informative but also pointed out that the data and strength of evidence for other conclusions were inadequate to support them. This expert agreed that the biopharmaceutical classification system was not more instructive than individual agent evaluations as stated in the report but pointed out that the data are no more informative than the rest of the review.

General conclusions taken from the abstract of the report: One expert thought the conclusions regarding carbamazepine are almost certainly still supported by the evidence but cited new evidence for the comparison of innovator versus generic medications. The other expert pointed out that the data and strength of evidence are inadequate for the conclusions and cited the subsequent journal article[23] that emphasized the insufficient or low strength of evidence as new evidence.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1: In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on health outcomes: mortality, hospitalizations, office/emergency department visits, composite endpoint of medical service utilization, health-related quality of life, seizures, secondary seizure injury, status epilepticus, loss of driver's license, and loss of employment?				
Newer antiepileptic medications did not significantly impact the risk of mortality versus their older counterparts carbamazepine, phenytoin, or valproic acid. However, many of these trials had followup times that might preclude observing an impact on a long-term outcome such as survival.	2 new studies were identified that reported on mortality: a cohort study reporting on phenytoin or valproate versus levetiracetam[5]and an RCT comparing lorazepam versus levetiracetam[19]	See KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusion is still valid, the other one thought that in particular combining all new AEDs is not useful and the journal article based on the review highlights that the strength of evidence is low for this conclusion	There is some new evidence and considering the existing criticism the conclusion is possibly out of date
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. Data supporting this is limited to four pharmaceutical industry-sponsored observational studies. These studies compared the use of long tolerated innovator antiepileptic medication with short-term results yielded after switching. The controlled observational studies did not state that they were limited to "A" rated products. The switch was not blinded, so patients' and clinicians' emotional or anxiety-related triggers for medical service utilization could have occurred. Use of claims data increases the risk of missing or misclassified data. Three out of the four studies showed that rates of hospitalization were higher with generic use compared with innovator, and one study found no difference. For the endpoint of hospital stay duration, all four studies found that generic use was associated with longer hospital stay duration than innovator use. And for the endpoint of outpatient service utilization, two studies found generic use was associated with higher outpatient service utilization and the other two studies found	2 new studies were identified that reported on emergency department visits and hospitalization: a retrospective cohort study on brand to generic phenytoin, lamotrigine, and divalproex[9] and a retrospective cohort study on brand to generic phenytoin[15]	See KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one cited the journal article based on the review highlighting that the strength of evidence is low for this conclusion, the other expert cited potential new evidence	There is some new evidence and considering the existing criticism the conclusion is possibly out of date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
no difference between the generic and innovator groups. Three separate, well-conducted controlled observational studies assessed a composite endpoint of medical service utilization. They did not compare innovator with generic products but rather the switch between "A" rated versions of products (innovator to generic, generic to generic, or generic to innovator). Two of the studies were supported by the pharmaceutical industry, used similar methods, had a similar composite endpoint (emergency department visit, ambulance service utilization, or hospitalization) and derived similar results. They matched for several important factors, limited the analyses to "A" rated products, and conducted subgroup analyses with similar results to the base case analysis. However, these studies did not control for comorbidities or changes in other medications and their associated dosages, which are known to impact seizure occurrence. As such, it is difficult to assure that the case population had the same baseline risk of an acute event requiring emergency services aside from their switch between antiepileptic medication versions. The third well-conducted case control study was sponsored by Express Scripts. In this study, significant increases in hospitalization of emergency room visits were seen in unadjusted analyses (odds ratio [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. Unlike the other two trials, this study's authors controlled for a person's risk of epilepsy exacerbation, change in disease severity, drug interactions, poor adherence, and change in patient diagnosis. This suggests that the difference in magnitude between these three studies may be due to inadequate confounder adjustment and/or the inclusion of ambulance service utilization in the two previous studies. All three of these controlled observational trials were				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
unblinded and used claims data. In total, two of the three observational studies suggest that switching from an antiepileptic 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).				
Several markers of epilepsy control were used in randomized controlled trials to compare newer versus older antiepileptic medications. The risk of being seizure free for either 6–12 or 24 months was significantly lower for newer antiepileptic medications versus carbamazepine. The risk of withdrawing due to lack of efficacy was also significantly higher for newer antiepileptic medications versus carbamazepine. No differences in 6–12- or 24-month freedom from seizures were seen for newer antiepileptic medications versus valproic acid, although this was based on a single controlled clinical trial, or for withdrawals due to lack of efficacy for newer antiepileptic medications versus phenytoin or valproic acid. The time to first seizure was increased for newer antiepileptic medications versus phenytoin, but not for newer antiepileptic medications versus carbamazepine or valproic acid. No significant difference in the risk of maintaining seizure freedom was seen when newer antiepileptic medications were compared versus carbamazepine, controlled/sustained-release carbamazepine, phenytoin, or valproic acid in controlled clinical trials, although data is limited for the comparison of newer antiepileptic medications versus controlled/sustained-release carbamazepine.	7 new studies reporting on epilepsy control were identified[5, 8, 11, 12, 19-21] reporting on the newer drugs levetiracetam, lamotrigine, topiramate, oxcarbazepine, gabapentin, zonisamide, felbamate, pregabalin, tiagabine, vigabatrin	See KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one indicated they did not entirely agree with the original conclusion but was not aware of additional information. The other expert thought the conclusion regarding carbamazepine was questionable	There is some new evidence and considering the existing criticism the conclusion is possibly out of date
For the comparison of innovator antiepileptic medications with their respective generic versions, we found that seizure occurrence and frequency were not significantly different between groups in controlled clinical trials. In addition, there were no	2 new studies were identified: a survey reporting on brand to generic phenytoin, carbamazepine, valproic acid, lamotrigine, oxcarbazepine,	See KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusion is still	There is some new evidence and considering the existing criticism the conclusion is

