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Comparative Effectiveness Review
Number 40

Effectiveness and Safety of Antiepileptic Medications in Patients With Epilepsy



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Effectiveness and Safety of Antiepileptic Medications in Patients With Epilepsy

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Effectiveness and Safety of Antiepileptic Medications in Patients With Epilepsy

Structured Abstract

Objectives: This is an evidence report prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center examining the comparative efficacy, safety, and tolerability of newer versus older and innovator versus generic antiepileptic medications.

Data Sources: MEDLINE (starting from 1950), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews, and Web of Science from the earliest possible date through March 23, 2011.

Review Methods: Controlled clinical trials and controlled observational studies were included in our comparative effectiveness review if they met the following inclusion criteria: compared older to newer antiepileptic medications or innovator to generic antiepileptic medications, conducted in patients with epilepsy, and reported data on prespecified clinical or humanistic outcomes. Using predefined criteria, data on study design, interventions, quality criteria, study population, baseline characteristics, and outcomes were extracted. All of the available data was qualitatively evaluated and where possible, statistically pooled. For dichotomous endpoints, we used relative risks, and for continuous endpoints, we used weighted mean differences or standardized mean differences. Both were calculated using a DerSimonian and Laird random effects model and reported with 95 percent confidence intervals. When mean change scores from baseline for each group were not reported, the difference between the mean baseline and mean followup scores for each group and the standard deviations of the change scores were calculated. I² was used to detect statistical heterogeneity and Egger's weighted regression statistics were used to assess for publication bias. The strength of the body of evidence for each outcome was rated as insufficient, low, moderate, or high.

Results: Patients given newer antiepileptic medications were less likely to be seizure free for 6–12 months or 24 months and had a greater risk of withdrawing due to a lack of efficacy than those receiving carbamazepine. The risk of withdrawing due to adverse events and the risk of several adverse events including fatigue, somnolence, dizziness, and skin rash were significantly reduced when patients received newer antiepileptic medications versus carbamazepine, but the risk of withdrawing for any reason was not significantly impacted. Similarly, patients receiving newer antiepileptic medications were more likely to withdraw due to a lack of efficacy than those receiving carbamazepine sustained or controlled release products but are more likely to withdraw due to adverse events and skin rash. The risk of withdrawing for any reason was not significantly impacted.

There was no significant difference in the risk of being seizure free for the study duration when newer antiepileptic medications were compared against phenytoin or valproic acid, or the risk of being seizure free at 6–12 or 24 months for valproic acid. No significant differences were seen for newer antiepileptic medications versus either phenytoin or valproic acid for withdrawals for

any reason, withdrawals due to lack of efficacy, or withdrawals due to adverse events. The risk of certain adverse events including fatigue, somnolence, nausea, and alopecia were significantly lower for newer antiepileptic medications versus valproic acid. The risks of vomiting and gum hyperplasia were significantly lower for newer antiepileptic medications versus phenytoin. For the comparison of innovator antiepileptic medications to their respective generic versions, we found that seizure occurrence, seizure frequency, total withdrawals, withdrawals due to lack of efficacy, or withdrawals due to adverse events were not significantly different in controlled clinical trials. Using data from observational studies, switching from an innovator to a generic antiepileptic medication may increase the risk of hospitalization, hospital stay duration, and the composite of medical service utilization but may not increase outpatient service utilization.

Conclusions: 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.

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.

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Executive Summary

Background

Epilepsy is a clinical phenomenon in which a person has recurrent seizures due to a chronic underlying process.^{1,2} Approximately 1 to 3 percent of people in the United States will develop epilepsy over the course of their lives.²⁻⁴ Epilepsy begins most commonly during the first 9 years of life, plateaus over the next 30 years, dips in patients 40 to 59 years of age, and then rises again in the elderly.^{1,4,5} Seizures in epilepsy can result in status epilepticus, a life-threatening unrelenting seizure, or can result in car accidents or falls that can lead to morbidity or mortality. In addition, uncontrolled seizures can result in patients losing their jobs or driving privileges.^{1,2,4} The main three types of seizures in patients with epilepsy include partial, generalized, and unclassified. There are several distinct subtypes of seizures.¹

Since 1993, the Food and Drug Administration (FDA) has approved several newer antiepileptic drugs (felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, zonisamide) for the treatment of epilepsy.⁶ This offered clinicians and patients many new options over the older antiepileptic medications that were approved between 1953 and 1983 (phenytoin, 1953; primidone, 1954; ethosuximide, 1960; carbamazepine, 1968; clonazepam, 1975; divalproex, 1978; valproic acid, 1983). The comparative benefits and harms of older versus newer antiepileptic drugs have been assessed in numerous randomized controlled trials with varying results.^{1,7,8}

Another important issue in the management of epilepsy is generic substitution of innovator antiepileptic medications. The American Academy of Neurology has issued two position papers stating that there is concern with generic antiepileptic medication substitution and that physicians should specifically approve all generic substitutions.^{9,10} The Italian League Against Epilepsy established a working group on generic products in epilepsy treatment. It concluded that generic medications offer a valuable and cost-effective choice in the management of epilepsy but that generic substitution is not recommended in patients who achieve seizure remission on an innovator product.¹¹ The FDA and the American Society of Health-System Pharmacists do not share the view that antiepileptic medications, or other narrow therapeutic index medications (medications where the difference between the minimum effective and minimum toxic concentrations are close together), should be treated differently as it pertains to generic substitution.¹²⁻¹⁵

A comparative effectiveness review (CER) of the benefits and harms associated with newer versus older and innovator versus generic antiepileptic treatments is needed to clarify these issues.

Objectives

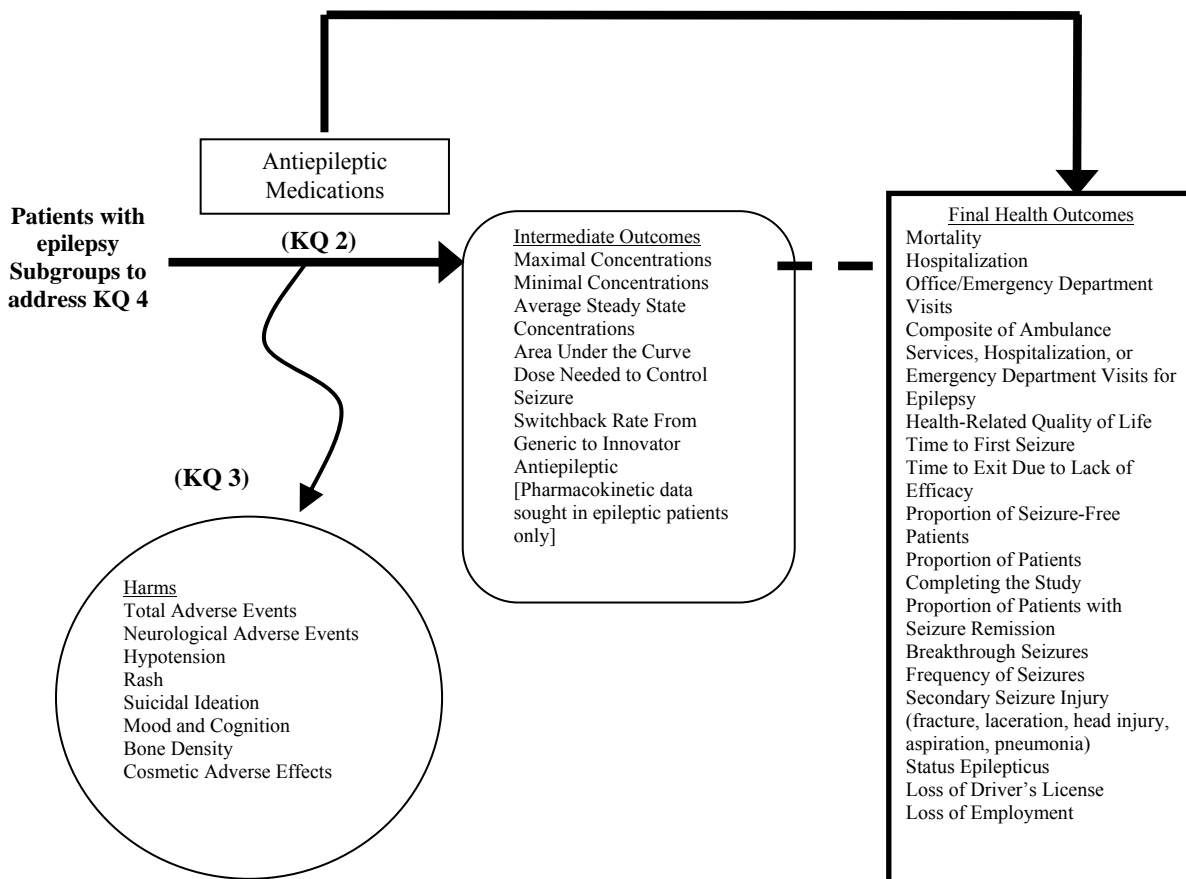
This CER utilized data on benefits and harms from direct comparative studies of newer versus older or innovator versus generic antiepileptic medications in patients with epilepsy. The analytic framework for the evaluation of effectiveness and safety of antiepileptic medication in patients with epilepsy is located in Figure A.

- 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?

- 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?
- 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?
- 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?

Figure A. Analytic framework for the evaluation of effectiveness and safety of antiepileptic medication in patients with epilepsy



KQ = Key Question

Methods

Input From Stakeholders

The Evidence-based Practice Center drafted a topic refinement document with proposed Key Questions after consulting with Key Informants. Our Key Informants did not have financial or other declared conflicts. The public was invited to comment on the topic refinement document and Key Questions. After reviewing the public commentary, responses to public commentary, and proposed revisions to the Key Questions, a preliminary protocol was generated and reviewed with the Technical Expert Panel. The Technical Expert Panel provided feedback on the feasibility and importance of our approach and provided their unique insight. Again, no conflict of interest was identified. The draft CER report underwent peer review and public commentary and revisions were made before the report was finalized.

Data Sources and Selection

Two independent investigators conducted systematic literature searches of MEDLINE (from 1950 to March 23, 2011), Web of Science from the earliest possible date through March 23, 2011, and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews from the earliest possible date through March 23, 2011. Separate search strategies were employed for the older versus newer antiepileptic medication evaluation and for the innovator versus generic antiepileptic evaluation. No language restriction was imposed, and a manual search of references from reports of clinical trials or review articles was also conducted.

Studies were included in the evaluation of Key Questions if they: (1) compared older antiepileptic medications (pre-1993 FDA-approved medications: phenytoin, carbamazepine, carbamazepine sustained release (SR) or controlled release (CR), valproic acid, clonazepam, phenobarbital, ethosuximide, primidone) with newer antiepileptic medications (1993 or later FDA approvals) or compared innovator antiepileptic medications with generic antiepileptic medications; (2) conducted in patients with epilepsy; and (3) reported data on prespecified clinical or humanistic outcomes.

Data Extraction and Quality Assessment

Using a standardized data abstraction tool, two reviewers independently collected data, with disagreement resolved through discussion. The following information was obtained from each study, where applicable: author identification, year of publication, source of study funding, study design characteristics and methodological quality criteria, study population (including study inclusion and exclusion criteria, run-in period, study withdrawals, antiepileptic medication utilized, length of study, and duration of patient followup), patient baseline characteristics (gender, age, ethnicity), patient pharmacogenetic profile, seizure etiology (partial, generalized, specific epilepsy syndrome), seizure type (new onset, chronic disease), types of antiepileptic medication (individual drug names, drug class, Biopharmaceutics Classification System [BCS] class), comorbidities, and use of concurrent standard medical therapies. Intermediate and final health and harms outcomes were collected where applicable. Authors were contacted for clarification or to provide additional data, where applicable.

Validity assessment was performed using the recommendations in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.¹⁶ Each study was rated as good, fair, or

poor. Applicability of individual studies was based on population, intervention, comparison, outcomes, and setting factors that limit overall applicability.

Data Synthesis and Analysis

In the evaluation of older versus newer antiepileptic medications, each newer antiepileptic medication was compared with an individual older epileptic medication as part of a direct comparative study. In the evaluation of innovator and generic medications, each innovator antiepileptic drug was compared with its corresponding generic medication separately as part of a direct comparative study. Comparative trials or studies could be qualitatively described or quantitatively synthesized. Controlled clinical trials could be pooled, as could controlled observational studies, but could not be pooled together.

When pooling continuous endpoints, a weighted mean difference along with 95 percent confidence intervals (CI) were calculated using a DerSimonian and Laird random effects model.¹⁷ In order to pool data of different antiepileptic medications together for continuous endpoints, we used an inverse variance weighting approach as standardized mean difference (mean difference between treatment and control groups divided by pooled standard deviation) and 95 percent CIs. In cases where mean change scores from baseline for each group were not reported, we calculated the difference between the mean baseline and mean followup scores for each group.¹⁸ When there was more than one treatment group versus control, each treatment group was treated as a separate trial for meta-analysis, dividing the control group sample size by the number of treatment arms.¹⁹

For dichotomous endpoints, weighted averages were reported as relative risks (RRs) with associated 95 percent CIs. As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model was used when pooling data and calculating RRs and 95 percent CIs.

Statistical heterogeneity was assessed using the I^2 statistic while Egger's weighted regression statistics were used to assess for the presence of publication bias.

Statistics was performed using StatsDirect statistical software, version 2.7.8 (StatsDirect Ltd, Cheshire, England). A p-value of <0.05 was considered statistically significant for all analyses.¹⁹

For the section on medical service utilization, the data was available as incidence rate ratios in the individual observational studies, therefore the data was described, but not pooled. For the section on time to first seizure, data were expressed in the trials as hazard ratios and are reported and pooled.

In subgroup analyses for the older versus newer evaluation, we evaluated the results in those with new onset versus chronic (refractory) disease and by seizure type (partial, generalized, and specific epilepsy syndrome), gender, and age. In subgroup analyses for the innovator versus generic evaluation, innovator medications were specifically studied against known "A" rated generics, and innovator medications within a BCS class (I, II, or III) were compared with their corresponding generic medications within that same class.

Results

For the newer versus older antiepileptic medication literature search, 5,773 nonduplicative citations were identified. After title and abstract screening and full text review, 5,505 and 200 citations were excluded, respectively. Sixty-eight and 49 studies were available for qualitative and quantitative synthesis, respectively. Newer versus older comparisons were largely limited to studies using carbamazepine or valproic acid and to a lesser extent phenytoin and

sustained/controlled-release carbamazepine. Comparisons versus clonazepam, phenobarbital, ethosuximide, or primidone were very limited or not conducted at all. Newer versus older comparisons were also largely limited to gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin. Comparisons versus felbamate, lacosamide, pregabalin, tiagabine, and zonisamide were very limited or not conducted at all.

For the innovator versus generic antiepileptic medication literature search, 356 nonduplicative citations were identified. After title and abstract screening and full text review, 267 and 18 citations were excluded, respectively. Seventy-one and 18 studies were available for qualitative and quantitative synthesis, respectively. Innovator versus generic antiepileptic medication comparisons are limited predominantly to studies of carbamazepine and to a lesser extent phenytoin and valproic acid. The use of an “A” rated generic could only be verified in one controlled clinical trial and a minority of controlled observational studies.

A summary of the results with ratings of the strength of the body of evidence for all Key Questions can be found in Table A. Please refer to the appendix of the full report for ratings of the strength of evidence and applicability for individual studies. We conducted evaluations for each newer antiepileptic medication versus each older generic antiepileptic medication individually and then as all newer versus each individual older medication. Similarly, we conducted each innovator medication versus its generic comparator analysis separately and then evaluated all innovator versus all generic analyses for each endpoint. However, we are not able to provide all of the individual analyses in the limited space within the executive summary. Please see the full report for the detailed results of these individual agent analyses, which are less prone to clinical heterogeneity and vital to a full understanding of the topic area.

Key Question 1

Newer antiepileptic medications did not significantly impact the risk of mortality versus their older counterparts carbamazepine, phenytoin, or valproic acid.²⁰⁻²⁹ However, many of these trials had followup times that might preclude observing an impact on a long-term outcome such as survival.

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.^{12,30-32} Data supporting this is limited to four pharmaceutical industry-sponsored observational studies.^{12,30-32} 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 no difference between the generic and innovator groups.

Three separate, well-conducted controlled observational studies assessed a composite endpoint of medical service utilization.³³⁻³⁵ 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.^{33,34} 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.³⁵ 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 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).^{33,35}

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,²⁴ 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.

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 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.³⁶ 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.³⁷ 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]).³⁷

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.

Key Question 2

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.

The average C_{max}, C_{min}, C_{ss}, T_{max}, 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).

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.^{12,30-32} 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.

Key Question 3

We could not adequately compare antiepileptic medications for hypotension, asthenia, ataxia, nystagmus, tremor, mood and cognition, or bone density.

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.

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.

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

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.

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.¹² 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). 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.

Table A. Summary of results and strength of evidence

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
KEY QUESTION 1 ENDPOINTS				
MORTALITY: Newer vs. Carbamazepine	6 RCTs	Yes	No effect, RR 0.75 (0.51, 1.12)	SOE: L
Newer vs. Phenytoin	3 RCTs	Yes	No effect, RR 0.30 (0.05, 1.95)	SOE: L
Newer vs. Valproic Acid	3 RCTs	Yes	No effect, RR 0.94 (0.31, 2.80)	SOE: L
OUTPATIENT SERVICE UTILIZATION: Innovator vs. Generic	4 OBS	No	Similar utilization of outpatient services during generic medication periods.	SOE: L
HOSPITALIZATIONS: Newer vs. Carbamazepine	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared with carbamazepine.	SOE: I
Newer vs. Valproic Acid	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared with valproic acid.	SOE: I
Newer vs. Ethosuximide	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared with ethosuximide.	SOE: I
Innovator vs. Generic	4 OBS	No	Increased risk of hospitalizations during generic medication periods.	SOE: L
HOSPITAL STAY DURATION: Innovator vs. Generic	4 OBS	No	Increased hospital stay during generic medication periods.	SOE: L
COMPOSITE OF MEDICAL SERVICE UTILIZATION (Ambulance service, hospitalization, or emergency department visit for epilepsy): Innovator vs. Generic	3 OBS	No	Increase in medical service utilization during periods when a patient's antiepileptic medication is switched to an "A" rated version of the product (innovator to generic, generic to generic, generic to innovator).	SOE: I

Table A. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
HEALTH-RELATED QUALITY OF LIFE:				
Newer vs. Carbamazepine	3 RCTs	No	Different scales and subscales, data inconclusive	SOE: I
Newer vs. Carbamazepine CR/SR	1 RCT	No	Different scales and subscales, data inconclusive	SOE: I
Newer vs. Phenytoin	2 RCTs	No	Different scales and subscales, data inconclusive	SOE: I
Newer vs. Valproic Acid	3 RCTs	No	Different scales and subscales, data inconclusive	SOE: I
TIME TO FIRST SEIZURE:				
Newer vs. Carbamazepine	4 RCTs	Yes	No effect, (HR 1.14 [0.98, 1.33])	SOE: L
Newer vs. Phenytoin	2 RCTs	Yes	Time to seizure increased for newer vs. phenytoin. (HR 1.59 [1.04, 2.43])	SOE: L
Newer vs. Valproic Acid	1 RCT	Yes	No effect, (HR 0.8 [0.63, 1.02])	SOE: L
SEIZURE OCCURRENCE:				
Innovator vs. Generic	7 RCTs	Yes	No effect, [0.87 [0.64, 1.18])	SOE: L
SEIZURE FREEDOM FOR STUDY DURATION:				
Newer vs. Carbamazepine	15 RCTs	Yes	No effect, (RR 0.94 [0.87, 1.03])	SOE: L
Newer vs. Carbamazepine CR/SR	2 RCTs	Yes	No effect, (RR, 0.90 [0.79, 1.02])	SOE: M
Newer vs. Phenytoin	4 RCTs	Yes	No effect, (RR 0.92 [0.85, 1.00])	SOE: M
Newer vs. Valproic Acid	12 RCTs	Yes	No effect, (RR 0.97 [0.87, 1.08])	SOE: M
SEIZURE FREQUENCY:				
Newer vs. Carbamazepine	1 RCT	No	No effect, [MD -3 [-6.32, 0.32])	SOE: I
Newer vs. Phenytoin	2 RCTs	No	Not enough data to evaluate effect	SOE: I
Newer vs. Valproic Acid	1 RCT	No	Not enough data to evaluate effect	SOE: I
Innovator vs. Generic	3 RCTs	Yes	No effect, [SMD 0.03 [-0.08, 0.14])	SOE: L

Table A. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
SEIZURE REMISSION 6- to 12-Month: Newer vs. Carbamazepine	2 RCTs	Yes	Patients on newer antiepileptic medications were less likely to have seizure remission vs. carbamazepine. (RR 0.81 [0.67, 0.99], NNT 9]	SOE: L
Newer vs. Valproic Acid	1 RCT	Yes	No effect, (RR 0.97 [0.89, 1.06])	SOE: M
24-Month: Newer vs. Carbamazepine	1 RCT	Yes	Patients on newer antiepileptic medication were less likely to have seizure remission vs. carbamazepine. (RR 0.82 [0.72, 0.94], NNT 13]	SOE: M
Newer vs. Valproic Acid	1 RCT	Yes	No effect, (RR 0.85 [0.73, 1.00])	SOE: M
STATUS EPILEPTICUS, SECONDARY INJURY FROM SEIZURES, LOSS OF DRIVER'S LICENSE/EMPLOYMENT: Innovator vs. Generic	No data	No	No data	SOE: I
TOTAL WITHDRAWALS: Newer vs. Carbamazepine	14 RCTs	Yes	No effect, (RR 0.90 [0.82, 1.00])	SOE: L
Newer vs. Carbamazepine CR/SR	2 RCTs	Yes	No effect, (RR 0.96 [0.78, 1.18])	SOE: L
Newer vs. Phenytoin	3 RCTs	Yes	No effect, (RR 0.91 [0.76, 1.09])	SOE: L
Newer vs. Valproic Acid	16 RCTs	Yes	No effect, (RR 0.96 [0.85, 1.09])	SOE: L
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.95 [0.53, 1.71])	SOE: I
Innovator vs. Generic	9 RCTs + 1 NRCT	Yes	No effect, (RR 0.90 [0.39, 2.08])	SOE: L
WITHDRAWALS DUE TO LACK OF EFFICACY: Newer vs. Carbamazepine	10 RCTs	Yes	Withdrawals due to lack of efficacy increased with newer agents vs. carbamazepine. (RR 1.59 [1.25, 2.02], NNT 50]	SOE: L
Newer vs. Carbamazepine CR/SR	1 RCT	No	Withdrawals due to lack of efficacy increased with newer agents vs. carbamazepine CR/SR. (RR 2.43 [1.32, 4.52], NNT 16]	SOE: I
Newer vs. Phenytoin	3 RCTs	Yes	No effect, (RR 1.03 [0.33, 3.23])	SOE: L
Newer vs. Valproic Acid	11 RCTs	Yes	No effect, (RR 1.10 [0.77, 1.56])	SOE: L
Innovator vs. Generic	9 RCTs + 1 NRCT	Yes	No effect, (RR 1.02 [0.41, 2.54])	SOE: L

Table A. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
KEY QUESTION 2 ENDPOINTS				
Maximum Concentration: Innovator vs. Generic	7 RCTs + 1 NRCT	Yes	No effect, [SMD 0.10 [-0.13, 0.32]]	SOE: L
Minimum Concentration: Innovator vs. Generic	5 RCTs + 1 NRCT	Yes	No effect, [SMD 0.05 [-0.21, 0.31]]	SOE: L
Steady State Concentration: Innovator vs. Generic	7 RCTs	Yes	No effect, [SMD 0.18 [-0.09, 0.45]]	SOE: L
Time to Maximal Concentration: Innovator vs. Generic	5 RCTs	Yes	No effect, [WMD 0.00 [-0.43, 0.43]] (Note: a WMD was calculated vs. an SMD for Tmax because only carbamazepine trials made up this evaluation).	SOE: I
AREA UNDER THE CURVE: Innovator vs. Generic	7 RCTs + 1 NRCT	Yes	No effect, [SMD 0.05 [-0.18, 0.28]]	SOE: L
DOSE REQUIREMENTS FOR SEIZURE CONTROL: Innovator vs. Generic	No data	No	No data	SOE: I
SWITCHBACK RATES: Innovator vs. Generic	4 OBS	No	Switchback rates from a generic back to an innovator antiepileptic medication varied from 12.4% to 44.1%	SOE: L

Table A. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
KEY QUESTION 3 ENDPOINTS				
WITHDRAWALS DUE TO ADVERSE EVENTS: Newer vs. Carbamazepine	18 RCTs	Yes	Withdrawals due to adverse events were reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.62 [0.53, 0.73], NNT 13)	SOE: M
Newer vs. Carbamazepine CR/SR	2 RCTs	Yes	Withdrawals due to adverse events were reduced with newer antiepileptic medications vs. carbamazepine CR/SR. (RR 0.69 [0.50, 0.95], NNT 16)	SOE: M
Newer vs. Phenytoin	3 RCTs	Yes	No effect, [0.38 [0.14, 1.03]]	SOE: I
Newer vs. Valproic Acid	16 RCTs	Yes	No effect, (RR 0.90 [0.75, 1.08])	SOE: L
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.71 [0.45, 1.12])	SOE: I
Innovator vs. Generic	9 RCTs + 1 NRCT	Yes	No effect, (RR 0.79 [0.28, 2.20])	SOE: L
HEADACHE: Newer vs. Carbamazepine	15 RCTs	Yes	No effect, (RR 0.92 [0.78, 1.08])	SOE: L
Newer vs. Carbamazepine SR/CR	2 RCTs	Yes	No effect, (RR 0.83 [0.63, 1.10])	SOE: L
Newer vs. Phenytoin	4 RCTs	Yes	No effect, (RR 0.74[0.53, 1.02])	SOE: L
Newer vs. Valproic Acid	15 RCTs	Yes	No effect, (RR 0.90 [0.70, 1.16])	SOE: L
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.66 [0.33, 1.29])	SOE: I
Innovator vs. Generic	3 RCTs	Yes	No effect, (RR 0.95 [0.55, 1.64])	SOE: I
FATIGUE: Newer vs. Carbamazepine	7 RCTs	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.57 [0.41, 0.80], NNT 11)	SOE: L
Newer vs. Carbamazepine SR/CR	1 RCT	Yes	No effect, (RR 1.17 [0.80, 1.72])	SOE: I
Newer vs. Phenytoin	1 RCT	No	No effect, (RR 1.05 [0.49, 2.25])	SOE: I
Newer vs. Valproic Acid	8 RCTs	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. valproic acid. (RR 0.61 [0.44, 0.85], NNT 23)	SOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.90 [0.45, 1.80])	SOE: I
Innovator vs. Generic	No data	No	No data	SOE: I

Table A. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
SOMNOLENCE: Newer vs. Carbamazepine	8 RCTs	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.47 [0.36, 0.61], NNT 14)	SOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	No	No effect, (RR 1.21 [0.75, 1.96])	SOE: I
Newer vs. Phenytoin	4 RCTs	Yes	No effect, (RR 0.72 [0.44, 1.18])	SOE: I
Newer vs. Valproic Acid	9 RCTs	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. valproic acid. (RR 0.65 [0.43, 0.98], NNT 25)	SOE: M
Newer vs. Ethosuximide	1 RCT	No	Risk of somnolence reduced with newer antiepileptic medications vs. ethosuximide. (RR 0.22 [0.07, 0.70], NNT 15)	SOE: I
Innovator vs. Generic	2 RCTs	Yes	No effect, (RR 0.90 [0.48, 1.70])	SOE: L
DIZZINESS: Newer vs. Carbamazepine	16 RCTs	Yes	Risk of dizziness reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.78 [0.67, 0.91], NNT 50)	SOE: M
Newer vs. Carbamazepine SR/CR	2 RCTs	Yes	No effect, (RR 0.96 [0.56, 1.66])	SOE: L
Newer vs. Phenytoin	3 RCTs	Yes	No effect, (RR 0.67 [0.43, 1.05])	SOE: L
Newer vs. Valproic Acid	12 RCTs	Yes	No effect, (RR 0.98 [0.71, 1.35])	SOE: L
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.46 [0.15, 1.38])	SOE: I
Innovator vs. Generic	No data	No	No data	SOE: I
COMBINED NEUROLOGICAL ADVERSE EVENTS: Innovator vs. Generic	1 RCT + 1 OBS	No	No effect, RCT: 4.3% vs 21.7%, p=0.189; OBS: 75.7 events per 1000 person years, 75.7 events per 1,000 person years, p=NS	SOE: L
DIPLOPIA: Innovator vs. Generic	2 RCT	Yes	No effect, [1.28 [0.38, 4.31])	SOE: L
HYPOTENSION, ASTHENIA, ATAXIA, NYSTAGMUS, TREMOR: Innovator vs. Generic	No data	No	No data	SOE: I

Table A. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
NAUSEA: Newer vs. Carbamazepine Newer vs. Carbamazepine SR/CR Newer vs. Phenytoin Newer vs. Valproic Acid Innovator vs. Generic	8 RCTs 1 RCT 4 RCTs 11 RCTs No data	Yes No Yes Yes No	No effect, (RR 0.69 [0.46, 1.02]) No effect, (RR 0.66 [0.39, 1.12]) No effect, (RR 0.88 [0.56, 1.37]) Risk of nausea reduced with newer antiepileptic medications vs. valproic acid. (RR 0.56 [0.41, 0.77], NNT 31) No data	SOE: L SOE: I SOE: L SOE: M SOE: I
VOMITING: Newer vs. Carbamazepine Newer vs. Phenytoin Newer vs. Valproic Acid Innovator vs. Generic	3 RCTs 1 RCT 5 RCTs No data	Yes No Yes No	No effect, (RR 1.25 [0.66, 2.35]) Risk of vomiting was reduced with newer antiepileptic medications vs. phenytoin (RR 0.09 [0.01, 0.89], NNT 19) No effect, (RR 0.69 [0.34, 1.42]) No data	SOE: L SOE: I SOE: L SOE: I
SKIN RASH: Newer vs. Carbamazepine Newer vs. Carbamazepine SR/CR Newer vs. Phenytoin Newer vs. Valproic Acid Innovator vs. Generic	13 RCTs 2 RCTs 4 RCTs 10 RCTs 2 RCTs	Yes Yes Yes Yes Yes	Risk of skin rash was reduced with newer antiepileptic medications vs. carbamazepine (RR 0.52 [0.39, 0.69], NNT 24) Risk of skin rash was reduced with newer antiepileptic medications vs. carbamazepine SR/CR (RR 0.47 [0.25, 0.89], NNT 27) No effect, (RR 0.76 [0.34, 1.66]) No effect, (RR 1.17 [0.55, 2.48]) No effect, (RR 0.77 [0.17, 3.57])	SOE: M SOE: L SOE: I SOE: L SOE: I
SUICIDAL IDEATION: Newer vs. Carbamazepine Innovator vs. Generic	1 Obs No data	No No	Risk of attempted suicide was increased with gabapentin vs. carbamazepine (RR 13.92 [1.82, 106.38]). No data	SOE: I SOE: I
MOOD AND COGNITION: Newer vs. Carbamazepine Newer vs. Phenytoin Newer vs. Valproic Acid Innovator vs. Generic	4 RCTs 1 RCT 5 RCTs 1 RCT	No No No No	Different scales and subscales, data inconclusive No effect Different scales and subscales, data inconclusive Only cognition evaluated. No significant differences between innovator of generic but 4 of 5 cognitive test measures showed better scores for innovator than generic.	SOE: I SOE: I SOE: I SOE: I

Table A. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
BONE DENSITY: Newer vs. Older Innovator vs. Generic	No data No data	No No	No data No data	SOE: I SOE: I
ALOPECIA: Newer vs. Carbamazepine Newer vs. Valproic Acid	6 RCTs 8 RCTs	Yes Yes	No effect, (RR 0.60 [0.23, 1.58]) Risk of alopecia was reduced with newer antiepileptic medications vs. valproic acid. (RR 0.18 [0.10, 0.31], NNT 10]	SOE: L SOE: M
ACNE: Newer vs. Phenytoin	1 RCT	No	No effect, (RR 2.78 [0.82, 9.53])	SOE: I
GUM HYPERPLASIA: Newer vs. Phenytoin	2 RCTs	Yes	Risk of gum hyperplasia was reduced with newer antiepileptic medications vs. phenytoin. (RR 0.10 [0.04, 0.27], NNT 6]	SOE: H

CR = controlled release; H = high; I = insufficient; L = low; M = moderate; MD = mean difference; SMD = standardized mean difference; NRCT = nonrandomized controlled trial; NNT = number needed to treat; OBS = observational study; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence; SR = sustained release; WMD = weighted mean difference

Discussion

Overview of Key Findings

Our evaluation of newer versus older antiepileptic medications was predominantly limited to newer antiepileptic medication comparisons versus carbamazepine, valproic acid, and to a lesser extent phenytoin. Carbamazepine had advantages in epilepsy control over the newer antiepileptic medications it was compared with but had more adverse effects. The risk of withdrawing due to lack of efficacy was decreased, and withdrawing due to adverse events was increased, leading to a neutral effect on withdrawing for any reason. Valproic acid and phenytoin provided similar epilepsy control to newer antiepileptic medications, although newer antiepileptic medications had a longer time to first seizure versus phenytoin. While the risk of withdrawing due to adverse events was not significantly different with valproic acid or phenytoin versus newer antiepileptic medications, there were adverse events that occurred more commonly with these older antiepileptic medications. 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.

In a patient who needs to initiate an antiepileptic medication, we could find no substantive differences in terms of benefits or harms associated with the use of a generic version versus an innovator product. Our data is limited predominantly to innovator versus generic versions of carbamazepine and to a lesser extent phenytoin and valproic acid. We could find no substantive differences in pharmacokinetic parameters between generic and innovator versions of the same antiepileptic medication either. While the source of the innovator and the generic (internationally versus domestically) may impact the variability in blood concentrations, the pharmacokinetic and final health outcomes results for initiating innovator versus generic medications seem congruent. In our literature set, patients were studied in a crossover or parallel design so when they were allocated to therapy or switched between therapies, the tendency for loss of efficacy or harm associated with switching might be similarly distributed across the groups. As such, this data cannot prove that intermediate or final health outcomes would be similar for the short-term period (several days to weeks) after an innovator or generic product is switched to another version of the medication versus maintaining the patient on their previous therapy. Switching from an innovator to a generic antiepileptic medication may increase the risk of hospitalization and hospital stay duration and may increase the risk of a composite of having an emergency department and hospitalization visit with or without ambulance service utilization. However, this is based on controlled observational study data, which has inherent limitations substantially reducing the strength of evidence. In addition, this data cannot be used to say that use of generic antiepileptic medications are less efficacious or safe than innovator versions for long-term therapy.^{12,30-35}

Only one outcome, the risk of gum hyperplasia with phenytoin versus newer antiepileptic medications, had a high strength of evidence. For the outcomes reported in the executive summary, the strength of evidence was predominantly moderate to low for the newer versus older antiepileptic medication evaluation and low to insufficient for the innovator versus generic evaluation. In many cases, strength of evidence was reduced for issues of inconsistency and imprecision. Pooling multiple newer antiepileptic medication comparisons versus a single older

antiepileptic medication enhanced power to detect differences but reduced consistency. Precision frequently was impacted negatively by having only a few small trials for an analysis. Analyses with only observational studies had a greater risk of bias which negatively impacted strength of evidence.

Applicability of evidence for both the newer versus older antiepileptic medication evaluation and the innovator versus generic evaluation was more evenly dispersed between insufficient, low, and moderate with no areas of high applicability. 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.

Limitations

This CER is limited by heterogeneity. A heterogeneous group of antiepileptic medications was placed into groups based on whether they were older, newer, innovator, or generic. A heterogeneous group of epilepsy types was also lumped together, and the diagnosis and detection of these different types have changed over time, making clear subgroup evaluations using these trials difficult. Patients with different pharmacodynamic and pharmacokinetic genetic polymorphisms were not elucidated in virtually all the trials but these factors could make some medications more or less preferable. The use of studies from different countries, different time periods, utilizing differing study durations, mixing of patients with different baseline seizure frequency rates and different environmental triggers, and the use of “A” rated and non-“A” rated products in some analyses may have also introduced heterogeneity.

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 evaluate some of the major potential sources of heterogeneity in subgroup analyses. Other sources of heterogeneity such as genomic differences, durations of therapy, mixing of patients with differing seizure frequencies should have been attenuated within a trial due to randomization. We are transparent in our presentation of the results since in the full report we provide individual agent comparisons and subgroup analyses for other potential sources of heterogeneity but could not report the results in the executive summary given wording limitations.

We did not include every possible endpoint of interest. We had to make some choices as to which endpoints would be included and which would not and we wanted to make those decisions a priori. We included myriad endpoints that while not exhaustive, are very broad but may not contain a specific endpoint that a particular practitioner may wish to see. For instance, we included loss of job or driving privileges but did not include school performance.

While we sought to evaluate the impact of newer versus older antiepileptic medications, only a few older antiepileptic medications were substantively evaluated and were compared to a greater or lesser extent with newer antiepileptic medications. In the full report, we provide the data for each individual newer antiepileptic medication versus each individual older antiepileptic medication. These data are more specific than the aggregate pooled data of all newer antiepileptic medication versus each older antiepileptic medication and decreases the clinical heterogeneity in the data. However, the power to detect differences in these individual analyses is substantially compromised. With future direct comparative clinical trials, the ability to use

individual newer versus individual older antiepileptic medication evaluations in agent selection could be enhanced.

Our evaluations of newer versus older antiepileptic medications provide populationwide insight into comparative benefits and harms but cannot account for individual patient factors that may make the use of a certain antiepileptic medication more or less desirable. Factors such as pregnancy, the 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 need more information on the benefits and harms associated with older and newer antiepileptic medications in different seizure types, and it needs to be understood that the classification of epilepsy types is an evolving science.

Our innovator versus generic antiepileptic medications evaluation is limited by the small size, short-term nature, and the almost entire lack of clinical trials specifying that they were comparing “A” rated products. In the United States, generic substitution is done between products with an “A” rating by the FDA. The observational nature and lack of full accounting for confounders in other studies is also an important limitation. The observational study by Devine and colleagues demonstrates the potential impact of more fully accounting for confounders in observational studies.

Future clinical trials should be conducted specifically evaluating the impact of switching patients from innovator to generic versions of medication. A proposed methodology would be to take a population of patients receiving either innovator or an “A” rated generic version of a medication and then randomize some patients to be switched and other patients to be maintained on initial therapy in a double blind manner. This would eliminate the potential impact of clinician or patient apprehension about the switch on resource utilization or to increase the risk of experiencing a seizure or an adverse event either directly or indirectly through noncompliance or dose alteration. Followup could be relatively brief (3 months) and should include a pharmacokinetic (using Bayesian population pharmacokinetics whereby only one or two samples from each patient would suffice) and final health outcome component (assessing for seizure occurrence, seizure frequency, health care utilization, and adverse events). Without randomization, blinding, and exclusive use of “A” rated products, future studies would share the substantial flaws of the current body of literature.

Our subgroup analyses could have been very important in helping identify which populations have an accentuated or attenuated effect versus the average, but due to a lack of power and methodological limitations, we were unable to generate data that could guide therapy in this manner. Future trials should report on their benefits and harms in these subpopulations even in the absence of power to judge significance because it allows systematic reviewers to pool the trials together.

Endpoints such as bone fracture and concussion should be assessed in everyone, loss of job or driving privileges should be assessed in adults, and school performance should be evaluated in children.

Glossary

“A” Rated Drug Products: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products. “A” products are those for which actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence.

Area Under the Curve (AUC): The area under the concentration versus time curve derived when an antiepileptic medication is dosed. Also referred to as the total systemic exposure to the drug over time.

Bioequivalent Drug Products: Pharmaceutical equivalent or alternative products that display comparable bioavailability when studied under similar experimental conditions.

Biopharmaceutics Classification System (BCS): Classification of antiepileptic medications based on properties and relegated into four classes; high solubility/high permeability (Class I, optimal class with lowest risk of absorption variability), low solubility/high permeability (Class II), high solubility/low permeability (Class III), and low solubility/low permeability (Class IV).

C_{max}: The maximal concentration of antiepileptic medication obtained after dosing.

Confidence Intervals (CIs): A range that is likely to include the given value. Usually presented as a percent (%). For example, a value with 95 percent confidence interval implies that when a measurement is made 100 times, it will fall within the given range 95 percent of the time.

Correlation Coefficient: A value (which usually ranges from zero to one) that indicates the degree of relationship between two variables. For example, a correlation coefficient of one would indicate a strong relationship.

C_{ss}: The concentration of antiepileptic medication obtained at steady state.

DerSimonian and Laird Random-Effects Model: A statistical method based on the assumption that the effects observed in different studies (in a meta-analysis) are truly different.

Egger’s Weighted Regression Statistics: A method of identifying and measuring publication bias.

Epilepsy: A clinical phenomenon in which a person has recurrent seizures due to a chronic underlying process. The main types of seizures include partial (simple partial, complex partial, partial with secondary generalization) and generalized (absence, tonic-clonic, tonic, atonic, myoclonic).

I²: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to 100.

Meta-analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.

Publication Bias: The possibility that published studies may not represent all the studies that have been conducted, and therefore, create bias by being left out of a meta-analysis.

Q Statistic: A test to assess the presence of statistical heterogeneity among several studies.

Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a non-exposed group in a given population. A ratio of one indicates no difference in the risk between the two groups.

Risk Difference: The absolute difference in the event rate between two comparison groups. A risk difference of zero indicates no difference between comparison groups.

Sensitivity Analysis: A “what if” analysis that helps determine the robustness of a study. Helps determine the degree of importance of each variable for a given outcome.

Standard Deviations (SDs): A measure of the variability of a dataset. For a simple dataset with numbers, standard deviation can be calculated using the following formula:

$$\sigma = ((\sum(x-x_m))^2/N)^{0.5}$$

σ is standard deviation.

x_m is the average.

$\sum(x-x_m)$ is the sum of x_m subtracted from each individual number x .

N is the total number of values.

Note: Other formulas also exist.

Statistical Heterogeneity: Variability in the observed effects among studies in a meta-analysis.

Therapeutic Equivalence: Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

Tmax: The time from administration until the Cmax (see Cmax above) is obtained.