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
significant differences between innovator antiepileptic medications and their respective generic versions in terms of total withdrawals or withdrawals due to lack of efficacy in controlled clinical trials. In one controlled observational trial, there was a significant increase in withdrawals for any reason, but this trial had marked differences in several demographic variables (age, insurance type, and concomitant migraine headache and cerebral palsy) and the investigators did not conduct adjusted analyses. This occurred even though many of the trials did not use FDA approved "A" rated generics. Many of these controlled clinical trials used a crossover design or randomized patients to either an innovator or generic product in a parallel fashion so they cannot be used to determine whether a switch from one antiepileptic medication to another "A" rated version would increase the risk of seizure occurrence or increase seizure frequency. In 2010, a meta-analysis of seven trials on seizure occurrence following the use of generic versus innovator antiepileptic medications was published. We did not include the trial by Wolf 1992 since it was comparing two established versions of a sustained-release carbamazepine product versus a new version that was not a generic of the original versions. The authors said they included data from Hartley 1991 but instead used the data from Hartley 1990. Even with these differences, our findings, using the six trials that were eligible for pooling within our analysis, are characteristically similar to that of their meta-analysis (OR 1.1 [0.9 to 1.2]).	zonisamide, gabapentin, levetiracetam, and topiramate[6] and a retrospective chart review on levetiracetam[7]		valid. The other expert cited the journal article based on the review which emphasized that the conclusions are based on low or insufficient strength of evidence and that the pooled result is possibly still supported but does not address the most critical clinical question (risk of switching)	possibly out of date
Health-related quality of life, loss of driver's license or employment, secondary seizure injury, and status epilepticus endpoints were unavailable or did not allow adequate data to determine comparative effectiveness.	2 new studies reporting on status epilepticus were identified: a cohort study comparing phenytoin or valproate versus levetiracetam[5] and an RCT comparing lorazepam and levetiracetam[19]	None relevant	The published critique is summarized in the text. Both experts reviewing the individual conclusions agreed that the conclusion is almost certainly still supported by the evidence	The conclusions regarding status epilepticus are possibly out of date, there is new evidence available

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 2: In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on intermediate outcomes: pharmacokinetics, the comparative dose of medication needed to control seizures, and switchback rates?				
This section is specifically focused on innovator versus generic antiepileptic medications. The data were derived predominantly from carbamazepine trials and to a lesser extent phenytoin and lamotrigine trials. As such, there is limited ability to extrapolate to all antiepileptic medications with generic versions.	No new studies comparing newer versus older but 3 cohort studies[7, 9, 15] and 2 bioequivalence comparison studies[16, 18] on innovator versus generic antiepileptic medication were identified reporting on other than carbamazepine, phenytoin and lamotrigine	None relevant	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one agreed that the data are too limited for conclusions and cited the journal article, the other expert pointed to new evidence	There is new evidence available, the conclusions are possibly out of date
The average Cmax, Cmin, Css, Tmax, and AUC values from a population of patients receiving innovator antiepileptic medications are not significantly different from that of their generic versions. A population of patients should derive similar concentrations on an innovator to using generic antiepileptic medications. However, our data do not allow us to determine if an individual patient or subset of patients would have an over- or under-accentuated pharmacokinetic response if they were switched from one version of the medication to the other (innovator to generic, generic to generic, generic to innovator).	3 new studies were identified: a retrospective cohort study investigating phenytoin[15], an inter-study comparison of FDA bioequivalence studies for carbamazepine, divalproex, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide[16]; and an inter-study comparison of bioequivalence studies submitted to the Dutch Medicines Evaluation Board reporting on topiramate and gabapentin[18]	None relevant	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one agreed that the data are limited and cited the journal article as new evidence, the other expert pointed to new evidence	There is new evidence but it does not contradict the conclusion, overall the conclusion can be considered still valid.
While 12 to 44 percent of patients in four observational studies switched back to innovator antiepileptics after taking a generic version of the medication, the main limitation of this type of data is that the patients and clinicians were not blinded. As such, the switchback from a generic to an innovator antiepileptic medication may or may not be due to real versus perceived differences in efficacy or adverse events.	1 retrospective chart review[7] was identified reporting on the switch back rate of brand to generic levetiracetam (43%)	See KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusion is still valid. The other expert agreed that the data are too limited for conclusions and cited the journal article based on the review which emphasized that the conclusions are based on low or insufficient strength of evidence	There is new evidence but it does not contradict the conclusion, overall the conclusion can be considered still valid.
Key Question 3: In patients with epilepsy, what is the comparative impact of antiepileptic medications on serious adverse events such as neurological adverse effects, hypotension, rash, suicidal ideation, mood and cognition, bone density, and cosmetic adverse effects?				
We could not adequately compare antiepileptic	2 new studies were identified: an	There was a label change for	The published critique is	There is new