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Introduction

Background

Seizures are single or paroxysmal events arising from abnormal, excessive, hypersynchronous discharges from central nervous system neurons, and range in severity from symptoms not readily apparent to an observer to dramatic convulsions.¹ Epilepsy describes a clinical phenomenon in which a person has recurrent seizures due to a chronic, underlying process.^{1,2}

Over a lifetime, approximately 10 percent of people in the United States will suffer a seizure, with 1 percent to 3 percent developing epilepsy.²⁻⁴ The annual incidence of epilepsy is about 50 per 100,000 with a prevalence of 5–10 per 1,000.^{4,5}

Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. Seizure classification is an important element in designing the treatment plan, since some antiepileptic drugs have different activities against various seizure types. The International League Against Epilepsy classifies the three main types of seizures: partial, generalized, and unclassified. The main subtypes are given in Table 1.¹ Partial seizure activity is restricted, at least initially, to discrete areas of the cerebral cortex while generalized seizure activity occurs in diffuse regions of the brain simultaneously. If consciousness is fully preserved during the partial seizure, it is termed a simple partial seizure. If consciousness is impaired during the partial seizure, it is termed a complex partial seizure. If a seizure begins as a partial seizure and then spreads diffusely throughout the cortex, it is termed a partial seizure with secondary generalization. Because of the focused nature of a partial seizure, only a specific area of the body is usually involved, at least initially. Generalized seizures are termed absence seizures if they are characterized by sudden, brief lapses of consciousness without loss of postural control. Absence seizures usually begin in childhood (ages 4–8) or early adolescence and are the main seizure type in 15–20 percent of children with epilepsy. Generalized seizures are termed generalized tonic-clonic seizures if they are characterized by generalized muscle contraction for a period followed by intermittent muscle contraction and relaxation. There is usually a postictal phase with confusion that accompanies the end of convulsions. Generalized seizures are the main seizure type in approximately 10 percent of people with epilepsy. Generalized seizures are termed atonic seizures if sudden loss and then regaining of postural muscle tone characterize them. While consciousness is briefly impaired, there is usually no postictal confusion in people with atonic seizures. Generalized seizures are termed myoclonus seizures if a sudden jerking movement of the skeletal muscle characterizes it. A patient with epilepsy may experience more than one subtype of seizure over their lifetime.¹

Epilepsy syndromes are disorders in which epilepsy is a predominant feature, and there is sufficient evidence to suggest a common underlying mechanism.¹ Three main epilepsy syndromes have been classified; one is associated with partial seizures (Mesial Temporal Lobe Epilepsy Syndrome) and the others are associated with generalized seizures (Juvenile Myoclonic Epilepsy Syndrome and Lennox-Gastaut Epilepsy Syndrome). Mesial Temporal Lobe Epilepsy Syndrome is associated with complex partial epilepsy and has distinctive clinical, electroencephalographic, and pathologic findings. High-resolution magnetic resonance imaging can detect the characteristic hippocampal sclerosis that appears to be essential in the pathophysiology of the syndrome. Epilepsy in people with this syndrome tends to be refractory to treatment with anticonvulsants but responds well to surgical intervention. Juvenile Myoclonic Epilepsy Syndrome is a generalized seizure disorder that appears in early adolescence. While

most of the seizures the patient experiences consist of bilateral myoclonic jerks, people may also experience tonic-clonic or absence seizures. The condition is otherwise benign, and although complete remission is uncommon, the seizures respond well to anticonvulsant medication. Lennox-Gastaut Epilepsy Syndrome occurs in children and is defined by the following triad: multiple seizure types (generalized tonic-clonic, atonic, and atypical absence), specific electroencephalographic findings (<3 Hz spike-and-wave discharges), and impaired cognitive function. Lennox-Gastaut Epilepsy Syndrome is associated with central nervous system delays or dysfunction from a variety of causes, including developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions. The multifactorial nature of this syndrome suggests that it is a nonspecific response of the brain to diffuse neural injury. Unfortunately, many patients have a poor prognosis due to the underlying central nervous system pathology and the consequences of severe, poorly controlled epilepsy.¹

Table 1. Classification of seizure types¹

Seizure Type	Subtypes
Partial Seizures	Simple partial seizures Complex partial seizures Partial seizures with secondary generalization
Generalized Seizures	Absence Tonic-clonic Tonic Atonic Myoclonic
Unclassified Seizures	Neonatal seizures Infantile spasms

The incidence of new-onset epilepsy is high during the first 9 years of life and then plateaus over the next 30 years.¹ The incidence drops in 40–59 year olds and then rises again in the elderly.^{4,5} The age of epilepsy onset is marked by different underlying causes as depicted in Table 2.^{1,2,5} Childhood marks the age at which many of the well-defined epilepsy syndromes present. During adolescence and early adulthood, there is a transition away from idiopathic or genetically based epilepsy to more cases secondary to acquired central nervous system lesions (e.g., head trauma, infections, brain tumors). A patient with a penetrating head wound, depressed skull fracture, intracranial hemorrhage, or prolonged posttraumatic coma or amnesia has a 40–50 percent risk of developing epilepsy, while a patient with a closed head injury and cerebral contusion has a 5–25 percent risk. The causes of seizures in older adults include cerebrovascular disease, trauma (e.g. blunt trauma and subdural hematoma), brain tumors, and degenerative diseases such as Alzheimer’s disease. Cerebrovascular disease may account for approximately 50 percent of new cases of epilepsy in patients older than 65 years.¹

Table 2. Epilepsy etiology based on age^{1,2,5}

Age Group	Epilepsy Causes
Children	Genetic disorders Developmental disorders Central nervous system infection Trauma Idiopathic
Adolescents/Young Adults	Trauma Genetic disorders Infection Brain Tumor Idiopathic
Older Adults	Trauma Cerebrovascular accidents Brain tumor Degenerative diseases (Alzheimer's disease) Idiopathic

The overall goals of antiepileptic therapy are to prevent seizures and avoid untoward side effects with a regimen that is convenient and easy to follow. People with epilepsy usually initiate treatment with one antiepileptic drug at the time of diagnosis, but 30 percent of patients will be refractory to this medication.⁶ While control of seizures is the overriding goal of therapy, selecting an effective drug with the least potential for side effects becomes a crucial decision for clinicians.

Table 3 identifies approved medications for the treatment of epilepsy, their known or suspected mechanism of action, type of seizures principally treated, adverse effects, drug interaction potential, and availability of a generic product.^{1,2,7-9} This is meant to be a brief overview, not an exhaustive review, of the mechanisms or characteristics.

Table 3. Important characteristics of antiepileptic medications^{1,2,7-9}

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Carbamazepine	Inhibition of Na ⁺ channel	Partial Tonic–Clonic	Neurological: dizziness, diplopia, ataxia, vertigo Non-neurological: aplastic anemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash*	Enzyme Substrate: CYP 3A4, 2C8 Enzyme Inducer: CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4 Enzyme Inhibitor: None	Yes
Ethosuximide	Inhibition of T-type Ca ²⁺ channel in thalamus	Absence	Neurological: ataxia, lethargy, headache Non-neurological: gastrointestinal irritation, skin rash, bone marrow suppression	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes, only Available in Generic

Table 3. Important characteristics of antiepileptic medications^{1,2,7-9} (continued)

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Felbamate	Antagonism of NMDA receptor and increase of GABA availability	Partial Lennox-Gastaut	Neurological: insomnia, dizziness, sedation, headache Non-neurological: aplastic anemia, hepatic failure, weight loss, gastrointestinal irritation	Enzyme Substrate: CYP 2E1, 3A4 Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	No, but patent expired 9/26/09
Gabapentin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: sedation, dizziness, ataxia, fatigue Non-neurological: gastrointestinal irritation, weight gain, edema	Enzyme Substrate: None Enzyme Inducer: None Enzyme Inhibitor: None	Yes
Lacosamide	Selective enhancement of slow inactivation of voltage-gated Na ⁺ channels	Partial	Neurological: headache, dizziness, diplopia, ataxia, fatigue, tremor, somnolence, blurred vision Non-neurological: Nausea, vomiting, diarrhea	Enzyme Substrate: CYP 2C19 Enzyme inducer: None Enzyme Inhibitor: CYP 2C19	No
Lamotrigine	Decrease of glutamate release	Partial Tonic-Clonic Atypical Absence Myoclonic Lennox-Gastaut	Neurological: dizziness, diplopia, sedation, ataxia, headache Non-neurological: skin rash*	Enzyme Substrate: UGT1A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes
Oxcarbazepine	Inhibition of Na ⁺ channel	Partial	Neurological: fatigue, ataxia, dizziness, diplopia Non-neurological: aplastic anemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash	Enzyme Substrate: CYP Enzyme Inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Phenobarbital	Potential of GABA receptor function	Partial Tonic-Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-neurological: Skin rash, hepatotoxicity	Enzyme Substrate: CYP 2C9, 2C19, 2E1 Enzyme Inducer: CYP 1A2, 2A6, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes, only available in generic
Phenytoin	Inhibition of Na ⁺ and Ca ²⁺ channel	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, confusion Non-neurological: gingival hyperplasia, peripheral neuropathy, lymphadenopathy, hirsutism, osteomalacia, hepatotoxicity, facial coarsening, skin rash*	Enzyme Substrate: CYP 2C9, 2C19, 3A4 Enzyme Inducer: CYP 2B6, 2C8, 2C9, 2C19, 3A4 and UDPGT Enzyme Inhibitor: None	Yes

Table 3. Important characteristics of antiepileptic medications^{1,2,7-9} (continued)

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Pregabalin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: ataxia, somnolence, dizziness, blurred vision, diplopia Non-neurological: peripheral edema, increased appetite	Enzyme Substrate: None Enzyme Inducer: None Enzyme Inhibitor: None	No
Primidone	Inhibition of neuronal firing	Partial Tonic–Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-neurological: Skin rash	Enzyme Substrate: None Enzyme inducer: CYP 1A2, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes
Tiagabine	Increase of GABA availability	Partial Tonic–Clonic	Neurological: confusion, sedation, depression, speech problems, paresthesias, psychosis Non-neurological: gastrointestinal irritation	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Topiramate	Inhibition of Na ⁺ channel	Partial Tonic–Clonic Lennox-Gastaut	Neurological: psychomotor slowing, sedation, speech problems, fatigue, paresthesias Non-neurological: kidney stones, glaucoma, weight loss, hypohidrosis	Enzyme Substrate: None Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Valproic Acid	Inhibition of T-type Ca ⁺⁺ channel in thalamus Increase of GABA availability	Partial Tonic–Clonic Absence Atypical Absence Myoclonic	Neurological: ataxia, sedation, tremor Non-neurological: Hepatotoxicity, thrombocytopenia, gastrointestinal irritation, weight gain, hyperammonemia	Enzyme Substrate: UGT 1A6, 1A9, 2B7, beta-oxidation Enzyme Inducer: CYP 2A6 Enzyme Inhibitor: CYP 2C9, 2C19, 2D6, 3A4	Yes
Vigabatrin	Analog of GABA Inhibition of GABA catabolism	Complex Partial	Neurological: headache, fatigue, drowsiness, dizziness, tremor, agitation, visual field defects, abnormal vision, diplopia Non-neurological: nausea, vomiting, diarrhea, weight gain, skin rash	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	No

Table 3. Important characteristics of antiepileptic medications^{1,2,7-9} (continued)

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Zonisamide	Inhibition of Na ⁺ channel	Partial	Neurological: sedation, dizziness, confusion, headache, psychosis Non-neurological: Anorexia, renal stones, hypohidrosis	Enzyme Substrate: CYP 2C19, 3A4 Enzyme Inducer: None Enzyme Inhibitor: None	Yes

Ca²⁺ = calcium ion; CYP = cytochrome P enzyme; GABA = gamma amino butyric acid; Na⁺ = sodium ion; NMDA= N-methyl D-aspartic acid

* Ddenotes skin rash risk (Steven's Johnson syndrome and toxic epidermal necrolysis) related to human leukocyte antigen (HLA)-phenotype.

Since 1993, the Food and Drug Administration (FDA) has approved several newer antiepileptic drugs (felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, zonisamide) for the treatment of epilepsy.⁶ This offered clinicians and patients many new options over the older antiepileptic medications approved between 1953 and 1983 (phenytoin, 1953; primidone, 1954; ethosuximide, 1960; carbamazepine, 1968; clonazepam, 1975; divalproex, 1978; valproic acid, 1983). While most newer antiepileptic drugs are approved as second-line agents for the treatment of refractory seizures, topiramate, oxcarbazepine, and lamotrigine are also approved for monotherapy in certain situations.⁶

According to the Biopharmaceutics Classification System (BCS), drugs are relegated into four classes; high solubility/high permeability (Class I, optimal class with lowest risk of absorption variability), low solubility/high permeability (Class II), high solubility/low permeability (Class III) and low solubility/low permeability (Class IV).¹⁰ A drug is considered to have high solubility when the highest dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1 to 7.5 at 37 degrees Celsius.^{11,12} A drug is considered to be highly permeable when the extent of absorption (bioavailability) is ≥ 90 percent.^{11,12} In 2000, the FDA started using the BCS to grant a waiver of in vivo bioavailability and bioequivalence testing of immediate release solid dosage forms for Class I drugs.¹³ The BCS classification for older and newer epilepsy medications is given in Table 4.^{11,14-27}

Table 4. Biopharmaceutics Classification System of antiepileptic medications^{11,14-27}

AED	BCS Solubility	BCS Permeability	BCS Class
Older Antiepileptic Drugs			
Carbamazepine	Low	High	II
Clonazepam	Low	High	II
Ethosuximide	High	High	I
Phenobarbital	High	High	I
Phenytoin	Low	High	II
Primidone	Low	High	II
Valproic Acid	High	High	I

Table 4. Biopharmaceutics Classification System of antiepileptic medications^{11,14-27} (continued)

AED	BCS Solubility	BCS Permeability	BCS Class
Newer Antiepileptic Drugs			
Felbamate	Low	High	II
Gabapentin	High	Low	III
Lamotrigine	High	High	I
Levetiracetam	High	High	I
Oxcarbazepine	Low	High	II
Pregabalin	High	High	I
Tiagabine	High	High	I
Topiramate	High	High	I
Zonisamide	High	High	I

AED = Antiepileptic Drug; BCS = Biopharmaceutics Classification System

The comparative benefits and harms of older antiepileptic drugs (pre-1993 FDA approved medications: phenytoin, carbamazepine, carbamazepine valproic acid, clonazepam, phenobarbital, ethosuximide, primidone) versus newer antiepileptic drugs (1993 or newer FDA approved medications) have been assessed in numerous randomized controlled trials (RCTs), with varying results. In the Standard And New Antiepileptic Drugs (SANAD) study, there were two treatment arms. In Arm A, carbamazepine was compared with other newer antiepileptic treatments (i.e. gabapentin, lamotrigine, topiramate, oxcarbazepine), while in Arm B, valproate was compared with newer antiepileptic agents (i.e., lamotrigine and topiramate). The efficacy, tolerability, and safety of newer antiepileptic agents were compared with their older counterparts. In this RCT, lamotrigine significantly extended the time to treatment failure versus carbamazepine in patients with partial seizures, but the time to treatment failure was similar between lamotrigine and valproate in patients with generalized seizures. However, other newer antiepileptic agents demonstrated similar or inferior 12-month remission rates compared with older antiepileptics.^{28,29} Many older and newer antiepileptic medications share mechanisms related to sodium channels and gamma-amino-butyric-acid and are used either alone or in combination to control seizures. As such, it is possible to determine their comparative effectiveness.

Another important issue in the management of epilepsy surrounds generic substitution of innovator antiepileptic medications. The American Academy of Neurology has issued two position papers stating that there is concern with generic antiepileptic medication substitution and that physicians should specifically approve all generic substitutions.^{30,31} The International League Against Epilepsy established a working group on generic products in epilepsy treatment. They concluded that generic medications offer a valuable and cost-effective choice in the management of epilepsy but that generic substitution is not recommended in patients who achieve seizure remission on an innovator product.³² The FDA and the American Society of Health-System Pharmacists do not share the view that antiepileptic medications, or other narrow therapeutic index medications (medications where the difference between the minimum effective and minimum toxic concentrations are close together), should be treated differently with respect to generic substitution.³³⁻³⁶ However, their responses have been related to the process of determining bioequivalence and therapeutic equivalence rather than specifically providing an evaluation of comparative effectiveness. As such, several states including Hawaii, Illinois, Tennessee, and Utah prevent automatic generic substitution for innovator antiepileptic medications and another 24 state legislatures (including California and New York) have discussed or are considering legislation preventing generic substitution.^{33,37-40} A common example of legislation includes: “Would prohibit a pharmacist from substituting or interchanging

any antiepileptic drug, innovator or generic, without notification to both the prescribing physician and the patient or the patient's representative."⁴⁰ Variations include written consent from the prescriber and/or patient before substitution can occur.

Opponents of generic substitution of antiepileptic medications oppose it on one or more of the following reasons: bioequivalence studies mandated by FDA are in normal volunteers and not in patients with epilepsy; bioequivalence may occur in the fasting but not the fed state (unless food is known to affect absorption when both are required); the acceptable limit for variance (90 percent confidence interval for the C_{max} and area under the curve for the generic falls within 0.80 and 1.25 (i.e., 20 percent over or under) of the innovator medication) is not narrow enough; generics may be close enough to the innovator to be bioequivalent but not to another generic medication (if one generic consistently but predictably achieves higher concentrations than the innovator and another consistently but predictably achieves lower concentrations than the two generic medications may not be bioequivalent); and bioequivalence may be seen for a generic and innovator medication within a group of patients but not necessarily within each individual patient with epilepsy.^{33,41}

Due to the inconclusive results of the SANAD study and other currently available studies, a comparative effectiveness review of the efficacy, tolerability, and safety of older versus newer antiepileptic treatments is needed. Similarly, given the controversy surrounding generic substitution of antiepileptic medications, a comparative effectiveness review of the efficacy, tolerability, and safety is needed.

Objective

The objective of this study was to perform a comparative effectiveness review of the efficacy, safety, and tolerability of antiepileptic medications and to address the issue of generic substitution by qualitatively and/or quantitatively comparing older versus newer antiepileptic medications and comparing innovator antiepileptic medications to their generic counterparts. The analytic framework for the evaluation of effectiveness and safety of antiepileptic medication in patients with epilepsy is located in Figure 1.

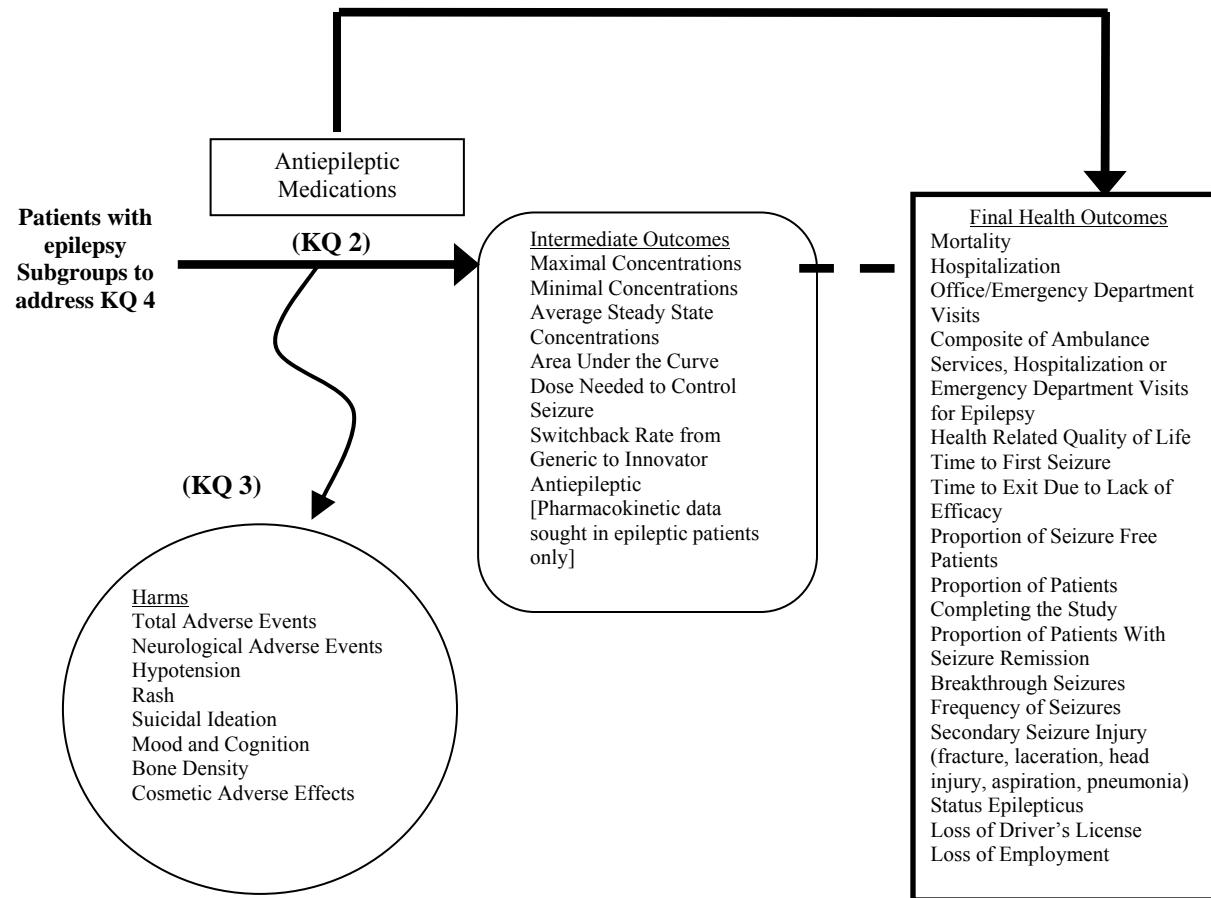
Key Questions

- 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 (ambulance services, hospitalizations, or emergency department visits for epilepsy), health-related quality of life, seizures (time to first seizure, time to exit for trial due to lack of efficacy, proportion of seizure-free patients, proportion of patients with seizure remission, breakthrough seizures, frequency of seizures), secondary seizure injury (fracture, laceration, head trauma, aspiration pneumonia), status epilepticus, loss of driver's license, and loss of employment?
- 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?

- 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?
- 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 (partial, generalized, specific epilepsy syndrome), seizure type (new onset disease, chronic disease), gender, ethnicity, patient age, and patient pharmacogenetic profile; and by types of antiepileptic medication (medication classes, individual medications and medications meeting the definition of having a narrow therapeutic index [BCS class II–IV])?

Analytic Framework

Figure 1. Analytic framework for the evaluation of effectiveness and safety of antiepileptic medication in patients with epilepsy



KQ = Key Question

Methods

Topic Refinement

The topic for this report was nominated via a public process. The Evidence-based Practice Center (EPC) drafted a topic refinement document with proposed Key Questions and solicited input from a panel of key informants on the questions and scope of the report. The public was then invited to comment on the topic refinement document and Key Questions. After a review of the public commentary, the Key Questions were finalized by the EPC and approved by the Agency for Healthcare Research and Quality (AHRQ).

Literature Search Strategy

Two independent investigators conducted systematic literature searches of MEDLINE (from 1950 to the March 23, 2011), Web of Science, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from the earliest possible date through March 23, 2011. For the older versus newer antiepileptic medication search, we utilized Cochrane's Highly Sensitive Search Strategy (Sensitivity Maximizing Version 2008) to limit the search to randomized controlled trials and the Scottish Intercollegiate Guidelines Network Observational Study Search Filter to limit the search to observational studies. The search for the innovator versus generic evaluation contained no search filters, but had to be a direct comparison of an antiepileptic medication versus another version of the same medication (innovator versus its generic, or for health care utilization, a generic to innovator, innovator to generic, or generic to generic comparison). We did not limit the search to "A" rated versions of products. No language restriction was imposed in either search and a manual search of references from reports of clinical trials or review articles was also conducted.

Detailed search strategies are provided in Appendix A.

Study Selection

Studies were included in the evaluation of key questions if they: (1) compared older antiepileptic medications (phenytoin, carbamazepine, valproic acid, clonazepam, phenobarbital, ethosuximide, primidone) to newer antiepileptic medications or compared innovator antiepileptic medications to generic antiepileptic medications (or in the case of health care utilization, compared generic to innovator, innovator to generic, or generic to generic version of the same medication); (2) conducted in patients with epilepsy; and (3) reported data on prespecified clinical or humanistic outcomes.

Data Abstraction

Through the use of a standardized data abstraction tool, two reviewers independently collected data, with disagreement resolved through discussion. The data extraction tools are available in Appendix B. The following information was obtained from each study, where applicable: author identification, year of publication, source of study funding, study design characteristics and methodological quality criteria, study population (including study inclusion and exclusion criteria, run-in period, study withdrawals, antiepileptic medication utilized, length of study, and duration of patient followup), patient baseline characteristics (gender, age, ethnicity), patient pharmacogenetic profile, seizure etiology (partial, generalized, specific

epilepsy syndrome), seizure type (new onset, chronic disease), types of antiepileptic medication (individual drug names, drug class and Biopharmaceutics Classification System [BCS] class), comorbidities, and use of concurrent standard medical therapies. Intermediate and final health and harms outcomes were collected where applicable. Authors were contacted for clarification or to provide additional data, where applicable.

We differentiate the outcomes for evaluation based on the following schemes in Table 5 and Table 6.

Table 5. Outcomes for innovator and generic antiepileptic evaluation

Pharmacokinetics	Comparative Efficacy	General Measures of Tolerance and Harms
Maximum concentration (C_{max})	Seizure frequency	Incidence of adverse events
Minimum concentration (C_{min})	Incidence of breakthrough seizure	Incidence of individual adverse events
Average steady-state concentration (C_{ss})	Incidence of status epilepticus	Incidence of adverse events resulting in therapy withdrawal
Area under the curve (AUC)	Dose needed to control seizures after switching from an innovator antiepileptic to its generic counterpart	Incidence of adverse events not resulting in therapy withdrawal
Time to maximum concentration (T_{max})	Secondary seizure injury; fracture, laceration, head trauma, aspiration pneumonia	Skin rash
	Incidence of breakthrough seizure	Neurologic adverse events
		Suicidal Ideation
		Mortality
		Medical service utilization; office/emergency department visits, hospitalizations
		Hypotension
		Hospital stay duration
		Loss of driver's license
		Loss of employment
		Rates of switching from generic antiepileptic back to its innovator counterpart for any reason

AUC = Area under the curve; C_{max} = Maximum concentration; C_{min} = Minimum concentration; C_{ss} = Average steady-state concentration; T_{max} = Time to maximum concentration

Table 6. Outcomes for older and newer antiepileptic evaluation

Comparative Efficacy	General Measures of Tolerance and Harms
Time to first seizure	Proportion of patients withdrawn due to adverse events
Time to study exit due to lack of efficacy	Cosmetic adverse events
Proportion of seizure-free patients	Incidence of adverse events
Proportion of patients completing the study	Incidence of individual adverse events
Proportion of patients achieving seizure remission	Incidence of adverse events resulting in therapy withdrawal
Seizure frequency	Incidence of adverse events not resulting in therapy withdrawal
	Skin rash
	Neurologic adverse events
	Suicidal Ideation
	Mortality
	Medical service utilization: office/emergency department visits, hospitalizations, ambulance use

Validity Assessment

Validity assessment was performed using the recommendations in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.⁴² Studies were given an overall score of good, fair, or poor (Table 7). This rating system does not attempt to assess the comparative validity across different types of study design. For example, a “fair” RCT was not judged to have the same methodological quality as a “fair” observational study. Both study design and quality rating were considered when interpreting the methodological quality of a study.

Table 7. Summary ratings of quality of individual studies

Quality Rating	Definition
Good (low risk of bias)	These studies have the least bias, and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality include the following: a formal randomized, controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; and clear reporting of dropouts.
Fair	These studies are susceptible to some bias, but it is not sufficient to invalidate results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies have significant flaws that imply biases of various types that may invalidate the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Literature Synthesis

In the evaluation of older versus newer antiepileptic medications, each newer antiepileptic medication was compared with an individual older epileptic medication as part of a direct comparative study. In the evaluation of innovator and generic medications, each innovator antiepileptic drug was compared with its corresponding generic medication separately as part of a direct comparative study. Comparative trials or studies could be qualitatively described or quantitatively synthesized while single-arm observational studies, case series, or case reports were termed descriptive studies.

Quantitative Analysis

Controlled clinical trials could be crossover or parallel trials but may or may not be randomized. Controlled observational studies were cohort or case-control studies and had to have a control group. Controlled clinical trials and controlled observational studies could be pooled separately, but clinical trials and observational studies could not be pooled together.

When pooling continuous endpoints, a weighted mean difference along with 95 percent confidence intervals (CI) were calculated using a DerSimonian and Laird random effects model.⁴³ In order to pool data of different AEDs together for continuous endpoints, we used an inverse variance weighting approach as standardized mean difference (mean difference between treatment and control groups divided by pooled standard deviation) and 95 percent CIs. In cases where mean change scores from baseline for each group were not reported, we calculated the difference between the mean baseline and mean followup scores for each group. Standard deviations (SDs) of the change scores were calculated from the SD of the baseline values and of the followup values, using the formula: $SD_{\text{baseline-followup}} = \sqrt{SD_{\text{baseline}}^2 + SD_{\text{followup}}^2 - 2 * (\text{correlation coefficient}) * SD_{\text{baseline}} * SD_{\text{followup}}}$. A correlation coefficient of 0.5 proposed by

Follman and colleagues was used.⁴⁴ In the event where there was more than one treatment group versus control, each treatment group was treated as a separate trial for meta-analysis, dividing the control group sample size by the number of treatment arms.

For dichotomous endpoints, weighted averages were reported as relative risks (RRs) with associated 95 percent CIs. As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model was used when pooling data and calculating RRs and 95 percent CIs.

Statistical heterogeneity was assessed using the I^2 statistic which assesses the degree of inconsistency not due to chance across studies and ranges from 0 to 100 percent with values of >50 percent representing important statistical heterogeneity, respectively. Egger's weighted regression statistics were used to assess for the presence of publication bias.

Statistical analysis was performed using StatsDirect statistical software, version 2.7.8 (StatsDirect Ltd, Cheshire, England). A p-value of <0.05 was considered statistically significant for all analyses.⁴⁵

For the section on medical service utilization, data were available as incidence rate ratios in the individual observational studies and were described but not pooled.

Subgroup and Sensitivity Analyses

To assess the effect of heterogeneity on our meta-analysis conclusions, subgroup and sensitivity analyses were conducted. In both the older versus newer and innovator versus generic evaluations, we performed subgroup analyses based on gender, ethnicity, patient age, and patient pharmacogenetic profile.

In subgroup analyses for the older versus newer evaluation, we evaluated the results in those with new onset versus chronic (refractory) disease and by seizure type (partial, generalized, and specific epilepsy syndrome), gender, and age. In subgroup analyses for the innovator versus generic evaluation, innovator medications were specifically studied against known "A" rated generics, and innovator medications within a BCS class (I, II, or III) were compared with their corresponding generic medications within that same class.

Grading the Strength of Evidence

We used the EPC methodology for grading, which is based on the criteria and methods of GRADE (Grading of Recommendations Assessment, Development) to assess the strength of evidence. This system uses four required domains: risk of bias, consistency, directness, and precision.⁴⁶ Additional domains will not be utilized because they are deemed not relevant to this review. All assessments will be made by two investigators (with disagreements resolved through discussion). The evidence pertaining to each Key Question will be classified into three broad categories: (1) "high," (2) "moderate," (3) or "low" grade (Table 8). If the evidence is too sparse, a grade of insufficient was assigned. Below we describe in more detail the features that determined the strength of evidence for the different outcomes evaluated in this report.

Table 8. Definitions for grading the strength of evidence

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect

Risk of Bias

Risk of bias is the degree to which the included studies for any given outcome or comparison has a high likelihood of adequate protection against bias. This can be assessed through the evaluation of both design and study limitations. For study design, whether the study was a randomized controlled trial or an observational study was recorded. Studies were also ranked as no limitations, serious limitations, or very serious limitations. Because all of the included studies were randomized controlled trials with few limitations, they were considered to have a low risk of bias.

Consistency

Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. This was assessed in two main ways: (1) the effect sizes had the same sign, in that they were on the same side of unity; (2) the range of effect sizes was narrow. We ranked this domain as no inconsistency, serious inconsistency, and very serious inconsistency. For outcomes whereby only a single study was included, consistency was not judged. We also considered measures of heterogeneity from our meta-analyses in evaluating consistency.

Directness

Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We ranked this domain as no indirectness, serious indirectness, and very serious indirectness.

Precision

Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis was performed, we evaluated the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. 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.

Rating Applicability

Trials had to meet five of the following seven criteria in order to be considered an effectiveness trial: used a primary care population, used less stringent eligibility criteria, assessed final health outcomes, had adequate study duration with clinically relevant treatment modalities, assessed adverse events, had an adequate sample size, and used intention-to-treat analysis. Those meeting fewer than five criteria were classified as efficacy trials and deemed to have less applicability.

The factors that are important for determining the applicability of a study to clinical practice are evaluated based on the patient population enrolled, the intervention given, the evaluation of a comparator, the types of outcomes evaluated and the setting where care was administered. The factors used to evaluate the applicability of a study to clinical practice are further defined in Table 9; those factors that were extracted into evidence tables for every study included in the report. By using all of the applicable studies to answer a Key Question, the applicability of the body of evidence was then determined and reported separately and qualitatively for each outcome of interest.

Table 9. Applicability PICOTS and data to extract

Feature	Condition That Limits Applicability	Features to be Extracted Into Evidence Table
Population	Differences between patients in the study and the community	Eligibility criteria, demographics
Population	Events rates markedly different than in the community	Event rates in treatment and control groups
Intervention	Treatment not reflective of current practice	Type of device, device name
Comparator	Use of substandard alternative therapy	Type of comparator
Outcomes	Intermediate end points, brief followup periods, improper definitions for outcomes, composite end points, lack of adverse event reporting	Outcomes (benefits and harms) and how they were defined
Settings	Settings where standards of care differ markedly from setting of interest	Clinical setting and geographic setting

PICOTS = Population, Intervention, Comparator, Outcomes, Settings

Peer Review and Public Commentary

A draft of this Evidence Report was sent to peer reviewers, the representatives of the AHRQ and the scientific review committee at Oregon Health and Science University. The draft report and posted to the Effective Health Care Web site for public comment. In response to the comments of the peer reviewers and the public, revisions were made to the Evidence Report, and a summary of the comments and their disposition was submitted to AHRQ.

Results

Results of Literature Search

Older Versus Newer Antiepileptic Drug Evaluation

A summary of search results is presented in Figure 2.

Upon conducting the literature search to identify articles that compared older antiepileptic medications to the newer ones, we retrieved 5,773 unique citations, and another 7 citations were identified from other sources. During the title and abstract review, 5,505 articles were excluded, and 200 articles were excluded during the full text review. A list of articles excluded during full text review can be found in Appendix C. A total of 68 articles were found to match our inclusion criteria. Although no language restrictions were imposed in the literature search, seven articles were excluded from the full-text review because they were not published in the English language. Given the small number of articles excluded, their small sample sizes, and the traditional medicine versus complementary medicine topic, we do not anticipate that their inclusion would have impacted our results in a meaningful way.⁴²

Innovator Versus Generic Antiepileptic Drug Evaluation

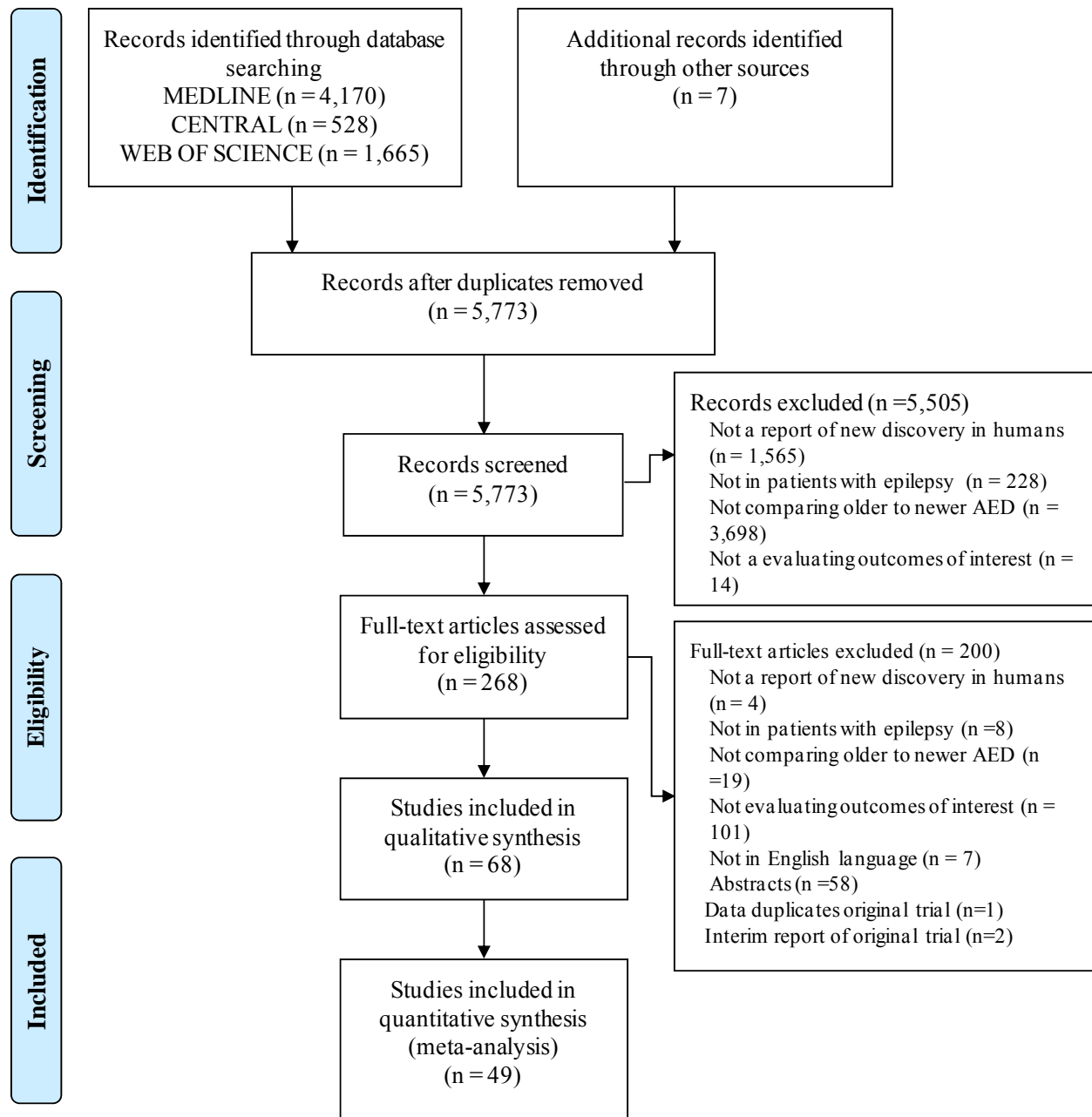
A summary of search results is presented in Figure 3.

Upon conducting the literature search to identify articles that compared innovator antiepileptic medications to its generic version, we retrieved 380 unique citations, and another 9 citations were identified from other sources. After removing duplicates, 356 citations were retrieved. Two hundred sixty-seven articles were excluded during the title and abstract review, and 18 articles were excluded during the full-text review. A list of articles excluded during full text review can be found in Appendix C. A total of 71 articles were found to match our inclusion criteria. Although no language restrictions were imposed in the literature search, one article was excluded from the full text review because it was not published in the English language. Given the small number of articles excluded, their small sample sizes, and the traditional medicine versus complementary medicine topic, we do not anticipate that their inclusion would have impacted our results in a meaningful way.⁴²

General Overview of Results

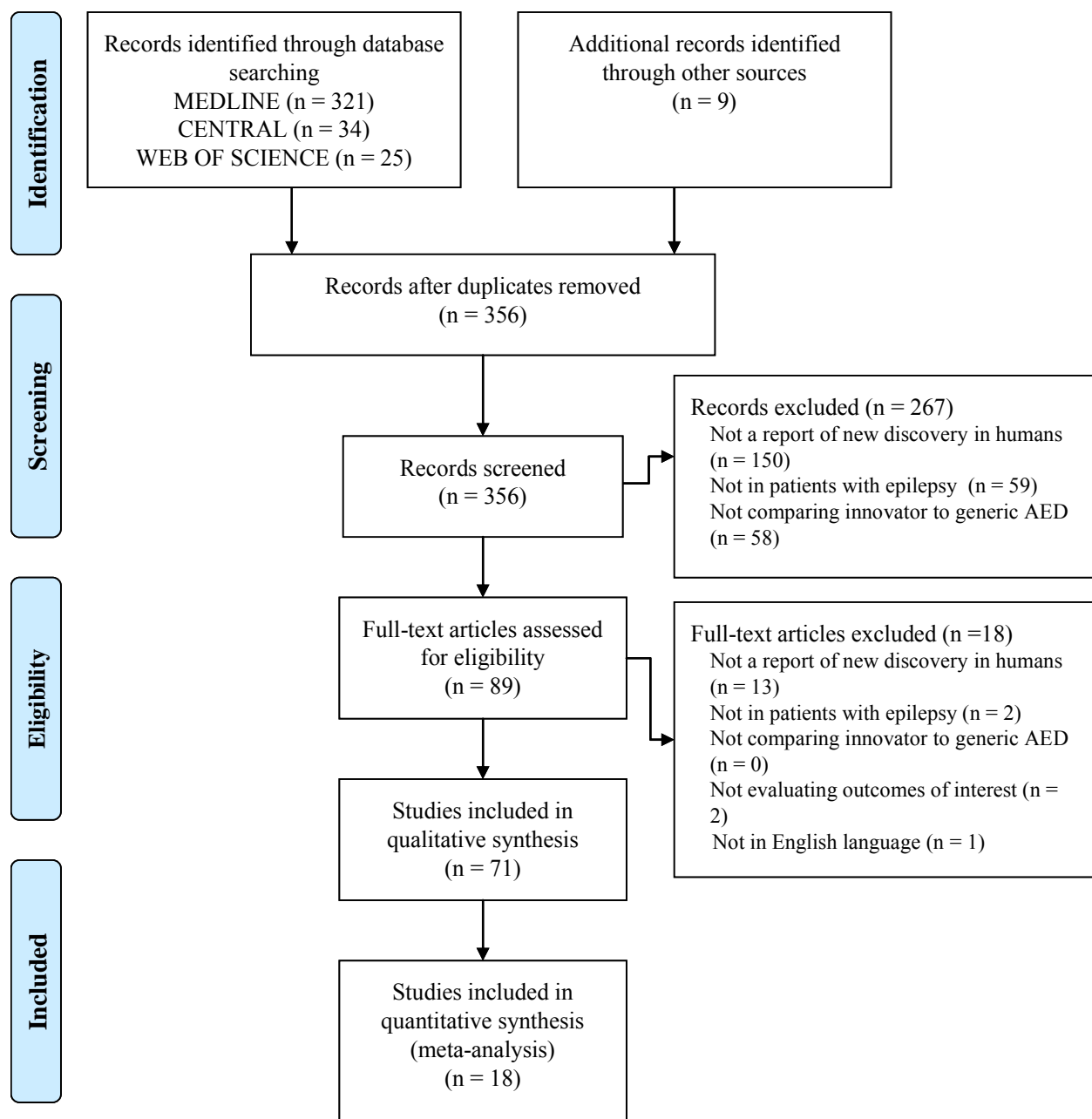
Table 10 delineates the results of the CER with a rating of the strength of evidence. The sections that follow provide much more detail into the analyses conducted and the nuances necessary to understand the analyses and how they apply to health care decisionmakers, clinicians, and patients.

Figure 2. PRISMA flow diagram of citations identified and evaluated in the older versus newer search



AED = antiepileptic drug; PRISMA = preferred reporting items for systematic reviews and meta-analyses

Figure 3. PRISMA flow diagram of citations identified and evaluated in the innovator versus generic search



AED = antiepileptic drug; PRISMA = preferred reporting items for systematic reviews and meta-analyses

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 (ambulance services, hospitalizations, or emergency department visits for epilepsy), health-related quality of life, seizures (time to first seizure, time to exit from trial due to lack of efficacy, proportion of seizure-free patients, proportion of patients with seizure remission, breakthrough seizures, frequency of seizures), secondary seizure injury (fracture, laceration, head trauma, aspiration pneumonia), status epilepticus, loss of driver's license, and loss of employment?

Key Points

- There was no difference observed in the risk of mortality when newer antiepileptic medications were compared with carbamazepine, phenytoin, or valproic acid. No other comparisons between newer and older antiepileptic medications were available.
- No 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.
- 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 with newer agents. When either gabapentin or oxcarbazepine was 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 with gabapentin or oxcarbazepine. When topiramate was compared with 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. No differences in 12- or 24-month seizure freedom were seen for newer antiepileptic 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.
- There was a significant increase in the time to first seizure when newer antiepileptic medications were compared versus phenytoin. No difference in the time to first seizure was seen between newer antiepileptic medications versus carbamazepine or valproic acid. However in individual newer agent versus carbamazepine or valproic acid analyses, significant reductions were seen for gabapentin and vigabatrin versus carbamazepine and for lamotrigine versus valproic acid.
- Five 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.
 - In a direct comparative trial, gabapentin, lamotrigine, oxcarbazepine, and topiramate similarly impacted health-related quality of life versus carbamazepine.

Tiagabine and carbamazepine both significantly improved subscales of health-related quality of life versus baseline in one trial, but lamotrigine significantly improved health-related quality of life versus baseline while carbamazepine did not in another trial.

- In one direct comparative trial, there was no significant difference in the median change from baseline in health-related quality of life when lamotrigine was compared to sustained-release carbamazepine.
- In a direct comparative trial, lamotrigine had a greater positive impact on health-related quality of life versus phenytoin. Tiagabine and phenytoin both significantly improved a subscale of health-related quality of life versus baseline in one trial.
- In one direct comparative trial, lamotrigine and topiramate yielded a similar effect to valproic acid and in another trial topiramate and valproic acid had similar effects on health-related quality of life. In another trial, lamotrigine had a greater positive effect on three subscales of health-related quality of life versus valproic acid.
- In controlled clinical trials, the available data on seizure occurrence or frequency for innovator and generic antiepileptic medications is confined to carbamazepine and to a lesser extent phenytoin and valproic acid.
 - The use of an “A” rated generic could only be verified in one controlled clinical trial and a minority of controlled observational studies.
- For a population of people, seizure occurrence, seizure frequency, withdrawals for any reason, and withdrawals due to lack of efficacy are similar during periods in which innovator and generic versions of antiepileptic agents are used.
 - The impact of switching patients stabilized on an innovator or generic version to an alternative version on these endpoints cannot be answered by the available controlled clinical trials or observational studies.
- Important final health outcomes including mortality, health-related quality of life, loss of driver’s license or employment, time to first seizure, seizure remission, secondary seizure injury, and status epilepticus could not be assessed.
- Controlled observational studies suggest that switching from one version of an antiepileptic medication (either innovator or generic) to another version may increase medical service utilization.
 - These observational studies, while well conducted, have inherent limitations, and controlled clinical trials will be needed to evaluate whether and to what extent this is true.
 - The preponderance of funding for these observational studies is by the pharmaceutical industry.

Detailed Analysis

Older Versus Newer Study Design and Population Characteristics

Forty-eight controlled trial reports (n=13,039) evaluated older versus newer antiepileptic medication comparisons and were eligible for inclusion (Appendix F Table 5).^{47-68,68-93}

Twenty-four reports were funded by the pharmaceutical industry,^{49,51,52,59,60,63,64,66-69,71-74,76-78,80-83,86,90,93} 5 reports were funded by government or foundation funding,^{78,85,89,91,92} and funding was not reported for 19 reports.^{47,48,50,53,55-58,61,62,65,66,70,75,84,87,94}

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 reports were 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 conducted in Australia and Europe;⁵⁵ one multinational report was conducted in 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 Three reports did not report any country.^{48,73,77}

Baseline characteristics are presented in Appendix F Tables 5–9. The average age is between 12 years and 77 years, and the percentage of male participants ranged from no male participants to 100 percent. Body weight ranged between 19 and 83.5 kg within the 15 trials that reported it.^{49,51,56-59,61,65,70,72,78,81,83,86,88,90} Ethnicity was reported by 10 trials.^{51,57,59,68,72,78,81,88-90} The percentage of Caucasian participants ranged from 47 to 92.1 in the 10 trials that reported the percentage of Caucasian participants,^{51,57,59,68,72,78,81,88-90} the percentage of Black patients ranged from 3 to 27.6 in the 10 trials that reported the percentage of Black participants,^{51,57,59,68,72,78,81,88-90} the percentage of Asian participants ranged from 0 to 11 in the 4 trials that reported the percentage of Asian participants,^{68,72,81,90} the percentage of Hispanic participants ranged from 0 to 8 in the four trials that reported the percentage of Hispanic participants,^{68,72,78,88} and the percentage of participants with another ethnicity ranged from 1.5 to 34 in the 7 trials that reported participants with another ethnicity.^{51,57,59,78,81,89,90}

Epilepsy history was only reported by 23 trials,^{50,51,55,57-60,62,65,68-70,72,75,76,80,82,83,85,86,88-90} and only 30 trials reported seizure type.^{47,49,51-53,56-60,63,64,68-70,72,74-78,80-82,84,85,88-90,94}

Fourteen trials reported the number of patients that were untreated with antiepileptic agents prior to enrollment.^{52,53,56,57,63,64,70,72,74,78,82,84,85,88} Prior or concurrent use of carbamazepine, phenytoin, valproic acid, phenobarbital, gabapentin, lorazepam, or other therapy was reported in 10 trials.^{47,62,68,69,72,76,84,85,88,95}

Fifteen observational reports (n=2469) evaluated older versus newer antiepileptic medication comparisons and were eligible for inclusion (Appendix F Table 5).^{54,54,79,95-106} Three reports were funded by pharmaceutical companies,^{96,97,103} five reports were funded by government or foundations, and^{54,102,105,106} seven reports did not report the role of funding.^{79,95,98-101,104} Three reports were conducted in the United States,^{96,97,102,103} one report was conducted in Denmark,⁵⁴ one report was conducted in Italy,⁹⁸ one report was conducted in Scotland,⁹⁹ one report was conducted in Hungary,⁹⁵ one report was conducted in Poland,⁷⁹ one report was conducted in Turkey,¹⁰⁰ two reports were conducted in Korea,^{101,104} one report was conducted in China,¹⁰⁵ and one report was conducted in Brazil.¹⁰⁶ (Appendix F Table 5)

Baseline characteristics are elucidated in Appendix F Tables 5–9. The average age ranged between 8.5 months and 36.9 years, and the percentage of male participants ranged from 25 to 60 percent. Body weight ranged from 38.15 to 73 kg in the two studies that reported body weight,^{100,102} and the percentage of Caucasian participants ranged from 61 to 76 percent in the study that reported the percentage of Caucasian participants (Appendix F Table 7).¹⁰² Epilepsy

history was reported in two observational studies,^{99,102} and only three of the studies reported the seizure type (Appendix F Table 8).^{79,98,100}

Four studies reported the number of patients that were untreated with antiepileptic agents prior to enrollment.^{54,98,99,101} Prior or concurrent use of carbamazepine, phenytoin, valproic acid, phenobarbital, gabapentin, lorazepam, or other therapy use was reported in four studies (Appendix F Table 9).^{79,95,100,102}

Descriptive studies were not included in the older versus newer antiepileptic medication evaluation.

Innovator Versus Generic Study Design and Population Characteristics

Seventeen controlled trial reports (n=365) evaluated innovator to generic or generic to innovator comparisons and were eligible for inclusion (Appendix F Table 1).¹⁰⁷⁻¹²³ Two phenytoin trials that appeared otherwise eligible for our analyses were excluded upon detailed evaluation.^{124,125} In the first trial, the products were coded by letter, and it could not be determined which products, if any, were innovator or generic. In the second trial, two innovator products from the same manufacturer but manufactured in different countries were compared with each other, and the generic versions were not of the same salt form (Appendix C Table 1).^{124,125}

Only 1 of the 17 reports specified that they were limited to “A” rated versions of the generic medications.¹¹² Four were funded by the pharmaceutical industry,^{107,110,112,119} and funding was not known for eight studies.^{111,113,115,116,118,120-122} Multiple studies were included in one of the reports.¹¹² Four reports were conducted in the United States,^{109,112,121,123} five were conducted in the United Kingdom,^{110,111,118,119,122} two in Finland^{107,113} and one each in Germany, Thailand, Netherlands, Denmark, Sweden and India (Appendix F Table 1).^{108,114-117,120}

Baseline characteristics are presented in Appendix F Tables 1–4. The average age ranged between 9.5 and 45.1 years, and the percentage of male participants ranged from 35 to 100 percent. Body weight ranged between 35.8 and 59.6 kg within the six studies that reported it.^{108,110,114,120,122,123} Ethnicity was not reported in any study (Appendix F Table 2). Epilepsy history was only reported by three trials (either new-onset or chronic epilepsy),^{110,115,120} and only six of the studies reported the seizure type (Appendix F Table 3).^{110,113-116,119}

Patients in these trials had been previously treated with antiepileptic medications. Prior or concurrent use of carbamazepine, phenytoin, or valproic acid was reported in 11 out of 16 trials (Appendix F Table 4).^{107-110,112-116,118,121} The use of combination therapy was reported in 8^{107-109,112,114-116,121} of the 17 trials and ranged between 0 and 80 percent.

Nine controlled observational reports (n=61,684), not constituted by patients in clinical trials, evaluated innovator to generic, generic to generic, or generic to innovator switches and were eligible for inclusion (Appendix F Table 1).^{33,126-133} Only three of the eight reports specified that they were limited to “A” rated versions of the generic medications.¹²⁶⁻¹²⁸ Eight of the reports were funded by the pharmaceutical industry,^{33,126,127,129-133} and one was funded by a health insurance provider.¹²⁸ Multiple studies were included in three of the reports.^{33,129,131} Five reports were conducted in the United States¹²⁶⁻¹³⁰ and the other four in Canada (Appendix F Table 1).^{33,131-133}

Baseline characteristics are elucidated in Appendix F tables 2 and 3. The average age ranged between 33.7 and 52.5 years and the percentage of male participants ranged from 32.3 to 50.8 percent. Body weight and ethnicity were not reported in these

observational studies (Appendix F Table 2). Epilepsy history was not reported in the observational studies, and only three of the studies reported the seizure type (either partial or generalized) (Appendix F Table 3).¹²⁶⁻¹²⁸

Patients in observational studies had been previously treated with antiepileptic medications (Appendix F Table 4).^{33,126-133} Prior or concurrent use of carbamazepine, phenytoin, or valproic acid was not reported. The use of combination therapy was reported in five^{33,128,131-133} of the eight trials, and the percent of patients on combination treatment ranged between 52 and 94 percent.

Twenty-nine descriptive reports (n=2,190) assessed innovator to generic, generic to generic, or generic to innovator switches. Seventeen (60.7 percent) of these descriptive studies were case reports or case series, four (14.3 percent) were pure surveys, one (3.6 percent) was a survey and a case series, and seven were other designs where patients were described but not compared with a control group.

Four of the reports were funded by the pharmaceutical industry,¹³⁴⁻¹³⁷ two of the reports were funded by the National Institutes of Health,^{138,139} and funding for all the other reports was not specified.^{116,140-161} Multiple descriptive studies were included in 10 of the reports.^{134-136,138,140-145} Fifteen reports were conducted in the United States,^{135,136,138,139,141,143-149,155,158,159} two reports were conducted in the United Kingdom,^{134,140} two reports were conducted in Poland,^{142,156} two reports were conducted in Germany^{153,157} and one report each was conducted in Switzerland, Italy, Canada, and Denmark.^{116,137,150,152} Study location for four other reports was unknown (Appendix F Table 1).^{151,154,160,161}

Baseline characteristics are reported in appendix tables 2 and 3 (Appendix F Table 2-3). The average age ranged between 6.0 and 66.0 years, and the percentage of male participants ranged from 0 to 100 percent. Body weight and ethnicity were not reported in these reports (Appendix F Table 2). Epilepsy history was only reported by five studies.^{145,147-149,158} Epilepsy duration ranged from 1 to 16 years.^{145,149,158} Four studies reported chronic onset of epilepsy which was either at birth or 1 year of age.^{147-149,158} Twelve studies reported seizure type as partial, simple partial, complex partial, generalized, tonic-clonic or absence and the proportion of patients with each type of seizure varied between studies (Appendix F Table 3).^{116,136,140,143,146-148,150,156,158,160,161}

Patients in fourteen studies had been previously treated with antiepileptic medications (Table 4).^{116,143,145-152,156-158,160} Prior or concurrent use of carbamazepine, phenytoin, or valproic acid was reported in eight studies.^{116,146-150,152,160} The use of combination therapy was reported in 12 of these trials^{116,143,145,147-152,156-158} and ranged between 21 and 100 percent.

Given the inherent limitations and biases associated with uncontrolled data, and the specific limitations associated with these reports in particular, these studies will not be discussed in the results section of this report.

Outcome Evaluations

Mortality

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Six randomized controlled trials reported the number of patients who died when receiving a newer antiepileptic compared with carbamazepine, and all six were amenable for pooling.^{55,62,63,76,78,85}

Two randomized controlled trials reported the number of patients who died when gabapentin was compared with carbamazepine, and both were amenable for pooling.^{78,85} The risk of death was nonsignificantly decreased by 8 percent when gabapentin was compared with carbamazepine (relative risk [RR] 0.92 [0.57 to 1.48]) (Appendix J Figure 1).

Five randomized controlled trials reported the number of patients who died when lamotrigine was compared with carbamazepine, and all five were amenable for pooling.^{55,62,76,78,85} The risk of death was nonsignificantly decreased by 37 percent when lamotrigine was compared with carbamazepine (RR 0.63 [0.37 to 1.04]) (Appendix J Figure 1). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.682$).

One randomized controlled trial reported the number of patients who died when oxcarbazepine was compared with carbamazepine.⁸⁵ The risk of death was nonsignificantly decreased by 50 percent when oxcarbazepine was compared with carbamazepine (RR 0.50 [0.19 to 1.27]) (Appendix J Figure 1).

One randomized controlled trial reported the number of patients who died when topiramate was compared with carbamazepine.⁸⁵ The risk of death was nonsignificantly decreased by 6 percent when topiramate was compared with carbamazepine (RR 0.94 [0.50 to 1.78]) (Appendix J Figure 1).

One randomized controlled trial reported the number of patients who died when vigabatrin was compared with carbamazepine.⁶³ The risk of death was nonsignificantly increased by 2.0-fold when vigabatrin was compared with carbamazepine (RR 2.01 [0.26 to 15.27]) (Appendix J Figure 1).

Six randomized controlled trials reported the number of patients who died when either gabapentin, lamotrigine, oxcarbazepine, or topiramate was compared with carbamazepine and all six were amenable for pooling.^{55,62,63,76,78,85} The risk of death was nonsignificantly decreased by 25 percent when all newer antiepileptics were compared with carbamazepine (RR 0.75 [0.51 to 1.12]) (Appendix J Figure 1). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.598$).

Phenytoin Versus Newer

Three randomized controlled trials reported the number of patients who died when newer antiepileptics were compared with phenytoin and all three were amenable for pooling.^{57,90}

One randomized controlled trial reported the number of patients who died when lamotrigine was compared with phenytoin.⁶⁴ The risk of death was nonsignificantly decreased by 78 percent when lamotrigine was compared with phenytoin (RR 0.22 [0.02 to 2.41]) (Appendix J Figure 2).

One randomized controlled trial reported the number of patients who died when oxcarbazepine was compared with phenytoin.⁵⁷ The risk of death was nonsignificantly decreased

by 80 percent when oxcarbazepine was compared with phenytoin (RR 0.20 [0.02 to 2.22]) (Appendix J Figure 2).

One randomized controlled trial reported the number of patients who died when topiramate was compared with phenytoin.⁹⁰ The risk of death was nonsignificantly decreased by 4 percent when topiramate was compared with phenytoin (RR 0.96 [0.06 to 16.60]) (Appendix J Figure 2).

Three randomized controlled trials reported the number of patients who died when either lamotrigine, oxcarbazepine or topiramate was compared with phenytoin and all three were amenable for pooling.^{57,64} The risk of death was nonsignificantly decreased by 70 percent when the newer agents were compared with phenytoin (RR 0.30 [0.05 to 1.95]) (Appendix J Figure 2). No significant statistical heterogeneity was detected (I^2 : 0 percent); however, tests for publication bias could not be performed.

Valproic Acid Versus Newer

Three randomized controlled trials reported the number of patients who died when newer antiepileptics were compared with valproic acid and all three were amenable for pooling.^{61,76,85}

Two randomized controlled trials reported the number of patients who died when lamotrigine was compared with valproic acid and both were amenable for pooling.^{76,85} The risk of death was nonsignificantly increased by 6 percent when lamotrigine was compared with valproic acid (RR 1.06 [0.30 to 3.76]) (Appendix J Figure 3).

One randomized controlled trial reported the number of patients who died when topiramate was compared with valproic acid.⁸⁵ The risk of death was nonsignificantly decreased by 25 percent when topiramate was compared with valproic acid (RR 0.75 [0.19 to 2.95]) (Appendix J Figure 3).

One randomized controlled trial reported the number of patients who died when vigabatrin was compared with valproic acid.⁶² The risk of death was nonsignificantly decreased by 1 percent when vigabatrin was compared with valproic acid (RR 0.99 [0.06 to 17.08]) (Appendix J Figure 3).

Three randomized controlled trials reported the number of patients who died when the newer antiepileptics lamotrigine, topiramate or vigabatrin were compared with valproic acid and all three were amenable for pooling.^{62,76,85} The risk of death was nonsignificantly decreased by 6 percent when newer agents were compared with valproic acid (RR 0.94 [0.31 to 2.80]) (Appendix J Figure 3). No publication bias (Egger's $p=0.448$) was detected.

Phenobarbital or Primidone Versus Newer

No data are available for this comparison.

Ethosuximide Versus Newer

No data are available for this comparison.

Innovator Versus Generic Antiepileptic Drug Evaluation

None of the available controlled clinical trials or observational studies reported on mortality as an endpoint.

Use of Medical Services

Older Versus Newer Antiepileptic Drug Evaluation

No data are available comparing newer versus older antiepileptic medications for any endpoint in this section.

Innovator Versus Generic Antiepileptic Drug Evaluation

Office or Emergency Room Visits

No controlled clinical trials and four controlled observational reports (n=3,852) evaluated innovator to generic, generic to generic, or generic to innovator switches and were eligible for inclusion and reported on at least one of the following endpoints: outpatient visits, hospitalizations, or hospital stay duration (Appendix G Table 3).^{33,129,132,133} None of the four reports specified that they were limited to “A” rated versions of the generic medications. The pharmaceutical industry funded all of the reports.^{33,129,132,133} Multiple studies were included in two of the reports.^{33,129} One report was conducted in the United States¹²⁹ and the other three in Canada (Appendix G Table 3).^{33,132,133}

Baseline characteristics are elucidated in appendix tables 2 and 3 (Appendix F Table 2, Appendix F Table 3). The average age ranged between 33.7 and 52.5 years, and the percentage of male participants ranged from 32.3 percent to 50.8 percent. Body weight and ethnicity were not reported in these observational studies (Appendix F Table 2). Epilepsy history or seizure type was also not reported in these observational studies (Appendix F Table 3).

Patients in these studies had been previously treated with antiepileptic medications (Appendix F Table 4).^{33,129,132,133} Prior or concurrent use of carbamazepine, phenytoin, or valproic acid was not well reported. The use of combination therapy was reported in three^{33,132,133} of the four trials and ranged between 70 percent and 94 percent.

No controlled clinical trials and three controlled observational reports (n=17,424) evaluated innovator to generic, generic to generic, or generic to innovator switches and were eligible for inclusion and reported on a composite endpoint of medical service utilization.¹²⁶⁻¹²⁸ All of the observational studies were conducted in the United States, two were funded by Abbott Laboratories and employed a similar methodology, and one was funded by Express Scripts. Baseline characteristics are elucidated in Appendix F tables 2 and 3. The average age ranged between 35.6 and 44 years, and the percentage of male participants ranged from 43.9 to 49 percent. Body weight and ethnicity were not reported in these observational studies (Appendix F Table 2). Epilepsy history or seizure type was also not reported in these observational studies (Appendix F Table 3).

Ambulance Services

There were no controlled clinical trials or observational studies that met our inclusion criteria that evaluated ambulance services as a sole endpoint.

Outpatient Medical Care Utilization

No controlled clinical trials and four large observational studies evaluated the impact of switching from innovator to generic, generic to innovator, or generic to generic antiepileptic medication^{33,129,133} on office or emergency room visits. One was conducted in the United States, and the other three studies were conducted in Canada. Two of the studies were supported by GlaxoSmithKline^{33,129} and the other two studies were supported by Ortho-McNeil-Janssen.^{132,133}

All four studies employed similar methodology, but none of the studies specified whether they were limited to “A” rated generic products. These trials are not amenable to statistical pooling and are discussed qualitatively.

In the first study, a retrospective open-cohort design was used to classify the duration of observations into two mutually exclusive periods of innovator and generic use of antiepileptic drugs.¹²⁹ Patients with epilepsy who had an ambulance ride, emergency department visit, or office visit between January 1, 2000, and October 31, 2007, were compared during innovator and generic use periods using a person-time approach. Incidence rates of outpatient visits (office and emergency room visits) were calculated for antiepileptic drugs. The duration of prescriptions was normalized to 28 days to enable incidence rate comparisons. Study results were further stratified into stable versus unstable epilepsy groups. The stable group was defined as patients with ≤ 2 outpatient services per year on average throughout the observation period and no emergency room visits associated with epilepsy or nonfebrile convulsions. All other patients were defined as having unstable epilepsy. For epilepsy-related medical resource use, observed differences in outpatient visits in both the stable and unstable group showed higher utilization rates during generic-use periods (2.52 [innovator] versus 2.92 [generic]; adjusted incidence rate ratio [IRR] 1.20 [1.19 to 1.21]) in the stable patient group and (23.33 [innovator] versus 28.36 [generic]; adjusted IRR 1.16 [1.16 to 1.17]) in the unstable patient group.

In the second study, a retrospective open-cohort design was used in patients with epilepsy who had any outpatient visits between April 1, 1998, and July 31, 2006. Incidence rates of outpatient visits were calculated and compared between periods of innovator versus generic use of lamotrigine.³³ Incidence rates were calculated as the number of events divided by the number of person-years of observation. To account for varying days of supply associated with different dispensations, the dispensation length was set to 28 days. Outpatient visits were more frequent during the generic period compared with the innovator periods (9.25 versus 8.24 visits per person per year; RR 1.13 [1.09 to 1.18]; $p < 0.0001$).

In the third study, a retrospective open-cohort design was used to classify the observation period into mutually exclusive periods of innovator topiramate use only, single-generic topiramate use, and multiple-generic topiramate use.¹³² Incidence rates of outpatient visits were calculated and compared between periods of innovator versus single-generic and multiple-generic use of topiramate. Incidence rates were calculated as the number of events divided by the number of person-years observed. The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Incidence rates for outcomes during the innovator period versus single-generic and multiple-generic periods were compared using incidence rate ratios. Outpatient visits showed no significant differences among the three studied periods (9.07 [innovator] versus 9.48 [single-generic] versus 8.74 [multiple-generic] visits per person per year; adjusted IRR 0.99 (0.94 to 1.04) for single-generic versus innovator and adjusted IRR 0.95 (0.88 to 1.02) for multiple-generic versus innovator).

In the fourth study, a retrospective open-cohort design was used to classify the observation period into mutually exclusive periods of innovator and generic use of topiramate.¹³³ Incidence rates of outpatient visits were expressed as frequency per person per year, and were calculated as the number of events divided by the number of person-years observed, and were compared between periods of innovator versus generic use of topiramate using IRRs. The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Outpatient visits showed no significant difference among the two periods (9.0 [innovator] versus 9.1 [generic] visits per person per year; adjusted IRR 0.99 [0.96 to 1.03] for innovator versus generic).

Hospitalizations

No controlled trials and four large observational studies evaluated the impact of switching from innovator to generic, generic to innovator, or generic to generic antiepileptic medication^{33,129,132,133} on hospitalizations. One study¹²⁹ was conducted in United States and the other three studies were conducted in Canada. Two of the studies were supported by GlaxoSmithKline^{33,129} and the other two studies were supported by Ortho-McNeil-Janssen.^{132,133} All four studies employed similar methodology, but none of the studies specified whether they were limited to “A” rated generic products. These trials are not amenable for statistical pooling and are discussed qualitatively.

In the first study, a retrospective open-cohort design was used to classify the duration of observations into two mutually exclusive periods of innovator and generic use of antiepileptic drugs. Patients with epilepsy who were hospitalized between January 1, 2000, and October 31, 2007, were compared during innovator and generic use periods using a person-time approach. Incidence rates of hospitalizations were calculated for antiepileptic drugs.¹²⁹ The duration of prescriptions was normalized to 28 days to enable incidence rate comparisons. Study results were further stratified into stable versus unstable epilepsy groups. The stable group was defined as patients with ≤ 2 outpatient services per year on average throughout the observation period and no ER visit associated with epilepsy or nonfebrile convulsions. All other patients were defined as having unstable epilepsy. For epilepsy-related medical resource use, observed differences in hospitalization in both the stable and unstable group showed higher utilization rates during generic-use periods (0.05 [innovator] versus 0.06 [generic]; adjusted IRR [incidence rate ratio] 1.31 [1.24 to 1.40]) in stable patient group and (0.34 [innovator] versus 0.47 [generic]; adjusted IRR 1.30 [1.25 to 1.36]) in unstable patient group.

In the second study, a retrospective open-cohort design was used in patients with epilepsy who had any outpatient visits between April 1, 1998, and July 31, 2006. Incidence rates of hospitalizations were calculated and compared between periods of innovator versus generic use of lamotrigine.³³ Incidence rates were calculated as the number of events divided by the number of person-years of observation. To account for varying days of supply associated with different dispensations, the dispensation length was set to 28 days. Rates of inpatient hospitalizations were not statistically different between the generic and innovator periods (0.56 versus 0.49 visits per person per year; RR 1.14 [0.96 to 1.35]; $p = 0.1264$).

In the third study, a retrospective open-cohort design was used to classify the observation period into mutually exclusive periods of innovator topiramate use, single-generic topiramate use, and multiple-generic topiramate use.¹³² Incidence rates of hospitalizations were calculated and compared between periods of innovator versus single-generic and multiple-generic use of topiramate. Incidence rates were calculated as the number of events divided by the number of person-years observed. The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Incidence rates for outcomes during the innovator period versus single-generic and multiple-generic periods were compared using IRRs. After covariate adjustment, multiple generic use was associated with significantly higher incidence of hospitalization relative to innovator-only use, while the difference between single-generic and innovator periods was not significant (0.48 [innovator] versus 0.52 [single-generic] versus 0.83 [multiple-generic] hospitalizations per person per year; adjusted IRR 1.08 [0.88 to 1.34] for single-generic versus innovator and adjusted IRR 1.65 [1.28 to 2.13] for multiple-generic versus innovator).

In the fourth study, a retrospective open-cohort design was used to classify the observation period into mutually exclusive periods of innovator and generic use of topiramate.¹³³ Incidence rates of hospitalizations were expressed as frequency per person per year, and were calculated as the number of events divided by the number of person-years observed, and were compared between periods of innovator versus generic use of topiramate using IRRs. The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Rates of hospitalization was significantly higher in generic use period compared with innovator periods (0.5 [innovator] versus 0.6 [generic] visits per person per year; adjusted IRR 1.17 [1.03 to 1.33]).

Hospital Stay Duration

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled trials and four large observational studies evaluated the impact of switching from innovator to generic, generic to innovator, or generic to generic antiepileptic medication^{33,129,133,162} on office or emergency room visits. One study¹²⁹ was conducted in United States and the other three studies were conducted in Canada. Two of the studies were supported by GlaxoSmithKline^{33,129} and the other two studies were supported by Ortho-McNeil-Janssen.^{132,133} All four studies employed similar methodology, but none of the studies specified whether they were limited to “A” rated generic products. These studies were not amenable to statistical pooling and are discussed qualitatively.

In the first study, a retrospective open-cohort design was used to classify the duration of observations into two mutually exclusive periods of innovator and generic use of antiepileptic drugs. Hospital duration of patients with epilepsy who were hospitalized between January 1, 2000, and October 31, 2007, was compared during innovator and generic use periods. Incidence rates of length of hospital stay was calculated for antiepileptic drugs.¹²⁹ The duration of prescriptions was normalized to 28 days to enable incidence rate comparisons. Study results were further stratified into stable versus unstable epilepsy groups. The stable group was defined as patients with ≤ 2 outpatient services per year on average throughout the observation period and no emergency room visit associated with epilepsy or nonfebrile convulsions. All other patients were defined as having unstable epilepsy. For epilepsy-related medical resource use, hospital stays lasted significantly longer on average during generic antiepileptic drug treatment in both stable and unstable group (1.02 [innovator] versus 1.38 [generic]; adjusted IRR 1.33 [1.30 to 1.36]) in stable patient group and (2.33 [innovator] versus 3.29 [generic]; adjusted IRR 1.34 [1.32 to 1.36]) in unstable patient group.

In the second study, a retrospective open-cohort design was used in patients with epilepsy who had any hospitalizations between April 1, 1998, and July 31, 2006. Incidence rates of length of hospital stay was calculated and compared between periods of innovator versus generic use of lamotrigine.³³ Incidence rates were calculated as the number of days divided by the number of person-years of observation. To account for varying days of supply associated with different dispensations, the dispensation length was set to 28 days. The average length of hospital stay was longer during the generic period compared with the innovator periods (4.86 versus 3.29 days per patient per year; RR 1.48 [confidence interval not reported]; $p < 0.0001$).

In the third study, a retrospective open-cohort design was used to classify the observation period into mutually exclusive periods of innovator topiramate only, single-generic topiramate use, and multiple-generic topiramate use.¹³² Incidence rates of length of hospital stay was calculated and compared between periods of innovator versus single-generic and multiple-generic use of topiramate. Incidence rates were calculated as the number of days divided by the

number of person-years observed. The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Incidence rates for outcomes during the innovator period versus single-generic and multiple-generic periods were compared using IRRs. Significantly longer mean hospital lengths of stay were observed for multiple-generic period and for single-generic period than for innovator period (2.55 [innovator] versus 3.22 [single-generic] versus 3.88 [multiple-generic] days per person per year; adjusted IRR 1.12 [1.03 to 1.23] for single-generic versus innovator and adjusted IRR 1.43 [1.27 to 1.60] for multiple-generic versus innovator).

In the fourth study, a retrospective open-cohort design was used to classify the observation period into mutually exclusive periods of innovator and generic use of topiramate.¹³³ Incidence rates of length of hospital stay was expressed as days per person per year, and were calculated as the number of days divided by the number of person-years observed, and were compared between periods of innovator versus generic use of topiramate using IRRs. The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Significantly longer average length of hospital stays were observed during generic period compared with innovator period (2.4 [innovator] versus 3.1 [generic] days per person per year; adjusted IRR 1.21 [1.15 to 1.28]).

Composite of Medical Services

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled trials and three large observational studies evaluated the impact of switching from innovator to generic, generic to innovator, or generic to generic antiepileptic medication on a composite of medical service utilization.¹²⁶⁻¹²⁸ All three of the observational studies were conducted in the United States, employed similar methodology, and were limited to “A” rated products. The first two were supported by Abbott Laboratories^{126,127} while the last was supported by the pharmacy benefit managing company Express Scripts, Inc.¹²⁸

In the first study, patients with epilepsy who had an ambulance ride, emergency department visit, or inpatient hospitalization between July 1, 2006, and December 31, 2006, without a previous acute event in the past 6 months were defined as cases, while those receiving an office visit for epilepsy during the same time period were defined as controls.¹²⁶ The percentage of patients switching from an “A” rated antiepileptic medication to another “A” rated version of the same antiepileptic medication was compared between groups. This could have been switching from innovator to generic, generic to innovator, or generic to generic. Patients were matched 1:3 (cases:controls) for diagnosis and age. Diagnosis was divided into seizure type (generalized, partial, or other) and whether the seizure type was intractable or not. Patients in the case group and control group were well matched for seizure type and severity, male gender, age, and region of the country. The cases were more likely to be insured by Medicaid than the controls. The cases were significantly 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 (odds ratio [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). However, these results are unadjusted and therefore may be biased.

In the second study, patients with epilepsy who received an ambulance service, emergency department visit, or inpatient hospitalization between October 1, 2005, and December 31, 2006, without a previous acute event in the past 6 months were cases while those receiving an office

visit for epilepsy during the same time period were controls.¹²⁷ The percentage of patients switching from an “A” rated antiepileptic medication to another “A” rated version of the same antiepileptic medication was compared between groups. This could have been from innovator to generic, generic to innovator, or generic to generic. Patients were matched 1:3 (cases:controls) for gender, age, and diagnosis. Diagnosis was divided into seizure type (generalized, partial, or other) and whether the seizure type was intractable or not. Patients in the case and control group were well matched for age, male gender, and seizure type and severity. The cases were more likely to be insured by Medicaid than the controls, and the regional distribution between cases and controls was different. The cases were significantly 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 1.84 [1.44, 2.36], 11.0 percent versus 6.3 percent), analysis excluding patients with a concurrent change in dosage (OR 2.86 [2.13, 3.83], 11.5 percent versus 4.4 percent), and analysis excluding patients with Medicaid coverage (OR 1.83 [95 percent CI 1.41 to 2.37], 10.6 percent versus 6.1 percent). No analysis was conducted based on geographic location.

In the third study, patients with epilepsy who had an emergency department visit, or inpatient hospitalization between January 1, 2006, and December 31, 2007, without a previous acute event in the past 6 months were defined as cases while controls were from the same population and matched on baseline epilepsy diagnosis and followup time since January 1, 2006.¹²⁸ The exposure was a switch between “A” rated antiepileptic drugs in the 90 days prior to the matching date. This could have been switching from innovator to generic, generic to innovator, or generic to generic. Each case was matched to three controls with the same baseline diagnosis code for epilepsy (the most recent medical claim prior to December 31, 2005), and a total time at risk greater than or equal to that of the index date of the case. Patients in the case and control group were well matched for seizure type and severity, gender, age, and region of the country. The authors also controlled for the following confounders: person’s risk of epilepsy exacerbation, change in disease severity, drug interactions, poor adherence, and change in patient diagnosis. The unadjusted odds ratio between switch and epilepsy exacerbation was 1.51 (1.29–1.76). After adjusting for potential confounders, the odds ratio was non significant 1.08 (0.91–1.29). The time evaluated for the number of antiepileptic drugs, the addition of a new antiepileptic drug, and the addition of a new interacting medication were extended to 180 days. This alternate analysis resulted in an increase in the total number of “A” rated switches by 523, for a total of 1,286. Upon reanalysis, the adjusted odds ratio of acute epilepsy exacerbations were non-significantly increased to 1.14 (0.99–1.31).

Health-Related Quality of Life

Older Versus Newer Antiepileptic Drug Evaluation

Five instruments, Quality of Life in Epilepsy-89 (QOLIE-89), Side Effect and Life Satisfaction Inventory (SEALS Inventory), Newly Diagnosed Epilepsy Quality of Life (NEWQOL), European Descriptive Health Related Quality of Life States (EQ-5D), and the World Health Organization-5 Well-Being Index (WHO-5) were employed to evaluate health-related quality of life (HRQoL) when newer antiepileptic drugs were compared with older antiepileptic drugs. The QOLIE-89 scale is a self-administered health-related quality of life inventory for adults with epilepsy. The inventory includes contains 17 multi-item measures of overall quality of life including: emotional well-being, role limitations due to emotional problems, social support, social isolation, energy/fatigue, worry about seizure, medication

effects, health discouragement, work/driving/social function, attention/concentration, language, memory, physical function, pain, role limitations due to physical problems, and health perceptions. Scores are calculated for the individual subscales and for the total with higher scores representing an improvement. The SEALS Inventory is a 38-question self-completed inventory that measures patient satisfaction with antiepileptic drug therapy. The 38 questions are divided into the following five subgroups of worry, temper, cognition, dysphoria, and tiredness. Each item is scored on a 4-point scale with 0 = never, 1 = occasionally, 2 = sometimes, 3 = many times. The score for each subscale is the total number of points for each of the items in the subscale. The total SEALS Inventory score is the sum of the scores of the five subscales. Lower scores indicate fewer symptoms and higher health-related quality of life. The NEWQOL is a 93-item self-administered battery that measures the quality of life in patients with new-onset epilepsy who are 16 years of age and older. The NEWQOL is made up of 93 items; 81 of the items comprise 8 multi-item subscales that measure several health parameters, including anxiety, depression, social activities, symptoms, locus of control/mastery, neuropsychological problems, social stigma, worry, and work. The remaining items are single-item subscales that include general health, number of seizures, social limitations, social support, self concept, ambition limitations, health transition, and general limitations. The EQ-5D is a descriptive system of health-related quality of life states with five dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression designed to measure health status. Each dimension has three levels of response based on severity including no problems, some or moderate problems, and extreme problems. The WHO-5 questionnaire assesses psychological well being using five positively worded items including, mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), and general interests (being interested in things).

Carbamazepine Versus Newer

Four randomized controlled trials reported information regarding HRQoL when newer antiepileptic drugs were compared with carbamazepine using the QOLIE-89, SEALS Inventory, and NEWQOL and EQ-5D instruments (Appendix G Table 14).^{28,67,69,163}

One trial reported information regarding HRQoL using the QOLIE-89 instrument when patients were receiving carbamazepine or tiagabine in addition to baseline phenytoin therapy.⁶⁹ This trial reported the total score and the subscales with statistically significant changes from baseline in the epilepsy domain for responders in each treatment group. For patients who received carbamazepine in addition to baseline phenytoin therapy, there were statistically significant improvements from baseline in the work-driving-social-relations ($p=0.004$) and seizure worry ($p=0.016$) subscales. For patients who received tiagabine in addition to baseline phenytoin therapy, there were statistically significant improvements from baseline in the attention-concentration ($p=0.002$), memory ($p=0.042$), language ($p=0.004$), and seizure worry ($p=0.03$) subscales.

Two trials reported information regarding HRQoL versus baseline using the SEALS Inventory when patients received lamotrigine or carbamazepine or sustained-release carbamazepine.^{67,163} The first trial reported the mean total SEALS Inventory scores recorded at baseline by treatment group. Patients in the lamotrigine group had a statistically significant improvement in SEALS scores from baseline ($p<0.001$). Patients in the carbamazepine had no significant change in SEALS scores from baseline ($p=0.394$).¹⁵⁰ The second trial reported the median difference in SEALS score from baseline to 40 weeks of treatment for the sustained-release carbamazepine and lamotrigine groups. The trial reported no statistically significant

difference in median SEALS score from baseline between the sustained-release carbamazepine and lamotrigine groups ($P=0.54$).¹⁶³

One trial reported information regarding HRQoL using the NEWQOL and EQ-5D inventories when newer antiepileptics, gabapentin, lamotrigine, oxcarbazepine, and topiramate were compared with carbamazepine.²⁸ The trial reported that there was no significant difference in anxiety, depression, adverse events profile, neurotoxicity, or global quality of life at 2 years when patients were receiving newer antiepileptics gabapentin, lamotrigine, oxcarbazepine, and topiramate versus patients receiving carbamazepine. The trial also reported that there was no significant difference in health related quality of life at 2 years when the newer antiepileptics gabapentin, lamotrigine, oxcarbazepine, and topiramate, were compared with carbamazepine using the EQ-5D.

One observational study reported information regarding HRQoL using the WHO-5 question questionnaire for patients who were not pretreated with any antiepileptic drug and who received either carbamazepine or levetiracetam.¹⁶⁴ The study reported that 31.7 percent of the patients treated with carbamazepine had an improvement in quality of life according to the WHO-5, while 4.9 percent had a decline in quality of life. In contrast, 21.9 percent of the patients treated with levetiracetam had an improvement in quality of life according to the WHO-5, while 1.4 percent had a decline in quality of life.

Phenytoin Versus Newer

Two randomized controlled trials reported information regarding HRQoL when newer antiepileptic drugs were compared with phenytoin using the QOLIE-89 scale the SEALS Inventory instruments (Appendix G Table 14).^{64,69}

One trial reported information regarding HRQoL using the QOLIE-89 instrument when patients were receiving phenytoin or tiagabine in addition to baseline carbamazepine therapy.⁶⁹ This trial reported the total score and the subscales with statistically significant changes from baseline in the epilepsy domain for responders in each treatment group. For patients who received phenytoin in addition to baseline carbamazepine therapy, there was a statistically significant improvement from baseline in the seizure worry subscale ($p=0.007$). For patients who received tiagabine in addition to baseline carbamazepine therapy, there were statistically significant improvements from baseline in the seizure worry ($p=0.03$) subscale.

One trial reported information regarding HRQoL using the SEALS Inventory when patients received lamotrigine compared with phenytoin.⁶⁴ This trial reported the mean total SEALS Inventory scores by visit and the estimated difference between treatments in the overall change from baseline. The estimated difference between treatments in the overall change from baseline was 4.0 points greater for the lamotrigine group compared with the phenytoin group ($p=0.02$).

Valproic Acid Versus Newer

Three randomized controlled trials reported information regarding HRQoL when newer antiepileptic drugs were compared with valproic acid using the QOLIE-89, NEWQOL and EQ-5D instruments (Appendix G Table 14).^{28,29,71,73}

One trial reported information regarding HRQoL using the NEWQOL, and EQ-5D inventories when the newer antiepileptic drugs lamotrigine and topiramate were compared with valproic acid.²⁸ The trial reported that there was no significant difference in anxiety, depression, adverse events profile, neurotoxicity or global quality of life at 2 years when patients were receiving the newer antiepileptic drugs lamotrigine or topiramate compared with patients receiving valproic acid using results from the NEWQOL. The trial also reported that there was

no significant difference in health related quality of life at 2 years when the newer antiepileptic drugs lamotrigine or topiramate were compared with valproic acid using results from the EQ-5D.

One trial reported information regarding HRQoL using the QOLIE-89 inventory when topiramate was compared with valproic acid.⁷³ The trial reported the mean total QOLIE-89 score at baseline and during maintenance treatment for patients receiving topiramate or valproic acid treatment. There was no significant improvement in total QOLIE-89 score when topiramate was compared with valproic acid (weighted mean difference [WMD] -2 [-1 to -3]).

One trial reported information regarding HRQoL using the QOLIE-89 inventory when lamotrigine was compared with valproic acid.⁷¹ The trial reported the likelihood that patients would have an improvement in HRQoL when lamotrigine was compared with valproic acid for health perception, energy/fatigue, social isolation, medication effects and attention/concentration subscales of the QOLIE-89 inventory. Patients treated with lamotrigine had a significant increase in the odds of improvement in the health perception (OR 4.0 [1.6 to 10.6]), energy/ fatigue (OR 2.3 [1.1 to 5.3]) and social isolation (OR 2.8 [1.1 to 7.6]) subscales compared with those treated with valproic acid.

Innovator Versus Generic Antiepileptic Drug Evaluation

None of the available controlled clinical trials or observational studies reported health-related quality of life as an endpoint.

Loss of Driver's License or Employment

Innovator Versus Generic Antiepileptic Drug Evaluation

None of the available controlled clinical trials or observational studies reported loss of driver's license or employment as an endpoint.

Seizure Outcomes

Time to First Seizure

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer. Six randomized controlled trials reported the time to first seizure for patients when newer antiepileptics were compared with carbamazepine^{52,55,63,74,77,85} and four trials were amenable for pooling.^{52,55,63,85}

One randomized controlled trial reported the time to first seizure when gabapentin was compared with carbamazepine.⁸⁵ The time to first seizure was significantly increased when gabapentin was compared with carbamazepine (HR 1.35 [1.14 to 1.60]) (Appendix J Figure 4).

Three randomized controlled trials reported the time to first seizure when lamotrigine was compared with carbamazepine and all three were amenable for pooling.^{52,55,85} The time to first seizure was nonsignificantly decreased when lamotrigine was compared with carbamazepine (HR 0.97 [0.73 to 1.28]) (Appendix J Figure 4). A high level of statistical heterogeneity was detected (I^2 : 56.5 percent) but publication bias was not detected (Egger's: $p=0.135$).

One randomized controlled trial reported the time to first seizure when oxcarbazepine was compared with carbamazepine.⁸⁵ The time to first seizure was nonsignificantly increased when oxcarbazepine was compared with carbamazepine (HR 1.06 [0.84 to 1.33]) (Appendix J Figure 4).

One randomized controlled trial reported the time to first seizure when topiramate was compared with carbamazepine.⁸⁵ The time to first seizure was nonsignificantly increased when topiramate was compared with carbamazepine (HR 1.05 [0.89 to 1.25]) (Appendix J Figure 4).

One randomized controlled trial reported the time to first seizure when vigabatrin was compared with carbamazepine.⁶³ The time to first seizure was significantly increased when vigabatrin was compared with carbamazepine (HR 1.79 [1.33 to 2.40]) (Appendix J Figure 4).

Four randomized controlled trials reported the time to first seizure for patients when gabapentin, lamotrigine, oxcarbazepine, topiramate and vigabatrin were compared with carbamazepine and all four trials were amenable for pooling.^{52,55,60,85} The time to first seizure was nonsignificantly increased when either newer agent was compared with carbamazepine (HR 1.14 [0.98 to 1.33]) (Appendix J Figure 4). A high level of statistical heterogeneity was detected (I^2 : 66.4 percent) but publication bias was not detected (Egger's: $p=0.382$).

Two trials were not included in the pooled analysis because the time to first seizure was reported for the whole patient population and not per treatment group but the significance of the inter-group comparison was given. A nonsignificant difference in the time to first seizure when topiramate was compared with carbamazepine was reported in these two trials (Appendix G Table 10).^{74,77}

Phenytoin Versus Newer. Two randomized controlled trials reported time to first seizure when newer antiepileptics were compared with phenytoin and both were amenable for pooling.^{64,90}

One randomized controlled trial reported time to first seizure when lamotrigine was compared with phenytoin.⁶⁴ The time to first seizure was nonsignificantly increased when lamotrigine was compared with phenytoin (HR 1.40 [0.80 to 2.30]) (Appendix J Figure 5). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported time to first seizure when topiramate was compared with phenytoin.⁹⁰ The time to first seizure was nonsignificantly increased when topiramate was compared with phenytoin (HR 2.00 [0.98 to 4.12]) (Appendix J Figure 5). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Two randomized controlled trials reported time to first seizure when lamotrigine or topiramate were compared with phenytoin and both were amenable for pooling.^{64,90} Time to first seizure was significantly increased when either newer agent was compared with phenytoin (HR 1.59 [1.04 to 2.43]) (Appendix J Figure 5). Since only two trials were available, tests for statistical heterogeneity and publication bias could not be performed.