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
medications for hypotension, asthenia, ataxia, nystagmus, tremor, mood and cognition, or bone density.	RCT comparing lorazepam and levetiracetam reported on hypotension, agitation, and rash[19]and a prospective cohort study reported on depression, anxiety, mood swings, and anger for carbamazepine versus levetiracetam[13]	topamax (topiramate), trileptal (oxcarbazepine), and zonegran (zonisamide) adding risk of suicidal behavior and ideation.	summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusions are still valid, the other thought there is data on differential cognitive effects, questioned the choice of side effects to review and thought it is inexcusable that teratogenic risks were not examined	evidence and the FDA warnings should be investigated systematically, the conclusions are probably out of date
Newer antiepileptic medications were not significantly different versus carbamazepine, carbamazepine SR/CR, phenytoin, valproic acid, or ethosuximide in risk of overall withdrawal and versus phenytoin, valproic acid, and ethosuximide in risk of withdrawal due to adverse events, although the phenytoin and ethosuximide evaluations for both outcomes are based on more limited data. Newer antiepileptic medications had a lower withdrawal rate due to adverse events but an offsetting higher withdrawal rate due to lack of efficacy versus carbamazepine and carbamazepine SR/CR.	No new study was identified.	See below	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusions are still valid, the other thought the conclusions not concerning carbamazepine are based on low strength of evidence and not justified	There is no new evidence but the strength of evidence should be stated clearly, the conclusion is possibly out of date
Newer antiepileptic medications had a significantly lower risk of developing fatigue, somnolence, dizziness, and skin rash than carbamazepine; skin rash versus carbamazepine SR/CR; vomiting and gum hyperplasia versus phenytoin; fatigue, somnolence, nausea, and alopecia versus valproic acid; and somnolence versus ethosuximide. No significant differences in the risk of headache with newer versus older antiepileptic medications was seen. Data on adverse events was very limited for carbamazepine SR/CR and ethosuximide analyses. In no case did newer antiepileptic medications exhibit a higher risk of adverse events than older antiepileptic medications.	3 new studies were identified: an RCT comparing carbamazepine-CR and levetiracetam reported on sleep outcomes[8], an RCT comparing lorazepam and levetiracetam reported an incidence of rash in the levetiracetam group[19], and a cohort study comparing carbamazepine, phenobarbital, phenytoin, valproate versus lamotrigine, gabapantine, and topiramate reported on gastrointestinal adverse events[14]	There was a label change for Topamax (topiramate) adding fetal toxicity (the benefits and risk should be considered when administering the drug in women of childbearing potential) to warnings and precautions; the adverse event hyperesthesia was added; the use in specific populations was updated (pregnancy: topamax can cause fetal harm when administered to a pregnant women); and the counseling information concerning eye disorders was updated	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusions are still valid, the other emphasized that several conclusions were based on low or insufficient strength of evidence	There is new evidence available, the conclusions are possibly out of date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
		(patients should seek immediate medical attention). There was a label change for Dilantin (phenytoin) adding allergic reactions, coarsening of facial features, systemic lupus erythematosus, periarteritis nodosa, immunoglobulin abnormalities; altered taste sensation, Peyronie's disease. FDA notification that Lamictal (lamotrigine) can cause aseptic meningitis. There is new safety information for tegretol (carbamazepine): serious dermatologic reactions, increased risk in some Asian countries, strong association with HLA-B gene in patients of Han Chinese ancestry, HLA-B 1502 genotyping could be used as a screening tool and use of tegretol should be avoided.		
No significant differences were noted between innovator and generic antiepileptic medications for evaluated adverse events including headache, somnolence, diplopia, or skin rash. Given the similar blood concentrations between innovator versus generic antiepileptic medications, this would be anticipated, but it has to be noted that the crossover and parallel comparative trials establish the impact of starting patients on innovator or generic therapy and not the short-term impact of switching from one version of the medication to the other.	1 new study[6] was identified: a survey comparing brand to generic phenytoin, carbamazepine, valproic acid, lamotrigine, oxcarbazepine, zonisamide, gabapentin, levetiracetam, topiramate reported 20.6% of participants reported increased side effects after switching to generic AEDs	See above	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one did not comment, the other emphasized the low or insufficient strength of evidence	There is new evidence available, the conclusions are possibly out of date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 4: In patients with epilepsy, what are the comparative benefits or harms for antiepileptic medications in subgroups of patients differentiated by seizure etiology, seizure type, gender, ethnicity, patient age, and patient pharmacogenetic profile; and by types of antiepileptic medication?				
The results of these a priori subgroup analyses are not very informative. Data were limited mostly to partial epilepsy, new onset epilepsy, and were generally in patients 18 years or younger. Gender, genetic profile, and polypharmacy's impact on results could not be determined. Splitting our newer antiepileptic medication versus carbamazepine, phenytoin, valproic acid, or ethosuximide analyses by seizure etiology, seizure type, gender, and patient age, we had limited power to detect differences. The sample sizes of the trials in each subpopulation were lower than the overall population. 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 of the subgroup analysis were similar to the base case evaluations, although, in the subgroup analysis, the results were less likely to show significance.	4 new studies comparing older versus newer medications were identified: 1 prospective cohort study reporting on women comparing carbamazepine versus levetiracetam or lamotrigine[13]; 1 study reporting on the North American AED Pregnancy Registry comparing carbamazepine, phenytoin, valproate, phenobarbital, or clonazepam versus lamotrigine, levetiracetam, topiramate, oxcarbazepine, gabapentin, or zonisamide[12]; 1 RCT exclusively in partial epilepsy patients compared carbamazepine-CR versus levetiracetam[8]; 1 cohort study exclusively in intractable epilepsy patients compared carbamazepine, phenobarbital, phenytoin, or valproate versus lamotrigine, gabapentine, or topiramate[14]	FDA states that women of childbearing age should be informed about increased risk for adverse effects associated with prenatal valproate exposure, alternative medications that have a lower risk of adverse birth outcomes should be considered. As outlined in KQ3, there was a label change for topamax (topiramate) specifying that it can cause fetal harm when administered to a pregnant woman, and the benefits and risks should be considered when administering the drug in women of childbearing potential	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one indicated the conclusion is almost certainly still supported by the evidence, the other agreed that the analyses are not very informative as stated in the conclusions	There is new published evidence and the potential harm for women of childbearing potential should be investigated systematically and be addressed in the conclusions; the conclusions are probably out of date
Innovator versus generic controlled clinical trials and controlled observational studies did not provide data in prespecified subgroups based on seizure etiology or type, or on genetic profile. No controlled clinical trials and one controlled observational study reported data on gender, age, and polypharmacy impact on switchback rates from generic to innovator versions. There was no statistically significant difference in women compared with men when switching back to innovator from generic versions of antiepileptic medications (HR 1.10 [0.97 to 1.24]; p=0.130). Younger patients were more likely to require a switchback to innovator medication compared with older patients (HR 0.993 [0.988 to 0.997];	No new studies were identified.	See above and KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusion is almost certainly still supported by the evidence, the other stated that the data and strength of evidence are inadequate for conclusions	The conclusions are still valid but the strength of evidence should be stated clearly

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
p=0.002). Patients receiving polytherapy were no more or less likely to switch back to innovator (HR 1.23 [0.995 to 1.515]; p=0.056).				
While data on BCS class for the innovator versus generic antiepileptic medication evaluation was presented directly in Key Questions 1, 2, and 3; the use of BCS class was not more instructive than individual agent evaluations.	No new studies were identified.	None relevant	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusion is almost certainly still supported by the evidence, the other stated that the BCS class data is no more informative than the rest of the CER	The conclusions are still valid.
General Conclusions (Abstract)				
Carbamazepine had advantages in epilepsy control over newer antiepileptic medications as a class but had more adverse effects. Valproic acid and phenytoin provided epilepsy control similar to newer antiepileptic medications, but there were adverse events that occurred more commonly with these older antiepileptic medications. However, these adverse events did not significantly increase the risk of withdrawals.	5 new studies[8, 12-14, 20] including one RCT reporting on carbamazepine specifically were identified and showed mixed results depending on the individual comparator, 5 studies investigating valproic acid showed mixed results depending on the individual comparator[5, 12, 14, 17, 20], 4 studies included phenytoin and reported mixed results depending on the comparator and investigated outcome[5, 12, 14, 20]	See KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought the conclusion is almost certainly still supported by the evidence, the other stated that the data and strength of evidence are inadequate for conclusions	There is new evidence and considering the existing criticism the conclusion is possibly out of date
In patients who need to initiate an antiepileptic medication, we could find no substantive differences in terms of benefits or harms associated with the use of an innovator versus a generic. 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	7 new studies were identified that compared innovator and generic medications[6, 7, 9, 10, 15, 16, 18]	See KQ3	The published critique is summarized in the text. Of the two experts reviewing the individual conclusions, one thought there was new available evidence, the other stated that the data and strength of evidence are inadequate for conclusions	There is new evidence and considering the existing criticism the conclusion is possibly out of date

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
service utilization.				