Valproic Acid Versus Newer. Three randomized controlled trials reported time to first seizure when newer antiepileptics were compared with valproic acid.^{74,77,85}

One randomized controlled trial reported time to first seizure when lamotrigine was compared with valproic acid.⁸⁵ The time to first seizure was significantly decreased when lamotrigine was compared with valproic acid (HR 0.71 [0.57 to 0.88]) (Appendix J Figure 6). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported time to first seizure when topiramate was compared with valproic acid.⁸⁵ The time to first seizure was nonsignificantly decreased when topiramate was compared with valproic acid (HR 0.91 [0.73 to 1.14]) (Appendix J Figure 6). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported the time to first seizure when lamotrigine or topiramate was compared with valproic acid.⁸⁵ The time to first seizure was nonsignificantly

decreased when either newer agent was compared with valproic acid (HR 0.8 [0.63 to 1.02]) (Appendix J Figure 6). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Two trials were not included in the pooled analysis because the time to first seizure was reported for the whole patient population and not per treatment group but the significance of the inter-group comparison was given. A nonsignificant difference in the time to first seizure was reported when topiramate was compared with valproic acid in these two trials.^{74,77}

Innovator Versus Generic Antiepileptic Drug Evaluation

None of the available controlled clinical trials or observational studies time to first seizure as an endpoint.

Seizure Occurrence/Breakthrough

Older Versus Newer Antiepileptic Drug Evaluation

None of the available controlled clinical trials or observational studies seizure occurrence or breakthrough as an endpoint.

Innovator Versus Generic Antiepileptic Drug Evaluation

Seven randomized controlled trials reported the occurrence of seizures while patients were receiving innovator versus their associated generic antiepileptic medications^{109,110,112,114,115,120,123} (Appendix J Figure 7).

Five trials reported data on the occurrence of seizures while patients were receiving innovator versus one or more generic versions of carbamazepine and were all suitable for meta-analysis.^{109,110,112,114,115} Only one of the trials¹¹² utilized a discernable “A” rated generic carbamazepine product. The risk of experiencing a seizure is nonsignificantly decreased by 14 percent when generic carbamazepine was used versus innovator carbamazepine (RR 0.86 [0.55 to 1.32]). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger’s: $p=0.178$) was detected.

One trial reported data on the occurrence of seizures while patients were receiving an innovator versus three generic versions of phenytoin¹²⁰ but did not use discernable Food and Drug Administration “A” rated generics. The risk of experiencing a seizure is nonsignificantly decreased by 60 percent when generic phenytoin is used versus innovator phenytoin (RR 0.40 [0.14 to 1.12]).

One trial reported data on the occurrence of seizures while patients were receiving innovator versus a generic version of valproic acid¹²³ but did not use discernable FDA “A” rated generics. The risk of experiencing a seizure is nonsignificantly increased by 5 percent when generic valproic acid is used versus innovator valproic acid (RR 1.05 [0.65 to 1.70]).

Seven trials reported data on the occurrence of seizures for any innovator versus generic versions of antiepileptic medication and were all suitable for meta-analysis.^{109,110,112,114,115,120,123} The risk of experiencing a seizure is nonsignificantly decreased by 13 percent when generic antiepileptic medications are used versus their associated innovator products (RR 0.87 [0.64 to 1.18]). No significant statistical heterogeneity was detected (I^2 : 0 percent), but publication bias was detected (Egger’s: $p=0.0004$).

The BCS Class I analysis was comprised of the single trial evaluating innovator versus generic versions of valproic acid the results were the same as the aforementioned analysis (RR 1.05 [0.65, 1.70]).

The BCS Class II analysis was comprised of the six trials comparing innovator and generic versions of carbamazepine and phenytoin.^{109,110,112,114,115,120} The risk of experiencing a seizure is nonsignificantly decreased by 24 percent when generic BCS Class II antiepileptic medications were used versus their associated innovator antiepileptic medications (RR 0.76 [0.51 to 1.14]). No significant statistical heterogeneity was detected (I^2 : 0 percent), but publication bias was detected (Egger's: $p=0.001$).

One randomized controlled trial reported data on the occurrence of seizures for an innovator versus a discernable FDA "A" rated generic product, in this case carbamazepine.¹¹² The risk of experiencing a seizure is nonsignificantly decreased by 50 percent when "A" rated generic carbamazepine is used versus innovator carbamazepine (RR 0.50 [0.11 to 2.09]).

Seizure Frequency

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer. One randomized controlled trial reported change from baseline in seizure frequency when oxcarbazepine was compared with carbamazepine.⁴⁹ Seizure frequency was nonsignificantly decreased from baseline when oxcarbazepine was compared with carbamazepine (MD -3 [-6.32 to 0.32]).

One observational study reported the mean percentage change from baseline in seizure frequency when the newer agent topiramate was compared with carbamazepine.⁸³ The study reported that there was no difference between the mean percentage change from baseline in seizure frequency during the maintenance period, but did not provide a measure of deviation.

Phenytoin Versus Newer. Two randomized controlled trials reported change from baseline in seizure frequency when the newer agent oxcarbazepine was compared with phenytoin.^{57,59} The weighted mean difference for the change in seizure frequency could not be calculated because neither trial reported a measure of deviation for the mean seizure frequency at baseline and both trials reported a different number of patients at baseline and during the maintenance period.

Valproic Acid Versus Newer. One randomized controlled trial reported the change from baseline in seizure frequency when the newer agent oxcarbazepine was compared with valproic acid.⁵⁸ The weighted mean difference for the change in seizure frequency could not be calculated because the trial did not report a measure of deviation for the mean seizure frequency at baseline and the number of patients at baseline was different than the number of patients during the maintenance period.

Innovator Versus Generic Antiepileptic Drug Evaluation

Three randomized controlled trials reported the occurrence of seizure frequency while patients were receiving innovator and their associated generic antiepileptic medications.^{109,112,123}

Two trials reported data on seizure frequency in patients receiving innovator carbamazepine versus a generic version and were both amenable to pooling.^{109,112} Only one of the trials utilized a discernable Food and Drug Administration (FDA) "A" rated generic carbamazepine product.¹¹² The seizure frequency is nonsignificantly higher in the generic carbamazepine groups versus innovator carbamazepine group (WMD 0.03 [-0.08 to 0.14] seizures over the evaluative period).

One trial reported data on seizure frequency in patients receiving innovator valproic acid versus a generic version but did not use a discernable FDA "A" rated generic.¹²³ The seizure frequency is nonsignificantly lower in the generic carbamazepine versus innovator carbamazepine group (MD -1.06 [-16.05 to 13.93] seizures over the evaluative period).

Three trials reported data on seizure frequency in patients receiving any innovator versus a generic version of antiepileptic medication and were all suitable for meta-analysis.^{109,112,123} (Appendix J Figure 8) The seizure frequency is nonsignificantly higher in the generic antiepileptic medication group versus the innovator group (standardized mean difference [SMD] 0.03 [-0.08 to 0.14] seizures over the evaluative period). No statistical heterogeneity was detected (I^2 : 0 percent), and publication bias could not be evaluated.

The Biopharmaceutics Classification System (BCS) Class I analysis is the same as that reported for the valproic acid analysis (WMD -1.06 [-16.05 to 13.93] seizures over the evaluative period) while the BCS Class II analysis is the same as the carbamazepine analysis (WMD 0.03 [-0.08 to 0.14] seizures over the evaluative period).

One randomized controlled trial reported on the comparison of an innovator to a discernable FDA “A” rated generic product, in this case carbamazepine.¹¹² The seizure frequency is nonsignificantly higher in the generic versus innovator carbamazepine group (MD 0.03 [-0.08 to 0.14] seizures over the evaluative period).

Total Withdrawals

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Twenty-one studies (16 randomized controlled trials and 5 observational studies) reported withdrawals for any reason while patients were receiving a newer antiepileptic medication compared with carbamazepine.^{47,52,53,55,60,62,63,70,74,76-80,83,85,98,99,101,103,104}

Sixteen randomized controlled trials reported data on withdrawals for any reason when newer antiepileptics were compared versus carbamazepine^{47,52,53,55,60,62,63,70,74,76-80,83,85} and 14 were all amenable to pooling.^{52,53,55,60,62,63,70,74,76,78-80,83,85}

Three randomized controlled trials reported data on withdrawals for any reason when gabapentin was compared versus carbamazepine and all three were amenable for pooling.^{60,78,85} The risk of withdrawal was nonsignificantly decreased by 1 percent when gabapentin was compared versus carbamazepine (RR 0.99 [0.83 to 1.17]) (Appendix J Figure 9). A high level of statistical heterogeneity was detected (I^2 : 64.1 percent), but publication bias was not detected (Egger’s: $p=0.739$).

Eight randomized controlled trials reported data on withdrawals for any reason when lamotrigine was compared versus carbamazepine and all eight were amenable for pooling.^{52,55,62,70,76,78,80,85} The risk of withdrawal was significantly decreased by 26 percent when lamotrigine was used versus carbamazepine (RR 0.74 [0.64 to 0.86]) (Appendix J Figure 9). Given the risk difference (RD) (RD -0.101 [-0.158 to -0.0453]), for every 10 patients treated, 1 less patient would withdraw from treatment with lamotrigine than with carbamazepine. Moderate statistical heterogeneity was detected (I^2 : 48.5 percent), but publication bias was not detected (Egger’s: $p=0.309$). Seven of eight trials had the same direction of effect but differed as to the magnitude of effect.

One randomized controlled trial reported data on withdrawal for any reason when oxcarbazepine was compared versus carbamazepine.⁸⁵ The risk of withdrawal was nonsignificantly decreased by 7 percent when oxcarbazepine was used versus carbamazepine (RR 0.93 [0.80 to 1.07]) (Appendix J Figure 9).

Three randomized controlled trials reported data on withdrawals for any reason when topiramate was compared versus carbamazepine and were amenable for pooling.^{74,83,85} The risk

of withdrawal was nonsignificantly increased by 6 percent when topiramate was used versus carbamazepine (RR 1.06 [0.96 to 1.17]) (Appendix J Figure 9). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.641$).

Three randomized controlled trials reported data on withdrawals for any reason when vigabatrin was compared versus carbamazepine and were amenable for pooling.^{53,63,79} The risk of withdrawal was nonsignificantly increased by 3 percent when vigabatrin was used versus carbamazepine (RR 1.03 [0.79 to 1.36]) (Appendix J Figure 9). A low level of statistical heterogeneity was detected (I^2 : 17.5 percent).

In the pooled analysis of 14 randomized trials reporting data on withdrawals for any reason when either lamotrigine, oxcarbazepine, topiramate, or vigabatrin were compared with carbamazepine.^{52,53,55,60,62,63,70,74,76,78-80,83,85} The risk of withdrawal was nonsignificantly decreased by 10 percent when all newer antiepileptics were used versus carbamazepine (RR 0.90 [0.82 to 1.00]) (Appendix J Figure 9). A high level of statistical heterogeneity was detected (I^2 : 55.2 percent), but publication bias was not detected (Egger's: $p=0.689$).

Two randomized controlled trials reported data on withdrawals for any reason when the newer antiepileptics gabapentin, lamotrigine, and topiramate were compared with carbamazepine, but these trials were not included in the pooled analysis because withdrawals were reported for the whole patient population and not per treatment group (Appendix G Table 12).^{47,77}

Two observational studies reported withdrawals for any reason when lamotrigine was compared versus carbamazepine.^{99,101} The risk of withdrawal was significantly decreased by 34 percent when lamotrigine was compared versus carbamazepine (RR 0.66 [0.49 to 0.89]) (Appendix J Figure 10). Given the RD (RD -0.11 [-0.33, 0.12]), for every 10 patients treated with lamotrigine, 1 less patient would withdraw compared with those treated with carbamazepine. Since only two studies were available, tests for statistical heterogeneity and publication bias could not be performed. However, the pooled result was driven almost entirely by one single study, and the effect of the direction differed between the two studies.

One observational study reported withdrawal for any reason when levetiracetam was compared versus carbamazepine.¹⁰³ The risk of withdrawal was nonsignificantly increased by 67 percent when levetiracetam was compared versus carbamazepine (RR 1.67 [0.73 to 4.35]) (Appendix J Figure 10).

One observational study reported withdrawal for any reason when topiramate was compared versus carbamazepine.¹⁰⁴ The risk of withdrawal was nonsignificantly decreased by 11 percent when topiramate was compared versus carbamazepine (RR 0.89 [0.74 to 1.05]) (Appendix J Figure 10).

One observational study reported withdrawal for any reason when vigabatrin was compared versus carbamazepine.⁹⁸ The risk of withdrawal was significantly increased by 20.5-fold when vigabatrin was compared versus carbamazepine (RR 20.52 [2.22 to 202.53]) (Appendix J Figure 10). Given the RD, (RD 0.24 [0.10 to 0.38]), for every five patients treated with vigabatrin, one additional patient would withdraw compared with those treated with carbamazepine.

Five observational studies reported withdrawals for any reason when lamotrigine, levetiracetam, or vigabatrin was compared with carbamazepine.^{98,99,101,103,104} The risk of withdrawal was nonsignificantly decreased by 7 percent when either newer agent was compared versus carbamazepine (RR 0.93 [0.61 to 1.40]) (Appendix J Figure 10). A high level of statistical heterogeneity was detected (I^2 : 60.9 percent), but no significant publication bias was detected (Egger's: $p=0.307$).

Two randomized controlled trials reported withdrawals for any reason when newer antiepileptics were compared with controlled or sustained release carbamazepine and both were amenable for pooling.^{81,86}

One randomized controlled trial reported withdrawals for any reason when lamotrigine was compared with sustained release carbamazepine.⁸⁶ The risk of withdrawal was nonsignificantly decreased by 18 percent when lamotrigine was compared versus sustained release carbamazepine (RR 0.82 [0.52 to 1.27]) (Appendix J Figure 11).

One randomized controlled trial reported withdrawals for any reason when levetiracetam was compared with controlled release carbamazepine.⁸¹ There was no significant difference in the risk of withdrawal when levetiracetam was compared versus controlled release carbamazepine in patients (RR 1.00 [0.79 to 1.26]) (Appendix J Figure 11).

Two randomized controlled trials reported withdrawals for any reason when lamotrigine or levetiracetam were compared with controlled or sustained release carbamazepine and both were amenable for pooling.^{81,86} The risk of withdrawal was nonsignificantly decreased by 4 percent when either newer agent was compared with controlled or sustained release carbamazepine (RR 0.96 [0.78 to 1.18]) (Appendix J Figure 11).

Phenytoin Versus Newer

Three randomized controlled trials reported withdrawals for any reason while patients were receiving a newer antiepileptic medication compared with phenytoin and all were amenable for pooling.^{57,59,64}

One randomized controlled trial reported data on withdrawals for any reason when lamotrigine was compared with phenytoin.⁶⁴ The risk of withdrawal was nonsignificantly decreased by 1 percent when lamotrigine was compared versus phenytoin (RR 0.99 [0.75 to 1.31]) (Appendix J Figure 12).

Two randomized controlled trials reported data on withdrawals for any reason when oxcarbazepine was compared with phenytoin and were amenable for pooling.^{57,59} The risk of withdrawal was nonsignificantly decreased by 15 percent when oxcarbazepine was compared versus phenytoin (RR 0.85 [0.66 to 1.09]) (Appendix J Figure 12).

In the pooled analysis of three randomized trials reporting data on withdrawals for any reason either lamotrigine or oxcarbazepine were compared versus phenytoin.^{57,59} The risk of withdrawal was nonsignificantly decreased by 9 percent when the newer agents were compared versus phenytoin (RR 0.91 [0.76 to 1.09]) (Appendix J Figure 12). No significant statistical heterogeneity was detected (I^2 : 0 percent), however tests for publication bias could not be performed.

Valproic Acid Versus Newer

Nineteen studies (17 randomized controlled trials and 2 observational studies) reported withdrawals for any reason while patients were receiving a newer antiepileptic medication compared with valproic acid.^{50,58,61,65,68,72-77,80,85,87-89,94,101}

Seventeen randomized controlled trials reported data on withdrawals for any reason when newer antiepileptics were compared versus valproic acid^{50,58,61,65,68,72-77,80,85,87-89,94} and 16 were amenable for pooling.^{50,58,61,65,68,72-76,80,85,87-89,94}

One randomized controlled trial reported data on withdrawals for any reason when felbamate was compared versus valproic acid.⁵⁰ There was no significant difference in the risk of overall withdrawal when felbamate was compared versus valproic acid (RR 1.00 [0.11 to 9.24])

(Appendix J Figure 13). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Ten randomized controlled trials reported data on withdrawals for any reason when lamotrigine was compared versus valproic acid and were amenable for pooling.^{68,72,75,76,80,85,87-89,94} The risk of withdrawal was significantly decreased by 12 percent when lamotrigine was compared versus valproic acid (RR 0.88 [0.78 to 0.99]) (Appendix J Figure 13). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.953$).

One randomized controlled trial reported data on withdrawals for any reason when oxcarbazepine was compared versus valproic acid.⁵⁸ The risk of withdrawal was nonsignificantly increased by 20 percent when oxcarbazepine was compared versus valproic acid (RR 1.20 [0.87 to 1.66]) (Appendix J Figure 13). Since only one trial was available, tests for statistical heterogeneity or publication bias could not be performed.

Four randomized controlled trials reported data on withdrawals for any reason when topiramate was compared versus valproic acid and were amenable for pooling.^{65,73,74,85} The risk of withdrawal was nonsignificantly decreased by 2 percent when topiramate was compared versus valproic acid (RR 0.98 [0.80 to 1.21]) (Appendix J Figure 13). A moderate level of statistical heterogeneity was detected (I^2 : 38.5 percent), but publication bias was not detected (Egger's: $p=0.922$).

One randomized controlled trial reported data on withdrawals for any reason when vigabatrin was compared versus valproic acid.⁶¹ The risk of withdrawal was nonsignificantly decreased by 32 percent when vigabatrin was compared versus valproic acid (RR 0.68 [0.42 to 1.08]) (Appendix J Figure 13). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

In the pooled analysis of 16 randomized controlled trials reporting data on withdrawals for any reason when felbamate, lamotrigine, oxcarbazepine, topiramate or vigabatrin was compared versus valproic acid.^{50,58,61,65,68,72-76,80,85,87-89,94} The risk of withdrawal was nonsignificantly decreased by 4 percent when the newer agents were compared versus valproic acid (RR 0.96 [0.85 to 1.09]) (Appendix J Figure 13). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's: $p=0.959$) was detected.

One randomized controlled trial reported data on withdrawals for any reason when topiramate was compared with valproic acid, but this trial was not included in the pooled analysis because withdrawals were reported for the whole patient population and not per treatment group (Appendix G Table 12).⁷⁷

Two observational studies reported withdrawals for any reason while patients were receiving newer antiepileptic medications compared with valproic acid and both were amenable for pooling.^{99,101}

Two observational studies reported withdrawals for any reason when lamotrigine was compared with valproic acid and were amenable for pooling.^{99,101} The risk of withdrawal was nonsignificantly decreased by 9 percent when lamotrigine were compared versus valproic acid (RR 0.91 [0.63 to 1.30]) (Appendix J Figure 14). Since only two studies were available, tests for statistical heterogeneity and publication bias could not be performed.

Ethosuximide Versus Newer

One randomized controlled trial reported withdrawals for any reason while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ The risk of overall withdrawal was nonsignificantly decreased by 5 percent when lamotrigine was compared versus ethosuximide

(RR 0.95 [0.53 to 1.71]). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Innovator Versus Generic Antiepileptic Drug Evaluation

Eleven studies (nine randomized controlled trials, one prospective nonrandomized trial, and one observational study) reported withdrawals for any reason while patients were receiving innovator and their associated generic antiepileptic medications.^{108-113,115,117,120,121,130}

Seven randomized controlled trials reported data on withdrawals for any reason for innovator versus one or more generic versions of carbamazepine^{108-113,115} and were all amenable to pooling. Only one trial¹¹² used discernable FDA “A” rated generics. The risk of withdrawals for any reason is nonsignificantly decreased by 15 percent when generic carbamazepine was used versus innovator carbamazepine (RR 0.85 [0.30 to 2.40]) (Appendix J Figure 15). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger’s: $p=0.42$). One observational study compared innovator carbamazepine to a generic version.¹³⁰ The risk of withdrawals for any reason is significantly increased by 17 percent when generic carbamazepine was used versus innovator carbamazepine (RR 1.17 [1.04 to 1.31]) (Appendix J Figure 15). Tests for statistical heterogeneity or publication bias could not be calculated.

Three controlled clinical trials (two randomized controlled trials,^{120,121} and one prospective nonrandomized trial)¹¹⁷ evaluated innovator phenytoin versus generic phenytoin and were suitable for meta-analysis. None of the trials used discernable FDA “A” rated generics. The risk of withdrawals for any reason was equivalent when generic phenytoin was used versus innovator phenytoin (RR 1.00 [0.24 to 4.14]) (Appendix J Figure 15). No significant statistical heterogeneity was detected (I^2 : 0 percent), but publication bias was detected (Egger’s: $p=0.04$).

Ten trials (nine randomized controlled trials,^{108-113,115,120,121} and one prospective nonrandomized trial)¹¹⁷ reported data on withdrawals for any reason for any innovator versus a generic version of antiepileptic medication and were all suitable for meta-analysis. The risk of withdrawals for any reason is nonsignificantly decreased by 10 percent when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications (RR 0.90 [0.39, 2.08]) (Appendix J Figure 15). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger’s: $p=0.45$). Analysis on any innovator versus generic antiepileptic medication for observational trials is the same as that reported for the carbamazepine observational trial analysis (RR 1.17 [1.04 to 1.31]) (Appendix J Figure 15).

None of the available trials or studies evaluated BCS Class I antiepileptic medications, so analysis was not possible. The BCS Class II analysis for controlled trials is the same as the “any antiepileptic medications” controlled trial analysis (RR 0.90 [0.39 to 2.08]) and the BCS Class II analysis for observational trials is the same as carbamazepine observational trial analysis (RR 1.17 [1.04 to 1.31]) (Appendix J Figure 15).

One randomized controlled trial reported on the comparison of an innovator to a discernable FDA “A” rated generic product, in this case carbamazepine.¹¹² The risk of withdrawals for any reason is nonsignificantly decreased by 20 percent when “A” rated generic carbamazepine was used versus innovator carbamazepine (RR 0.80 [0.12 to 5.16]) (Appendix J Figure 15). Tests for statistical heterogeneity or publication bias could not be calculated.

Withdrawals Due to Lack of Efficacy

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Sixteen studies (11 randomized controlled trials and 5 observational studies) reported withdrawals due to lack of efficacy while patients were receiving a newer antiepileptic medication compared with carbamazepine.^{49,52,53,55,62,63,74,77,78,80,85,98,99,101,104,105}

Eleven randomized controlled trials reported data on withdrawals due to lack of efficacy when newer antiepileptics were compared versus valproic acid.^{49,52,53,55,62,63,74,77,78,80,85} and 10 were amenable for pooling.^{49,52,53,55,62,63,74,78,80,85}

Two randomized controlled trials reported data on withdrawals due to lack of efficacy when gabapentin was compared versus carbamazepine and were amenable for pooling.^{78,85} The risk of withdrawal was significantly increased by 2.3-fold when gabapentin was compared versus carbamazepine (RR 2.25 [1.64 to 3.08]) (Appendix J Figure 16). Given the RD (RD 0.08 [-0.09 to 0.25]), for every 13 patients treated with gabapentin, 1 additional patient would withdraw due to lack of effective treatment compared with those treated with carbamazepine. Since only two trials were available, tests for statistical heterogeneity and publication bias could not be performed.

Six randomized controlled trials reported data on withdrawals due to lack of efficacy when lamotrigine was compared versus carbamazepine and were amenable for pooling.^{52,55,62,78,80,85} The risk of withdrawal due to lack of efficacy was significantly increased by 43 percent when lamotrigine was compared versus carbamazepine (RR 1.43 [1.03 to 1.99]) (Appendix J Figure 16). Given the RD, (RD 0.023 [0.0025 to 0.044]), for every 44 patients treated with lamotrigine, 1 additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.759$).

Two randomized controlled trials reported data on withdrawals due to lack of efficacy when oxcarbazepine was compared versus carbamazepine and were amenable for pooling.^{49,85} The risk of withdrawal due to lack of effective treatment was nonsignificantly increased by 1 percent when oxcarbazepine was compared versus carbamazepine (RR 1.01 [0.64 to 1.59]) (Appendix J Figure 16). Since only two trials were available, tests for statistical heterogeneity and publication bias could not be performed.

Two randomized controlled trials reported data on withdrawals due to lack of efficacy when topiramate was compared versus carbamazepine and were amenable for pooling.^{74,85} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 28 percent when topiramate was compared versus carbamazepine (RR 1.28 [0.93 to 1.78]) (Appendix J Figure 16). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Two randomized controlled trials reported data on withdrawals due to lack of efficacy when vigabatrin was compared versus carbamazepine and were amenable for pooling.^{53,63} The risk of withdrawal due to lack of efficacy was significantly increased by 3.0-fold when vigabatrin was compared versus carbamazepine (RR 2.98 [1.58 to 5.61]) (Appendix J Figure 16). Given the RD (RD 0.14 [0.02 to 0.26]), for every eight patients treated with vigabatrin, one additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine. Since only two trials were available, tests for statistical heterogeneity and publication bias could not be performed.

Ten randomized controlled trials reported data on withdrawals due to lack of efficacy when gabapentin, lamotrigine, oxcarbazepine, topiramate, or vigabatrin was compared versus carbamazepine and were amenable for pooling.^{49,52,53,55,62,63,74,78,80,85} The risk of withdrawal due to lack of efficacy was significantly increased by 59 percent when newer agents were compared versus carbamazepine (RR 1.59 [1.25 to 2.02]) (Appendix J Figure 16). Given the RD (RD 0.02 [0.003 to 0.04]), for every 50 patients treated with either newer agent, 1 additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.747$).

One randomized controlled trial reported data on withdrawals due to lack of efficacy when topiramate was compared versus carbamazepine.⁷⁷ The data from this trial was not included in the pooled analysis because withdrawals due to lack of efficacy were reported for the whole population and not per treatment group (Appendix J Figure 16).

Five observational studies reported withdrawals due to lack of efficacy while patients were receiving a newer antiepileptic medications compared with carbamazepine and all five were amenable for pooling.^{98,99,101,104,105}

Two observational studies reported withdrawals due to lack of efficacy when lamotrigine was compared versus carbamazepine and were amenable for pooling.^{99,101} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 3 percent when lamotrigine was compared versus carbamazepine (RR 1.03 [0.66 to 1.60]) (Appendix J Figure 17). Since only two trials were available, tests for statistical heterogeneity or publication bias could not be performed.

Two observational studies reported withdrawal due to lack of efficacy when topiramate was compared versus carbamazepine and were amenable for pooling.^{104,105} The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 19 percent when topiramate was compared versus carbamazepine (RR 0.81 [0.45 to 1.45]) (Appendix J Figure 17). Since only two trials were available, tests for statistical heterogeneity or publication bias could not be performed.

One observational study reported withdrawal due to lack of efficacy when vigabatrin was compared versus carbamazepine.⁹⁸ The risk of withdrawal due to lack of efficacy was significantly increased by 18.4-fold when vigabatrin was compared versus carbamazepine (RR 18.36 [1.97 to 182.09]) (Appendix J Figure 17). Given the RD (RD 0.21 [0.08 to 0.35]), for every five patients treated with vigabatrin, one additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine. Since only one trial was available, tests for statistical heterogeneity or publication bias could not be performed.

Five observational studies reported withdrawals due to lack of efficacy when lamotrigine, topiramate, or vigabatrin was compared with carbamazepine.^{98,99,101,104,105} The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 3 percent when newer agents were compared versus carbamazepine (RR 0.97 [0.60 to 1.56]) (Appendix J Figure 17). A lower level of statistical heterogeneity was detected (I^2 : 35.3 percent), but publication bias was not detected (Egger's: $p=0.522$).

One randomized controlled trial reported withdrawals due to lack of efficacy when levetiracetam was compared with controlled release carbamazepine.⁸¹ The risk of withdrawal due to lack of efficacy was significantly increased by 2.4-fold when levetiracetam was compared versus controlled release carbamazepine (RR 2.43 [1.32 to 4.52]). Given the RD, (RD 0.064 [0.021 to 0.11]), for every 16 patients treated with levetiracetam, 1 additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine. Since only

one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Phenytoin Versus Newer

Three randomized controlled trials reported withdrawals due to lack of efficacy while patients were receiving newer antiepileptic medications versus phenytoin and all three were amenable for pooling.^{57,59,64}

One randomized controlled trial reported data on withdrawal due to lack of efficacy when lamotrigine was compared versus phenytoin.⁶⁴ The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 45 percent when lamotrigine was compared versus phenytoin (RR 0.55 [0.07 to 4.15]) (Appendix J Figure 18). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Two randomized controlled trials reported data on withdrawal due to lack of efficacy when oxcarbazepine was compared versus phenytoin and were amenable for pooling.^{57,59} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 24 percent when oxcarbazepine was compared versus phenytoin (RR 1.24 [0.34 to 4.55]) (Appendix J Figure 18). Since only two trials were available, tests for statistical heterogeneity and publication bias could not be performed.

In the pooled analysis of three randomized controlled trials reporting data on withdrawals due to lack of efficacy, either lamotrigine or oxcarbazepine were compared versus phenytoin.^{57,59,64} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 3 percent when either newer agent was compared versus phenytoin (RR 1.03 [0.33 to 3.23]) (Appendix J Figure 18). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Valproic Acid Versus Newer

Fifteen studies (12 randomized controlled trials and 3 observational studies) reported withdrawals due to lack of efficacy while patients were receiving a newer antiepileptic medication compared with valproic acid.^{58,61,65,74,75,77,80,84,85,87,88,94,99,101,105}

Twelve randomized controlled trials reported data on withdrawals due lack of efficacy when newer antiepileptics were compared versus valproic acid^{58,61,65,74,75,77,80,84,85,87,88,94} and 11 were amenable for pooling.^{58,61,65,74,75,80,84,85,87,88,94}

Six randomized controlled trials reported data on withdrawals due to lack of efficacy when lamotrigine was compared versus valproic acid and were amenable for pooling.^{75,80,85,87,88,94} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 53 percent when lamotrigine was compared versus valproic acid (RR 1.53 [0.74 to 3.17]) (Appendix J Figure 19). A higher level of statistical heterogeneity was detected (I^2 : 52.2 percent), but publication bias was not detected (Egger's: $p=0.724$).

One randomized controlled trial reported data on withdrawals due to lack of efficacy when oxcarbazepine was compared versus valproic acid.⁵⁸ The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 5 percent when oxcarbazepine was compared versus valproic acid (RR 0.95 [0.33 to 2.71]) (Appendix J Figure 19). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Four randomized controlled trials reported data on withdrawals due to lack of efficacy when topiramate was compared versus valproic acid and were amenable for pooling.^{65,74,84,85} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 12 percent when

topiramate was compared versus valproic acid (RR 1.12 [0.74 to 1.70]) (Appendix J Figure 19). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.487$).

One randomized controlled trial reported data on withdrawals due to lack of efficacy when vigabatrin was compared versus valproic acid.⁶¹ The risk of withdrawal due lack of efficacy was nonsignificantly decreased by 43 percent when vigabatrin was compared versus valproic acid (RR 0.57 [0.29 to 1.13]) (Appendix J Figure 19). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Eleven randomized controlled trials reported data on withdrawals due to lack of efficacy when either lamotrigine, oxcarbazepine, topiramate or vigabatrin were compared versus valproic acid and were amenable for pooling.^{28,58,61,65,74,75,80,84,87,88,94} The risk of withdrawal was nonsignificantly increased by 10 percent when all newer agents were compared versus valproic acid (RR 1.10 [0.77 to 1.56]) (Appendix J Figure 19). A lower level of statistical heterogeneity was detected (I^2 : 26.6 percent), but publication bias was not detected (Egger's: $p=0.982$).

One randomized controlled trial reported data on withdrawals due to lack of efficacy when topiramate was compared versus valproic acid, but this trial was not included in the pooled analysis because withdrawals were reported for the whole patient population and not per treatment group (Appendix G Table 10).⁷⁷

Three observational studies reported withdrawals due to lack of efficacy when lamotrigine or topiramate were compared versus valproic acid and all three were amenable for pooling.^{99,101,105}

Two observational studies reported data on withdrawals due to lack of efficacy when lamotrigine was compared versus valproic acid and were amenable for pooling.^{99,101} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 1 percent when lamotrigine was compared versus valproic acid (RR 1.01 [0.61 to 1.66]) (Appendix J Figure 20). Since only two trials were available, tests for statistical heterogeneity and publication bias could not be performed.

One observational study reported data on withdrawals due to lack of efficacy when topiramate was compared versus valproic acid.¹⁰⁵ The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 2 percent when topiramate was compared versus valproic acid (RR 1.02 [0.65 to 1.60]) (Appendix J Figure 20). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Three observational studies reported data on withdrawals due to lack of efficacy when either lamotrigine or topiramate were compared versus valproic acid and were amenable for pooling.^{99,101,105} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 2 percent when newer agents were compared versus valproic acid (RR 1.02 [0.73 to 1.42]) (Appendix J Figure 20). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Innovator Versus Generic Antiepileptic Drug Evaluation

Ten trials (nine randomized controlled trials^{108-113,115,120,121} and one prospective nonrandomized trial)¹¹⁷ reported withdrawals due to lack of efficacy while patients were receiving innovator and their associated generic antiepileptic medications.

Seven randomized controlled trials reported data on withdrawals due to lack of efficacy for innovator carbamazepine versus one or more generic versions^{108-113,115} and they were all suitable for meta-analysis. Only one of the trials utilized a discernable FDA "A" rated generic carbamazepine product.¹¹² The risk of withdrawals due to ineffective treatment is nonsignificantly decreased by 13 percent when generic carbamazepine was used versus

innovator carbamazepine (RR 0.87 [0.29 to 2.63]) (Appendix J Figure 21). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.99$).

Three trials (two randomized controlled trials^{120,121} and one prospective nonrandomized trial¹¹⁷) reported withdrawals due to lack of efficacy while patients were receiving innovator phenytoin versus three generic versions and were all suitable for meta-analysis but the trials did not use discernable FDA "A" rated generics. The risk of withdrawals due to ineffective treatment is nonsignificantly increased by 45 percent when generic phenytoin was used versus innovator phenytoin (RR 1.45 [0.28 to 7.53]) (Appendix J Figure 21). No significant statistical heterogeneity was detected (I^2 : 0 percent), but publication bias was detected (Egger's: $p=0.03$).

Ten trials (nine randomized controlled trials^{108-113,115,120,121} and one prospective nonrandomized trial¹¹⁷) reported withdrawals due to lack of efficacy for any innovator versus generic version of antiepileptic medication and were all suitable for meta-analysis. The risk of withdrawals due to ineffective treatment is nonsignificantly increased by 2 percent when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications (RR 1.02 [0.41 to 2.54]) (Appendix J Figure 21). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.434$).

None of the available drugs were in BCS Class I, so analysis was not possible. The BCS Class II analysis is the same as the analysis for any antiepileptic medications (RR 1.02 [0.41 to 2.54]) (Appendix J Figure 21).

One randomized controlled trial reported on the comparison of an innovator to a discernable FDA "A" rated generic product, in this case carbamazepine.¹¹² The risk of withdrawals due to ineffective treatment is nonsignificantly decreased by 25 percent when "A" rated carbamazepine generic was used versus innovator carbamazepine (RR 0.75 [0.15 to 3.73]) (Appendix J Figure 21). Tests for statistical heterogeneity or publication bias could not be calculated.

Seizure Remission

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Two randomized controlled trials reported the number of patients who achieved 12-month seizure remission when newer antiepileptics were compared with carbamazepine.^{28,63}

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when gabapentin was compared with carbamazepine.²⁸ The risk of achieving 12-month seizure remission was significantly decreased by 15 percent when gabapentin was compared with carbamazepine (RR 0.85 [0.76 to 0.95]) (Appendix J Figure 22). Given the RD (RD -0.10 [-0.17 to -0.03]), for every 10 patients treated, 1 less patient would achieve 12-month seizure remission when treated with gabapentin versus carbamazepine.

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when lamotrigine was compared with carbamazepine.²⁸ The risk of achieving 12-month seizure remission was nonsignificantly decreased by 4 percent when lamotrigine was compared with carbamazepine (RR 0.96 [0.87 to 1.06]) (Appendix J Figure 22).

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when oxcarbazepine was compared with carbamazepine.²⁸ The risk of achieving 12-month seizure remission was significantly decreased by 52 percent when oxcarbazepine was compared with carbamazepine (RR 0.48 [0.39 to 0.59]) (Appendix J Figure 22). Given the RD ([RD -0.36 [-0.44 to -0.28]), for every three patients treated, one less patient

would achieve 12-month seizure remission when treated with oxcarbazepine versus carbamazepine.

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when topiramate was compared with carbamazepine.²⁸ The risk of achieving 12-month seizure remission was significantly decreased by 10 percent when topiramate was compared with carbamazepine (RR 0.90 [0.81 to 0.99]) (Appendix J Figure 22). Given the RD (RD -0.073 [-0.142 to -0.004]), for every 14 patients treated, 1 less patient would achieve 12 month seizure remission when treated with topiramate versus carbamazepine.

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when vigabatrin was compared with carbamazepine.⁶³ The risk of achieving 12-month seizure remission was nonsignificantly decreased by 5 percent when vigabatrin was compared with carbamazepine (RR 0.95 [0.79 to 1.14]) (Appendix J Figure 22).

Two randomized controlled trials reported the number of patients who achieved 12-month seizure remission when gabapentin, lamotrigine, oxcarbazepine, topiramate or vigabatrin was compared with carbamazepine and were amenable for pooling.^{28,63} The risk of achieving 12-month seizure remission was significantly decreased by 19 percent when newer agents were compared with carbamazepine (RR 0.81 [0.67 to 0.99]) (Appendix J Figure 22). Given the RD (RD -0.12 [-0.23 to -0.001]), for every nine patients treated, one less patient would achieve 12-month seizure remission when treated with either newer agent versus carbamazepine. A high level of statistical heterogeneity was detected (I^2 : 84.7 percent), but publication bias was not detected (Egger's: $p=0.069$).

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when newer antiepileptics were compared with carbamazepine.²⁸ This randomized controlled trial reported the number of patients who achieved 24-month seizure remission when gabapentin was compared with carbamazepine.²⁸ The risk of achieving 24-month seizure remission was significantly decreased by 21 percent when gabapentin was compared with carbamazepine (RR 0.79 [0.66 to 0.94]) (Appendix J Figure 23). Given the RD (RD -0.10 [-0.17 to -0.02]), for every 10 patients treated, 1 less patient would achieve 12-month seizure remission when treated with gabapentin versus carbamazepine. Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when lamotrigine was compared with carbamazepine.²⁸ The risk of achieving 24-month seizure remission was nonsignificantly decreased by 8 percent when lamotrigine was compared with carbamazepine (RR 0.92 [0.78 to 1.08]) (Appendix J Figure 23). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when oxcarbazepine was compared with carbamazepine.²⁸ The risk of achieving 24-month seizure remission was significantly decreased by 27 percent when oxcarbazepine was compared with carbamazepine (RR 0.73 [0.58 to 0.91]) (Appendix J Figure 23). Given the RD (RD -0.12 [-0.21 to -0.04]), for every nine patients treated, one less patient would achieve 12-month seizure remission when treated with oxcarbazepine versus carbamazepine. Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when topiramate was compared with carbamazepine.²⁸ The risk of achieving 24-month seizure remission was significantly decreased by 16 percent when topiramate was

compared with carbamazepine (RR 0.84 [0.71 to 0.94]) (Appendix J Figure 23). Given the RD (RD -0.07 [-0.15 to -0.001]), for every 15 patients treated, 1 less patient would achieve 12-month seizure remission when treated with topiramate versus carbamazepine. Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when gabapentin, lamotrigine, oxcarbazepine, or topiramate was compared with carbamazepine.²⁸ The risk of achieving 24-month seizure remission was significantly decreased by 18 percent when these newer antiepileptic medications were compared with carbamazepine (RR 0.82 [0.72 to 0.94]) (Appendix J Figure 23). Given the RD (RD -0.08 [-0.14 to -0.02]), for every 13 patients treated with a newer antiepileptic medication, 1 less patient would achieve 12-month seizure remission when treated with a newer agent versus carbamazepine. Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

Valproic Acid Versus Newer

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when newer antiepileptics were compared with valproic acid.²⁹

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when lamotrigine was compared with valproic acid.²⁹ The risk of achieving 12-month seizure remission was nonsignificantly decreased by 6 percent when lamotrigine was compared with valproic acid (RR 0.94 [0.84 to 1.04]) (Appendix J Figure 24). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when topiramate was compared with valproic acid.²⁹ The risk of achieving 12-month seizure remission remained the same when topiramate was compared with valproic acid (RR 1.00 [0.90 to 1.10]) (Appendix J Figure 24).

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when lamotrigine or topiramate was compared with valproic acid.²⁹ The risk of achieving 12-month seizure remission was nonsignificantly decreased when either newer agent was compared with valproic acid (RR 0.97 [0.89 to 1.06]) (Appendix J Figure 24).

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when newer antiepileptics were compared with valproic acid.⁸⁵

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when lamotrigine was compared with valproic acid.⁸⁵ The risk of achieving 24-month seizure remission was nonsignificantly decreased by 17 percent when lamotrigine was compared with valproic acid (RR 0.83 [0.68 to 1.00]) (Appendix J Figure 25).

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when topiramate was compared with valproic acid.⁸⁵ The risk of achieving 24-month seizure remission was nonsignificantly decreased by 12 percent when topiramate was compared with valproic acid (RR 0.88 [0.73 to 1.05]) (Appendix J Figure 25).

One randomized controlled trial reported the number of patients who achieved 24-month seizure remission when lamotrigine or topiramate was compared with valproic acid.⁸⁵ The risk of achieving 24-month seizure remission was nonsignificantly decreased by 15 percent when either newer antiepileptic was compared with valproic acid (RR 0.85 [0.73 to 1.00]) (Appendix J Figure 25).

Innovator Versus Generic Antiepileptic Drug Evaluation

There were no controlled clinical trials or controlled observational studies that reported data on seizure remission.

Seizure Freedom for Study Duration

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Twenty-one studies (15 randomized controlled trials and 6 observational studies) reported data on seizure freedom for the duration of the study while receiving a newer antiepileptic medications compared with carbamazepine.^{48,49,52-56,62,70,74,76-78,80,82,83,98,99,103,105,164}

Fifteen randomized controlled trials reported data on seizure freedom for the duration of the study when newer antiepileptics were compared versus carbamazepine^{48,49,52,53,55,56,62,70,74,76-78,80,82,83} and were all amenable to pooling.

One randomized controlled trial comparing gabapentin to carbamazepine reported data on seizure freedom for the study duration.⁷⁸ The risk of remaining seizure free for the duration of the study is significantly decreased by 26 percent when gabapentin is used versus carbamazepine (RR 0.74 [0.56 to 0.97]) (Appendix J Figure 26).

Seven randomized controlled trials comparing lamotrigine to carbamazepine reported data on seizure freedom for the study duration.^{52,55,62,70,76,78,80} The risk of remaining seizure free for the duration of study is nonsignificantly decreased by 6 percent when lamotrigine is used versus carbamazepine (RR 0.94 [0.83 to 1.05]) (Appendix J Figure 26). A low level of statistical heterogeneity was detected (I^2 : 35.5 percent), but no significant publication bias was detected (Egger's $p=0.073$).

Three trials comparing oxcarbazepine to carbamazepine reported data on seizure freedom for the study duration.^{48,49,82} The risk of remaining seizure free for the duration of study is nonsignificantly decreased by 4 percent when oxcarbazepine is used versus carbamazepine (RR 0.96 [0.77 to 1.19]) (Appendix J Figure 26). No statistical heterogeneity was detected (I^2 : 0 percent).