Legend: AED: antiepileptic drug; CER: Comparative Effectiveness Review; KQ: Key Question; RCT: Randomized Controlled Trial; SCEPC: Southern California Evidence-based Practice Center

References

1. Talati R, Scholle JM, Phung OJ, et al. Effectiveness and Safety of Antiepileptic Medications in Patients with Epilepsy. Comparative Effectvess Review No. 40. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 11(12)-EHC082-EF Agency for Healthcare Research and Quality. Rockville, MD: December 2011.

2. Welty TE, Faught E, Schmidt D, et al. Be sure to read the fine print: the agency for healthcare research and quality comparative effectiveness report on antiepileptic drugs. Epilepsy Curr. 2012 May;12(3):84-6. PMID 22690134.

3. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) (Prepared by the Southern California Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality; October 2009.

4. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007 Aug 21;147(4):224-33. PMID 17638714.

5. Alvarez V, Januel J-M, Burnand B, et al. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia. 2011 Jul;52(7):1292-6. PMID 21480881.

6. Bautista RED, Gonzales W, Jain D. Factors associated with poor seizure control and increased side effects after switching to generic antiepileptic drugs. Epilepsy Research. 2011 Jun;95(1-2):158-67. PMID 21530177.

7. Chaluvadi S, Chiang S, Tran L, et al. Clinical experience with generic levetiracetam in people with epilepsy. Epilepsia. 2011 Apr;52(4):810-5. PMID 21426334.

8. Cho YW, Kim DH, Motamedi GK. The effect of levetiracetam monotherapy on subjective sleep quality and objective sleep parameters in patients with epilepsy: compared with the effect of carbamazepine-CR monotherapy. Seizure. 2011 May;20(4):336-9. PMID 21316267.

9. Erickson SC, Le L, Ramsey SD, et al. Clinical and pharmacy utilization outcomes with brand to generic antiepileptic switches in patients with epilepsy. Epilepsia. 2011 Jul;52(7):1365-71. PMID 21692778.

10. Fitzgerald CL, Jacobson MP. Generic substitution of levetiracetam resulting in increased incidence of breakthrough seizures. Annals of Pharmacotherapy. 2011 May;45(5):e27. PMID 21521860.

11. Gilioli I, Vignoli A, Visani E, et al. Focal epilepsies in adult patients attending two epilepsy centers: classification of drug-resistance, assessment of risk factors, and usefulness of "new" antiepileptic drugs. Epilepsia. 2012 Apr;53(4):733-40. PMID 22360822.

12. Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012 May 22;78(21):1692-9. PMID 22551726.

13. Herzog AG, Smithson SD, Fowler KM, et al. Premenstrual dysphoric disorder in women with epilepsy: relationships to potential epileptic, antiepileptic drug, and reproductive endocrine factors. Epilepsy & Behavior. 2011 Aug;21(4):391-6. PMID 21724471.

14. Jahromi SR, Togha M, Fesharaki SH, et al. Gastrointestinal adverse effects of antiepileptic drugs in intractable epileptic patients. Seizure. 2011 May;20(4):343-6. PMID 21236703.

15. Kinikar SA, Delate T, Menaker-Wiener CM, et al. Clinical outcomes associated with brand-to-generic phenytoin interchange. Annals of Pharmacotherapy. 2012 May;46(5):650-8. PMID 22550275.

16. Krauss GL, Caffo B, Chang Y-T, et al. Assessing bioequivalence of generic antiepilepsy drugs. Annals of Neurology. 2011 Aug;70(2):221-8. PMID 21717495.

17. Machado RA, Espinosa AG, Melendrez D, et al. Suicidal risk and suicide attempts in people treated with antiepileptic drugs for epilepsy. Seizure. 2011 May;20(4):280-4. PMID 21269844.

18. Maliepaard M, Banishki N, Gispen-de Wied CC, et al. Interchangeability of generic anti-epileptic drugs: a quantitative analysis of topiramate and gabapentin. European Journal of Clinical Pharmacology. 2011 Oct;67(10):1007-16. PMID 21494766.

19. Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol. 2012 Apr;259(4):645-8. PMID 21898137.

20. Poolos NP, Warner LN, Humphreys SZ, et al. Comparative efficacy of combination drug therapy in refractory epilepsy. Neurology. 2012 Jan 3;78(1):62-8. PMID 22170887.

21. Stephen LJ, Forsyth M, Kelly K, et al. Antiepileptic drug combinations--have newer agents altered clinical outcomes? Epilepsy Research. 2012 Feb;98(2-3):194-8. PMID 21982026.

22. Epilepsy Foundation. Epilepsy Community Has Major Concern Over Release of Anticonvulsant Drug Comparison Report. February 16, 2012. http://www.epilepsyfoundation.org/news/Epilepsy-Community-Has-Major-Concern-Over-Release-of-Anticonvulsant-Drug-Comparison-Report.cfm.

23. Talati R, Scholle JM, Phung OP, et al. Efficacy and safety of innovator versus generic drugs in patients with epilepsy: a systematic review. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2012 Apr;32(4):314-22. PMID 22461121.

Appendices

Appendix A: Search Methodology

Appendix B: Evidence Tables

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

Search Strategy Innovator versus Generic Antiepileptic Drug Evaluation

(original search strategy modified to capture new studies not fully indexed)

1 generic.mp.
2 innovator.mp.
3 nonproprietary.mp.
4 exp drugs, generic
5 generic$.mp
6 (therapeutic adj equivalency).mp.
7 exp therapeutic equivalency
8 (brand adj name).mp.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 epilepsy.mp.
11 epilep$.mp
12 exp epilespy
13 seiz$.mp.
14 convuls$.mp.
15 10 or 11 or 12 or 13 or 14
16 9 and 15
17 Non-proprietary.mp.
18 9 or 17
19 15 and 18
20 21 and 2011:2012. (sa year)

Search strategy for older versus newer antiepileptic drug evaluations

Journal ranking by number of antiepileptic drug publications

WEB OF SCIENCE TOP 10 JOURNALS

Publication Dates: 1980 - present

Source Titles	records	% of 25006
EPILEPSIA	3873	15.488
EPILEPSY RESEARCH	934	3.735
NEUROLOGY	913	3.651
EPILEPSY BEHAVIOR	853	3.411
SEIZURE EUROPEAN JOURNAL OF EPILEPSY	656	2.623
REVISTA DE NEUROLOGIA	376	1.504
JOURNAL OF CHILD NEUROLOGY	304	1.216
ACTA NEUROLOGICA SCANDINAVICA	269	1.076
PEDIATRIC NEUROLOGY	269	1.076
EUROPEAN JOURNAL OF NEUROLOGY	263	1.052

Search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10
12. epidemiologic studies/
13. exp case control studies/
14. exp cohort studies/
15. case control.tw.
16. (cohort adj (study or studies)).tw.
17. cohort.analy$.tw.
18. (follow up adj (study or studies)).tw.
19. longitudinal.tw.
20. retrospective.tw.
21. cross sectional.tw.
22. cross-sectional studies/
23. or/12-22
24. 11 or 23
25. Epilepsy/ or epilepsy.mp.
26. epilep$.mp.
27. seiz$.mp.
28. convuls$.mp.
29. 25 or 26 or 27 or 28
30. felbamate.mp.
31. gabapentin.mp.
32. lacosamide.mp.
33. lamotrigine.mp.
34. levetiracetam.mp.
35. oxcarbazepine.mp.
36. pregabalin.mp.
37. rufinamide.mp.
38. tiagabine.mp.
39. topriamate.mp.
40. vigabatrin.mp.
41. zonisamide.mp.
42. 30 or 31 or 32 or 33 or 34 or 35 of 36 or 37 of 38 or 39 or 40 or 41
43. 29 and 42
44. 43 and (11 or 24)
45. 44 or drug$ and medicat*

Citations were limited to English-language publications in these journals:

Annals of Internal Medicine
New England Journal of Medicine
Journal of the American Medical Association
Lancet
British Medical Journal
Epilepsia
Epiepsy research
Neurology
Epilepsy Behavior
Seizure European Journal of Epilepsy

Latest search date: 8/10/2012

Appendix B. Evidence Tables

Evidence Table Key Question 1. In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on health outcomes: mortality, hospitalizations, office/emergency department visits, composite endpoint of medical service utilization, health-related quality of life, seizures, secondary seizure injury, status epilepticus, loss of driver's license, and loss of employment?

Study	Design	Interventions	Outcomes	Finding
Older versus Newer				
Alvarez, 2011[5]	Cohort study	Phenytoin or valproate versus levetiracetam	Mortality, status epilepticus episodes, deadly etiology	Valproate failed to control status epilepticus in 25.4%, phenytoin in 41.4%, and levetiracetam in 48.3% of episodes; a deadly etiology was more frequent in the valproate group, status epilepticus episodes tended to be more severe in the phenytoin group; levetiracetam failed more often than valproate (OR 2.69; CI 1.19–6.08); 16.8% (95% CI: 6.0–31.4%) of second-line treatment failures could be attributed to levetiracetam; phenytoin was not statistically different from the other two compounds
Cho, 2011[8]	Longitudinal RCT	Carbamazepine-CR versus levetiracetam	Seizure reduction, National Hospital Seizure Severity Scale	The overall effect on seizure reduction was comparable, although there were some differences in the effects on individuals
Gilioli, 2012[11]	Cohort study	Older AEDs versus lamotrigine, levetiracetam, felbamate, gabapentin, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide	Seizure free status	The patients previously considered resistant to two or more AEDs, 53% became seizure-free while receiving a new AED
Hernandez-Diaz, 2012[12]	Cohort study (North American AED Pregnancy Registry)	Carbamazepine, phenytoin, valproate, phenobarbital, clonazepam versus lamotrigine, levetiracetam, topiramate, oxcarbazepine, gabapentin, zonisamide	Seizures	Seizures during pregnancy ranged from 20.2% (phenobarbital) to 27.7% (carbamazepine) in older AEDs versus 23.6% (zonisamide) to 44.8% (gabapentin)
Misra, 2012[19]	RCT	Lorazepam Versus levetiracetam	Status epilepticus management24-hour seizure free, mortality	Both were equally effective; in the first instance, status epilepticus was controlled by levetiracetam in 76.3% and by lorazepam in 75.6% of patients; in those resistant to the regimen, levetiracetam controlled status epilepticus in 70.0% and lorazepam in 88.9% of patients; 24-h freedom from seizure was comparable (levetiracetam: 79%,

Study	Design	Interventions	Outcomes	Finding
				lorazepam: 68%)
Poolos, 2012[20]	Retrospective chart review	Carbamazepine, phenytoin, valproate versus levetiracetam, lamotrigine, topiramate, zonisamide	Seizure control	Seizure frequency ratio of lamotrigine was significantly superior to valproate, and lamotrigine was superior to valproate plus phenytoin
Stephen, 2012[21]	Retrospective cohort study	Antiepileptic drug combinations in 2000 versus combinations used in 2010 (levetiracetam and topiramate most commonly represented in successful combinations)	Seizure free	In 2000 21% of patients required polytherapy to remain seizure-free for at least 1 year compared to 20% in 2010. Data tend to imply that drug substitution rather than addition has largely led to the marginally improved results; newer agents appear not to have impacted substantially on the likelihood of producing seizure freedom
Innovator versus Generic				
Bautista, 2011[6]	Survey	Brand to generic phenytoin, carbamazepine, valproic acid, lamotrigine, oxcarbazepine, zonisamide, gabapentin, levetiracetam, topiramate	Seizure frequency	25.7% participants reported increased seizure frequency after switching to generic AEDs
Chaluvadi, 2011[7]	Retrospective chart review	Brand to generic levetiracetam	Seizure frequency in patients switching back to brand name	43% of patients were switched back to brand name, reasons included increase in seizure frequency (19.6% versus 1.6%, $p<0.0001$); careful monitoring is imperative because a compulsory switch from brand to generic levetiracetam may lead to poor clinical outcomes, with risk of AEs and increased seizure frequency
Erickson, 2011[9]	Retrospective cohort study	Brand or generic phenytoin, lamotrigine, divalproex	All-cause emergency department visit, hospitalization	Brand to generic switching of phenytoin, lamotrigine, and divalproex was not associated with more clinical events
Fitzgerald, 2011[10]	4 cases	Keppra to generic levetiracetam	Breakthrough seizures	Increased incidence of breakthrough seizures after changing to generic, seizure frequency returned to baseline when switched back
Kinikar, 2012[15]	Retrospective cohort study	Brand to generic phenytoin (Dilantin)	Emergency department visit, hospitalization	There were low proportions of patients with confirmed seizure events that resulted in an emergency department visit / inpatient hospitalization in both periods; the proportion of patients with confirmed seizure events diagnosed at a medical office visit was not significantly different