Three trials comparing topiramate to carbamazepine reported data on seizure freedom for the study duration.^{74,77,83} The risk of remaining seizure free for the 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). No significant statistical heterogeneity was detected (I^2 : 0 percent), but publication bias was detected (Egger's $p=0.021$).

Two trials comparing vigabatrin to carbamazepine reported data on seizure freedom for the study duration.^{53,56} The risk of remaining seizure free for the 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).

Fifteen randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for the study duration.^{48,49,52,53,55,56,62,70,74,76-78,80,82,83} The risk of remaining seizure free for the duration of study is nonsignificantly decreased by 6 percent when newer antiepileptic drugs (AEDs) are used versus carbamazepine (RR 0.94 [0.87 to 1.03]) (Appendix J Figure 26). A low level of statistical heterogeneity was detected (I^2 : 21.5 percent), and a trend toward publication bias was detected (Egger's $p=0.054$).

Six observational studies reported seizure freedom for study duration while patients were receiving newer antiepileptic medications compared with carbamazepine and all six were amenable for pooling.^{54,98,99,103,105,164}

One observational study comparing lamotrigine to carbamazepine reported data on seizure freedom for study duration.⁹⁹ The risk of remaining seizure free for the duration of study is significantly increased by 48 percent when lamotrigine is used versus carbamazepine (RR 1.48 [1.16 to 1.87]) (Appendix J Figure 27).

Two observational studies comparing levetiracetam to carbamazepine reported data on seizure freedom for study duration.^{103,164} The risk of remaining seizure free for the duration of study is nonsignificantly increased by seven percent when levetiracetam is used versus carbamazepine (RR 1.07 [0.93 to 1.24]) (Appendix J Figure 27).

One observational study comparing oxcarbazepine to carbamazepine reported data on seizure freedom for study duration.⁵⁴ The risk of remaining seizure free for the duration of study is nonsignificantly decreased by 31 percent when oxcarbazepine is used versus carbamazepine (RR 0.69 [0.31 to 1.37]) (Appendix J Figure 27).

One observational study comparing topiramate to carbamazepine reported data on seizure freedom for study duration.¹⁰⁵ The risk of remaining seizure free for the duration of study is nonsignificantly increased by 5 percent when topiramate is used versus carbamazepine (RR 1.05 [0.87 to 1.29]) (Appendix J Figure 27).

One observational study comparing vigabatrin to carbamazepine reported data on seizure freedom for study duration.⁹⁸ The risk of remaining seizure free for the duration of study is nonsignificantly decreased by 18 percent when vigabatrin is used versus carbamazepine (RR 0.82 [0.58 to 1.13]) (Appendix J Figure 27).

Six observational studies comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration.^{54,98,99,103,105,164} The risk of remaining seizure free for the duration of the study is nonsignificantly increased by 7 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.75 [0.90 to 1.29]) (Appendix J Figure 27). A low level of statistical heterogeneity was detected (I^2 : 20.8 percent), but publication bias was not detected (Egger's $p=0.0945$).

Two randomized controlled trials reported data on seizure freedom for study duration when newer antiepileptics were compared with controlled or sustained release carbamazepine and both were amenable for pooling.^{81,86}

One randomized controlled trial reported data on seizure freedom for study duration when lamotrigine was compared with sustained release carbamazepine.⁸⁶ The risk of remaining seizure free for the study duration was nonsignificantly decreased by 18 percent when lamotrigine was used versus sustained release carbamazepine (RR 0.82 [0.64 to 1.03]) (Appendix J Figure 28).

One randomized controlled trial reported data on seizure freedom for study duration when levetiracetam was compared with controlled-release carbamazepine.⁸¹ The risk of remaining seizure free for the study duration was nonsignificantly decreased by 6 percent when levetiracetam is used versus controlled-release carbamazepine (RR 0.94 [0.80 to 1.10]) (Appendix J Figure 28).

Two randomized controlled trials reported data on seizure freedom for study duration when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86} The risk of remaining seizure free for the study duration was nonsignificantly decreased by 10 percent when either newer agent was compared with controlled- or sustained-release carbamazepine (RR 0.90 [0.79 to 1.02]) (Appendix J Figure 28).

Phenytoin Versus Newer

Four randomized controlled trials reported seizure freedom for study duration while patients were receiving a newer antiepileptic medications compared with phenytoin^{57,59,64,90} and were all amenable to pooling.

One randomized controlled trial comparing lamotrigine to phenytoin reported data on seizure freedom for study duration.⁶⁴ The risk of remaining seizure free for the study duration is nonsignificantly decreased by 5 percent when lamotrigine is used versus phenytoin (RR 0.95 [0.56 to 1.63]) (Appendix J Figure 29).

Two trials comparing oxcarbazepine to phenytoin reported data on seizure freedom for study duration.^{57,59} The risk of remaining seizure free for the study duration is nonsignificantly decreased by 3 percent when oxcarbazepine is used versus phenytoin (RR 0.97 [0.84 to 1.12]) (Appendix J Figure 29).

One trial comparing topiramate to phenytoin reported data on seizure freedom for study duration.⁹⁰ The risk of remaining seizure free for the study duration is significantly decreased by 11 percent when topiramate is used versus phenytoin (RR 0.89 [0.80 to 0.98]) (Appendix J Figure 29). Given the RD (RD 0.89 [0.82 to 0.98]), for every two patients treated with topiramate, one less patient would remain seizure free for the duration of the study when treated with phenytoin.

Four trials comparing newer antiepileptic medications to phenytoin reported data on seizure freedom for study duration.^{57,59,64,90} The risk of remaining seizure free for the study duration is significantly decreased by 8 percent when newer antiepileptic medications are used versus phenytoin (RR 0.92 [0.85 to 1.00]) (Appendix J Figure 29). No statistical heterogeneity was detected (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.257$).

One observational study comparing oxcarbazepine to phenytoin reported data on seizure freedom on study duration.⁵⁴ The risk of remaining seizure free for the study duration is nonsignificantly decreased by 39 percent when newer antiepileptic medications are used versus phenytoin (RR 0.61 [0.28 to 1.15]).

Valproic Acid Versus Newer

Fifteen studies (12 randomized controlled trials and 3 observational studies) reported seizure freedom for study duration while patients were receiving newer antiepileptic medications compared with valproic acid.^{54,58,68,72,74,76,77,80,82,84,87,88,94,99,105}

Twelve randomized controlled trials reported data on seizure freedom for study duration when newer antiepileptics were compared versus valproic acid^{58,68,72,74,76,77,80,82,84,87,88,94} and were all amenable to pooling.

Seven trials comparing lamotrigine to valproic acid reported data on seizure freedom for study duration.^{23,68,72,80,87,88,94} The risk of remaining seizure free for the study duration is nonsignificantly decreased by 5 percent when lamotrigine is used versus valproic acid (RR 0.95 [0.76 to 1.19]) (Appendix J Figure 30). A moderate level of statistical heterogeneity was detected (I^2 : 47.3 percent), but publication bias was not detected (Egger's $p=0.132$).

Two trials comparing oxcarbazepine to valproic acid reported data on seizure freedom for study duration.^{58,82} The risk of remaining seizure free for the study duration is nonsignificantly increased by 1 percent when oxcarbazepine is used versus valproic acid (RR 1.01 [0.81 to 1.26]) (Appendix J Figure 30).

Three trials comparing topiramate to valproic acid reported data on seizure freedom for study duration.^{74,77,84} The risk of remaining seizure free for the study duration is nonsignificantly increased by 8 percent when topiramate is used versus valproic acid (RR 1.08 [0.86 to 1.36])

(Appendix J Figure 30). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.997$).

Twelve trials comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration.^{58,68,72,74,76,77,80,82,84,87,88,94} The risk of remaining seizure free for the 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). A low level of statistical heterogeneity was detected (I^2 : 5 percent), but statistically significant publication bias was detected (Egger's $p=0.039$).

Three observational studies reported seizure freedom for study duration while patients were receiving newer antiepileptic medications compared with valproic acid and all were amenable for pooling.^{54,99,105}

One observational study comparing lamotrigine to valproic acid reported data on seizure freedom for the study duration.⁹⁹ The risk of remaining seizure free for study duration is nonsignificantly increased by 5 percent when lamotrigine is used versus valproic acid (RR 1.05 [0.82 to 1.34]) (Appendix J Figure 31).

One observational study comparing oxcarbazepine to valproic acid reported data on seizure freedom for study duration.⁵⁴ The risk of remaining seizure free for the study duration is nonsignificantly decreased by 21 percent when oxcarbazepine is used versus valproic acid (RR 0.79 [0.34 to 1.67]) (Appendix J Figure 31).

One observational study comparing topiramate to valproic acid reported data on seizure freedom for study duration.¹⁰⁵ The risk of remaining seizure free for the study duration is nonsignificantly decreased by 20 percent when topiramate is used versus valproic acid (RR 0.80 [0.68 to 0.92]) (Appendix J Figure 31).

Three observational study comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration.^{54,99,105} The risk of remaining seizure free for the study duration is nonsignificantly decreased by 11 percent when newer antiepileptic medications are used versus valproic acid (RR 0.89 [0.72 to 1.10]) (Appendix J Figure 31). A moderate level of statistical heterogeneity was detected (I^2 : 46.3 percent), but tests for publication bias could not be performed.

Innovator Versus Generic Drug Evaluation

There were no controlled clinical trials or controlled observational studies that reported data on seizure freedom for study duration.

Secondary Seizure Injury

Innovator Versus Generic Drug Evaluation

There were no controlled clinical trials or controlled observational studies that reported secondary seizure injury.

Status Epilepticus

Innovator Versus Generic Drug Evaluation

There were no controlled clinical trials or controlled observational studies that reported secondary status epilepticus.

Discussion

The newer antiepileptic medications did not 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.

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. However, there was a trend towards a reduction in the risk of maintaining seizure freedom when newer antiepileptic medications were compared with phenytoin and there was a significant reduction in the risk of maintaining seizure freedom when topiramate was compared with phenytoin. Data is limited for the comparisons of newer antiepileptic medications versus controlled/sustained release carbamazepine.

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 antiepileptic medications versus valproic acid, although this was based on a single controlled clinical trial.

There was a significant increase in the time to first seizure when newer antiepileptic medications were compared versus phenytoin. No difference in the time to first seizure was seen between newer antiepileptic medications versus carbamazepine or valproic acid. However, in individual newer agent versus carbamazepine or valproic acid analyses, significant reductions were seen for gabapentin and vigabatrin versus carbamazepine and for lamotrigine versus valproic acid.

Statistical heterogeneity in some of the analyses of older versus newer antiepileptic medications was likely due to the pooling of different newer antiepileptic medications together and pooling patients with generalized epilepsy, partial epilepsy, new onset epilepsy, and chronic epilepsy together. We performed a priori-defined subgroup analyses to explore heterogeneity due to these factors as well as gender and age.

For the comparison of innovator antiepileptic medications to their respective generic versions, we found that seizure occurrence and frequency was similar between groups in controlled clinical trials. In addition, there were no 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 study had marked differences in several demographic variables (age, insurance type, and concomitant migraine headache and cerebral palsy), but the study investigators did not conduct adjusted analyses.

In 2010, a meta-analysis on seizure occurrence following the use of generic versus innovator antiepileptic medications was published.¹⁶⁵ In this meta-analysis, the authors pooled seven trials evaluating the occurrence of seizures together. We did not include the trial by Wolf 1992 since they were comparing two established versions of a sustained release carbamazepine product versus a new version. The new version was not a generic of the original versions and was not included. The authors said they included data from Hartley 1991 but instead used the data from Hartley 1990. Our findings, using the six trials that were eligible for pooling within our analysis

(RR 0.89 [0.57 to 1.39]), are characteristically similar to that of the meta-analysis by Kesselheim 2010 (OR 1.1 [0.9 to 1.2]).

When viewed together, the data suggest that generic antiepileptic medication use, predominantly with carbamazepine, phenytoin, and valproic acid, provides a similar level of efficacy to a population of people with epilepsy as their respective innovator products. This occurred even though many of the trials did not use FDA approved “A” rated generics, which would have likely resulted in less variability in concentrations between the different forms of the medications. It would be difficult to extrapolate these findings from controlled clinical trials to other antiepileptic medications since they were not represented in the analyses.

Many of the 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 form of the medication, whether an innovator or generic, would increase the risk of seizure occurrence or increase seizure frequency. Unfortunately, this has not been directly assessed in any controlled clinical trial or controlled observational trial. It has been reported in descriptive trials, but these uncontrolled observations are prone to such a high degree of bias, they cannot be used to reliably gauge comparative efficacy.

In the absence of controlled clinical trial data, controlled observational studies can be used to provide insight into the impact of innovator to generic switching on other endpoints. However, the inherent limitations of observational data need to be appreciated and negatively impact internal validity, even when sophisticated statistical methods are used to create more comparable control groups. Even under the best of circumstances, investigators can only control for those factors that are known or suspected to impact results, and the sample size limits the number of variables that can be controlled for. Additionally, as with the controlled clinical trials, it is hard to extrapolate the results on these studies to that of other antiepileptic medications that were not evaluated.

Four controlled observational trials have evaluated the impact of switching from one version of an antiepileptic medication (either an innovator or generic) to another version of the medication on outpatient resource utilization, hospitalization, and hospital stay duration. These controlled observational studies compared periods of innovator medication use versus periods of generic use. All of the observational studies were sponsored by the pharmaceutical industry. Two controlled observational trials (one evaluating several antiepileptic medications together as one group and another focusing on lamotrigine) found an increased incidence of utilizing outpatient resources^{33,129} but two other trials focusing on topiramate did not.^{133,162} One of the four trials found significant increases in hospitalization rates during periods of generic use, one found significant increases in both evaluated subpopulations, one trial found a trend towards an increase in the hospitalization rate, and another found a significant increase in the hospitalization rate in one subpopulation and a trend in the other. All four controlled observational studies found a significant increase in hospital length of stay.

These controlled observational studies, while well conducted, have four important limitations. First, they set their observational periods to coincide with the generic introduction of an antiepileptic medication. As such, they were evaluating patients who were likely stabilized on the innovator therapy, were switched to the generic medication and if they had an issue, were switched back. As such, these studies cannot be used to differentiate the comparative efficacy of innovator versus generic antiepileptic medications since the circumstances for which they were used is different. The studies do provide insight into the impact of switching from one

medication to another version of the same medication. Second, it was not specified that the controlled observational studies were limited to “A” rated generics. If generic versions that would not meet the FDA guidance for an “A” rated generic were included, the differences between the innovator and generic groups may be greater than when limited to “A” rated versions. Third, the switch was not blinded. As such, patients and clinicians may have been aware the switch had occurred and emotional or anxiety related triggers for medical service utilization not related to the comparability of the innovator and generic products could have occurred. Fourth, the studies used claims data increasing the risk that data was missing or misclassified.

Three well-conducted controlled observational studies assessed a composite endpoint of medical service utilization. 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 for some other factors found to be disparate between groups with similar results to the base case analysis. As such, these observational trials were well conducted. However, they could not control for comorbidities or changes in other medications and their associated dosages which are known to impact seizure occurrence. Only one of the studies matched for gender and the other study had a different regional distribution of patients between cases and controls. Given the enrolled population, 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 versions of the same antiepileptic medication. It would have increased the internal validity if they found a similar number of office visits in the 6 to 12 months preceding the switch between “A” rated versions of the antiepileptic medications. If the cases had more office visits preceding the switch it would suggest that the patients were not comparable. A third important case control study was conducted by Devine and colleagues and was sponsored by Express Scripts.¹²⁸ In this study, significant increases in hospitalization of emergency room visits were seen in unadjusted analyses, but no significant difference was found after adjusting for confounders. Unlike the other two trials,^{126,127} this study’s authors controlled for person’s risk of epilepsy exacerbation, change in disease severity, drug interactions, poor adherence, and change in patient diagnosis.¹²⁸ This suggests that the difference in magnitude between these three studies may be due to inadequate confounder adjustment. 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.¹²⁶⁻¹²⁸ Since the controlled observational studies by Zachry and colleagues and Rascati and colleagues used a composite endpoint that included ambulance service utilization and Devine and colleagues did not, this may also explain differences in magnitude between the three studies. All three of these controlled observational trials were unblinded and used claims data increasing the risk that data was missing or misclassified.

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?

Key Points

- This Key Question focused on the innovator versus generic comparison. Pharmacokinetic data was derived from carbamazepine and to a lesser extent phenytoin, and lamotrigine studies, as there is limited ability to extrapolate to all antiepileptic medications.
- The average maximum concentration (C_{max}), minimum concentration (C_{min}), time to maximum concentration (T_{max}), and area under the curve (AUC) values from a population of patients receiving innovator antiepileptic medications are similar to that of their generic versions.
- The average Steady-state concentration (C_{ss}) values from a population of patients receiving innovator antiepileptic medication are similar overall to that of their generic counterparts.
 - There was a significantly increase in the weighted mean difference for C_{ss} with generic versus innovator phenytoin.
- While the average pharmacokinetic parameters of patients receiving innovator and their generic versions are similar, we cannot demonstrate whether or not an individual patient stabilized on an innovator or generic product will experience a marked change when switched to alternate therapy, leading to loss of efficacy or adverse events.
- There are high rates of switching from innovator to generic versions of antiepileptic medications as evidenced by high rates of switching back from generic to innovator products.

Detailed Analysis

Study Design and Population Characteristics

Studies used to answer this Key Question will be the same as those comparing innovator to generic antiepileptic medications used to answer Key Question 1.

Outcome Evaluations

Pharmacokinetics

Maximum Concentration

Eight trials (seven randomized controlled trial and one prospective nonrandomized trial) reported the maximal blood concentrations (C_{max}) of patients receiving innovator and their associated generic antiepileptic medications.^{110-116,122}

Six randomized controlled trials reported data on C_{max} in patients receiving innovator carbamazepine versus generic versions and were all suitable for meta-analysis.¹¹⁰⁻¹¹⁵ Only one of

the trials utilized a discernable FDA “A” rated generic carbamazepine product.¹¹² The weighted mean difference for Cmax in the generic carbamazepine group was nonsignificantly higher than the innovator carbamazepine group (WMD 0.28 [-0.17 to 0.72] mcg/mL) (Appendix J Figure 32). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger’s: $p=0.277$) was detected.

One prospective nonrandomized trial reported data on Cmax in patients receiving innovator lamotrigine against a generic version but did not use a discernable FDA “A” rated generic.¹¹⁶ The weighted mean difference in the generic lamotrigine group was nonsignificantly lower than the innovator lamotrigine group (WMD -0.11 [-8.82 to 8.60] mcg/mL) (Appendix J Figure 32). Statistical heterogeneity and publication bias could not be determined.

One randomized controlled trial reported data on Cmax in patients receiving innovator phenytoin versus a several generic versions but did not use a discernable FDA “A” rated generic.¹²² The weighted mean difference in the generic phenytoin group was nonsignificantly lower than the innovator phenytoin group (WMD -1.08 [-4.35 to 2.19] mcg/mL) (Appendix J Figure 32). No statistical heterogeneity was found (I^2 : 0 percent), but publication bias was detected (Egger’s: $p=0.001$).

Eight trials, seven of which were randomized, reported data on Cmax in patients receiving innovator versus generic versions of antiepileptic medication and were all suitable for meta-analysis.^{110-116,122} The standardized mean difference in the generic antiepileptic medication group was nonsignificantly higher than the innovator antiepileptic medication group (SMD 0.10 [-0.13 to 0.32]) (Appendix J Figure 32). No statistical heterogeneity (I^2 : 0 percent) was found, but there was a trend towards detectable publication bias (Egger’s: $p=0.086$).

The BCS Class I analysis is the same as that reported for lamotrigine (WMD -0.11 [-8.82 to 8.60] mcg/mL). Seven randomized controlled trials reported data on BCS Class II antiepileptic medications suitable for meta-analysis.^{110-115,122} The standardized mean difference in the generic BCS Class II antiepileptic medication group was nonsignificantly lower than the innovator BCS Class II antiepileptic medication group (SMD 0.10 [-0.13 to 0.33]) (Appendix J Figure 32). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger’s: $p=0.103$) was detected.

One randomized controlled trial reported on the comparison of an innovator to a discernable FDA “A” rated generic product, in this case carbamazepine.¹¹² The weighted mean difference in the generic carbamazepine group was nonsignificantly higher than the innovator carbamazepine group (WMD 0.20 [-0.73 to 1.13] mcg/mL) (Appendix J Figure 32). Tests for statistical heterogeneity and publication bias could not be calculated.

Minimum Concentration

Six trials (four randomized controlled trials, one prospective before and after nonblinded trial, and one prospective nonrandomized trial) reported the minimal blood concentrations (Cmin) of patients receiving innovator and their associated generic antiepileptic medications.^{107,110,113-116}

Five trials (four randomized controlled trials and one prospective before and after nonblinded trial) reported data on Cmin in patients receiving innovator carbamazepine versus generic versions and were all suitable for meta-analysis.^{107,110,113-115} None of the trials used a discernable FDA “A” rated generic carbamazepine product. The weighted mean difference in the generic carbamazepine group was nonsignificantly higher than the innovator carbamazepine group (WMD 0.15 [-0.25 to 0.56] mcg/mL) (Appendix J Figure 33). No statistical heterogeneity was found (I^2 : 0 percent), but publication bias was trending towards significance (Egger’s: $p=0.056$).

One prospective nonrandomized trial reported data on C_{min} in patients receiving innovator lamotrigine versus a generic version but did not use a discernable FDA “A” rated generic.¹¹⁶ The weighted mean difference in the generic lamotrigine group was nonsignificantly higher than the innovator lamotrigine group (WMD 0.89 [-6.07 to 7.85] mcg/mL) (Appendix J Figure 33). Statistical heterogeneity and publication bias could not be determined.

Six trials (four randomized controlled trials^{110,113-115} one prospective before and after nonblinded trial,¹⁰⁷ and one prospective nonrandomized trial¹¹⁶) reported data on C_{max} in patients receiving innovator versus generic version of antiepileptic medications and were all suitable for meta-analysis. The standardized mean difference in the generic group was nonsignificantly higher than the generic antiepileptic medication group (SMD 0.05 [-0.21 to 0.31]) (Appendix J Figure 33). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger’s: $p=0.341$) was detected.

The BCS Class I analysis is the same as that reported for lamotrigine (WMD 0.89 [-6.07 to 7.85] mcg/mL). The BCS Class II analysis is the same as reported for carbamazepine (WMD 0.15 [-0.25 to 0.56] mcg/mL) (Appendix J Figure 33). There were no discernable “A” rated generics available to analyze.

Steady-State Concentration

Seven randomized controlled trials reported steady state concentration (C_{ss}) of patients receiving innovator and their associated generic antiepileptic medications.^{108,109,111,113,118,120,121}

Four randomized controlled trials reported data on C_{ss} in patients receiving innovator carbamazepine versus generic versions and were all suitable for meta-analysis.^{108,109,111,113} None of the trials utilized a discernable FDA “A” rated generic carbamazepine product. The weighted mean difference for C_{ss} in generic carbamazepine group was nonsignificantly higher than the innovator carbamazepine group (WMD 0.34 [-0.31 to 0.99]) (Appendix J Figure 34). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger’s: $p=0.085$) was detected.

Three randomized controlled trials reported data on C_{ss} in patients receiving innovator phenytoin versus one or more generic versions of phenytoin.^{118,120,121} None of the trials utilized a discernable FDA “A” rated generic. The weighted mean difference in the generic phenytoin group was significantly higher than the innovator phenytoin group (WMD 2.96 [0.65 to 5.28] mcg/mL) (Appendix J Figure 34). No statistical heterogeneity was found (I^2 : 0 percent), but publication bias was detected (Egger’s: $p=0.045$).

Seven randomized controlled trials reported data on innovator versus generic versions of antiepileptic medications suitable for meta-analysis.^{108,109,111,113,118,120,121} The standardized mean difference in the generic group was nonsignificantly higher than the innovator antiepileptic medication group (SMD 0.18 [-0.09 to 0.45]) (Appendix J Figure 34). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger’s: $p=0.300$) was detected.

None of the available drugs were in BCS Class I, so analysis was not possible. The BCS Class II analysis is the same as antiepileptic medication analysis (SMD 0.18 [-0.09 to 0.45]) (Appendix J Figure 34). There were no discernable “A” rated generics available to analyze.

Time to Maximum Concentration

Five randomized controlled trials reported time to maximum concentration (T_{max}) of patients receiving innovator and their associated generic antiepileptic medications.¹¹¹⁻¹¹⁵

Five randomized controlled trials reported data on T_{max} in patients receiving innovator carbamazepine versus generic versions and were all suitable for meta-analysis.¹¹¹⁻¹¹⁵ Only one of the trials utilized a discernable FDA “A” rated generic carbamazepine product.¹¹² The weighted

mean difference for Tmax in generic carbamazepine group was the same as the innovator carbamazepine group (WMD 0.00 [-0.43 to 0.43] hours) (Appendix J Figure 35). High and significant statistical heterogeneity (I^2 : 60.2 percent) was detected, but publication bias (Egger's: $p=0.400$) was not detected. The heterogeneity was driven by the Aldenkamp 1996 trial. The weighted mean difference after exclusion of Aldenkamp 1996 was significantly lower in the innovator antiepileptic medication group (WMD -0.37 [-0.69 to -0.04]) with no statistical heterogeneity ($I^2=0$ percent) (Appendix J Figure 35). We assessed potential reasons why the Aldenkamp 1996 trial would find a different direction of effect from the other trials. Aldenkamp had a short study duration (3 days per phase) versus the Hartley 1991 (6 weeks per phase) and Oles 1992 (3 months per phase), had an older mean age of 45 years versus the other trials (35 and 11 years), and was conducted more recently (1998 versus 1992 and 1991), respectively. Gender and country of study conduction were not likely explanations for the heterogeneity. Patients' seizure history was not reported adequately enough to allow assessment of this variable.

The "any antiepileptic" medication analysis and the BCS Class II analysis is the same as the carbamazepine analysis (WMD 0.00 [-0.43 to 0.43]) (Appendix J Figure 35). None of the available drugs were in BCS Class I, so analysis was not possible.

One randomized controlled trial reported on the comparison of an innovator to a discernable FDA "A" rated generic product, in this case carbamazepine.¹¹² The WMD in the generic carbamazepine group was nonsignificantly lower than the innovator carbamazepine group (WMD -0.25 [-0.85 to 0.35]) (Appendix J Figure 35). Tests for statistical heterogeneity and publication bias could not be calculated.

Area Under the Curve

Eight trials (seven randomized controlled trials and one prospective nonrandomized trial) reported AUC of patients receiving innovator and their associated generic antiepileptic medications.^{110-116,122}

Six randomized controlled trials reported data on AUC in patients receiving innovator carbamazepine to generic versions and were all suitable for meta-analysis.^{108,111-115} Only one of the trials utilized a discernable FDA "A" rated generic carbamazepine product.¹¹² The WMD in the generic carbamazepine group was nonsignificantly higher than the innovator carbamazepine group (WMD 2.34 [-1.59 to 6.28]) (Appendix J Figure 36). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's: $p=0.932$) was detected.

One prospective nonrandomized trial reported data on AUC in patients receiving innovator lamotrigine versus a generic version but did not use a discernable FDA "A" rated generic.¹¹⁶ The WMD in the generic lamotrigine group was nonsignificantly lower than the innovator lamotrigine group (WMD -10.50 [-86.08 to 65.08] mcg/mL) (Appendix J Figure 36). Tests for statistical heterogeneity and publication bias could not be calculated.

One randomized controlled trial reported data on AUC in patients receiving innovator phenytoin versus a several generic versions but did not use a discernable FDA "A" rated generic.¹²² The WMD in the generic phenytoin group was nonsignificantly lower than the innovator phenytoin group (WMD -18.78 [-52.60 to 15.06]) (Appendix J Figure 36). No significant statistical heterogeneity (I^2 : 0 percent) was detected, but publication bias was detected (Egger's: $p=0.048$).

Eight trials (seven randomized controlled trials^{108,111-115,122} and one prospective nonrandomized trial¹¹⁶) reported data on innovator versus generic versions of antiepileptic medication suitable for meta-analysis. The SMD in the generic group was nonsignificantly higher than the innovator antiepileptic medication group (SMD 0.05 [-0.18 to 0.28]) (Appendix J

Figure 36). No statistical heterogeneity (I^2 : 0 percent) was detected, but publication bias was detected (Egger's: $p=0.004$).

The BCS Class I analysis is the same as that reported for lamotrigine (WMD -10.50 [-86.08 to 65.08] mcg/mL). Seven randomized controlled trials reported data on BCS Class II antiepileptic medications suitable for meta-analysis.^{110-115,122} The standardized mean difference in the generic BCS Class II antiepileptic medication group was nonsignificantly higher than the innovator BCS Class II antiepileptic medication group (SMD 0.06 [-0.17 to 0.30]) (Appendix J Figure 36). No statistical heterogeneity (I^2 : 0 percent) was detected, but publication bias (Egger's: $p=0.006$) was detected.

One randomized controlled trial reported on the comparison of an innovator to a discernable FDA "A" rated generic product, in this case carbamazepine.¹¹² The WMD in the "A" rated generic carbamazepine group was nonsignificantly higher than the innovator carbamazepine group (WMD 1.44 [-3.60 to 6.49]) (Appendix J Figure 36). Tests for statistical heterogeneity and publication bias could not be calculated.

Dose Requirements for Seizure Control

There were no controlled clinical trials or observational studies that reported data on this endpoint.

Switchback Rates

Four observational studies reported switchback rates, the percentage of patients switching back to an innovator antiepileptic medication after taking a generic version. In the first study,¹²⁹ switchback rate in the stable epilepsy patients was 26.5 percent, whereas in the unstable epilepsy patients, the switchback rate was 31.1 percent. In the other three studies, switchback rates were divided by antiepileptic medications. Switchback rate for carbamazepine was 20.8 percent and 12.2 percent,^{33,132} divalproex was 14 percent,¹³² valproic acid was 20.9 percent and 23.9 percent,^{131,132} clobazam was 20.5 percent, 44.1 percent, and 23 percent,^{33,131,162} gabapentin was 30.9 percent and 19.5 percent,^{33,132} lamotrigine was 13 percent, 27.5 percent, and 12.4 percent^{33,131,132}, and topiramate was 12.5 percent.¹³²

Discussion

This section is specifically focused on innovator versus generic antiepileptic medications and does not pertain to older versus newer agents. While we evaluated the impact of using innovator versus generic antiepileptic medications on several pharmacokinetic parameters, the data was derived from carbamazepine and to a lesser extent phenytoin, and lamotrigine studies. Therefore, there is limited ability to extrapolate to all antiepileptic medications.

The average C_{max} , C_{min} , T_{max} , and AUC values from a population of patients receiving innovator antiepileptic medications are similar to that of their generic versions in the combined and individual drug analyses. The average C_{ss} values from a population of patients receiving innovator antiepileptic medication are similar overall to that of their generic counterparts. However, there was a significantly increase in the weighted mean difference for C_{ss} with generic versus innovator phenytoin.

When taken together, a population of patients should derive similar concentrations on an innovator as they would using a generic antiepileptic medication. However, our data do not allow us to determine if an individual patient or subset of patients would have an over- or

underaccentuated pharmacokinetic response if they were switched from one version of the medication to the other.

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 a result, 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

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?

Key Points

- While the risk of withdrawing for any reason is not different for newer antiepileptic medications versus either carbamazepine or controlled/sustained carbamazepine in controlled clinical trials, this is due to an offsetting increase in the risk of withdrawals due to lack of efficacy and a decrease in withdrawals due to adverse events.
- No difference was found in the risk of withdrawals for any reason or withdrawals due to adverse events when newer antiepileptic medications were compared with ethosuximide, although this is based on a single trial with lamotrigine.
- No difference was found in the risk of withdrawals for any reason, withdrawals due to lack of efficacy, or withdrawals due to adverse events when newer antiepileptic medications were compared with either phenytoin or valproic acid, although the phenytoin comparisons were based on limited trial data with only lamotrigine and oxcarbazepine as comparators.
- The risk of dizziness was significantly lower with newer antiepileptic medications versus carbamazepine and in individual comparisons between lamotrigine or topiramate versus carbamazepine. No differences were noted between newer antiepileptic medications versus either phenytoin or valproic acid, although the phenytoin evaluation had limited data. No data were available for controlled/sustained-release carbamazepine.
- The risk of fatigue was significantly lower with newer antiepileptic medications versus carbamazepine and in individual comparisons between gabapentin, lamotrigine, or topiramate versus carbamazepine. Similarly, the risk of fatigue was significantly lower with newer antiepileptic medications versus valproic acid and in an individual comparison between topiramate versus carbamazepine. No differences were noted between newer antiepileptic medications versus either controlled/sustained-release carbamazepine or phenytoin, although these evaluations had limited data.
- No difference was found in the risk of headache when newer antiepileptic medications were compared versus carbamazepine, controlled/sustained release carbamazepine, phenytoin, or valproic acid, although the phenytoin and controlled/sustained-release carbamazepine evaluations were based on limited data. The risk of headache was significantly lower when oxcarbazepine was compared versus valproic acid.

- No difference was found in the risk of nausea when newer antiepileptic medications were compared versus carbamazepine, controlled/sustained-release carbamazepine, or phenytoin, although the controlled/sustained release carbamazepine evaluations were based on limited data and a significantly lower risk of nausea was noted in individual agent analysis when topiramate was compared versus carbamazepine. The risk of nausea was significantly lower when newer antiepileptic medications were compared versus valproic acid and in individual comparisons where lamotrigine or topiramate had a significantly lower risk of nausea than valproic acid.
- No difference in the risk of vomiting was noted for newer antiepileptic medications versus carbamazepine or valproic acid but was significantly lower when compared versus phenytoin. The risk of vomiting was based on limited data for the carbamazepine and phenytoin comparisons, and no data was available evaluating newer antiepileptic medications and controlled/sustained-release carbamazepine.
- The risk of skin rash was significantly lower with newer antiepileptic medications versus carbamazepine and in individual comparisons between gabapentin, lamotrigine, topiramate, or vigabatrin versus carbamazepine. Similarly, the risk of skin rash was significantly lower with newer antiepileptic medications versus controlled/sustained-release carbamazepine. No differences were noted between newer antiepileptic medications versus either phenytoin or valproic acid although in individual agent analysis, the risk of skin rash was significantly reduced for topiramate versus either phenytoin or valproic acid but was significantly increased for lamotrigine versus valproic acid.
- The risk of somnolence was significantly lower with newer antiepileptic medications versus carbamazepine and in individual comparisons between gabapentin or lamotrigine versus carbamazepine. Similarly, the risk of somnolence was significantly lower with newer antiepileptic medications versus valproic acid. No differences were noted between newer antiepileptic medications versus either controlled/sustained-release carbamazepine or phenytoin, although the controlled/sustained-release evaluation had limited data and there was a significantly lower risk of somnolence in individual agent analysis when lamotrigine was compared versus phenytoin.
- No differences in the risk of alopecia was noted when newer antiepileptic medications and carbamazepine. Newer antiepileptic medications decreased the risk of experiencing alopecia when compared with valproic acid and when lamotrigine and topiramate were individually compared with valproic acid.
- No difference in the risk of acne was seen when newer antiepileptic medications were compared versus phenytoin, but this was based on a single study. However, newer antiepileptic medications (only oxcarbazepine was evaluated) had a lower risk of gum hyperplasia when compared with phenytoin.
- Cognition was evaluated for several newer antiepileptic medications versus carbamazepine and valproic acid with very limited data with phenobarbital and phenytoin.
 - Carbamazepine had better effects in some measures of cognition versus topiramate, similar effects to oxcarbazepine and tiagabine, and may not impact some measures of cognition as well as vigabatrin, although this latter statement is based on cross extrapolation of change from baseline data and not a direct comparison of the two agents.

- Phenobarbital had better effects on the mini-mental state exam than lamotrigine but worse than levetiracetam while exhibiting similar effects on the Alzheimer Disease Assessment Scale – Cognitive test to lamotrigine and inferior effects versus levetiracetam.
- Phenytoin and tiagabine had a similar impact on cognition.
- Valproic acid has better effects in some measures of cognition versus topiramate but has similar effects in several other measures. In a single study, valproic acid and oxcarbazepine had similar effects on cognition.
- Mood was not as extensively evaluated as cognition, and in several places, lack of significant effects was noted but data were not provided.
 - Carbamazepine had better impact on mood than tiagabine.
 - Phenytoin had a similar impact on mood as tiagabine.
 - Valproic acid had a similar effect on mood to topiramate but inferior effects on mood to lamotrigine.
 - Phenobarbital had inferior effects on mood compared with lamotrigine but may be similar to levetiracetam.
- No clinical trial evidence was available evaluating bone mineral density in patients receiving older and newer antiepileptic medications. These studies have higher risk of inherent biases and may be underpowered.
 - One study found that the use of either newer or older agents decreased bone mineral density versus normal controls. One study found no difference in bone mineral density when lamotrigine was compared against older antiepileptic drugs (carbamazepine, phenytoin, valproic acid). A final study found that carbamazepine reduced bone mineral density versus baseline but valproic acid and lamotrigine did not.
- Data on withdrawal rates due to adverse events were only available for innovator versus generic carbamazepine and phenytoin, limiting the ability to extrapolate findings to other antiepileptic medications.
- The withdrawals due to adverse events were similar between the innovator and generic versions of antiepileptic medications.

Detailed Analysis

Study Design and Population Characteristics

Older Versus Newer Antiepileptic Drug Evaluation

Studies to answer Key Question 3 are derived from the same set of studies used to evaluate Key Question 1 and are summarized in Appendix G Tables 15-19.

Innovator Versus Generic Antiepileptic Drug Evaluation

Studies to answer Key Question 3 are derived from the same set of studies used to evaluate Key Question 1 and are summarized in Appendix G Table 5, 7-9.

Outcome Evaluations

Withdrawals Due to Adverse Events

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Twenty-four trials (18 randomized controlled trials and 6 observational studies) reported withdrawals due to adverse events while patients were receiving a newer antiepileptic medication compared with carbamazepine.^{48,49,52,53,55,56,60,62,63,70,74,76-80,83,85,95,98,99,101,103,104}

Eighteen randomized controlled trials reported data on withdrawals due to adverse events when newer antiepileptics were compared versus carbamazepine and were amenable for pooling.^{48,49,52,53,55,56,60,62,63,70,74,76-80,83,85}

Three randomized controlled trials reported data on withdrawals due to adverse events when gabapentin was compared versus carbamazepine and were amenable for pooling.^{60,78,85} The risk of withdrawal was significantly decreased by 49 percent when gabapentin was compared versus carbamazepine (RR 0.51 [0.33 to 0.79]) (Appendix J Figure 37). Given the RD, (RD -0.12 [-0.17 to -0.08]), for every nine patients treated with gabapentin, one fewer patient would withdraw due to an adverse event compared with those treated with carbamazepine. A higher level of statistical heterogeneity was detected (I^2 : 56.5 percent), but publication bias was not detected (Egger's: $p=0.089$).

Eight randomized controlled trials reported data on withdrawals due to adverse events when lamotrigine was compared versus carbamazepine and were amenable for pooling.^{52,55,62,70,76,78,80,85} The risk of withdrawal was significantly decreased by 48 percent when lamotrigine was compared versus carbamazepine (RR 0.52 [0.43 to 0.61]) (Appendix J Figure 37). Given the RD (RD -0.17 [-0.14 to -0.07]), for every six patients treated with lamotrigine, one fewer patient would withdraw due to an adverse event compared with those treated with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's: $p=0.222$) was detected.

Three randomized controlled trials reported data on withdrawal due to adverse events when oxcarbazepine was compared versus carbamazepine and were amenable for pooling.^{48,49,85} The risk of withdrawal was nonsignificantly decreased by 24 percent when oxcarbazepine was compared versus carbamazepine (RR 0.76 [0.56 to 1.04]) (Appendix J Figure 37). A lower level of statistical heterogeneity was detected (I^2 : 9.1 percent), but tests for publication bias could not be performed.

Four randomized controlled trials reported data on withdrawals due to adverse events when topiramate was compared versus carbamazepine and were amenable for pooling.^{74,77,83,85} The risk of withdrawal was nonsignificantly increased by 4 percent when topiramate was used versus carbamazepine (RR 1.04 [0.86 to 1.26]) (Appendix J Figure 37). No statistical heterogeneity (I^2 : 0 percent), or publication bias was detected (Egger's: $p=0.496$).

Four randomized controlled trials reported data on withdrawals due to adverse events when vigabatrin was compared versus carbamazepine.^{53,56,63,79} The risk of withdrawal was nonsignificantly decreased by 42 percent when vigabatrin was used versus carbamazepine (RR 0.58 [0.23 to 1.45]) (Appendix J Figure 37). A moderate level of statistically significant statistical heterogeneity was detected (I^2 : 42.7 percent), but publication bias was not detected (Egger's: $p=0.442$).

In the pooled analysis of 18 randomized trials reporting data on withdrawals due to adverse events when either gabapentin, lamotrigine, oxcarbazepine, topiramate, or vigabatrin were compared versus carbamazepine.^{48,49,52,53,55,56,60,62,63,70,74,76-80,83,85} The risk of withdrawal was significantly decreased by 37 percent when all newer antiepileptics were used versus carbamazepine (RR 0.63 [0.53 to 0.73]) (Appendix J Figure 37). Given the RD (RD -0.08 [-0.11 to -0.053]), for every 13 patients treated with a newer agent, 1 fewer patient would withdraw due to an adverse event compared with those treated with carbamazepine. A moderate level of statistically significant statistical heterogeneity was detected (I^2 : 35.4 percent), but publication bias was not detected (Egger's: $p=0.063$).

Six observational studies reported withdrawals due to adverse events while patients were receiving newer antiepileptic medications compared with carbamazepine and all six were amenable for pooling.^{95,98,99,101,103,104}

Two observational studies reported withdrawals due to adverse events when lamotrigine was compared versus carbamazepine and were amenable for pooling.^{99,101} The risk of withdrawal was significantly decreased by 60 percent when lamotrigine was compared versus carbamazepine (RR 0.40 [0.20 to 0.78]) (Appendix J Figure 38). Given the RD, (RD -0.10 [-0.27 to 0.07]), for every 10 patients treated with lamotrigine, 1 less patient would withdraw compared with those treated with carbamazepine.

One observational study reported withdrawal due to adverse events when levetiracetam was compared versus carbamazepine.¹⁰³ The risk of withdrawal was nonsignificantly increased by 2.4-fold when levetiracetam was compared versus carbamazepine (RR 2.42 [0.45 to 14.69]) (Appendix J Figure 38).

One observational study reported withdrawal due to adverse events when oxcarbazepine was compared versus carbamazepine.⁹⁵ The risk of withdrawal was nonsignificantly increased by 3-fold when oxcarbazepine was compared versus carbamazepine (RR 3.00 [0.26 to 35.71]) (Appendix J Figure 38).

One observational study reported withdrawal due to adverse events when topiramate was compared versus carbamazepine.¹⁰⁴ The risk of withdrawal was nonsignificantly decreased by 63 percent when topiramate was compared versus carbamazepine (RR 0.37 [0.06 to 2.14]) (Appendix J Figure 38).

One observational study reported withdrawal due to adverse events when vigabatrin was compared versus carbamazepine.⁹⁸ The risk of withdrawal was nonsignificantly increased by 8 percent when vigabatrin was compared versus carbamazepine (RR 1.08 [0.06 to 18.74]) (Appendix J Figure 38).

In the pooled analysis of six observational studies reporting data on withdrawals due to adverse events, either lamotrigine, levetiracetam, oxcarbazepine, topiramate, or vigabatrin was compared versus carbamazepine.^{95,98,99,101,103,104} The risk of withdrawal was significantly increased by 49 percent when either newer agent was compared versus carbamazepine (RR 0.51 [0.28 to 0.92]) (Appendix J Figure 38). Given the RD (RD -0.020 [-0.098 to 0.057]), for every 50 patients treated with a newer agent, 1 less patient would withdraw compared with those treated with carbamazepine. No significant statistical heterogeneity (I^2 : 0 percent) or publication (Egger's: $p=0.098$) was detected.