Note: AED: antiepileptic drug

Evidence Table Key Question 2. In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on intermediate outcomes: pharmacokinetics, the comparative dose of medication needed to control seizures, and switchback rates?

Study	Design	Interventions	Outcomes	Finding
Innovator versus Generic				
Chaluvadi, 2011[7]	Retrospective chart review	Brand to generic levetiracetam	Switchback rate	43% of patients were switched back to brand name by their treating physician
Erickson, 2011[9]	Retrospective cohort study	Brand or generic phenytoin, lamotrigine, divalproex	Strength change, discontinuation of index medication, add-on therapy	Brand to generic switching of phenytoin was associated with increased index drug discontinuations, dose changes, or therapy augmentations; lamotrigine and divalproex brand to generic switching was not associated with increased utilization changes compared with patients remaining on the branded product; changes in utilization may be more sensitive than emergency department visits and hospitalizations for detecting adverse outcomes
Kinikar, 2012[15]	Retrospective cohort study	Brand to generic phenytoin (Dilantin)	Serum concentration	Low serum concentrations were detected more often in the post-interchange study period
Krauss, 2011[16]	Inter-study comparison of FDA bioequivalence studies	Generic products of carbamazepine, divalproex, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, zonisamide	Cmax, total drug exposure AUC	AUC_{0-t} values of approved reference and generic formulations differed by <15% in 99% of studies; C_{max} differed by <15% in 89% of studies; food affected variability of C_{max} but not AUC_{0-t}; inter-subject variability was small and similar for reference and generic products; in simulated switches estimated AUC_{0-t} differed by >15% for 17% of pairs; estimated C_{max} differed by >15% for 39%; AEDs with low bioavailability and solubility (e.g., oxcarbazepine) had the greatest variability; most generic AED products provide total drug delivery similar to reference products; differences in peak concentrations between formulations are more common; switches between generic AED products may cause greater changes in plasma drug concentrations than generic substitutions of reference products
Maliepaard, 2011[18]	Inter-study comparison of bioequivalence studies submitted to the Dutch Medicines Evaluation Board	Topiramate (topamax), gabapentin (neurontin)	AUC, Cmax	In a number of cases 90% CIs outside the 80–125% criterion were found upon interchanging generics; however, a similar pattern of 90% CIs outside the criterion was observed for innovator arms, despite the fact that the innovator was identical in all studies; the so-called drifting problem upon generic – generic substitution does not result in important differences in exposure upon exchanging topiramate generics or gabapentin generics

Note: AED: antiepileptic drug; AUC: area under the curve; CI: confidence interval

Evidence Table Key Question 3. In patients with epilepsy, what is the comparative impact of antiepileptic medications on serious adverse events such as neurological adverse effects, hypotension, rash, suicidal ideation, mood and cognition, bone density, and cosmetic adverse effects?

Study	Design	Interventions	Outcomes	Findings
Older versus Newer				
Cho, 2011[8]	Longitudinal RCT, before-after data reported	Carbamazepine-CR versus levetiracetam	Polysomnography, sleep questionnaires, depression, hospital anxiety scale	There were no significant differences in effects on sleep between the treatment groups
Herzog, 2011[13]	Prospective cohort study	Carbamazepine versus levetiracetam or lamotrigine	Depression, anxiety, mood swings, anger	Depression, mood swings, and anger were associated with higher average daily scores for levetiracetam compared to carbamazepine over the entire cycle and especially premenstrually
Jahromi, 2011[14]	Cohort study	Carbamazepine, phenobarbital, phenytoin, valproate versus lamotrigine, gabapentine, topiramate	Gastrointestinal adverse effects	Nausea and vomiting were significantly higher in carbamazepine and valproic acid; when phenytoin, gabapentine, or valproic acid was added to the other AEDs, the risk of the occurrence of diarrhea, dysphagia, or heartburn was significantly increased, respectively; addition of gabapentine to the other AEDs in multiple drug therapy was accompanied with the highest frequency of GI complications
Machado, 2011[17]	Prospective cohort study	Phenobarbital, carbamazepine, valproate, primidone, phenytoin versus lamotrigine, topiramate	Suicidal risk, suicide attempts	Antiepileptic drugs probably do not have an impact on suicidality
Misra, 2012[19]	RCT	Lorazepam versus levetiracetam	Hypotension, agitation, rash	Lorazepam was associated with insignificantly higher frequency of hypotension; other adverse events: agitation (4 vs 0), rash (1 vs 0) comparing levetiracetam versus lorazepam
Innovator versus Generic				
Bautista, 2011[6]	Survey	Brand to generic phenytoin, carbamazepine, valproic acid, lamotrigine, oxcarbazepine, zonisamide, gabapentin, levetiracetam, or topiramate	Side effects	20.6% participants reported increased side effects after switching to generic AEDs

Note: AED: antiepileptic drug

Evidence Table Key Question 4. In patients with epilepsy, what are the comparative benefits or harms for antiepileptic medications in subgroups of patients differentiated by seizure etiology, seizure type, gender, ethnicity, patient age, and patient pharmacogenetic profile; and by types of antiepileptic medication?

Study	Design	Subgroup	Intervention	Outcomes	Findings
Older versus Newer					
Cho, 2011[8]	Longitudinal RCT	Seizure type: Partial epilepsy	Carbamazepine-CR versus levetiracetam	Seizure reduction, National Hospital Seizure Severity Scale, polysomnography, sleep questionnaires, depression, hospital anxiety scale	The overall effect on seizure reduction was comparable, although there were some differences in the effects on individuals; there were no significant differences in effects on sleep between the treatment groups
Hernandez-Diaz, 2012[12]	Cohort study (North American AED Pregnancy Registry)	Gender: Women	Carbamazepine, phenytoin, valproate, phenobarbital, clonazepam versus lamotrigine, levetiracetam, topiramate, oxcarbazepine, gabapentin, zonisamide	Seizures	Seizures during pregnancy ranged from 20.2% (phenobarbital) to 27.7% (carbamazepine) in older AEDs versus 23.6% (zonisamide) to 44.8% (gabapentin)
Herzog, 2011[13]	Prospective cohort study	Gender: Women	Carbamazepine versus levetiracetam or lamotrigine	Depression, anxiety, mood swings, anger	Depression, mood swings, and anger were associated with higher average daily scores for levetiracetam compared to carbamazepine over the entire cycle and especially premenstrually
Jahromi, 2011[14]	Cohort study	Seizure type: Intractable epilepsy	Carbamazepine, phenobarbital, phenytoin, valproate versus lamotrigine, gabapentine, topiramate	Gastrointestinal adverse effects	Nausea and vomiting were significantly higher in carbamazepine and valproic acid; when phenytoin, gabapentine, or valproic acid was added to the other AEDs, the risk of the occurrence of diarrhea, dysphagia, or heartburn was significantly increased, respectively; addition of gabapentine to the other AEDs in multiple drug therapy was accompanied with the highest frequency of gastrointestinal complications

Note: AED: antiepileptic drug

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: **Effectiveness of Safety of Antiepileptic Medications in Patients with Epilepsy**

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on health outcomes: mortality, hospitalizations, office/emergency department visits, composite endpoint of medical service utilization, health-related quality of life, seizures, secondary seizure injury, status epilepticus, loss of driver's license, and loss of employment?			
Newer antiepileptic medications did not significantly impact the risk of mortality versus their older counterparts carbamazepine, phenytoin, or valproic acid. However, many of these trials had followup times that might preclude observing an impact on a long-term outcome such as survival.	☐	New Evidence:	☐
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. Data supporting this is limited to four pharmaceutical industry-sponsored observational studies. These studies compared the use of long tolerated innovator antiepileptic medication with short-term results yielded after switching. The controlled observational studies did not state that they were limited to "A" rated products. The switch was not blinded, so patients' and clinicians' emotional or anxiety-related triggers for medical service utilization could have occurred. Use of claims data increases the risk of missing or misclassified data. Three out of the four studies showed that rates of hospitalization were higher with generic use compared with innovator, and one study found no difference. For the endpoint of hospital stay duration, all four studies found that generic use was associated with longer hospital	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
stay duration than innovator use. And for the endpoint of outpatient service utilization, two studies found generic use was associated with higher outpatient service utilization and the other two studies found no difference between the generic and innovator groups.			
Three separate, well-conducted controlled observational studies assessed a composite endpoint of medical service utilization. They did not compare innovator with generic products but rather the switch between "A" rated versions of products (innovator to generic, generic to generic, or generic to innovator). Two of the studies were supported by the pharmaceutical industry, used similar methods, had a similar composite endpoint (emergency department visit, ambulance service utilization, or hospitalization) and derived similar results. They matched for several important factors, limited the analyses to "A" rated products, and conducted subgroup analyses with similar results to the base case analysis. However, these studies did not control for comorbidities or changes in other medications and their associated dosages, which are known to impact seizure occurrence. As such, it is difficult to assure that the case population had the same baseline risk of an acute event requiring emergency services aside from their switch between antiepileptic medication versions. The third well-conducted case control study was sponsored by Express Scripts. In this study, significant increases in hospitalization of emergency room visits were seen in unadjusted analyses (odds ratio [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. Unlike the other two trials, this study's authors controlled for a person's risk of epilepsy exacerbation, change in disease severity, drug interactions, poor adherence, and change in patient diagnosis. This suggests that the difference in magnitude between these three studies may be due to inadequate	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
confounder adjustment and/or the inclusion of ambulance service utilization in the two previous studies. All three of these controlled observational trials were unblinded and used claims data. In total, two of the three observational studies suggest that switching from an antiepileptic 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).			
Several markers of epilepsy control were used in randomized controlled trials to compare newer versus older antiepileptic medications. The risk of being seizure free for either 6–12 or 24 months was significantly lower for newer antiepileptic medications versus carbamazepine. The risk of withdrawing due to lack of efficacy was also significantly higher for newer antiepileptic medications versus carbamazepine. No differences in 6–12- or 24-month freedom from seizures were seen for newer antiepileptic medications versus valproic acid, although this was based on a single controlled clinical trial, or for withdrawals due to lack of efficacy for newer antiepileptic medications versus phenytoin or valproic acid. The time to first seizure was increased for newer antiepileptic medications versus phenytoin, but not for newer antiepileptic medications versus carbamazepine or valproic acid. No significant difference in the risk of maintaining seizure freedom was seen when newer antiepileptic medications were compared versus carbamazepine, controlled/sustained-release carbamazepine, phenytoin, or valproic acid in controlled clinical trials, although data is limited for the comparison of newer antiepileptic medications versus controlled/sustained-release carbamazepine.	☐	New Evidence:	☐
For the comparison of innovator antiepileptic medications with their respective generic versions, we found that seizure occurrence and frequency were not significantly different between groups in controlled clinical trials. In	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
addition, there were no significant differences between innovator antiepileptic medications and their respective generic versions in terms of total withdrawals or withdrawals due to lack of efficacy in controlled clinical trials. In one controlled observational trial, there was a significant increase in withdrawals for any reason, but this trial had marked differences in several demographic variables (age, insurance type, and concomitant migraine headache and cerebral palsy) and the investigators did not conduct adjusted analyses. This occurred even though many of the trials did not use FDA approved "A" rated generics. Many of these controlled clinical trials used a crossover design or randomized patients to either an innovator or generic product in a parallel fashion so they cannot be used to determine whether a switch from one antiepileptic medication to another "A" rated version would increase the risk of seizure occurrence or increase seizure frequency.			
In 2010, a meta-analysis of seven trials on seizure occurrence following the use of generic versus innovator antiepileptic medications was published. We did not include the trial by Wolf 1992 since it was comparing two established versions of a sustained-release carbamazepine product versus a new version that was not a generic of the original versions. The authors said they included data from Hartley 1991 but instead used the data from Hartley 1990. Even with these differences, our findings, using the six trials that were eligible for pooling within our analysis, are characteristically similar to that of their meta-analysis (OR 1.1 [0.9 to 1.2]).	☐	New Evidence:	☐
Health-related quality of life, loss of driver's license or employment, secondary seizure injury, and status epilepticus endpoints were unavailable or did not allow adequate data to determine comparative effectiveness.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 2: In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on intermediate outcomes: pharmacokinetics, the comparative dose of medication needed to control seizures, and switchback rates?			
This section is specifically focused on innovator versus generic antiepileptic medications. The data were derived predominantly from carbamazepine trials and to a lesser extent phenytoin and lamotrigine trials. As such, there is limited ability to extrapolate to all antiepileptic medications with generic versions.	☐	New Evidence:	☐
The average Cmax, Cmin, Css, Tmax, and AUC values from a population of patients receiving innovator antiepileptic medications are not significantly different from that of their generic versions. A population of patients should derive similar concentrations on an innovator to using generic antiepileptic medications. However, our data do not allow us to determine if an individual patient or subset of patients would have an over- or under-accentuated pharmacokinetic response if they were switched from one version of the medication to the other (innovator to generic, generic to generic, generic to innovator).	☐	New Evidence:	☐
While 12 to 44 percent of patients in four observational studies switched back to innovator antiepileptics after taking a generic version of the medication, the main limitation of this type of data is that the patients and clinicians were not blinded. As such, the switchback from a generic to an innovator antiepileptic medication may or may not be due to real versus perceived differences in efficacy or adverse events.	☐	New Evidence:	☐
Key Question 3: In patients with epilepsy, what is the comparative impact of antiepileptic medications on serious adverse events such as neurological adverse effects, hypotension, rash, suicidal ideation, mood and cognition, bone density, and cosmetic adverse effects?			
We could not adequately compare antiepileptic medications for hypotension, asthenia, ataxia, nystagmus, tremor, mood and cognition, or bone density.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Newer antiepileptic medications were not significantly different versus carbamazepine, carbamazepine SR/CR, phenytoin, valproic acid, or ethosuximide in risk of overall withdrawal and versus phenytoin, valproic acid, and ethosuximide in risk of withdrawal due to adverse events, although the phenytoin and ethosuximide evaluations for both outcomes are based on more limited data. Newer antiepileptic medications had a lower withdrawal rate due to adverse events but an offsetting higher withdrawal rate due to lack of efficacy versus carbamazepine and carbamazepine SR/CR.	☐	New Evidence:	☐
Newer antiepileptic medications had a significantly lower risk of developing fatigue, somnolence, dizziness, and skin rash than carbamazepine; skin rash versus carbamazepine SR/CR; vomiting and gum hyperplasia versus phenytoin; fatigue, somnolence, nausea, and alopecia versus valproic acid; and somnolence versus ethosuximide. No significant differences in the risk of headache with newer versus older antiepileptic medications was seen. Data on adverse events was very limited for carbamazepine SR/CR and ethosuximide analyses. In no case did newer antiepileptic medications exhibit a higher risk of adverse events than older antiepileptic medications.	☐	New Evidence:	☐
No significant differences were noted between innovator and generic antiepileptic medications for evaluated adverse events including headache, somnolence, diplopia, or skin rash. Given the similar blood concentrations between innovator versus generic antiepileptic medications, this would be anticipated, but it has to be noted that the crossover and parallel comparative trials establish the impact of starting patients on innovator or generic therapy and not the short-term impact of switching from one version of the medication to the other.			