Two randomized controlled trials reported withdrawals due to adverse events when newer antiepileptics were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86}

One randomized controlled trial reported withdrawals due to adverse events when lamotrigine was compared with sustained-release carbamazepine.⁸⁶ The risk of withdrawal was nonsignificantly decreased by 45 percent when lamotrigine was compared with sustained-release carbamazepine (RR 0.55 [0.30 to 1.01]) (Appendix J Figure 39).

One randomized controlled trial reported withdrawals due to adverse events when levetiracetam was compared versus controlled-release carbamazepine.⁸¹ The risk of withdrawal was nonsignificantly decreased by 25 percent when levetiracetam was compared with controlled-release carbamazepine (RR 0.75 [0.52 to 1.08]).

Two randomized controlled trials reported withdrawals due to adverse events when lamotrigine or levetiracetam was compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86} The risk of withdrawal was significantly decreased by 31 percent when either newer agent was compared with controlled- or sustained-release carbamazepine (RR 0.69 [0.50 to 0.95]) (Appendix J Figure 39). Given the RD (RD -0.0063 [-0.012 to -0.0090]), for every 159 patients treated with a newer agent, 1 less patient would withdraw compared with those treated with controlled or sustained release carbamazepine.

Phenytoin Versus Newer

Three randomized controlled trials reported withdrawals due to adverse events while patients were receiving a newer antiepileptic medication compared with phenytoin and all three were amenable for pooling.^{57,59,64}

One randomized controlled trial reported data on withdrawals due to adverse events when lamotrigine was compared with phenytoin.⁶⁴ The risk of withdrawal was nonsignificantly decreased by 20 percent when lamotrigine was compared versus phenytoin (RR 0.80 [0.42 to 1.51]) (Appendix J Figure 40).

Two randomized controlled trials reported data on withdrawals due to adverse events when oxcarbazepine was compared with phenytoin and were amenable for pooling.^{57,59} The risk of withdrawal was significantly decreased by 75 percent when oxcarbazepine was compared versus phenytoin (RR 0.25 [0.11 to 0.55]) (Appendix J Figure 40). Given the RD (RD

-0.095 [-0.14 to -0.05]), for every 11 patients treated with oxcarbazepine, 1 less would withdraw due to adverse events compared with those treated with carbamazepine.

In the pooled analysis of three randomized trials reporting data on withdrawals due to adverse events either lamotrigine or oxcarbazepine were compared versus phenytoin and were amenable for pooling.^{57,59,64} The risk of withdrawal was nonsignificantly decreased by 62 percent when the newer agents were compared versus phenytoin (RR 0.38 [0.14 to 1.03]) (Appendix J Figure 40). Significant statistical heterogeneity was detected (I^2 : 66.8 percent), but tests for publication bias could not be performed.

Valproic Acid Versus Newer

Eighteen studies (16 randomized controlled trials and 2 observational studies) reported withdrawals due to adverse events while patients were receiving a newer antiepileptic medication compared with valproic acid.^{58,62,68,72-77,80,84,85,87-89,94,99,101}

Sixteen randomized controlled trials reported data on withdrawals due to adverse events when newer antiepileptics were compared versus valproic acid and all were amenable for pooling.^{58,61,68,72-77,80,84,85,87-89,94}

Ten randomized controlled trials reported data on withdrawals due to adverse events when lamotrigine was compared versus valproic acid and were amenable for pooling.^{68,72,75,76,80,85,87-89,94} The risk of withdrawal was significantly decreased by 28 percent when lamotrigine was

compared versus valproic acid (RR 0.72 [0.57 to 0.91]) (Appendix J Figure 41). Given the RD (RD -0.02 [-0.05 to 0.004]), for every 50 patients treated, 1 less patient would withdrawal overall on lamotrigine therapy compared versus valproic acid therapy. No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's: $p=0.066$) was detected.

One randomized controlled trial reported data on withdrawals due to adverse events when oxcarbazepine was compared versus valproic acid.⁵⁸ The risk of withdrawal was nonsignificantly increased by 42 percent oxcarbazepine when was compared versus valproic acid (RR 1.42 [0.68 to 2.99]) (Appendix J Figure 41).

Five randomized controlled trials reported data on withdrawals due to adverse events when topiramate was compared versus valproic acid and were amenable for pooling.^{73,74,77,84,85} The risk of withdrawal was nonsignificantly increased by 6 percent when topiramate was compared versus valproic acid (RR 1.06 [0.70 to 1.61]) (Appendix J Figure 41). A moderate level of statistical heterogeneity was detected (I^2 : 40.6 percent) however, publication bias was not detected (Egger's: $p=0.153$).

One randomized controlled trial reported data on withdrawals due to adverse events when vigabatrin was compared versus valproic acid.⁶¹ The risk of withdrawal was nonsignificantly decreased by 1 percent when vigabatrin was compared versus valproic acid (RR 0.9 [0.47 to 2.07]) (Appendix J Figure 41).

In the pooled analysis of 16 randomized controlled trials reporting data on withdrawals due to adverse events when lamotrigine, oxcarbazepine, topiramate, or vigabatrin were compared versus valproic acid.^{58,61,68,72-77,80,84,85,87-89,94} The risk of withdrawal was nonsignificantly decreased by 10 percent when the newer agents were compared versus valproic acid in patients (RR 0.90 [0.75 to 1.08]) (Appendix J Figure 41). A low level of statistical heterogeneity (I^2 : 3.1 percent) was detected, but publication bias was not detected (Egger's: $p=0.840$).

Ethosuximide Versus Newer

One randomized controlled trial reported withdrawals due to adverse events while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ The risk of overall withdrawal was nonsignificantly decreased by 29 percent when lamotrigine was compared versus ethosuximide (RR 0.71 [0.45 to 1.12]).

Innovator Versus Generic Drug Evaluation

Ten trials (nine randomized controlled trials^{108-113,115,120,121} and one prospective nonrandomized trial)¹¹⁷ reported withdrawals due to adverse events while patients were receiving innovator and their associated generic antiepileptic medications.

Seven randomized controlled trials reported on withdrawals due to adverse events for innovator carbamazepine versus one or more generic versions and were suitable for meta-analysis.^{108-113,115} Only one of the trials utilized a discernable Food and Drug Administration (FDA) "A" rated generic carbamazepine product.¹¹² The risk of withdrawals due to adverse effects is nonsignificantly decreased by 15 percent when generic carbamazepine was used versus innovator carbamazepine (RR 0.85 [0.25 to 2.88]) (Appendix J Figure 43). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.5877$).

Three trials (two randomized controlled trials,^{120,121} and one prospective nonrandomized trial¹¹⁷) reported on withdrawals due to adverse events for innovator phenytoin versus three generic versions and were all suitable for meta-analysis. None of the trials used discernable FDA "A" rated generics. The risk of withdrawals due to adverse effects is nonsignificantly decreased by 34 percent when generic phenytoin was used versus innovator phenytoin (RR 0.66 [0.10 to

4.42]) (Appendix J Figure 43). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.108$).

Ten trials (nine randomized controlled trials,^{108-113,115,120,121} and one prospective nonrandomized trial¹¹⁷) reported on withdrawals due to adverse events for any innovator versus generic versions of antiepileptic medication and they were all suitable for meta-analysis. The risk of withdrawals due to adverse effects is nonsignificantly decreased by 21 percent when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications (RR 0.79 [0.28 to 2.20]) (Appendix J Figure 43). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.282$).

None of the available drugs were in BCS Class I, so analysis was not possible. The BCS Class II analysis is the same as any analysis for any antiepileptic medications (RR 0.79 [0.28 to 2.20]) (Appendix J Figure 43).

One randomized controlled trial reported on the comparison of an innovator to a discernable FDA "A" rated generic product, in this case carbamazepine.¹¹² The risk of withdrawals due to adverse effects is equivalent when "A" rated generic carbamazepine was used versus innovator carbamazepine (RR 1.00 [0.11 to 9.22]) (Appendix J Figure 43).

Neurological Adverse Events

Headache

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer. Seventeen studies (15 randomized controlled trials and 2 observational studies) reported headache while patients were receiving a newer antiepileptic medications compared with carbamazepine.^{47,52,53,55,56,60,62,63,70,74,76-78,82,85,99,105}

Fifteen randomized controlled trials reported data on headache when newer antiepileptics were compared versus carbamazepine^{47,52,53,55,56,60,62,63,70,74,76-78,82,85} and were all amenable to pooling.

Three trials comparing gabapentin to carbamazepine reported data on headache.^{60,78,85} Risk of headache is nonsignificantly decreased by 7 percent when gabapentin is used versus carbamazepine (RR 0.93 [0.67 to 1.28]) (Appendix J Figure 44). No statistical heterogeneity was detected (I^2 : 0 percent), but significant publication bias was detected (Egger's $p=0.046$).

Seven trials comparing lamotrigine to carbamazepine reported data on headache.^{52,55,62,70,76,78,85} Risk of headache is nonsignificantly increased by 6 percent when lamotrigine is used versus carbamazepine (RR 1.06 [0.84 to 1.33]) (Appendix J Figure 44). A low level of statistical heterogeneity (I^2 : 13.8 percent) was detected, but no publication bias was detected (Egger's $p=0.880$).

Three trials comparing oxcarbazepine to carbamazepine reported data on headache.^{47,82,85} Risk of headache is nonsignificantly decreased by 15 percent when oxcarbazepine is used versus carbamazepine (RR 0.85 [0.44 to 1.66]) (Appendix J Figure 44). No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Three trials comparing topiramate to carbamazepine reported data on headache.^{74,77,85} Risk of headache is significantly decreased by 37 percent when topiramate is used versus carbamazepine (RR 0.63 [0.41 to 0.96]) (Appendix J Figure 44). Given the RD (RD -0.057

[-0.144 to 0.030]), for every 18 patients treated, 1 less patient would develop headache from treatment with topiramate than with carbamazepine. A low level of statistical heterogeneity (I^2 : 33.3 percent) was detected, but no publication bias was detected (Egger's $p=0.308$).

Three trials comparing vigabatrin to carbamazepine reported data on headache.^{53,56,63} Risk of headache is nonsignificantly increased by 13 percent when vigabatrin is used versus carbamazepine (RR 1.13 [0.55 to 2.32]) (Appendix J Figure 44). A low level of statistical heterogeneity was detected (I^2 : 10.5 percent), but tests for publication bias could not be performed.

Fifteen trials comparing newer antiepileptic medications to carbamazepine reported data on headache.^{47,52,53,55,56,60,62,63,70,74,76-78,82,85} Risk of headache is nonsignificantly decreased by 8 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.92 [0.78 to 1.08]) (Appendix J Figure 44). A low level of statistical heterogeneity was detected (I^2 : 8.6 percent), but no publication bias was detected (Egger's $p=0.689$).

Five observational studies reported data on headache while patients were receiving a newer antiepileptic medication compared with carbamazepine and all five were amenable for pooling.^{95,99,103-105}

One observational study comparing lamotrigine to carbamazepine reported data on headache.⁹⁹ Risk of headache is nonsignificantly decreased by 55 percent when lamotrigine is used versus carbamazepine (RR 0.45 [0.11 to 1.74]) (Appendix J Figure 45).

One observational study comparing topiramate to carbamazepine reported data on headache.¹⁰⁵ Risk of headache is nonsignificantly decreased by 58 percent when topiramate is used versus carbamazepine (RR 0.42 [0.12 to 1.50]) (Appendix J Figure 45).

Two observational studies comparing newer antiepileptic medications to carbamazepine reported data on headache.^{99,105} Risk of headache is nonsignificantly decreased by 57 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.43 [0.16 to 1.18]) (Appendix J Figure 45).

Two randomized controlled trials reported data on headache when newer antiepileptics were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86}

One randomized controlled trial reported data on headache when lamotrigine was compared with sustained-release carbamazepine.⁸⁶ The risk of headache was nonsignificantly decreased by 1 percent when lamotrigine was compared versus sustained-release carbamazepine (RR 0.99 [0.44 to 2.22]) (Appendix J Figure 46).

One randomized controlled trial reported data on headache when levetiracetam was compared with controlled-release carbamazepine.⁸¹ The risk of headache was nonsignificantly decreased by 19 percent when levetiracetam was compared versus controlled-release carbamazepine (RR 0.81 [0.60 to 1.10]) (Appendix J Figure 46).

Two randomized controlled trials reported data on headache when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86} The risk of headache was nonsignificantly decreased by 17 percent when either newer agent was compared with controlled- or sustained-release carbamazepine [RR 0.83 (0.63 to 1.10)] (Appendix J Figure 46).

Phenytoin Versus Newer. Four trials reported data on headache while patients were receiving a newer antiepileptic medications compared with phenytoin^{57,59,64,90} and were all amenable to pooling.

One trial comparing lamotrigine to phenytoin reported data on headache.⁶⁴ Risk of headache is nonsignificantly decreased by 45 percent when lamotrigine is used versus phenytoin (RR 0.55 [0.26 to 1.14]) (Appendix J Figure 47).

Two trials comparing oxcarbazepine to phenytoin reported data on headache.^{57,59} Risk of headache is nonsignificantly decreased by 18 percent when oxcarbazepine is used versus phenytoin (RR 0.82 [0.54 to 1.25]) (Appendix J Figure 47).

One trial comparing topiramate to phenytoin reported data on headache.⁹⁰ Risk of headache is nonsignificantly decreased by 29 percent when topiramate is used versus phenytoin (RR 0.71 [0.34 to 1.45]) (Appendix J Figure 47).

Four trials comparing newer antiepileptic medications to phenytoin reported data on headache.^{57,59,64,90} Risk of headache is nonsignificantly decreased by 26 percent when newer antiepileptic medications are used versus phenytoin (RR 0.74 [0.53 to 1.02]) (Appendix J Figure 47). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.623$).

Valproic Acid Versus Newer. Seventeen (15 randomized controlled trials and 2 observational studies) reported headache while patients were receiving a newer antiepileptic medications compared with valproic acid.^{50,51,58,68,72,74-77,82,84,85,88,89,94,99,105}

Fifteen trials reported data on headache when newer antiepileptics were compared versus valproic acid^{50,51,58,68,72,74-77,82,84,85,88,89,94} and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on headache.⁵¹ Risk of headache is nonsignificantly decreased by 66 percent when felbamate is used versus valproic acid (RR 0.34 [0.11 to 1.07]) (Appendix J Figure 48).

Eight trials comparing lamotrigine to valproic acid reported data on headache.^{68,72,75,76,85,88,89,94} Risk of headache is nonsignificantly increased by 3 percent when lamotrigine is used versus valproic acid (RR 1.03 [0.73 to 1.45]) (Appendix J Figure 48). A low level of statistical heterogeneity was detected (I^2 : 6.8 percent), but no significant publication bias was detected (Egger's $p=0.158$).

Two trials comparing oxcarbazepine to valproic acid reported data on headache.^{58,82} Risk of headache is significantly decreased by 46 percent when oxcarbazepine is used versus valproic acid (RR 0.54 [0.32 to 0.93]) (Appendix J Figure 48). Given the RD (RD -0.083 [-0.160 to -0.007]), for every 13 patients treated, 1 less patient would develop headache from treatment with oxcarbazepine than with valproic acid.

Four trials comparing topiramate to valproic acid reported data on headache.^{74,77,84,85} Risk of headache is nonsignificantly decreased by 6 percent when topiramate is used versus valproic acid (RR 0.94 [0.62 to 1.43]) (Appendix J Figure 48). No statistical heterogeneity was detected (I^2 : 0 percent), but statistically significant publication bias was detected (Egger's $p=0.048$).

Fifteen trials comparing newer antiepileptic medications to valproic acid reported data on headache.^{50,51,58,68,72,74-77,82,84,85,88,89,94} Risk of headache is nonsignificantly decreased by 10 percent when newer antiepileptic medications are used versus valproic acid (RR 0.90 [0.70 to 1.16]) (Appendix J Figure 48). A low level of statistical heterogeneity (I^2 : 12.9 percent) and a trend towards significant publication bias was detected (Egger's $p=0.082$).

Two observational studies reported on headache while patients were receiving a newer antiepileptic medication compared with valproic acid and all were amenable for pooling.^{99,105}

One observational study comparing lamotrigine to valproic acid reported data on headache.⁹⁹ Risk of headache is nonsignificantly increased by 36 percent when lamotrigine is used versus valproic acid (RR 1.36 [0.29 to 6.19]) (Appendix J Figure 49).

One observational study comparing topiramate to valproic acid reported data on headache.¹⁰⁵ Risk of headache is nonsignificantly decreased by 45 percent when topiramate is used versus valproic acid (RR 0.55 [0.16 to 1.82]) (Appendix J Figure 49).

Two observational studies comparing newer antiepileptic medications to valproic acid reported data on headache.^{99,105} Risk of headache is nonsignificantly decreased by 23 percent when newer antiepileptic medications are used versus valproic acid (RR 0.77 [0.28 to 2.13]) (Appendix J Figure 49).

Ethosuximide Versus Newer. One randomized controlled trial reported data on headache while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ The risk of headache was nonsignificantly decreased by 34 percent when lamotrigine was compared versus ethosuximide (RR 0.66 [0.33 to 1.29]).

Innovator Versus Generic Drug Evaluation

Two randomized controlled trials reported data on headache when generic carbamazepine was compared to innovator carbamazepine.^{109,110} Headache is nonsignificantly increased by 4 percent when generic carbamazepine was used versus innovator carbamazepine (RR 1.04 [0.59 to 1.82]). Headache was nonsignificantly decreased by 68 percent when generic phenytoin was used versus innovator phenytoin (RR 0.32 [0.04 to 2.40]). Analysis for any antiepileptic drug showed that headache was nonsignificantly decreased by 5 percent when generic antiepileptic medications were used versus innovator antiepileptic medications (RR 0.95 [0.55 to 1.64]). BCS Class II antiepileptic medications analysis is the same as any antiepileptic drug analysis. No data was available to perform BCS Class I antiepileptic medications analysis.

Fatigue

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer. Seven randomized controlled trials reported data on fatigue when newer antiepileptics were compared versus carbamazepine^{56,60,63,74,77,80,82} and were all amenable to pooling.

One trial comparing gabapentin to carbamazepine reported data on fatigue.⁶⁰ Risk of fatigue is significantly decreased by 63 percent when gabapentin is used versus carbamazepine (RR 0.37 [0.22 to 0.62]) (Appendix J Figure 50). Given the RD (RD -0.188 [-0.300 to -0.076]), for every six patients treated, one less patient would develop fatigue from treatment with gabapentin than with carbamazepine.

One trial comparing lamotrigine to carbamazepine reported data on fatigue.⁸⁰ Risk of fatigue is significantly decreased by 66 percent when lamotrigine is used versus carbamazepine (RR 0.34 [0.20 to 0.58]) (Appendix J Figure 50). Given the RD (RD -0.284 [-0.411 to -0.157]), for every four patients treated, one less patient would develop fatigue from treatment with lamotrigine than with carbamazepine.

One trial comparing oxcarbazepine to carbamazepine reported data on fatigue.⁸² Risk of fatigue is nonsignificantly decreased by 11 percent when oxcarbazepine is used versus carbamazepine (RR 0.89 [0.31 to 2.70]) (Appendix J Figure 50).

Two trials comparing topiramate to carbamazepine reported data on fatigue.^{74,77} Risk of fatigue is significantly decreased by 46 percent when topiramate is used versus carbamazepine (RR 0.54 [0.35 to 0.83]) (Appendix J Figure 50). Given the RD (RD -0.099 [-0.172 to -0.027]), for every 11 patients treated, 1 less patient would develop fatigue from treatment with topiramate than with carbamazepine. A low level of statistical heterogeneity was detected (I^2 : 10.5 percent), but no significant publication bias was detected (Egger's $p=0.092$).

Two trials comparing vigabatrin to carbamazepine reported data on fatigue.^{56,63} Risk of fatigue is nonsignificantly increased by 2 percent when vigabatrin is used versus carbamazepine (RR 1.02 [0.59 to 1.76]) (Appendix J Figure 50).

Seven trials comparing newer antiepileptic medications to carbamazepine reported data on fatigue.^{56,60,63,74,77,80,82} Risk of fatigue is significantly decreased by 43 percent when newer AEDs are used versus carbamazepine (RR 0.57 [0.41 to 0.80]) (Appendix J Figure 50). Given the RD (RD -0.098 [-0.167 to -0.029]), for every 11 patients treated, 1 less patient would develop fatigue from treatment with newer AED than with carbamazepine. A high level of statistical heterogeneity was detected (I^2 : 50.2 percent), but no publication bias was seen (Egger's $p=0.952$).

One randomized controlled trial reported data on fatigue while patients were receiving levetiracetam compared with controlled-release carbamazepine.⁸¹ Risk of fatigue is nonsignificantly increased by 17 percent when levetiracetam is used versus controlled-release carbamazepine (RR 1.17 [0.80 to 1.72]).

Phenytoin Versus Newer. One randomized controlled trials reported fatigue while patients were receiving a newer antiepileptic medication (topiramate) compared with phenytoin.⁹⁰ Risk of fatigue is nonsignificantly increased by 5 percent when topiramate is used versus phenytoin (RR 1.05 [0.49 to 2.25]).

Valproic Acid Versus Newer. Eight randomized controlled trials reported data on fatigue when newer antiepileptics were compared versus valproic acid^{50,51,74,77,80,82,84,89} and were all amenable to pooling.

Two trials comparing felbamate to valproic acid reported data on fatigue.^{50,51} Risk of fatigue is nonsignificantly decreased by 18 percent when felbamate is used versus valproic acid (RR 0.82 [0.13 to 5.10]) (Appendix J Figure 51).

Two trials comparing lamotrigine to valproic acid reported data on fatigue.^{80,89} Risk of fatigue is nonsignificantly decreased by 32 percent when lamotrigine is used versus valproic acid (RR 0.68 [0.37 to 1.23]) (Appendix J Figure 51).

One trial comparing oxcarbazepine to valproic acid reported data on fatigue.⁸² Risk of fatigue is nonsignificantly increased by 85 percent when oxcarbazepine is used versus valproic acid (RR 1.85 [0.48 to 7.58]) (Appendix J Figure 51).

Three trials comparing topiramate to valproic acid reported data on fatigue.^{74,77,84} Risk of fatigue is significantly decreased by 49 percent when topiramate is used versus valproic acid (RR 0.51 [0.33 to 0.78]) (Appendix J Figure 51). Given the RD (RD -0.111 [-0.196 to -0.025]), for every 10 patients treated, 1 less patient would develop fatigue from treatment with topiramate than with valproic acid. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.475$).

Eight trials comparing newer antiepileptic medications to valproic acid reported data on fatigue.^{50,51,74,77,80,82,84,89} Risk of fatigue is significantly decreased by 39 percent when newer antiepileptic medications are used versus valproic acid (RR 0.61 [0.44 to 0.85]) (Appendix J Figure 51). Given the RD (RD -0.045 [-0.085 to -0.004]), for every 23 patients treated, 1 less patient would develop fatigue from treatment with newer AED than with valproic acid. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.459$).

Ethosuximide Versus Newer. One randomized controlled trial reported data on fatigue while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ The risk of fatigue was nonsignificantly decreased by 10 percent when lamotrigine was compared versus ethosuximide (RR 0.90 [0.45 to 1.80]).

Innovator Versus Generic Drug Evaluation

Data given in general adverse event section below.

Somnolence

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer. Twelve studies (eight randomized controlled trials and four observational studies) reported somnolence while patients were receiving a newer antiepileptic medications compared with carbamazepine.^{52,55,60,62,70,76,77,79,83,99,103,105}

Eight trials reported data on somnolence when newer antiepileptics were compared versus carbamazepine^{52,55,60,62,70,76,77,83} and were all amenable to pooling.

One trial comparing gabapentin to carbamazepine reported data on somnolence.⁶⁰ Risk of somnolence is significantly decreased by 59 percent when gabapentin is used versus carbamazepine (RR 0.41 [0.18 to 0.93]) (Appendix J Figure 52). Given the RD (RD -0.081 [-0.165 to 0.002]), for every 13 patients treated, 1 less patient would develop somnolence from treatment with gabapentin than with carbamazepine. No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Five trials comparing lamotrigine to carbamazepine reported data on somnolence.^{52,55,62,70,76} Risk of somnolence is significantly decreased by 56 percent when lamotrigine is used versus carbamazepine (RR 0.44 [0.33 to 0.58]) (Appendix J Figure 52). Given the RD (RD -0.085 [-0.117 to -0.052]), for every 12 patients treated, 1 less patient would develop somnolence from treatment with lamotrigine than with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.163$).

Two trials comparing topiramate to carbamazepine reported data on somnolence.^{77,83} Risk of somnolence is the same when topiramate is used versus carbamazepine (RR 1.00 [0.43 to 2.30]) (Appendix J Figure 52). No significant statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Eight trials comparing newer antiepileptic medications to carbamazepine reported data on somnolence.^{52,55,60,62,70,76,77,83} Risk of somnolence is significantly decreased by 53 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.47 [0.36 to 0.61]) (Appendix J Figure 52). Given the RD (RD -0.075 [-0.104 to -0.046]), for every 14 patients treated, 1 less patient would develop somnolence from treatment with newer AED than with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.784$).

Four observational studies reported on somnolence while patients were receiving a newer antiepileptic medication compared with carbamazepine and all were amenable for pooling.^{79,99,103,105}

One observational study comparing lamotrigine to carbamazepine reported data on somnolence.⁹⁹ Risk of somnolence is nonsignificantly decreased by 59 percent when lamotrigine is used versus carbamazepine (RR 0.41 [0.04 to 3.97]) (Appendix J Figure 53).

One observational study comparing levetiracetam to carbamazepine reported data on somnolence.¹⁰³ Risk of somnolence is significantly decreased by 77 percent when levetiracetam

is used versus carbamazepine (RR 0.23 [0.09 to 0.57]) (Appendix J Figure 53). Given the RD (RD -0.309 [-0.535 to -0.083]), for every four patients treated, one less patient would develop somnolence from treatment with levetiracetam than with carbamazepine.

One observational study comparing topiramate to carbamazepine reported data on somnolence.¹⁰⁵ Risk of somnolence is nonsignificantly decreased by 72 percent when topiramate is used versus carbamazepine (RR 0.28 [0.02 to 3.38]) (Appendix J Figure 53).

One observational study comparing vigabatrin to carbamazepine reported data on somnolence.⁷⁹ Risk of somnolence is nonsignificantly decreased by 46 percent when vigabatrin is used versus carbamazepine (RR 0.54 [0.12 to 2.13]) (Appendix J Figure 53).

Four observational studies comparing newer antiepileptic medications to carbamazepine reported data on somnolence.^{79,99,103,105} Risk of somnolence is significantly decreased by 70 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.30 [0.14 to 0.62]) (Appendix J Figure 53). Given the RD (RD -0.044 [-0.117 to 0.029]), for every 23 patients treated, 1 less patient would develop somnolence from treatment with newer AED than with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.409$).

One randomized controlled trial reported data on somnolence while patients were receiving levetiracetam compared with controlled release carbamazepine.⁶² Risk of somnolence is nonsignificantly increased by 21 percent when levetiracetam is used versus carbamazepine-CR (RR 1.21 [0.75 to 1.96]).

Phenytoin Versus Newer. Four trials reported somnolence while patients were receiving a newer antiepileptic medications compared with phenytoin^{57,59,64,90} and were all amenable to pooling.

One trial comparing lamotrigine to phenytoin reported data on somnolence.⁶⁴ Risk of somnolence is significantly decreased by 75 percent when lamotrigine is used versus phenytoin (RR 0.25 [0.11 to 0.54]) (Appendix J Figure 54). Given the RD (RD -0.21 [-0.32 to -0.11]), for every five patients treated with lamotrigine, one less patient would develop somnolence compared with those treated with phenytoin.

Two trials comparing oxcarbazepine to phenytoin reported data on somnolence.^{57,59} Risk of somnolence is nonsignificantly decreased by 4 percent when oxcarbazepine is used versus phenytoin (RR 0.96 [0.72 to 1.28]) (Appendix J Figure 54).

One trial comparing topiramate to phenytoin reported data on somnolence.⁹⁰ Risk of somnolence is nonsignificantly decreased by 14 percent when topiramate is used versus phenytoin (RR 0.86 [0.46 to 1.59]) (Appendix J Figure 54).

Four trials comparing newer antiepileptic medications to phenytoin reported data on somnolence.^{57,59,64,90} Risk of somnolence is nonsignificantly decreased by 28 percent when newer antiepileptic medications are used versus phenytoin (RR 0.72 [0.44 to 1.18]) (Appendix J Figure 54). A high level of statistical heterogeneity was detected (I^2 : 70.1 percent), but publication bias was not detected (Egger's $p=0.124$).

Valproic Acid Versus Newer. Eleven studies (nine randomized controlled trials and two observational studies) reported somnolence while patients were receiving a newer antiepileptic medications compared with valproic acid.^{50,51,58,68,72,76,77,84,89,99,105}

Nine randomized controlled trials reported data on somnolence when newer antiepileptics were compared versus valproic acid.^{50,51,58,68,72,76,77,84,89} and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on somnolence.⁵¹ Risk of somnolence is nonsignificantly decreased by 49 percent when felbamate is used versus valproic acid (RR 0.51 [0.07 to 3.78]) (Appendix J Figure 55).

Five trials comparing lamotrigine to valproic acid reported data on somnolence.^{50,68,72,76,89} Risk of somnolence is nonsignificantly increased by 27 percent when lamotrigine is used versus valproic acid (RR 0.73 [0.36 to 1.45]) (Appendix J Figure 55). A low level of statistical heterogeneity was detected (I^2 : 41.3 percent), but publication bias was not detected (Egger's $p=0.869$).

One trial comparing oxcarbazepine to valproic acid reported data on somnolence.⁵⁸ Risk of somnolence is nonsignificantly decreased by 25 percent when oxcarbazepine is used versus valproic acid (RR 0.75 [0.43 to 1.28]) (Appendix J Figure 55).

Two trials comparing topiramate to valproic acid reported data on somnolence.^{77,84} Risk of somnolence is nonsignificantly decreased by 62 percent when topiramate is used versus valproic acid (RR 0.38 [0.12 to 1.21]) (Appendix J Figure 55). A low level of statistical heterogeneity was detected (I^2 : 25.7 percent), but tests for publication bias could not be performed.

Nine trials comparing newer antiepileptic medications to valproic acid reported data on somnolence.^{50,51,58,68,72,76,77,84,89} Risk of somnolence is significantly decreased by 35 percent when newer antiepileptic medications are used versus valproic acid (RR 0.65 [0.43 to 0.98]) (Appendix J Figure 55). Given the RD (RD -0.041 [-0.092 to 0.010]), for every 25 patients treated, 1 less patient would develop somnolence from treatment with newer antiepileptic medications than with valproic acid. A low level of statistical heterogeneity was detected (I^2 : 19.9 percent), but publication bias was not detected (Egger's $p=0.639$).

Two observational studies reported on somnolence while patients were receiving a newer antiepileptic medication compared with valproic acid and both were amenable for pooling.^{99,105}

One observational study comparing lamotrigine to valproic acid reported data on somnolence.⁹⁹ Risk of somnolence is nonsignificantly increased by 29 percent when lamotrigine is used versus valproic acid (RR 1.29 [0.14 to 12.28]) (Appendix J Figure 56).

One observational study comparing topiramate to valproic acid reported data on somnolence.¹⁰⁵ Risk of somnolence is nonsignificantly decreased by 77 percent when topiramate is used versus valproic acid (RR 0.23 [0.02 to 2.46]) (Appendix J Figure 56).

Two observational studies comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with new onset epilepsy.^{99,105} Risk of somnolence is nonsignificantly decreased by 42 percent when newer antiepileptic medications are used versus valproic acid (RR 0.58 [0.08 to 4.38]) (Appendix J Figure 56).

Ethosuximide Versus Newer. One randomized controlled trial reported data on somnolence while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ The risk of somnolence was significantly decreased by 78 percent when lamotrigine was compared versus ethosuximide (RR 0.22 [0.07 to 0.70]). Given the RD (-0.07 [-0.12 to -0.020]), for every 15 patients treated with lamotrigine, 1 less patient would develop somnolence compared with those treated with ethosuximide.

Innovator Versus Generic Drug Evaluation

Somnolence is nonsignificantly decreased by 10 percent when generic carbamazepine was used versus innovator carbamazepine (RR 0.90 [0.48 to 1.70]). Analysis for any antiepileptic medications and BCS Class II antiepileptic medications is the same as carbamazepine analysis. No data was available to perform BCS Class I antiepileptic medications analysis.

Dizziness

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer. Nineteen studies (16 randomized controlled trials and 3 observational studies) reported data on dizziness while patients were receiving a newer antiepileptic medications compared with carbamazepine.^{52,53,55,56,60,62,63,70,74,76-78,82,83,85,90,99,103,105}

Sixteen randomized controlled trials reported data on dizziness when newer antiepileptics were compared versus carbamazepine^{52,53,55,56,60,62,63,70,74,76-78,82,83,85,90} and were all amenable to pooling.

Three trials comparing gabapentin to carbamazepine reported data on dizziness.^{60,78,85} Risk of dizziness is nonsignificantly decreased by 2 percent when gabapentin is used versus carbamazepine (RR 0.98 [0.75 to 1.28]) (Appendix J Figure 57). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.785$).

Seven trials comparing lamotrigine to carbamazepine reported data on dizziness.^{52,55,62,70,76,78,85} Risk of dizziness is significantly decreased by 21 percent when lamotrigine is used versus carbamazepine (RR 0.79 [0.64 to 0.97]) (Appendix J Figure 57). Given the RD (RD -0.015 [-0.034 to 0.005]), for every 67 patients treated, 1 less patient would develop dizziness from treatment with lamotrigine than with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.085$).

Two trials comparing oxcarbazepine to carbamazepine reported data on dizziness.^{82,85} Risk of dizziness is nonsignificantly increased by 78 percent when oxcarbazepine is used versus carbamazepine (RR 1.78 [0.87 to 3.63]) (Appendix J Figure 57).

Five trials comparing topiramate to carbamazepine reported data on dizziness.^{74,77,83,85,90} Risk of dizziness is significantly decreased by 34 percent when topiramate is used versus carbamazepine (RR 0.66 [0.49 to 0.90]) (Appendix J Figure 57). Given the RD (RD -0.032 [-0.073 to 0.008]), for every 32 patients treated, 1 less patient would develop vomiting from treatment with topiramate than with carbamazepine. No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.292$).

Three trials comparing vigabatrin to carbamazepine reported data on dizziness.^{53,56,63} Risk of dizziness is nonsignificantly decreased by 56 percent when vigabatrin is used versus carbamazepine (RR 0.44 [0.13 to 1.50]) (Appendix J Figure 57). A high level of statistical heterogeneity was detected (I^2 : 70.4 percent), but tests for publication bias could not be performed.

Sixteen trials comparing newer antiepileptic medications to carbamazepine reported data on dizziness.^{52,53,55,56,60,62,63,70,74,76-78,82,83,85,90} Risk of dizziness is significantly decreased by 22 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.78 [0.67 to 0.91]) (Appendix J Figure 57). Given the RD (RD -0.020 [-0.041 to -0.0001]), for every 50 patients treated, 1 less patient would develop dizziness from treatment with newer AED than with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.256$).

Three observational studies reported dizziness while patients were receiving a newer antiepileptic medication compared with carbamazepine and all were amenable for pooling.^{99,103,105}

One observational study comparing lamotrigine to carbamazepine reported data on dizziness.⁹⁹ Risk of dizziness is nonsignificantly decreased by 87 percent when lamotrigine is used versus carbamazepine (RR 0.13 [0.01 to 1.24]) (Appendix J Figure 58).

One observational study comparing topiramate to carbamazepine reported data on dizziness.¹⁰⁵ Risk of dizziness is nonsignificantly decreased by 58 percent when topiramate is used versus carbamazepine (RR 0.42 [0.06 to 3.17]) (Appendix J Figure 58).

Three observational studies comparing newer antiepileptic medications to carbamazepine reported data on dizziness.^{99,103,105} Risk of dizziness is significantly decreased by 79 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.21 [0.05 to 0.89]) (Appendix J Figure 58). Given the RD (RD -0.028 [-0.062 to 0.005]), for every 36 patients treated, 1 less patient would develop dizziness from treatment with newer AED than with carbamazepine. No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

One observational study comparing newer antiepileptic medications with carbamazepine reported data on dizziness in patients with new partial epilepsy.¹⁰³ Risk of dizziness is nonsignificantly decreased by 85 percent when levetiracetam is used versus carbamazepine (RR 0.15 [0.02 to 1.13]) (Appendix J Figure 58).

Two randomized controlled trials reported data on dizziness when newer antiepileptics were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86}

One randomized controlled trial reported data on dizziness when lamotrigine was compared with sustained-release carbamazepine.⁸⁶ The risk of dizziness was nonsignificantly increased by 43 percent when lamotrigine was used versus sustained release carbamazepine (RR 1.43 [0.66 to 3.13]) (Appendix J Figure 59).

One randomized controlled trial reported data on dizziness when levetiracetam was compared with controlled-release carbamazepine.⁸¹ The risk of dizziness was nonsignificantly decreased by 21 percent when levetiracetam is used versus carbamazepine-CR (RR 0.79 [0.51 to 1.22]) (Appendix J Figure 59).

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.^{81,86} The risk of dizziness was nonsignificantly decreased by 4 percent when either newer agent was compared with controlled- or sustained-release carbamazepine (RR 0.96 [0.56 to 1.66]) (Appendix J Figure 59).

Phenytoin Versus Newer. Three randomized controlled trials reported dizziness while patients were receiving newer antiepileptic medications compared with phenytoin^{57,59,64} and were all amenable to pooling.

One trial comparing lamotrigine to phenytoin reported data on dizziness.⁶⁴ Risk of dizziness is nonsignificantly decreased by 20 percent when lamotrigine is used versus phenytoin (RR 0.80 [0.35 to 1.85]) (Appendix J Figure 60).

Two trials comparing oxcarbazepine to phenytoin reported data on dizziness.^{57,59} Risk of dizziness is nonsignificantly decreased by 38 percent when oxcarbazepine is used versus phenytoin (RR 0.62 [0.31 to 1.24]) (Appendix J Figure 60).

Three trials comparing newer antiepileptic medications to phenytoin reported data on dizziness.^{57,59,64} Risk of dizziness is nonsignificantly decreased by 33 percent when newer antiepileptic medications are used versus phenytoin (RR 0.67 [0.43 to 1.05]) (Appendix J Figure 60). No statistical heterogeneity was detected (I^2 : 18.1 percent) but tests for publication bias could not be performed.

One observational study comparing newer antiepileptic medications to phenytoin reported data on dizziness in children 18 years of age or younger.⁵⁹ Risk of dizziness is significantly

decreased by 58 percent when newer antiepileptic medications are used versus phenytoin (RR 0.42 [0.20 to 0.85]). Given the RD (RD -0.130 [-0.232 to -0.027]), for every eight patients treated, one less patient would develop dizziness from treatment with newer AED than with phenytoin.

Valproic Acid Versus Newer. Fourteen studies (12 randomized controlled trials and 2 observational studies) reported dizziness while patients were receiving a newer antiepileptic medications compared with valproic acid.^{51,58,68,72,74,76,77,82,84,85,88,89,99,105}

Twelve randomized controlled trials reported data on dizziness when newer antiepileptics were compared versus valproic acid^{51,58,68,72,74,76,77,82,84,85,88,89} and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on dizziness.⁵¹ Risk of dizziness is nonsignificantly decreased by 49 percent when felbamate is used versus valproic acid (RR 0.51 [0.07 to 3.78]) (Appendix J Figure 61).

Six trials comparing lamotrigine to valproic acid reported data on dizziness.^{68,72,76,85,88,89} Risk of dizziness is nonsignificantly increased by 34 percent when lamotrigine is used versus valproic acid (RR 1.34 [0.85 to 2.12]) (Appendix J Figure 61). No statistical heterogeneity was detected (I^2 : 0 percent), but statistically significant publication bias was detected (Egger's $p=0.006$).

Two trials comparing oxcarbazepine to valproic acid reported data on dizziness.^{58,82} Risk of dizziness is nonsignificantly increased by 15 percent when oxcarbazepine is used versus valproic acid (RR 1.15 [0.33 to 3.97]) (Appendix J Figure 61).

Four trials comparing topiramate to valproic acid reported data on dizziness.^{74,77,84,85} Risk of dizziness is nonsignificantly decreased by 27 percent when topiramate is used versus valproic acid (RR 0.73 [0.36 to 1.49]) (Appendix J Figure 61). A low level of statistical heterogeneity (I^2 : 16.3 percent) was detected, but no publication bias was detected (Egger's $p=0.113$).

Twelve trials comparing newer antiepileptic medications to valproic acid reported data on dizziness.^{51,58,68,72,74,76,77,82,84,85,88,89} Risk of dizziness is nonsignificantly decreased by 2 percent when newer antiepileptic medications are used versus valproic acid (RR 0.98 [0.71 to 1.35]) (Appendix J Figure 61). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.111$).

Two observational studies reported dizziness while patients were receiving a newer antiepileptic medication compared with carbamazepine and both were amenable for pooling.^{99,105}

One observational study comparing lamotrigine to valproic acid reported data on dizziness.⁹⁹ Risk of dizziness is nonsignificantly decreased by 57 percent when lamotrigine is used versus valproic acid (RR 0.43 [0.04 to 5.17]) (Appendix J Figure 62).

One observational study comparing topiramate to valproic acid reported data on dizziness.¹⁰⁵ Risk of dizziness is nonsignificantly decreased by 45 percent when topiramate is used versus valproic acid (RR 0.55 [0.08 to 3.76]) (Appendix J Figure 62).

Two observational studies comparing newer antiepileptic medications to valproic acid reported data on dizziness.^{99,105} Risk of dizziness is nonsignificantly decreased by 50 percent when newer antiepileptic medications are used versus valproic acid (RR 0.50 [0.08 to 3.18]) (Appendix J Figure 62).

Ethosuximide Versus Newer. One randomized controlled trial reported data on dizziness while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ The risk of dizziness was nonsignificantly decreased by 54 percent when lamotrigine was compared versus ethosuximide (RR 0.46 [0.15 to 1.38]).

Innovator Versus Generic Drug Evaluation

Dizziness is nonsignificantly decreased by 50 percent when generic carbamazepine was used versus innovator carbamazepine (RR 0.50 [0.07 to 3.33]) in the one trial that reported this.¹⁰⁹ Results for any antiepileptic medications and BCS Class II antiepileptic medications is the same as carbamazepine results. No data was available for BCS Class I antiepileptic medications.

Combined Neurological Events and Neurological Components

Innovator Versus Generic Drug Evaluation

One controlled clinical trial¹¹⁰ and one controlled observational study¹³⁰ reported data on combined neurological adverse events. Results from the clinical trial showed that 5 out of 23 patients experienced neurological adverse events while receiving generic carbamazepine while only 1 out of 23 patients experienced neurological adverse event while on innovator carbamazepine. This difference was not statistically significant. Data from the observational trial is reported as events per 1,000 person-years (percent) for innovator and generic carbamazepine. In the generic group (n=705), there were 145.7 events per 1,000 person-years (percent), whereas in the innovator group (n=275), there were 75.7 events per 1,000 person-years (percent). This difference is also not statistically significant. None of the trials used discernable FDA “A” rated generics.

Results for any antiepileptic medications and BCS Class II antiepileptic drugs are the same as carbamazepine results given above. Data on BCS Class I antiepileptic medications were not available.

Three controlled clinical trials^{109,110,119} and no controlled observational studies reported individual neurological adverse events. Headache was reported by all three trials, diplopia and somnolence was reported by two trials,^{109,110} and dizziness was reported by only one trial.¹⁰⁹ None of the trials used discernable FDA “A” rated generics.

Diplopia was nonsignificantly increased by 28 percent when generic carbamazepine was used versus innovator carbamazepine (RR 1.28 [0.38 to 4.31]). Analysis for any antiepileptic medications and BCS Class II antiepileptic medications is the same as carbamazepine analysis. No data was available to perform BCS Class I antiepileptic medications analysis.

No controlled clinical trials or controlled observational studies reported data on asthenia, ataxia, nystagmus, or tremor.

Hypotension

Innovator Versus Generic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on hypotension.

Nausea

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Eight randomized controlled trials reported data on nausea when newer antiepileptics were compared versus carbamazepine^{47,52,55,56,74,76,77,85} and were all amenable to pooling.

One trial comparing gabapentin to carbamazepine reported data on nausea.⁸⁵ Risk of nausea is nonsignificantly decreased by 22 percent when gabapentin is used versus carbamazepine (RR 0.78 [0.30 to 2.00]) (Appendix J Figure 63).

Four trials comparing lamotrigine to carbamazepine reported data on nausea.^{52,55,76,85} Risk of nausea is nonsignificantly decreased by 5 percent when lamotrigine is used versus carbamazepine (RR 0.95 [0.56 to 1.60]) (Appendix J Figure 63). A low level of statistical heterogeneity was detected (I^2 : 25.9 percent), but significant publication bias was detected (Egger's $p=0.005$).

Two trials comparing oxcarbazepine to carbamazepine reported data on nausea.^{47,85} Risk of nausea is nonsignificantly increased by 87 percent when oxcarbazepine is used versus carbamazepine (RR 1.87 [0.34 to 10.40]) (Appendix J Figure 63).

Three trials comparing topiramate to carbamazepine reported data on nausea.^{74,77,85} Risk of nausea is significantly decreased by 51 percent when topiramate is used versus carbamazepine (RR 0.49 [0.33 to 0.74]) (Appendix J Figure 63). Given the RD (RD -0.073 [-0.166 to 0.019]), for every 14 patients treated, 1 less patient would develop nausea from treatment with topiramate than with carbamazepine. No significant statistical heterogeneity (I^2 : 0 percent) and no publication bias was detected (Egger's $p=0.300$).

One trial comparing vigabatrin to carbamazepine reported data on nausea.⁵⁶ Risk of nausea is nonsignificantly decreased by 76 percent when vigabatrin is used versus carbamazepine (RR 0.24 [0.04 to 1.47]) (Appendix J Figure 63).

Eight trials comparing newer antiepileptic medications to carbamazepine reported data on nausea.^{47,52,55,56,74,76,77,85} Risk of nausea is nonsignificantly decreased by 31 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.69 [0.46 to 1.02]) (Appendix J Figure 63). A low level of statistical heterogeneity was detected (I^2 : 32.7 percent), but no publication bias were detected (Egger's $p=0.218$).

One randomized controlled trial reported data on nausea while patients were receiving levetiracetam compared with controlled-release carbamazepine.⁸¹ Risk of nausea is nonsignificantly decreased by 34 percent when levetiracetam is used versus controlled-release carbamazepine (RR 0.66 [0.39 to 1.12]).

Phenytoin Versus Newer

Four randomized controlled trials reported nausea while patients were receiving a newer antiepileptic medication compared with phenytoin^{57,59,64,90} and were all amenable to pooling.

One trial comparing lamotrigine to phenytoin reported data on nausea.⁶⁴ Risk of nausea is nonsignificantly increased by 93 percent when lamotrigine is used versus phenytoin (RR 1.93 [0.63 to 6.02]) (Appendix J Figure 64).

Two trials comparing oxcarbazepine to phenytoin reported data on nausea.^{57,59} Risk of nausea is nonsignificantly decreased by 20 percent when oxcarbazepine is used versus phenytoin (RR 0.80 [0.45 to 1.45]) (Appendix J Figure 64).

One trial comparing topiramate to phenytoin reported data on nausea.⁹⁰ Risk of nausea is nonsignificantly decreased by 28 percent when topiramate is used versus phenytoin (RR 0.72 [0.32 to 1.62]) (Appendix J Figure 64).

Four trials comparing newer antiepileptic medications to phenytoin reported data on nausea.^{57,59,64,90} Risk of nausea is nonsignificantly decreased by 12 percent when newer antiepileptic medications are used versus phenytoin (RR 0.88 [0.56 to 1.37]) (Appendix J Figure 64). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.500$).

Valproic Acid Versus Newer

Eleven randomized controlled trials reported data on nausea when newer antiepileptics were compared versus valproic acid^{51,58,68,72,74,76,77,84,85,88,89} and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on nausea.⁵¹ Risk of nausea is nonsignificantly decreased by 66 percent when felbamate is used versus valproic acid (RR 0.34 [0.03 to 4.04]) (Appendix J Figure 65).

Six trials comparing lamotrigine to valproic acid reported data on nausea.^{68,72,76,85,88,89} Risk of nausea is significantly decreased by 52 percent when lamotrigine is used versus valproic acid (RR 0.48 [0.27 to 0.86]) (Appendix J Figure 65). Given the RD (RD -0.043 [-0.086 to -0.001]), for every 24 patients treated, 1 less patient would develop nausea from treatment with lamotrigine than with valproic acid. A low level of statistical heterogeneity was detected (I^2 : 33.8 percent), but publication bias was not detected (Egger's $p=0.982$).

One trial comparing oxcarbazepine to valproic acid reported data on nausea.⁵⁸ Risk of nausea is nonsignificantly decreased by 26 percent when oxcarbazepine is used versus valproic acid (RR 0.74 [0.36 to 1.54]) (Appendix J Figure 65).

Four trials comparing topiramate to valproic acid reported data on nausea.^{74,77,84,85} Risk of nausea is nonsignificantly decreased by 39 percent when topiramate is used versus valproic acid (RR 0.61 [0.36 to 1.04]) (Appendix J Figure 65). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.170$).

Eleven trials comparing newer antiepileptic medications to valproic acid reported data on nausea.^{51,58,68,72,74,76,77,84,85,88,89} Risk of nausea is significantly decreased by 44 percent when newer antiepileptic medications are used versus valproic acid (RR 0.56 [0.41 to 0.77]) (Appendix J Figure 65). Given the RD (RD -0.033 [-0.056 to -0.010]), for every 31 patients treated, 1 less patient would develop nausea from treatment with newer AED than with valproic acid. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.272$).

Innovator Versus Generic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on nausea.

Vomiting

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Three randomized controlled trials reported data on vomiting when newer antiepileptics were compared versus carbamazepine.^{52,62,77} and were all amenable to pooling.

Two trials comparing lamotrigine to carbamazepine reported data on vomiting.^{52,62} Risk of vomiting is nonsignificantly increased by 34 percent when lamotrigine is used versus carbamazepine (RR 1.34 [0.67 to 2.68]) (Appendix J Figure 66).

One trial comparing topiramate to carbamazepine reported data on vomiting.⁷⁷ Risk of vomiting is nonsignificantly decreased by 12 percent when topiramate is used versus carbamazepine (RR 0.88 [0.19 to 4.12]) (Appendix J Figure 66).

Three trials comparing newer antiepileptic medications to carbamazepine reported data on vomiting.^{52,62,77} Risk of vomiting is nonsignificantly increased by 25 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.25 [0.66 to 2.35]) (Appendix J Figure 66). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.315$).

Three trials comparing newer antiepileptic medications to carbamazepine reported data on vomiting in patients with new onset epilepsy.^{52,62,77} Risk of vomiting is nonsignificantly increased by 25 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.25 [0.66 to 2.35]) (Appendix J Figure 66). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.315$).

Phenytoin Versus Newer

Only one randomized controlled trial reported data on vomiting while patients were receiving a newer antiepileptic medication (oxcarbazepine) compared with phenytoin.⁵⁹ This trial was in children 18 years of age or younger. Risk of vomiting is significantly decreased by 91 percent when oxcarbazepine is used versus phenytoin (RR 0.09 [0.01 to 0.89]) (Appendix J Figure 67). Given the RD (RD -0.053 [-0.102 to -0.004]), for every 19 patients treated, 1 less patient would develop vomiting from treatment with oxcarbazepine than with phenytoin.

Valproic Acid Versus Newer

Five randomized controlled trials reported data on vomiting while patients were receiving a newer antiepileptic medications compared with valproic acid.^{51,72,72,77,88}

One trial comparing felbamate to valproic acid reported data on vomiting.⁷⁶ Risk of vomiting is nonsignificantly increased by 3 percent when felbamate is used versus valproic acid (RR 1.03 [0.19 to 5.61]) (Appendix J Figure 68).

Three trials comparing lamotrigine to valproic acid reported data on vomiting.^{68,72,88} Risk of vomiting is nonsignificantly decreased by 34 percent when lamotrigine is used versus valproic acid (RR 0.66 [0.22 to 2.00]) (Appendix J Figure 68). A low level of statistical heterogeneity was detected (I^2 : 55.9 percent), but tests for publication bias could not be performed.

One trial comparing topiramate to valproic acid reported data on vomiting.⁷⁷ Risk of vomiting is nonsignificantly increased by 65 percent when topiramate is used versus valproic acid (RR 1.65 [0.21 to 12.79]) (Appendix J Figure 68).

Five trials comparing newer antiepileptic medications to valproic acid reported data on vomiting.^{51,68,72,77,88} Risk of vomiting is nonsignificantly decreased by 31 percent when newer antiepileptic medications are used versus valproic acid (RR 0.69 [0.34 to 1.42]) (Appendix J Figure 68). A low level of statistical heterogeneity was detected (I^2 : 16.5 percent) and statistically significant publication bias was detected (Egger's $p=0.036$).

Innovator Versus Generic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on vomiting.

Skin Rash

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Eighteen studies (13 randomized controlled trials and 5 observational studies) reported skin rash while patients were receiving a newer antiepileptic medications compared with carbamazepine.^{52,53,55,56,62,63,70,74,78,80,82,83,85,95,99,103-105}

Thirteen randomized controlled trials reported data on skin rash when newer antiepileptics were compared versus carbamazepine^{52,53,55,56,62,63,70,74,78,80,82,83,85} and were all amenable to pooling.

Two randomized controlled trials comparing gabapentin to carbamazepine reported data on skin rash and were amenable for pooling.^{78,85} Risk of skin rash is significantly decreased by 69 percent when gabapentin is used versus carbamazepine (RR 0.31 [0.14 to 0.69]) (Appendix J Figure 69). Given the RD (RD -0.049 [-0.084 to -0.015]), for every 20 patients treated, 1 less patient would develop skin rash from treatment with gabapentin than with carbamazepine.

Seven randomized controlled trials comparing lamotrigine to carbamazepine reported data on skin rash.^{52,55,62,70,78,80,85} Risk of skin rash is significantly decreased by 34 percent when lamotrigine is used versus carbamazepine (RR 0.66 [0.46 to 0.94]) (Appendix J Figure 69). Given the RD (RD -0.032 [-0.053 to -0.012]), for every 32 patients treated, 1 less patient would develop skin rash from treatment with lamotrigine than with carbamazepine. A low level of statistical heterogeneity was detected (I^2 : 39.1 percent), but publication bias was not detected (Egger's $p=0.234$).

Two trials comparing oxcarbazepine to carbamazepine reported data on skin rash.^{82,85} Risk of skin rash is nonsignificantly decreased by 9 percent when oxcarbazepine is used versus carbamazepine (RR 0.91 [0.56 to 1.48]) (Appendix J Figure 69).

Three trials comparing topiramate to carbamazepine reported data on skin rash.^{74,83,85} Risk of skin rash is significantly decreased by 62 percent when topiramate is used versus carbamazepine (RR 0.38 [0.24 to 0.59]) (Appendix J Figure 69). Given the RD (RD -0.061 [-0.090 to -0.033]), for every 17 patients treated, 1 less patient would develop skin rash from treatment with topiramate than with carbamazepine. No significant statistical heterogeneity was detected (I^2 : 0 percent), but publication bias was detected (Egger's $p=0.050$).

Three trials comparing vigabatrin to carbamazepine reported data on skin rash.^{53,56,63} Risk of skin rash is significantly decreased by 71 percent when vigabatrin is used versus carbamazepine (RR 0.29 [0.13 to 0.62]) (Appendix J Figure 69). Given the RD (RD -0.075 [-0.125 to -0.026]), for every 14 patients treated, 1 less patient would develop skin rash from treatment with vigabatrin than with carbamazepine. No significant statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Thirteen randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on skin rash.^{52,53,55,56,62,63,70,74,78,80,82,83,85} Risk of skin rash is significantly decreased by 48 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.52 [0.39 to 0.69]) (Appendix J Figure 69). Given the RD (RD -0.043 [-0.058 to -0.028]), for every 24 patients treated, 1 less patient would develop skin rash from treatment with newer AED than with carbamazepine. A low level of statistical heterogeneity was detected (I^2 : 35.2 percent) and significant publication bias was detected (Egger's $p=0.001$).

Five observational studies reported data on skin rash while patients were receiving a newer antiepileptic medication compared with carbamazepine and all five were amenable for pooling.^{95,99,103-105}

One observational trial comparing lamotrigine to carbamazepine reported data on skin rash.⁹⁹ Risk of skin rash is nonsignificantly decreased by 63 percent when lamotrigine is used versus carbamazepine (RR 0.37 [0.12 to 1.11]) (Appendix J Figure 70).

One observational study comparing levetiracetam to carbamazepine reported data on skin rash.¹⁰³ Risk of skin rash is nonsignificantly decreased by 7 percent when levetiracetam is used versus carbamazepine (RR 0.93 [0.08 to 11.16]) (Appendix J Figure 70).

One observational study comparing oxcarbazepine to carbamazepine reported data on skin rash.⁹⁵ Risk of skin rash is nonsignificantly increased 3-fold when oxcarbazepine is used versus carbamazepine (RR 3.00 [0.26 to 35.71]) (Appendix J Figure 70).

Two observational studies comparing topiramate to carbamazepine reported data on skin rash.^{104,105} Risk of skin rash is significantly decreased by 90 percent when topiramate is used versus carbamazepine (RR 0.10 [0.02 to 0.49]) (Appendix J Figure 70). Given the RD (RD - 0.073 [-0.171 to 0.025]), for every 14 patients treated, 1 less patient would develop skin rash from treatment with topiramate than with carbamazepine.

Five observational studies comparing newer antiepileptic medications to carbamazepine reported data on skin rash.^{95,99,103-105} Risk of skin rash is nonsignificantly decreased by 67 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.33 [0.10 to 1.05]) (Appendix J Figure 70). A low level of statistical heterogeneity was detected (I^2 : 28.1 percent), but publication bias was not detected (Egger's $p=0.671$).

Two randomized controlled trials reported data on skin rash when newer antiepileptics were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86}

One randomized controlled trial reported data on skin rash when lamotrigine was compared with sustained release carbamazepine.⁸⁶ The risk of skin rash was nonsignificantly decreased by 59 percent when lamotrigine was used versus sustained release carbamazepine (RR 0.41 [0.16 to 1.07]) (Appendix J Figure 71).

One randomized controlled trial reported data on skin rash when levetiracetam was compared with controlled-release carbamazepine.⁸¹ The risk of skin rash was nonsignificantly decreased by 49 percent when levetiracetam is used versus controlled-release carbamazepine (RR 0.51 [0.23 to 1.15]) (Appendix J Figure 71).

Two randomized controlled trials reported data on skin rash when lamotrigine or levetiracetam was compared with controlled- or sustained-release carbamazepine and both were amenable for pooling.^{81,86} The risk of skin rash was significantly decreased by 53 percent when either newer agent was compared with controlled- or sustained-release carbamazepine (RR 0.47 [0.25 to 0.89]) (Appendix J Figure 71). Given the RD (RD [-0.038 [-0.081 to 0.005]), for every 27 patients treated with a newer agent, 1 less patient would develop skin rash compared with those treated with controlled- or sustained-release carbamazepine.

Phenytoin Versus Newer

Four randomized controlled trials reported skin rash while patients were receiving a newer antiepileptic medication compared with phenytoin^{57,59,64,90} and were all amenable to pooling.

One randomized controlled trial comparing lamotrigine to phenytoin reported data on skin rash.⁶⁴ Risk of skin rash is nonsignificantly increased by 47 percent when lamotrigine is used versus phenytoin (RR 1.47 [0.6 to 3.26]) (Appendix J Figure 72).

Two trials comparing oxcarbazepine to phenytoin reported data on skin rash.^{57,59} Risk of skin rash is nonsignificantly decreased by 22 percent when oxcarbazepine is used versus phenytoin (RR 0.78 [0.42 to 1.46]) (Appendix J Figure 72).

One trial comparing topiramate to phenytoin reported data on skin rash.⁹⁰ Risk of skin rash is significantly decreased by 90 percent when topiramate is used versus phenytoin (RR 0.10 [0.02 to 0.57]) (Appendix J Figure 72). Given the RD (RD -0.071 [-0.120 to -0.022]), for every 15 patients treated, 1 less patient would develop skin rash from treatment with topiramate than with phenytoin.

Four trials comparing newer antiepileptic medications to phenytoin reported data on skin rash.^{57,59,64,90} Risk of skin rash is nonsignificantly decreased by 24 percent when newer antiepileptic medications are used versus phenytoin (RR 0.76 [0.34 to 1.66]) (Appendix J Figure 72). A high level of statistical heterogeneity was detected (I^2 : 54 percent), but publication bias was not detected (Egger's $p=0.256$).

Valproic Acid Versus Newer

Twelve studies (10 randomized controlled trials and 2 observational studies) reported skin rash while patients were receiving a newer antiepileptic medications compared with valproic acid.^{51,72,74,75,80,82,84,85,88,94,99,105}

Ten randomized controlled trials reported data on skin rash when newer antiepileptics were compared versus valproic acid.^{51,72,74,75,80,82,84,85,88,94} and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on skin rash.⁵¹ Risk of skin rash is increased by 3 percent when felbamate is used versus valproic acid (RR 1.03 [0.11 to 9.62]) (Appendix J Figure 73). Given the RD (RD 0.001 [-0.070 to 0.072]), for every 1,000 patients treated, 1 less patient would develop skin rash from treatment with felbamate than with valproic acid.

Six trials comparing lamotrigine to valproic acid reported data on skin rash.^{72,75,80,85,88,94} Risk of skin rash is significantly increased over 2.7-fold when lamotrigine is used versus valproic acid (RR 2.69 [1.07 to 6.77]) (Appendix J Figure 73). Given the RD (RD 0.039 [0.008 to 0.070]), for every 26 patients treated, 1 less patient would develop skin rash from treatment with lamotrigine than with valproic acid. A low level of statistical heterogeneity was detected (I^2 : 26.6 percent), but publication bias was not detected (Egger's $p=0.202$).

One trial comparing oxcarbazepine to valproic acid reported data on skin rash.⁸² Risk of skin rash is nonsignificantly increased by 4.8-fold when oxcarbazepine is used versus valproic acid (RR 4.78 [0.49 to 49.52]) (Appendix J Figure 73).

Three trials comparing topiramate to valproic acid reported data on skin rash.^{74,84,85} Risk of skin rash is significantly decreased by 65 percent when topiramate is used versus valproic acid (RR 0.35 [0.14 to 0.86]) (Appendix J Figure 73). Given the RD (RD -0.035 [-0.104 to 0.034]), for every 29 patients treated, 1 less patient would develop skin rash from treatment with topiramate than with valproic acid. No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.398$) was detected.

Ten trials comparing newer antiepileptic medications to valproic acid reported data on skin rash.^{51,72,74,75,80,82,84,85,88,94} Risk of skin rash is nonsignificantly increased by 17 percent when newer antiepileptic medications are used versus valproic acid (RR 1.17 [0.55 to 2.48]) (Appendix J Figure 73). A low level of statistical heterogeneity was detected (I^2 : 33.6 percent), but publication bias was not detected (Egger's $p=0.400$).

Two observational studies reported data on skin rash while patients were receiving a newer antiepileptic medication compared with valproic acid and both were amenable for pooling.^{99,105}

One observational study comparing lamotrigine to valproic acid reported data on skin rash.⁹⁹ Risk of skin rash is nonsignificantly increased by 9.1-fold when lamotrigine is used versus valproic acid (RR 9.05 [0.86 to 96.19]) (Appendix J Figure 74).

One observational study comparing topiramate to valproic acid reported data on skin rash.¹⁰⁵ Risk of skin rash is nonsignificantly decreased by 18 percent when topiramate is used versus valproic acid (RR 0.82 [0.11 to 6.19]) (Appendix J Figure 74).

Two observational studies comparing newer antiepileptic medications to valproic acid reported data on skin rash.^{99,105} Risk of skin rash is nonsignificantly increased by over 2.3-fold when newer antiepileptic medications are used versus valproic acid (RR 2.33 [0.22 to 25.11]) (Appendix J Figure 74).

Innovator Versus Generic Drug Evaluation

Two trials reported data on skin rash.^{109,110} Incidence of skin rash is nonsignificantly decreased by 23 percent when generic carbamazepine is used versus innovator carbamazepine (RR 0.77 [0.17 to 3.57]). Analysis for any antiepileptic medications and BCS Class II antiepileptic medications is the same as carbamazepine analysis. No data was available to perform BCS Class I antiepileptic medications analysis.

Suicidal Ideation

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Paterno and colleagues performed a cohort study to determine the risk of suicidal acts, combined suicidal acts and violent death in patients beginning the use of an anticonvulsant medication compared to patients taking a reference anticonvulsant medication.¹⁶⁶ Patients aged 15 years and older who began taking an anticonvulsant between July 2001 and December 2006, and had 6 months of continuous health plan enrollment preceding drug initiation date and were identified through the HealthCore Integrated Research Database. Patients were excluded if they had received any anticonvulsant medication or multiple anticonvulsant medications in the past 6 months prior to the index date. Patients were also excluded if they had a recorded diagnosis of attempted suicide or medical conditions that could have influenced the risk of suicidal acts in the 6 months prior to the index date. Suicide attempts were identified through emergency department visits and hospitalizations with a diagnosis of suicide and self-inflicted injury. Patients were followed up for 180 days, until drug discontinuation or switching, study outcome, end of continuous health plan enrollment or the end of the observation period, whichever came first. A subgroup analysis was performed to identify the risk of suicidal events in patients beginning anticonvulsant use for epilepsy and seizure disorder; patients treated with carbamazepine served as the reference. Gabapentin when compared with carbamazepine was found to be associated with suicidality risk within 180 days among patients with a diagnosis of epilepsy or seizure disorders (RR 13.92 [1.82 to 106.38]). The newer antiepileptics oxcarbazepine (RR 0.73 [0.16 to 3.28]) and topiramate (RR 0.67 [0.37 to 1.19]) were not found to be associated with suicidality risk within 180 days.

Innovator Versus Generic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on suicidal ideation.

Mood and Cognition

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

A total of six studies evaluated the impact of newer antiepileptic medications on cognition as compared with carbamazepine, three in an adult population,^{53,164,167} and three in pediatric/adolescent populations.^{66,82,83}

One randomized controlled clinical trial evaluated the impact of newer antiepileptic medications on mood as compared with carbamazepine.⁶⁶ A randomized controlled trial in adult patients with newly diagnosed epilepsy by Kalviainen et al. showed that patients who were successfully treated with vigabatrin (n=25) had improvements from baseline in verbal fluency, delayed recall of the List Learning Test, and the Alternating S task ($p<0.05$ for all).⁵³ Those who were successfully treated with carbamazepine (n=24) did not see improvements in any of these tests. Vigabatrin and carbamazepine intergroup differences are unknown since direct statistical tests were not performed and could not be calculated. No differences from baseline were seen in any other tests for either the vigabatrin or carbamazepine groups.

Another randomized, open label, active controlled trial of children and adolescents by Dodrill et al. found statistically significant improvements on tests for verbal fluency ($p=0.014$) and perpetual/motor speed ($p=0.009$) with tiagabine adjunctive therapy versus carbamazepine in patients already receiving phenytoin⁶⁶ but tiagabine use resulted in poorer scores on measures of overall mood as evaluated by the Profile of Mood States (POMS) scale ($p=0.017$) and financial concern ($p=0.029$) versus adjunctive carbamazepine.

A randomized, open label, active control trial evaluated the cognitive effects of therapy in a pediatric population with partial seizures.⁸² Donati et al found no significant differences between oxcarbazepine and carbamazepine on various cognitive variables including psychomotor speed, alertness, memory and learning, and attention during the 6-month followup period.

A fourth study by Kang et al. was a 4-week randomized, open label, parallel group trial comparing the impact of topiramate versus carbamazepine on cognition and behavior in a Korean pediatric population.⁸³ Although most measures of cognition improved from baseline in both groups, the changes were more profound in the carbamazepine participants. In particular, carbamazepine performed significantly better than topiramate on the maze ($p=0.026$), arithmetic ($p=0.037$), and prefrontal function tests ($p=0.039$).

An open-label, randomized study by Lee and colleagues compared the cognitive and behavioral effects of lamotrigine and carbamazepine at 16 and 48 weeks of treatment in patients with newly diagnosed or untreated partial epilepsy in Korean population from the ages of 16 to 60.¹⁶⁷ A significant group-by-time interaction was only observed in the lamotrigine group in the test of phonemic fluency of COWAT (Controlled Oral Word Association Task) ($p=0.0032$) and the Stroop Color-Word Interference test ($p=0.0283$). Group-by-time interaction was not significant for any test in the carbamazepine group. The lamotrigine group was significantly better than the carbamazepine group at 16 ($p=0.0002$) and 48 ($p<0.0001$) weeks in phonemic fluency and in the Stroop Color-Word Interference at 48 weeks ($p=0.0002$). All other cognitive tests did not show any significant group-by-time interactions.

An open-label, noninterventive, controlled-surveillance study evaluated the cognitive outcomes of patients who were administered levetiracetam or carbamazepine as primary treatment or as substitution for previous treatment using the EpiTrack, a screening tool used to track adverse cognitive effects of antiepileptic medications and a shortened version of the

German verbal learning and memory test.¹⁶⁴ EpiTrack assesses working memory and not episodic memory through learning and immediate recall of a 15-item word list. In the nonpretreated group that received levetiracetam, 15.9 percent experienced an improvement in EpiTrack results, while 5.8 percent experienced a decline. In the nonpretreated group that received carbamazepine, 8.3 percent experienced an improvement in cognition based on EpiTrack, while 16.7 percent experienced a decline in cognition.

Phenytoin Versus Newer

A single study evaluated the impact of tiagabine on mood and cognition as compared with phenytoin for adjunctive therapy.⁶⁶ In adult patients with complex partial seizures already taking carbamazepine, Dodrill et al. showed no significant differences on any test of ability including the Lafayette grooved pegboard, Stroop Test, Benton Visual Retention Test, Controlled Oral Word Association Test, Symbol Digit Modalities Test, Rey Auditory Verbal Learning Test, Wonderlic Personnel Test, and the Digit Cancellation Test when phenytoin was compared with tiagabine. Additionally, there were no significant differences in test of adjustment or mood using the POMS scale, the Washington Psychosocial Seizure Inventory and the Mood Rating Scale with phenytoin versus tiagabine. The authors concluded that no changes in cognition were seen when phenytoin was used as add-on therapy to background carbamazepine therapy as compared with the newer AED tiagabine.

Valproic Acid Versus Newer

A total of six studies evaluated the impact of newer antiepileptic medications on cognition as compared with valproic acid.^{65,73,82,92,106,168} Five of these studies used the newer agent topiramate as the comparator.^{65,73,92,106,168} Four randomized controlled clinical trials evaluated the impact of newer antiepileptic medications on mood compared with valproic acid.^{65,73,93,168} A randomized, controlled trial by Aldenkamp et al evaluated the effect of valproic acid or topiramate on cognitive function and mood when given as add-on therapy to carbamazepine in 53 adult patients with partial-onset seizures.⁶⁵ By and large, tests of motor speed/fluency, alertness/reaction speed, information processing speed, and memory were not different between the groups, although many endpoints had p-values close to statistical significance (p=0.06 to 0.08). The Rey learning test of immediate recall was significantly improved with topiramate as compared with valproic acid (p=0.02). Thus, it appears that a larger patient sample may have produced more significant differences in cognitive function between groups. The trial also reported that there were no statistically significant differences in mood between the groups when mood was evaluated using the POMS scale.

A 20-week randomized, double blind study by Meador et al. evaluated differential cognitive, behavioral, and mood effects of valproic acid versus the topiramate in 76 adult patients with partial seizures.⁷³ They showed that topiramate performed worse than valproic acid on both the Symbol Digit Modalities Test and the Controlled Oral Word Association Test at the end of the followup period (p<0.05 for both). Significant differences between the groups were not seen for any other cognitive measures. Additionally, there were no significant differences between the groups when mood was evaluated using the POMS scales.

A cross-sectional study of 42 patients with juvenile myoclonic epilepsy evaluated the relationship between factors related to epilepsy and cognitive dysfunction between those treated with valproic acid or topiramate.¹⁰⁶ Although both agents performed similarly for most of the tests of cognitive function, valproic acid was better on the Digit Span (forward) (p=0.046), Symbol Search evaluating short-term memory and attention (p=0.048), and FAS Test assessing

verbal fluency ($p=0.001$) than topiramate. The last study by Sun et al was a randomized evaluation of 38 adult patients with untreated epilepsy comparing the impact of valproic acid and topiramate on measures of cognition over a 3-month period.⁹² Using the Wechsler Adult Intelligence Scale (WAIS-CR), the authors demonstrated that full-scale intelligence quotient ($p<0.05$), verbal intelligence quotient ($p=0.001$), and the average intelligence quotient ($p=0.023$) all decreased from baseline in the topiramate group, whereas no changes were seen in the valproic acid group. Taken together, these four studies suggested that topiramate worsens measures of cognition compared with valproic acid, although varying populations, endpoints, and study designs should be taken into account when evaluating these results.

A study by Zheleznova and colleagues compared the effects of valproic acid and topiramate on mental impairment during initial treatment of epilepsy in women of reproductive age using the symptom checklist-90 (SCL-90).¹⁶⁸ The SCL-90 is a list of 90 symptoms administered for patient self-assessment. The levels of anxiety ($p=0.03$), aggression ($p=0.028$) and lack of confidence ($p=0.042$) in social contacts were significantly greater in patients taking valproic acid than topiramate.

A single study evaluated the impact of oxcarbazepine on cognition as compared with valproic acid.⁸² Similar to the comparison with carbamazepine, Donati et al. found no significant differences between oxcarbazepine and valproic acid on cognitive variables including psychomotor speed, alertness, memory and learning, and attention during the 6-month followup period. One randomized controlled trial evaluated mood when lamotrigine was compared with valproic acid using the Beck Depression Inventory, the Cornell Dysthymia Rating Scale, and the POMS scale.⁹³ The trial reported a greater improvement in the Beck Depression Inventory and the Cornell Dysthymia Scale from baseline after 32 weeks of therapy when lamotrigine was compared with valproic acid. Patients receiving lamotrigine experienced an improvement in POMS scales scores from baseline after 32 weeks of therapy, but patients receiving valproic acid did not experience an improvement in POMS scale scored from baseline after 32 weeks of therapy.

Phenobarbital or Primidone Versus Newer

A single study evaluated the impact of lamotrigine or levetiracetam on cognition and mood as compared with phenobarbital.⁹¹ Cumbo et al. conducted a randomized, parallel group, case control trial of 95 patients with Alzheimer's disease and epileptic seizures and reported on cognitive and mood endpoints during a 12-month followup period. 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 ($P<0.05$). Patients treated with lamotrigine experienced an improvement in mood scored in the Cornell scale for depression from baseline to 12 months, but those treated with levetiracetam and phenobarbital experienced a worsening in mood score from baseline to 12 months. Lamotrigine produced a superior effect on mood, i.e. depression compared to levetiracetam and phenobarbital ($p's<.05$). However, patients treated with levetiracetam experienced significantly less depression than patients treated with PB ($p<.05$).

Multiple Older Versus Newer Antiepileptic Drugs

A total of three studies evaluated the impact of newer AEDs on cognition as compared with various older antiepileptic drugs.^{54,96,97} Sabers et al. evaluated the impact of AEDs on cognitive function in 87 patients with various epilepsy types over a 4-month period.⁵⁴ Patients were divided into one of three groups: Group A patients with untreated newly diagnosed epilepsy and received either carbamazepine (n=11), oxcarbazepine (n=10), valproic acid (n=11), phenobarbital (n=9), or phenytoin (n=11); Group B patients receiving carbamazepine (n=13) or valproic acid (n=14) monotherapy and had therapy withdrawn following a 3-year seizure free period; and Group C patients treated with phenytoin monotherapy who were switched to carbamazepine treatment (n=8). Cognitive function was assessed using a number of WAIS test subsets including, but not limited to, vocabulary, Block Design Test, and Digit Span Forwards and Backwards. Applicable to the current report, none of the agents used in Group A patients resulted in significant changes in any of the cognitive function tests as compared with baseline, although comparative statistics between agents were not provided. A large observational study of 1,694 adults with epilepsy by Arif et al. evaluated the impact of 14 AEDs on the rate of cognitive side effects.⁹⁷ Cognitive side effects (CSEs) were categorized as language problems, word-finding trouble, poor concentration or memory, psychomotor slowing, and confusion or disorientation. When evaluating older versus newer antiepileptics drugs in patients with epilepsy newly started on therapy (n=1,189), rates of CSEs were significantly higher with topiramate (26.2 percent) than with carbamazepine (11.7 percent; $p<0.001$) and valproic acid (9.2 percent; $p<0.001$). No other comparisons were statistically significant. Similarly, rates of cognitive side effects leading to drug discontinuation were higher with topiramate (13.8 percent) than with both carbamazepine (2.7 percent; $p<0.001$) and valproic acid (5.5 percent; $p=0.03$), but was lower with lamotrigine (3.9 percent) than phenytoin (9.4 percent; $p=0.02$). All other comparisons of older versus newer antiepileptic drugs were not statistically significant. Arif et al also conducted a comparative effectiveness study using a retrospective design aimed at evaluating 10 antiepileptic drugs and reporting the incidence of cognitive adverse events.⁹⁶ A cognitive adverse event was defined as it was in the last study.⁹⁷ The incidence of adverse events leading to either dose changes and/or treatment discontinuation was reported as ranges and indicated with (+) signs as follows: (+) 2 to 4.9 percent, (++) 5 to 9.9 percent, (+++) 10 to 19.9 percent, and (+++++) 20 percent or more. As a note, no statistical analysis was conducted comparing different agents. Topiramate (+++++) had the highest report incidence of cognitive adverse events followed by zonisamide (+++), gabapentin (+++), levetiracetam (++), lamotrigine (++), and phenytoin (++). Ranges were not provided for any other older or newer AEDs.

Innovator Versus Generic Drug Evaluation

No controlled clinical trial or controlled observational study evaluated mood and only one controlled clinical trial reported data on cognition.¹¹⁵ Overall, none of the five primary cognitive test variables (finger tapping, visual reaction time, binary choice reaction time, visual searching task, and recognition task) show statistically significant differences between three carbamazepine formulations. For the binary choice reaction time test, a significant time-effect ($P = 0.003$) was found, caused by fluctuations during the day without a consistent pattern. For the computerized visual searching task, statistical testing yielded a significant time- effect ($P = 0.002$), caused by the increase in speed during the day for this task, possibly caused by a “learning effect.” The major conclusion is, therefore, that significant switches between innovator carbamazepine and the investigated generic forms of carbamazepine formulations do not result in different cognitive profiles. Despite these results, it must be mentioned that four of the five cognitive test variables

show better scores for the innovator form of carbamazepine. Although none of the comparisons in the study yielded a statistically significant difference, it is possible that genuine differences do exist but that these differences are too small to be detected in the relatively limited sample size of 12 patients.

Bone Density

Older Versus Newer Antiepileptic Drug Evaluation

One prospective case control study reported bone mineral density measurements for the lumbar vertebrae 1 through 4 and for the total lumbar vertebrae when patients were receiving one of three antiepileptic medications (oxcarbazepine, carbamazepine, valproic acid) or control (Appendix G Table 18).¹⁰⁰ Bone mineral density values for the total lumbar vertebrae and lumbar vertebrae 1 through 4 ($p=0.010$ for lumbar vertebrae 1, $p=0.026$ for lumbar vertebrae 2, $p=0.049$ for lumbar vertebrae 3, $p=0.031$ for lumbar vertebrae 4 and $p=0.021$ for the total lumbar vertebrae) were significantly lower for antiepileptic medications (oxcarbazepine, carbamazepine, and valproic acid) compared with healthy controls. However, they did not compare the antiepileptic medications against each other.

One observational study reported bone mineral density measurements for the lumbar spine, femoral neck, and total hip at baseline and after 1 year of treatment when lamotrigine was compared with older antiepileptic medications (carbamazepine, phenytoin, and valproic acid) (Appendix G Table 18).¹⁰² The study reported that there was no significant bone loss at the lumbar spine ($p=0.25$), femoral neck ($p=0.41$), or the total hip ($p=0.39$) when lamotrigine was compared with these older agents after 1 year of treatment. However, comparisons of lamotrigine versus each individual older agent were not conducted.

One observational study reported the bone mineral density z score before and after 6 months of treatment with lamotrigine, carbamazepine, or valproic acid (Appendix G Table 19).¹⁰¹ The study reported that bone mineral density was significantly decreased in patients who received carbamazepine treatment ($p=0.043$), but was not significantly decreased when patients received lamotrigine ($p=0.100$) or valproic acid ($p=0.068$) treatment.

Innovator Versus Generic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on bone density.

Cosmetic Adverse Effects

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer

Six randomized controlled trials reported data on alopecia when newer antiepileptics were compared versus carbamazepine.^{49,53,74,76,77,82} and were all amenable to pooling.

One trial comparing lamotrigine to carbamazepine reported data on alopecia.⁷⁶ Risk of alopecia is nonsignificantly increased by 41 percent when lamotrigine is used versus carbamazepine (RR 1.41 [0.21 to 9.73]) (Appendix J Figure 75).

Two trials comparing oxcarbazepine to carbamazepine reported data on alopecia.^{49,82} Risk of alopecia is nonsignificantly decreased by 81 percent when oxcarbazepine is used versus carbamazepine (RR 0.19 [0.02 to 1.71]) (Appendix J Figure 75).

Two trials comparing topiramate to carbamazepine reported data on alopecia.^{74,77} Risk of alopecia is nonsignificantly decreased by 49 percent when topiramate is used versus carbamazepine (RR 0.51 [0.14 to 1.93]) (Appendix J Figure 75). A low level of statistical heterogeneity was detected (I^2 : 0 percent), but no significant publication bias was detected (Egger's $p=0.009$).

One trial comparing vigabatrin to carbamazepine reported data on alopecia.⁵³ Risk of alopecia is nonsignificantly increased by 3.1-fold when vigabatrin is used versus carbamazepine (RR 3.14 [0.26 to 37.78]) (Appendix J Figure 75).

Six trials comparing newer AEDs to carbamazepine reported data on alopecia.^{49,53,74,76,77,82} Risk of alopecia is nonsignificantly decreased by 40 percent when newer antiepileptic drugs are used versus carbamazepine (RR 0.60 [0.23 to 1.58]) (Appendix J Figure 75). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.095$).

Phenytoin Versus Newer

One trial comparing oxcarbazepine to phenytoin reported data on acne in patients with new onset epilepsy.⁵⁷ Risk of acne is nonsignificantly increased by 2.8-fold when oxcarbazepine is used versus phenytoin (RR 2.78 [0.82 to 9.53]).

Two randomized controlled trials reported data on gum hyperplasia when newer antiepileptics were compared versus valproic acid.^{57,59} and were all amenable to pooling.

Two trials comparing oxcarbazepine to phenytoin reported data on gum hyperplasia in patients with new onset epilepsy.^{57,59} Risk of gum hyperplasia is significantly decreased by 90 percent when oxcarbazepine is used versus phenytoin (RR 0.10 [0.04 to 0.27]) (Appendix J Figure 76). Given the RD (RD -0.17 [-0.29 to -0.04]), for every six patients treated with oxcarbazepine, one less patient would develop gum hyperplasia compared with those treated with phenytoin.

Valproic Acid Versus Newer

Eight randomized controlled trials reported data on alopecia when newer antiepileptics were compared versus valproic acid.^{58,68,72,74,76,77,82,84} and were all amenable to pooling.

Three trials comparing lamotrigine to valproic acid reported data on alopecia.^{68,72,76} Risk of alopecia is significantly decreased by 81 percent when lamotrigine is used versus valproic acid (RR 0.19 [0.06 to 0.58]) (Appendix J Figure 77). Given the RD (RD -0.093 [-0.150 to -0.036]), for every 11 patients treated, 1 less patient would develop alopecia from treatment with lamotrigine than with valproic acid. No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Two trials comparing oxcarbazepine to valproic acid reported data on alopecia.^{58,82} Risk of alopecia is nonsignificantly decreased by 66 percent when oxcarbazepine is used versus valproic acid (RR 0.34 [0.08 to 1.51]) (Appendix J Figure 77).

Three trials comparing topiramate to valproic acid reported data on alopecia.^{74,77,84} Risk of alopecia is significantly decreased by 89 percent when topiramate is used versus valproic acid (RR 0.11 [0.05 to 0.24]) (Appendix J Figure 77). Given the RD (RD -0.162 [-0.236 to -0.088]), for every seven patients treated, one less patient would develop alopecia from treatment with topiramate than with valproic acid. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.904$).

Eight trials comparing newer AEDs to valproic acid reported data on alopecia.^{58,68,72,74,76,77,82,84} Risk of alopecia is significantly decreased by 82 percent when newer antiepileptic drugs are used versus valproic acid (RR 0.18 [0.10 to 0.31]) (Appendix J Figure

77). Given the RD (RD -0.106 [-0.135 to -0.078]), for every 10 patients treated, 1 less patient would develop alopecia from treatment with newer antiepileptic drugs than with valproic acid. A low level of statistical heterogeneity was detected (I^2 : 24.9 percent) and significant publication bias was detected (Egger's $p=0.035$).

Innovator Versus Generic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on cosmetic adverse events.

Discussion

Withdrawals can be due to lack of efficacy, adverse events, or other factors. We could not find any significant difference in the risk of withdrawing for any reason when newer antiepileptic medications were compared with carbamazepine, controlled/sustained-release carbamazepine, ethosuximide, phenytoin, or valproic acid. However, in the case of carbamazepine and controlled/sustained-release carbamazepine, this was due to an offsetting significant increase in the risk of withdrawals due to lack of efficacy and a significant decrease in withdrawals due to adverse events. The data comparing newer antiepileptic medications versus controlled/sustained-release carbamazepine were limited with only two trials available and only levetiracetam and lamotrigine as comparators. Such an offsetting effect was not evident for the other analyses of newer antiepileptic medications versus ethosuximide, phenytoin, or valproic acid, but the number of studies evaluating the comparative impact on withdrawals for ethosuximide and phenytoin was limited.

Several of the newer antiepileptic medication versus an older antiepileptic medication analyses had a higher level of statistical heterogeneity. This was likely due to the pooling of different newer antiepileptic medications together. This was especially true of the overall withdrawal analysis, which showed a significant reduction in withdrawals with lamotrigine versus carbamazepine, but not with the other individual newer antiepileptic medications versus carbamazepine. In addition, pooling patients with generalized epilepsy, partial epilepsy, new onset epilepsy, and chronic epilepsy together also likely increased heterogeneity. We performed a priori-defined subgroup analyses to explore heterogeneity due to these factors as well as gender and age.

In this analysis, we compared newer antiepileptic medications to older epileptic medications for dizziness, fatigue, headache, nausea, skin rash, and somnolence.

Taken together, patients taking newer antiepileptic medications had a significantly lower risk of developing dizziness, fatigue, skin rash, and somnolence versus those taking carbamazepine. Patients taking newer antiepileptic medications had a significantly lower risk of developing fatigue, nausea, and somnolence versus those patients taking valproic acid. Statistical heterogeneity occurred in some places and was likely due to the pooling of different newer antiepileptic medications together and pooling patients with different seizure types together.

In many cases, the controlled/sustained-release carbamazepine and phenytoin analyses were based on limited data. However, the risk of skin rash was significantly lower with newer antiepileptic medications versus controlled/sustained-release carbamazepine. The risk of vomiting was significantly reduced when newer antiepileptic medications were compared versus phenytoin.

For cosmetic adverse events, newer antiepileptic medications had a lower risk of alopecia than valproic acid but not versus carbamazepine. Newer antiepileptic medications also had a lower risk of causing gum hyperplasia versus phenytoin.

In some pooled analyses, statistical heterogeneity occurred and was likely due to the pooling of different newer antiepileptic medications together and pooling patients with generalized epilepsy, partial epilepsy, new onset epilepsy, and chronic epilepsy together. We performed a priori-defined subgroup analyses to explore heterogeneity due to these factors as well as gender and age. In several cases, significant differences in risk for adverse events were seen when certain newer antiepileptic medications were compared versus their older comparators but not other newer antiepileptic medications, and in one case, the risk of skin rash was significantly increased when lamotrigine was compared with valproic acid and significantly reduced when topiramate was compared versus valproic acid.