Key Question 4: In patients with epilepsy, what are the comparative benefits or harms for antiepileptic medications in subgroups of patients differentiated by seizure etiology, seizure type, gender, ethnicity, patient age, and patient pharmacogenetic profile; and by types of antiepileptic medication?			
The results of these a priori subgroup analyses are not very informative. Data were limited mostly to partial epilepsy, new onset epilepsy, and were generally in patients 18 years or younger. Gender, genetic profile, and polypharmacy's impact on results could not be determined. Splitting our newer antiepileptic medication versus carbamazepine, phenytoin, valproic acid, or ethosuximide analyses by seizure etiology, seizure type, gender, and patient age, we had limited power to detect differences. The sample sizes of the trials in each subpopulation were lower than the overall population. 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 of the subgroup analysis were similar to the base case evaluations, although, in the subgroup analysis, the results were less likely to show significance.	☐	New Evidence:	☐
Innovator versus generic controlled clinical trials and controlled observational studies did not provide data in prespecified subgroups based on seizure etiology or type, or on genetic profile. No controlled clinical trials and one controlled observational study reported data on gender, age, and polypharmacy impact on switchback rates from generic to innovator versions. There was no statistically significant difference in women compared with men when switching back to innovator from generic versions of antiepileptic medications (HR 1.10 [0.97 to 1.24]; p=0.130). Younger patients were more likely to require a switchback to innovator medication compared with older patients (HR 0.993 [0.988 to 0.997]; p=0.002). Patients receiving polytherapy were no more or less likely to switch back to innovator (HR 1.23 [0.995 to 1.515]; p=0.056).	☐	New Evidence:	☐
While data on BCS class for the innovator versus generic antiepileptic medication evaluation was presented directly in Key Questions 1, 2, and 3; the use of BCS class was not more instructive than individual agent evaluations.	☐	New Evidence:	☐

General conclusions (abstract)			
Carbamazepine had advantages in epilepsy control over newer antiepileptic medications as a class but had more adverse effects. Valproic acid and phenytoin provided epilepsy control similar to newer antiepileptic medications, but there were adverse events that occurred more commonly with these older antiepileptic medications. However, these adverse events did not significantly increase the risk of withdrawals.	☐	New Evidence:	☐
In patients who need to initiate an antiepileptic medication, we could find no substantive differences in terms of benefits or harms associated with the use of an innovator versus a generic. 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.	☐	New Evidence:	☐

Are there new data that could inform the key questions that might not be addressed in the conclusions?