The newer antiepileptic medication topiramate may not be as good as the older antiepileptic medications carbamazepine or valproic acid in improving some aspects of cognition. The other newer antiepileptic drugs were similar to that of their older counterparts in cognition with the exceptions of vigabatrin and levetiracetam, which may have some advantages in cognition versus carbamazepine and phenobarbital, respectively. However, several different scales were used and employed many subscales. These trials were not amenable for pooling because of the variability in what was being evaluated and the way in which the data was presented in the manuscripts.

The impact on mood was not as extensively evaluated. It seems as if tiagabine may be similar to phenytoin and inferior to carbamazepine, topiramate may be similar to but lamotrigine may be superior to valproic acid, and lamotrigine may be superior to and levetiracetam may be similar to phenobarbital.

Data on withdrawal rates due to adverse events were only available for innovator versus generic carbamazepine and phenytoin limiting the ability to extrapolate findings to other antiepileptic medications.

The withdrawals due to adverse events were similar between the innovator and generic versions of antiepileptic medications. These results are in agreement with the overall withdrawal rates reported in Key Question 1.

While our data suggest that tolerability is similar in a population of patients receiving an innovator versus generic version of antiepileptic medication, we cannot say that an individual patient would not have changes in tolerability upon switching either due to changes in pharmacokinetics or as a result of the anxiety that they feel from switching.

Data on combined neurological adverse events were only available for carbamazepine, limiting the ability to extrapolate findings to other antiepileptic medications. There was no statistically significant difference in the combined neurological adverse events between the innovator and generic carbamazepine. However, in the single controlled trial and single observational study, the occurrence of neurological adverse events was qualitatively greater.

For individual neurological adverse events, data on headache were only reported for carbamazepine and phenytoin, which showed no statistically significant difference between the innovator and generic versions carbamazepine or phenytoin. Data on dizziness, somnolence, and diplopia were only reported for carbamazepine, which also showed no statistically significant difference between the innovator and generic versions of carbamazepine.

Data on incidence of rash were only available for carbamazepine, which showed no statistically significant difference between the innovator and generic version of carbamazepine.

No data were available for mood, but data on cognition were available for only carbamazepine, which showed no statistically significant difference between the innovator and generic versions of carbamazepine.

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 (partial, generalized, specific epilepsy syndrome), seizure type (new onset disease, chronic disease), gender, ethnicity, patient age, and patient pharmacogenetic profile; and by types of antiepileptic medication (medication classes, individual medications and medications meeting the definition of having a narrow therapeutic index [Biopharmaceutics Classification System (BCS) class II – IV])?

Key Points

- By splitting our newer antiepileptic medication versus carbamazepine, phenytoin, valproic acid, or ethosuximide by seizure etiology, 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.
 - If more than 90 percent of a population was constituted with a predefined subpopulation of interest (for example, females), we included the study in our subgroup analyses.
 - For many subgroup analyses, one subpopulation was evaluated (for example, females) but the other subpopulation (for example, males) was not. This precludes our ability to infer the differential effect in one subpopulation versus another.
 - The results of subgroup analyses generally followed those in the base case evaluations, although they were much less likely to be significantly different.
- Innovator versus generic controlled clinical trials and controlled observational studies did not provide data in prespecified subgroups based on seizure etiology or type.
- No data were available to evaluate ethnicity or genetic profile as a subgroup for either newer versus older or for innovator versus generic.
- Ethosuximide data was limited to one controlled clinical trial in patients with new onset epilepsy that is generalized or absence epilepsy in patients at or less than 18 years.
- Most of the trials comparing newer antiepileptic medications versus carbamazepine and phenytoin provided data for seizure etiology in partial epilepsy.
 - There was more balance in the number of trials with data in partial and generalized epilepsy comparing newer antiepileptic medications versus valproic acid.
- Most of the trials comparing newer antiepileptic medications to carbamazepine were in new onset epilepsy, as were all of the phenytoin trials.

- There was more balance in the number of trials with data in new onset versus chronic epilepsy comparing newer antiepileptic medications versus valproic acid
- Gender was not frequently evaluated as a subpopulation in newer versus older antiepileptic medications, with only one controlled clinical trial in males meeting our criteria for carbamazepine and only one controlled clinical trial in females meeting our criteria for females.
- No controlled clinical trials and one controlled observational study reported data on gender differences.³³ Results showed that women compared with men were more likely to switch from innovator to generic (hazard ratio [HR] 0.95 [95% CI 0.91 to 0.99]; p=0.0057), and there was no statistically significant difference in women compared with men when switching back to innovator from generic (HR 1.10 [0.97 to 1.24]; p=0.130).
- Almost all of the trials comparing newer versus older antiepileptic medications that could be separated into age categories (≤ 18 years, 18-65 years, ≥ 65 years) were conducted in patients ≤ 18 years.
- No controlled clinical trial and one observational study reported data on age differences.³³ Results showed that 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).
- No data was available in the evaluation of newer versus older antiepileptic medication in patients with polypharmacy.
- No controlled clinical trial and one observational trial reported data on differences in medication use.³³ Patients receiving polytherapy were less likely to switch to generic (HR 0.76 (0.69 to 0.83); p=0.056), but no more or less likely to switch back to innovator (HR 1.23 [0.995 to 1.515]; p=0.056).
- For the innovator versus generic antiepileptic medication evaluation, data on BCS class was presented directly in Key Questions 1, 2, and 3. The use of BCS class was not more instructive than individual agent evaluations.
- Given the large number of outcomes for subgroup and sensitivity analyses to be performed, subgroup and sensitivity analysis was not performed based on study quality.

Detailed Analysis

Study Design and Population Characteristics

The study designs and population characteristics are the same as that described previously in Key Questions 1 and 3.

Outcome Evaluations

For this key question, we used newer antiepileptic medications versus each older antiepileptic medication for each analysis. We do not report each individual newer agent versus each individual older antiepileptic medication analysis separately. In the text, we define which newer agents were compared versus the older antiepileptic medication for transparency. Further subdivision would have diminished the ability to identify useful information.

Seizure Etiology

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer Efficacy.

Partial Epilepsy. One randomized controlled trial reported the time to first seizure when vigabatrin was compared with carbamazepine in patients with partial epilepsy.⁶³ The time to first seizure was significantly increased when vigabatrin was compared with carbamazepine in patients with partial epilepsy (HR 1.79 [1.33 to 2.40]) (Appendix J Figure 4).

Four randomized controlled trials reported data on withdrawals for any reason in patients with partial epilepsy when lamotrigine, topiramate, or vigabatrin was compared versus carbamazepine.^{63,79,80,83} The risk of withdrawal was nonsignificantly decreased by 1 percent when these newer agents were compared versus carbamazepine (RR 0.99 [0.81 to 1.22]) (Appendix J Figure 9). A low level of statistical heterogeneity was detected (I^2 : 5.8 percent), but publication bias was not detected (Egger's: $p=0.412$).

Two observational studies reported withdrawals for any reason when vigabatrin or levetiracetam was compared with carbamazepine in patients with partial epilepsy.^{98,103} The risk of withdrawal was nonsignificantly increased by 4.3-fold when either newer agent was compared versus carbamazepine in patients with partial epilepsy (RR 4.33 [0.31 to 59.98]) (Appendix J Figure 10).

Two randomized controlled trials reported data on withdrawals due to lack of efficacy in patients with partial epilepsy when lamotrigine or vigabatrin was compared versus carbamazepine.^{63,80} The risk of withdrawal due to lack of efficacy was significantly increased by 2.5-fold when newer agents were compared versus carbamazepine in patients with partial epilepsy (RR 2.54 [1.22 to 5.27]) (Appendix J Figure 16). Given the RD (RD 0.032 [-0.048 to 0.11]), for every 32 patients with partial epilepsy treated with either newer agent, 1 additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine.

One observational study reported withdrawal due to lack of efficacy when vigabatrin was compared with carbamazepine in patients with partial epilepsy.⁹⁸ The risk of withdrawal due to lack of efficacy was significantly increased by 18.4-fold when vigabatrin was compared versus carbamazepine in patients with partial epilepsy (RR 18.36 [1.97 to 182.09]) (Appendix J Figure 17). Given the RD, (RD 0.21 [0.08 to 0.35]), for every five patients treated with vigabatrin, one additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine.

Six randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in patients with partial epilepsy.^{52,56,74,80,82,83} The risk of remaining seizure free for duration of study is nonsignificantly decreased by 6 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.94 [0.84 to 1.05]) (Appendix J Figure 26). No significant statistical heterogeneity (I^2 : 1 percent) or publication bias was detected (Egger's $p=0.562$).

Two observational studies comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in patients with partial epilepsy.^{98,103} The risk of remaining seizure free for duration of study is nonsignificantly decreased by 16 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.84 [0.62 to 1.16]) (Appendix J Figure 27).

One randomized controlled trial reported the number of patients who achieved 12-month seizure remission when vigabatrin was compared with carbamazepine in patients with partial epilepsy.⁶³ The risk of achieving 12-month seizure remission was nonsignificantly decreased by 5 percent when vigabatrin was compared with carbamazepine in patients with partial epilepsy (RR 0.95 [0.79 to 1.14]) (Appendix J Figure 22).

Generalized Epilepsy. Two randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in patients with generalized epilepsy.^{52,74} The risk of remaining seizure free for duration of study is nonsignificantly increased by 8 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.08 [0.90 to 1.29]) (Appendix J Figure 26). No significant statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Safety.

Partial Epilepsy. Six randomized controlled trials reported data on withdrawals due to adverse events in patients with partial epilepsy when lamotrigine, topiramate, or vigabatrin was compared versus carbamazepine.^{56,63,70,79,80,83} The risk of withdrawal due to adverse events was significantly decreased by 27 percent when these newer agents were compared versus carbamazepine (RR 0.73 [0.58 to 0.91]) (Appendix J Figure 37). Given the RD (RD -0.051 [-0.088 to -0.014]), for every 20 patients treated with lamotrigine, topiramate, or vigabatrin, 1 less patient would withdraw compared with those treated with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's: $p=0.629$) was detected.

Two observational studies reported withdrawals due to adverse events when levetiracetam or oxcarbazepine was compared with carbamazepine in patients with partial epilepsy and were amenable for pooling.^{95,103} The risk of withdrawal was nonsignificantly increased by 2.6-fold when either newer agent was compared versus carbamazepine in patients with partial epilepsy (RR 2.58 [0.47 to 14.09]) (Appendix J Figure 38).

Two trials comparing newer antiepileptic medications to carbamazepine reported data on headache in patients with partial epilepsy.^{56,82} Risk of headache is nonsignificantly increased by over 2-fold when newer antiepileptic medications are used versus carbamazepine (RR 2.11 [0.54 to 8.19]) (Appendix J Figure 44).

Three trials comparing newer antiepileptic medications to carbamazepine reported data on fatigue in patients with partial epilepsy.^{56,80,82} Risk of fatigue is nonsignificantly decreased by 26 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.74 [0.26 to 2.13]) (Appendix J Figure 50). A high level of statistical heterogeneity was detected (I^2 : 71.7 percent), but tests for publication bias could not be performed.

One trial comparing newer antiepileptic medications to carbamazepine reported data on somnolence in patients with partial epilepsy.⁸³ Risk of somnolence is nonsignificantly increased by 30 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.30 [0.46 to 3.71]) (Appendix J Figure 52).

One observational study comparing newer antiepileptic medications to carbamazepine reported data on somnolence in patients with new partial epilepsy.¹⁰³ Risk of somnolence is significantly decreased by 72 percent when levetiracetam is used versus carbamazepine (RR 0.28 [0.13 to 0.63]) (Appendix J Figure 53). Given the RD (RD -0.177 [-0.431 to 0.078]), for every six patients treated, one less patient would develop somnolence from treatment with newer AED than with carbamazepine.

Three trials comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients with partial epilepsy.^{56,82,83} Risk of dizziness is nonsignificantly decreased

by 37 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.63 [0.07 to 6.00]) (Appendix J Figure 57). A high level of statistical heterogeneity was detected (I^2 : 58.1 percent), but tests for publication bias could not be performed.

One observational study comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients with partial epilepsy.¹⁰³ Risk of dizziness is nonsignificantly decreased by 85 percent when levetiracetam is used versus carbamazepine (RR 0.15 [0.02 to 1.13]) (Appendix J Figure 58).

One trial comparing newer antiepileptic medications to carbamazepine reported data on nausea in patients with partial epilepsy.⁵⁶ Risk of nausea is nonsignificantly decreased by 76 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.24 [0.04 to 1.47]) (Appendix J Figure 63).

Four randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on skin rash in patients with partial epilepsy.^{56,80,82,83} Risk of skin rash is nonsignificantly decreased by 51 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.49 [0.23 to 1.05]) (Appendix J Figure 69). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.350$).

One trial comparing newer AED to carbamazepine reported data on alopecia in patients with partial epilepsy.⁸² Risk of alopecia is nonsignificantly decreased by 83 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.17 [0.01 to 2.04]) (Appendix J Figure 75).

Phenytoin Versus Newer Efficacy.

Partial Epilepsy. One randomized controlled trial reported time to first seizure when lamotrigine was compared with phenytoin in patients with partial epilepsy.⁶⁴ The time to first seizure was not altered when lamotrigine was compared with phenytoin in patients with partial epilepsy (HR 1.00 [0.50 to 2.20]) (Appendix J Figure 5).

Three trials comparing newer antiepileptic medications to phenytoin reported data on seizure freedom for study duration in patients with partial epilepsy.^{57,59,64} The risk of remaining seizure free for study duration is nonsignificantly increased by 1 percent when newer antiepileptic medications are used versus phenytoin (RR 1.01 [0.86 to 1.19]) (Appendix J Figure 29). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Valproic Acid Versus Newer Efficacy.

Partial Epilepsy. Four randomized controlled trials reported data on withdrawals for any reason in patients with partial epilepsy when felbamate, topiramate, or vigabatrin was compared versus valproic acid and were amenable for pooling.^{50,61,65,73} The risk of withdrawal was nonsignificantly increased by 5 percent when either newer agent was compared versus valproic acid in patients with partial epilepsy (RR 1.05 [0.57 to 1.92]) (Appendix J Figure 13). A moderate level of statistical heterogeneity was detected (I^2 : 31.5 percent), but publication bias was not detected (Egger's: $p=0.310$).

Three trials comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration in patients with partial epilepsy.^{58,74,82} The risk of remaining seizure free for study duration is nonsignificantly increased by 2 percent when newer antiepileptic medications are used versus valproic acid (RR 1.02 [0.86 to 1.22]) (Appendix J

Figure 30). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's $p=0.207$) was detected.

Two randomized controlled trials reported data on withdrawals due to lack of efficacy in patients with partial epilepsy when topiramate or vigabatrin was compared versus valproic acid and were amenable for pooling.^{61,65} The risk of withdrawal due lack of efficacy was nonsignificantly decreased by 44 percent when the newer agents were compared versus valproic acid in partial epilepsy (RR 0.56 [0.28 to 1.10]) (Appendix J Figure 19). Since only two trials were available, tests for statistical heterogeneity and publication bias could not be performed.

Generalized Epilepsy. Three randomized controlled trials reported data on withdrawals for any reason in patients with generalized epilepsy when lamotrigine was compared versus valproic acid and were amenable for pooling.^{75,80,89} The risk of withdrawal was nonsignificantly increased by 30 percent when lamotrigine was compared versus valproic acid in patients with generalized epilepsy (RR 1.30 [0.78 to 2.18]) (Appendix J Figure 13). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Three randomized controlled trials reported data on withdrawals due to lack of efficacy in patients with generalized epilepsy when lamotrigine was compared versus valproic acid and were amenable for pooling.^{75,80,84} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 2.3-fold when lamotrigine was compared versus valproic acid in generalized epilepsy (RR 2.28 [0.79 to 6.58]) (Appendix J Figure 19). No statistical heterogeneity (I^2 : 0 percent) was detected, but tests for publication bias could not be performed.

Four trials comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration in patients with generalized epilepsy.^{58,74,80,84} The risk of remaining seizure free for study duration is nonsignificantly decreased by 11 percent when newer antiepileptic medications are used versus valproic acid (RR 0.89 [0.77 to 1.02]) (Appendix J Figure 30). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.589$).

Safety.

Partial Epilepsy. Two randomized controlled trials reported data on withdrawals due to adverse events in patients with partial epilepsy when topiramate or vigabatrin was compared versus valproic acid and were amenable for pooling.^{61,73} The risk of withdrawal was nonsignificantly increased by 13 percent when either newer agent was compared versus valproic acid in patients with partial epilepsy (RR 1.13 [0.60 to 2.10]) (Appendix J Figure 41).

Three trials comparing newer antiepileptic medications to valproic acid reported data on headache in patients with partial epilepsy.^{50,51,82} Risk of headache is nonsignificantly decreased by 36 percent when newer antiepileptic medications are used versus valproic acid (RR 0.64 [0.21 to 1.98]) (Appendix J Figure 48). A high level of statistical heterogeneity was detected (I^2 : 70.3 percent), but tests for publication bias was could not be performed.

Three trials comparing newer antiepileptic medications to valproic acid reported data on fatigue in patients with partial epilepsy.^{50,51,82} Risk of fatigue is nonsignificantly increased by 30 percent when newer antiepileptic medications are used versus valproic acid (RR 1.30 [0.45 to 3.73]) (Appendix J Figure 51). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Two trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with partial epilepsy.^{50,51} Risk of somnolence is nonsignificantly increased by 55 percent when newer antiepileptic medications are used versus valproic acid (RR 1.55 [0.54 to 4.43]) (Appendix J Figure 55).

Three trials comparing newer antiepileptic medications to valproic acid reported data on dizziness in patients with partial epilepsy.^{50,51,82} Risk of dizziness is nonsignificantly increased by 59 percent when newer antiepileptic medications are used versus valproic acid (RR 1.59 [0.48 to 5.28]) (Appendix J Figure 61). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

One trial comparing newer antiepileptic medications to valproic acid reported data on nausea in patients with partial epilepsy.⁵¹ The risk of nausea is nonsignificantly decreased by 66 percent when newer antiepileptic medications are used versus valproic acid (RR 0.34 [0.03 to 4.04]) (Appendix J Figure 65).

One trial comparing newer antiepileptic medications to valproic acid reported data on vomiting in patients with partial epilepsy.⁵¹ Risk of vomiting is nonsignificantly increased by 3 percent when felbamate is used versus valproic acid (RR 1.03 [0.19 to 5.61]) (Appendix J Figure 68).

Two trials comparing newer antiepileptic medications to valproic acid reported data on skin rash in patients with partial epilepsy.^{51,82} Risk of skin rash is nonsignificantly increased by over 2.1-fold when newer antiepileptic medications are used versus valproic acid (RR 2.13 [0.29 to 15.49]) (Appendix J Figure 73).

One trial comparing newer AED to valproic acid reported data on alopecia in patients with partial epilepsy.⁸² Risk of alopecia is significantly decreased by 92 percent when newer antiepileptic medications are used versus valproic acid (RR 0.08 [0.01 to 0.78]) (Appendix J Figure 77). Given the RD (RD -0.109 [-0.229 to 0.010]), for every 10 patients treated, 1 less patient would develop alopecia from treatment with newer AED than with valproic acid.

Generalized Epilepsy. Four randomized controlled trials reported data on withdrawals for any reason in patients with generalized epilepsy when lamotrigine was compared versus valproic acid and were amenable for pooling.^{75,80,84,89} The risk of withdrawal was nonsignificantly decreased by 23 percent when lamotrigine was compared versus valproic acid in patients with generalized epilepsy (RR 0.77 [0.50 to 1.16]) (Appendix J Figure 41). No statistical heterogeneity was detected (I^2 : 0 percent), and publication bias was not detected (Egger's: $p=0.288$).

Three trials comparing newer antiepileptic medications to valproic acid reported data on headache in patients with generalized epilepsy.^{75,84,89} Risk of headache is nonsignificantly increased by 20 percent when newer antiepileptic medications are used versus valproic acid (RR 1.20 [0.60 to 2.41]) (Appendix J Figure 48). No statistical heterogeneity was detected (I^2 : 0 percent), and tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to valproic acid reported data on fatigue in patients with generalized epilepsy.^{80,84,89} Risk of fatigue is nonsignificantly decreased by 39 percent when newer antiepileptic medications are used versus valproic acid (RR 0.61 [0.35 to 1.08]) (Appendix J Figure 51). No statistical heterogeneity was detected (I^2 : 0 percent), but test for publication bias could not be performed.

Two trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with generalized epilepsy.^{84,89} Risk of somnolence is nonsignificantly decreased by 6 percent when newer antiepileptic medications are used versus valproic acid (RR 0.94 [0.25 to 3.53]) (Appendix J Figure 55).

Two trials comparing newer antiepileptic medications to valproic acid reported data on dizziness in patients with generalized epilepsy.^{84,89} Risk of dizziness is nonsignificantly increased by 52 percent when newer antiepileptic medications are used versus valproic acid (RR 1.52 [0.39 to 5.87]) (Appendix J Figure 61).

Two trials comparing newer antiepileptic medications to valproic acid reported data on nausea in patients with generalized epilepsy.^{84,89} Risk of nausea is significantly decreased by 82 percent when newer antiepileptic medications are used versus valproic acid (RR 0.18 [0.05 to 0.62]) (Appendix J Figure 65). Given the RD (RD -0.117 [-0.333 to 0.098]), for every nine patients treated, one less patient would develop nausea from treatment with newer AED than with valproic acid.

Three trials comparing newer antiepileptic medications to valproic acid reported data on skin rash in patients with generalized epilepsy.^{75,80,84} Risk of skin rash is nonsignificantly increased by 33 percent when newer antiepileptic medications are used versus valproic acid (RR 1.33 [0.09 to 19.38]) (Appendix J Figure 73). A high level of statistical heterogeneity was detected (I^2 : 58.7 percent), but tests for publication bias could not be performed.

One trial comparing newer antiepileptic drugs to valproic acid reported data on alopecia in patients with generalized epilepsy.⁸⁴ Risk of alopecia is nonsignificantly decreased by 68 percent when newer antiepileptic medications are used versus valproic acid (RR 0.32 [0.07 to 1.40]) (Appendix J Figure 77).

Ethosuximide Versus Newer Efficacy.

Generalized Epilepsy. One randomized controlled trial reported withdrawals for any reason while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤ 18 years of age.⁸⁹ The risk of overall withdrawal was nonsignificantly decreased by 5 percent when lamotrigine was compared versus ethosuximide (RR 0.95 [0.53 to 1.71]). This same trial reported withdrawals due to adverse events while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ The risk of overall withdrawal was nonsignificantly decreased by 29 percent when lamotrigine was compared versus ethosuximide (RR 0.71 [0.45 to 1.12]).

Safety.

Generalized Epilepsy. One randomized controlled trial reported data on headache while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤ 18 years of age.⁸⁹ The risk of headache was nonsignificantly decreased by 34 percent when lamotrigine was compared versus ethosuximide (RR 0.66 [0.33 to 1.29]). This trial found the risk of fatigue was nonsignificantly decreased by 10 percent when lamotrigine was compared versus ethosuximide (RR 0.90 [0.45 to 1.80]). This trial found the risk of somnolence was significantly decreased by 78 percent when lamotrigine was compared versus ethosuximide (RR 0.22 [0.07 to 0.70]). Given the RD (RD -0.04 [-0.11 to 0.03]), for every 25 patients treated with lamotrigine, 1 less patient would experience headache. This trial found the risk of dizziness was nonsignificantly decreased by 54 percent when lamotrigine was compared versus ethosuximide (RR 0.46 [0.15 to 1.38]).

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on seizure etiology.

Seizure Type

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer Efficacy.

New Onset Epilepsy. Three randomized controlled trials reported the number of patients with new onset epilepsy who died when gabapentin, vigabatrin, or lamotrigine was compared with carbamazepine and all 3 were amenable for pooling.^{62,63,78} The risk of death was nonsignificantly decreased by 37 percent when all newer antiepileptics were compared with carbamazepine in new onset epilepsy (RR 0.63 [0.34 to 1.18]) (Appendix J Figure 1). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.788$).

Two randomized controlled trials reported the time to first seizure when lamotrigine or vigabatrin was compared with carbamazepine in patients with new onset epilepsy.^{52,63} The time to first seizure was nonsignificantly increased when either newer agent was compared with carbamazepine in new onset epilepsy (HR 1.20 [0.55 to 2.65]) (Appendix J Figure 4).

Seven randomized controlled trials reported data on withdrawals for any reason in patients with new onset epilepsy when gabapentin, lamotrigine, or vigabatrin were compared versus carbamazepine.^{52,53,60,62,63,78,80} The risk of withdrawal for any reason was significantly decreased by 16 percent when newer agents were compared versus carbamazepine (RR 0.84 [0.73 to 0.97]) (Appendix J Figure 9). Since the RD was (RD -0.086 [-0.15 to -0.017]), for every 12 patients treated with gabapentin, lamotrigine, or vigabatrin, 1 less patient would withdraw compared with those treated with carbamazepine. A high level of statistical heterogeneity was detected (I^2 : 54.8 percent), but publication bias was not detected (Egger's: $p=0.719$).

Four observational studies reported withdrawals for any reason when lamotrigine, levetiracetam, or vigabatrin were compared with carbamazepine in patients with new onset epilepsy.^{98,99,101,103} The risk of withdrawal was nonsignificantly increased by 47 percent when either newer agent was compared versus carbamazepine in patients with new onset epilepsy (RR 1.47 [0.46 to 4.72]) (Appendix J Figure 10). A high level of statistical heterogeneity (I^2 : 70 percent) was detected, but no publication bias was detected (Egger's: $p=0.178$).

Six randomized controlled trials reported data on withdrawals due to lack of efficacy in patients with new onset epilepsy when gabapentin, lamotrigine, or vigabatrin were compared versus carbamazepine.^{52,53,62,63,78,80} The risk of withdrawal due to lack of efficacy was significantly increased by 2.3-fold when newer agents were compared versus carbamazepine in patients with new onset epilepsy (RR 2.31 [1.41 to 3.78]) (Appendix J Figure 16). Given the RD (RD 0.02 [-0.006 to 0.05]), for every 50 patients with new onset epilepsy treated with either newer agent, 1 additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's: $p=0.289$).

Five observational studies reported withdrawals due to lack of efficacy when lamotrigine, topiramate or vigabatrin were compared with carbamazepine in patients with new onset epilepsy.^{98,99,101,104,105} The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 3 percent when either newer agent was compared with carbamazepine in patients with new onset epilepsy (RR 0.97 [0.60 to 1.56]) (Appendix J Figure 17). A lower level of statistical heterogeneity was detected (I^2 : 35.3 percent), but publication bias was not detected (Egger's: $p=0.751$).

Five randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in patients with new onset epilepsy.^{53,62,70,74,78} The risk of remaining seizure free for duration of study is nonsignificantly decreased by 9 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.91 [0.77 to 1.09]) (Appendix J Figure 26). A high level of statistical heterogeneity was detected (I^2 : 54 percent), but publication bias was not detected (Egger's $p=0.712$).

Four observational studies comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in patients with new onset epilepsy.^{98,99,103,105} The risk of remaining seizure free for duration of study is nonsignificantly increased by 11 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.11 [0.84 to 1.47]) (Appendix J Figure 27). A high level of statistical heterogeneity was detected (I^2 : 67.4 percent), but publication bias was not detected (Egger's $p=0.865$).

Two randomized controlled trials reported withdrawals for any reason when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.^{81,86} The risk of withdrawal was nonsignificantly decreased by 4 percent when either newer agent was compared with controlled or sustained release carbamazepine in patients with new onset epilepsy (RR 0.96 [0.78 to 1.18]) (Appendix J Figure 11).

One randomized controlled trial reported withdrawals due to lack of efficacy when levetiracetam was compared with controlled-release carbamazepine.⁸¹ This trial included patients with new onset epilepsy and the risk of withdrawal due to lack of efficacy was significantly increased by 2.4-fold when levetiracetam was compared versus controlled-release carbamazepine in patients with new onset epilepsy (RR 2.43 [1.32 to 4.52]). Given the RD, (RD 0.064 [0.021 to 0.11]), for every 16 patients treated with levetiracetam, 1 additional patient would withdraw due to lack of efficacy compared with those treated with carbamazepine.

Two randomized controlled trials reported data on seizure freedom for study duration when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.^{81,86} The risk of remaining seizure free for study duration was nonsignificantly decreased by 10 percent when either newer agent was compared with controlled- or sustained-release carbamazepine (RR 0.90 [0.79 to 1.02]) (Appendix J Figure 28).

Chronic Epilepsy. One randomized controlled trial reported the number of patients with chronic epilepsy who died when lamotrigine was compared with carbamazepine.⁷⁶ The risk of death was nonsignificantly increased by 2.4-fold when lamotrigine was compared with carbamazepine in chronic epilepsy (RR 2.36 [0.22 to 26.14]) (Appendix J Figure 1).

Two randomized controlled trials reported data on withdrawals for any reason in patients with chronic epilepsy when lamotrigine or vigabatrin was compared versus carbamazepine.^{76,79} The risk of withdrawal was nonsignificantly increased by 2.2-fold when newer agents were compared versus carbamazepine (RR 2.22 [0.36 to 13.79]) (Appendix J Figure 9).

One randomized controlled trial comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in patients with chronic epilepsy.⁷⁶ The risk of remaining seizure free for duration of study is nonsignificantly increased by 31 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.31 [0.72 to 2.59]) (Appendix J Figure 26).

Safety.

New Onset Epilepsy. Ten randomized controlled trials reported data on withdrawals due to adverse events in patients with new onset epilepsy when gabapentin, lamotrigine, topiramate, or vigabatrin were compared versus carbamazepine and were amenable for pooling.^{48,52,53,56,60,62,63,77,78,80}

The risk of withdrawal was significantly decreased by 50 percent when newer agents were compared versus carbamazepine (RR 0.50 [0.37 to 0.66]) (Appendix J Figure 37). Given the RD (RD -0.11 [-0.16 to -0.06]), for every 10 patients treated with gabapentin, lamotrigine, or vigabatrin, 1 less patient would withdraw compared with those treated with carbamazepine. A low level of statistical heterogeneity was detected (I^2 : 38.6 percent), but publication bias was not detected (Egger's: $p=0.181$).

Four observational studies reported withdrawals due to adverse events when lamotrigine, levetiracetam or vigabatrin were compared with carbamazepine in patients with new onset epilepsy and were amenable for pooling.^{98,99,101,103} The risk of withdrawal was nonsignificantly decreased by 44 percent when either newer agent was compared versus carbamazepine in patients with new onset epilepsy (RR 0.56 [0.24 to 1.30]) (Appendix J Figure 38). A low level of statistical heterogeneity (I^2 : 9.1 percent) was detected, but publication bias was not detected (Egger's: $p=0.299$).

Two observational studies comparing newer antiepileptic medications to carbamazepine reported data on headache in patients with new onset epilepsy.^{99,105} Risk of headache is nonsignificantly decreased by 57 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.43 [0.16 to 1.18]) (Appendix J Figure 45).

Four trials comparing newer antiepileptic medications to carbamazepine reported data on somnolence in patients with new onset epilepsy.^{52,60,62,77} Risk of somnolence is significantly decreased by 52 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.48 [0.33 to 0.69]) (Appendix J Figure 52). Given the RD (RD -0.075 [-0.104 to -0.046]), for every 14 patients treated, 1 less patient would develop somnolence from treatment with newer antiepileptic medications than with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.779$).

Three observational studies comparing newer antiepileptic medications to carbamazepine reported data on somnolence in patients with new onset epilepsy.^{99,103,105} Risk of somnolence is significantly decreased by 74 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.26 [0.11 to 0.58]) (Appendix J Figure 53). Given the RD (RD -0.041 [-0.020 to 0.038]), for every 25 patients treated, 1 less patient would develop somnolence from treatment with newer antiepileptic medications than with carbamazepine. No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Nine trials comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients with new onset epilepsy.^{52,53,56,62,63,77,78,82,90} Risk of dizziness is significantly decreased by 21 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.79 [0.66 to 0.94]) (Appendix J Figure 57). Given the RD (RD -0.045 [-0.085 to -0.005]), for every 23 patients treated, 1 less patient would develop dizziness from treatment with newer antiepileptic medications than with carbamazepine. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.115$).

Three observational studies comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients with new onset epilepsy.^{99,103,105} Risk of dizziness is significantly decreased by 79 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.21 [0.05 to 0.89]) (Appendix J Figure 58). Given the RD (RD -0.028 [-

0.062 to 0.005]), for every 36 patients treated, 1 less patient would develop dizziness from treatment with newer antiepileptic medications than with carbamazepine. No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to carbamazepine reported data on nausea in patients with new onset epilepsy.^{52,56,77} Risk of nausea is nonsignificantly decreased by 44 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.56 [0.19 to 1.65]) (Appendix J Figure 63). A low level of statistical heterogeneity was detected (I^2 : 52.9 percent) and significant publication bias was detected (Egger's $p=0.001$).

Eight randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on skin rash in patients with new onset epilepsy.^{52,53,56,62,63,78,80,82} Risk of skin rash is significantly decreased by 55 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.45 [0.26 to 0.77]) (Appendix J Figure 69). Given the RD (RD -0.048 [-0.072 to -0.024]), for every 21 patients treated, 1 less patient would develop skin rash from treatment with newer antiepileptic medications than with carbamazepine. A low level of statistical heterogeneity was detected (I^2 : 42.4 percent), but significant publication bias was detected (Egger's $p=0.031$).

Three observational studies comparing newer antiepileptic medications to carbamazepine reported data on skin rash in patients with new onset epilepsy.^{99,103,105} Risk of skin rash is nonsignificantly decreased by 76 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.24 [0.06 to 1.03]) (Appendix J Figure 70). A low level of statistical heterogeneity was detected (I^2 : 41.5 percent), but tests for publication bias could not be performed.

Two trials comparing newer antiepileptic medications to carbamazepine reported data on alopecia in patients with new onset epilepsy.^{77,82} Risk of alopecia is nonsignificantly decreased by 84 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.16 [0.02 to 1.06]) (Appendix J Figure 75). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Two randomized controlled trials reported withdrawals due to adverse events when lamotrigine or levetiracetam was compared with controlled- or sustained-release carbamazepine in patients with new onset epilepsy and both were amenable for pooling.^{81,86} The risk of withdrawal was significantly decreased by 31 percent when either newer antiepileptic medications were compared with controlled- or sustained-release carbamazepine in patients with new onset epilepsy (RR 0.69 [0.50 to 0.95]) (Appendix J Figure 39). Given the RD (RD -0.063 [-0.117 to 0.009]), for every 16 patients treated with either newer agent 1 less patient would withdraw due to adverse events compared with patients treated with controlled- or sustained-release carbamazepine.

Nine trials comparing newer antiepileptic medications to carbamazepine reported data on headache in patients with new onset epilepsy.^{52,53,56,60,62,63,77,78,82} Risk of headache is nonsignificantly increased by 3 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.03 [0.85 to 1.25]) (Appendix J Figure 44). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.566$).

Two randomized controlled trials reported data on headache when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.^{62,86} The risk of headache was nonsignificantly decreased by 17 percent when either newer agent was compared with controlled- or sustained-release carbamazepine (RR 0.83 [0.63 to 1.10]) (Appendix J Figure 46).

One randomized controlled trial reported data on somnolence while patients were receiving levetiracetam compared with controlled-release carbamazepine in a population of patients with new onset epilepsy.⁸¹ Risk of somnolence is nonsignificantly increased by 21 percent when levetiracetam is used versus controlled-release carbamazepine (RR 1.21 [0.75 to 1.96]).

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 in patients with new onset epilepsy.^{81,86} 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).

One randomized controlled trial reported data on nausea while patients were receiving levetiracetam compared with controlled-release carbamazepine in a population of patients with new onset epilepsy.⁸¹ Risk of nausea is nonsignificantly decreased by 34 percent when levetiracetam is used versus controlled-release carbamazepine (RR 0.66 [0.39 to 1.12]).

Two randomized controlled trials reported data on skin rash when lamotrigine or levetiracetam were compared with controlled- or sustained-release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.^{81,86} The risk of skin rash was significantly decreased by 53 percent when either newer agent was compared with controlled- or sustained-release carbamazepine (RR 0.47 [0.25 to 0.89]) (Appendix J Figure 71).

Chronic Epilepsy. One randomized controlled trial reported data on withdrawals due to adverse events in patients with chronic epilepsy when lamotrigine was compared versus carbamazepine.⁷⁶ The risk of withdrawal was nonsignificantly decreased by 45 percent when newer agents were compared versus carbamazepine (RR 0.55 [0.28 to 1.09]) (Appendix J Figure 37).

One observational study reported withdrawals due to adverse events when oxcarbazepine was compared versus carbamazepine in patients with chronic epilepsy.⁹⁵ The risk of withdrawal was nonsignificantly increased by 3-fold when oxcarbazepine was compared versus carbamazepine in patients with chronic epilepsy (RR 3.00 [0.26 to 35.71]) (Appendix J Figure 38).

Two trials comparing newer antiepileptic medications to carbamazepine reported data on headache in patients with chronic epilepsy.^{47,76} Risk of headache is nonsignificantly decreased by 45 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.55 [0.17 to 1.78]) (Appendix J Figure 44).

One trial comparing newer antiepileptic medications to carbamazepine reported data on somnolence in patients with chronic epilepsy.⁷⁶ Risk of somnolence is nonsignificantly decreased by 49 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.51 [0.26 to 1.02]) (Appendix J Figure 52). Tests for statistical heterogeneity or publication bias could not be performed.

One observational study comparing newer antiepileptic medications to carbamazepine reported data on somnolence in patients with chronic epilepsy.⁷⁹ Risk of somnolence is nonsignificantly decreased by 46 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.54 [0.12 to 2.13]) (Appendix J Figure 53).

One trial comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients with chronic epilepsy.⁷⁶ Risk of dizziness is nonsignificantly decreased by 27 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.73 [0.38 to 1.43]) (Appendix J Figure 57).

Two trials comparing newer antiepileptic medications to carbamazepine reported data on nausea in patients with chronic epilepsy.^{47,76} Risk of nausea is nonsignificantly decreased by 83 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.17 [0.03 to 1.01]) (Appendix J Figure 63).

Two trials comparing newer antiepileptic medications to carbamazepine reported data on alopecia in patients with chronic epilepsy.^{53,76} Risk of alopecia is nonsignificantly increased by 84 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.84 [0.30 to 11.43]) (Appendix J Figure 75).

Phenytoin Versus Newer

Efficacy.

New Onset Epilepsy. Two randomized controlled trials reported the number of patients with new onset epilepsy who died when either lamotrigine or oxcarbazepine was compared with phenytoin.^{57,64} The risk of death was nonsignificantly decreased by 79 percent when either newer agent was compared with phenytoin in new onset epilepsy (RR 0.21 [0.02 to 1.79]) (Appendix J Figure 2).

One randomized controlled trial reported time to first seizure when lamotrigine was compared with phenytoin in patients with new onset epilepsy.⁶⁴ The time to first seizure was nonsignificantly increased when lamotrigine was compared with phenytoin in patients with new onset epilepsy (HR 1.40 [0.80 to 2.30]) (Appendix J Figure 5).

Three randomized controlled trials reporting data on withdrawals for any reason either lamotrigine or oxcarbazepine were compared versus phenytoin in patients with new onset epilepsy.^{57,59,64} The risk of withdrawal was nonsignificantly decreased by 9 percent when the newer agents were compared versus phenytoin (RR 0.91 [0.76 to 1.09]) (Appendix J Figure 12). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Three randomized controlled trials reporting data on withdrawals due to lack of efficacy when lamotrigine or oxcarbazepine were compared with phenytoin in patients with new onset epilepsy and were amenable for pooling.^{57,59,64} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 3 percent when either newer agent was compared versus phenytoin in patients with new onset epilepsy (RR 1.03 [0.33 to 3.23]) (Appendix J Figure 18). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to phenytoin reported data on seizure freedom for study duration in patients with new onset epilepsy.^{57,59,64} The risk of remaining seizure free for study duration is nonsignificantly decreased by 3 percent when newer antiepileptic medications are used versus phenytoin (RR 0.97 [0.84 to 1.12]) (Appendix J Figure 29). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Safety.

New Onset Epilepsy. Three randomized controlled trials reporting data on withdrawals due to adverse events either lamotrigine or oxcarbazepine were compared versus phenytoin in patients with new onset epilepsy and were amenable for pooling.^{57,59,64} The risk of withdrawal was nonsignificantly decreased by 62 percent when the newer agents were compared versus phenytoin (RR 0.38 [0.14 to 1.03]) (Appendix J Figure 40). Significant statistical heterogeneity was detected (I^2 : 66.8 percent), however tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to phenytoin reported data on headache in patients with new onset epilepsy.^{57,59,64} Risk of headache is nonsignificantly decreased by 25 percent when newer antiepileptic medications are used versus phenytoin (RR 0.75 [0.52 to 1.08]) (Appendix J Figure 47). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to phenytoin reported data on somnolence in patients with new onset epilepsy.^{57,59,64} Risk of somnolence is nonsignificantly decreased by 34 percent when newer antiepileptic medications are used versus phenytoin (RR 0.66 [0.34 to 1.30]) (Appendix J Figure 54). A high level of statistical heterogeneity was detected (I^2 : 80.2 percent), but tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to phenytoin reported data on nausea in patients with new onset epilepsy.^{57,59,64} Risk of nausea is nonsignificantly decreased by 5 percent when newer antiepileptic medications are used versus phenytoin (RR 0.95 [0.56 to 1.62]) (Appendix J Figure 64). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to phenytoin reported data on skin rash in patients with new onset epilepsy.^{57,59,64} Risk of skin rash is nonsignificantly decreased by 1 percent when newer antiepileptic medications are used versus phenytoin (RR 0.99 [0.60 to 1.62]) (Appendix J Figure 72). No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

Valproic Acid Versus Newer Efficacy.

New Onset Epilepsy. Five randomized controlled trials reported data on withdrawals for any reason in patients with new onset epilepsy when lamotrigine or oxcarbazepine were compared versus valproic acid and were amenable for pooling.^{58,75,80,87,89} The risk of withdrawal was nonsignificantly increased by 3 percent when the newer agents were compared versus valproic acid in patients with new onset epilepsy (RR 1.03 [0.77 to 1.38]) (Appendix J Figure 13). No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Two observational studies reported withdrawals for any reason when lamotrigine was compared with valproic acid in patients with new onset epilepsy and were amenable for pooling.^{99,101} The risk of withdrawal was nonsignificantly decreased by 9 percent when lamotrigine was compared versus valproic acid in patients with new onset epilepsy (RR 0.91 [0.63 to 1.30]) (Appendix J Figure 14).

Four randomized controlled trials reported data on withdrawals due to lack of efficacy in patients with new onset epilepsy when lamotrigine or oxcarbazepine were compared versus valproic acid and were amenable for pooling.^{58,75,80,87} The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 2 percent when either newer agent was compared versus valproic acid in new onset epilepsy (RR 0.98 [0.55 to 1.78]) (Appendix J Figure 19). A

lower level of statistical heterogeneity was detected (I^2 : 10.8 percent), but publication bias was not detected (Egger's: $p=0.130$).

Three observational studies reported data on withdrawals due to lack of efficacy in patients with new onset epilepsy when lamotrigine or topiramate was compared versus valproic acid and were amenable for pooling.^{99,101,105} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 2 percent when newer agents were compared versus valproic acid (RR 1.02 [0.73 to 1.42]) (Appendix J Figure 20). No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Five trials comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration in patients with new onset epilepsy.^{58,77,80,82,87} The risk of remaining seizure free for study duration is nonsignificantly decreased by 4 percent when newer antiepileptic medications are used versus valproic acid (RR 0.96 [0.83 to 1.11]) (Appendix J Figure 30). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.484$).

Two observational studies comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration in patients with new onset epilepsy.^{99,105} The risk of remaining seizure free for study duration is nonsignificantly decreased by 10 percent when newer antiepileptic medications are used versus valproic acid (RR 0.90 [0.69 to 1.18]) (Appendix J Figure 31).

Chronic Epilepsy. Two randomized controlled trials reported the number of patients who died when lamotrigine or vigabatrin was compared with valproic acid in patients with chronic epilepsy and both were amenable for pooling.^{61,76} The risk of death was nonsignificantly increased by 28 percent when either newer agent was compared with valproic acid in patients with chronic epilepsy (RR 1.28 [0.11 to 15.14]) (Appendix J Figure 3).

Four randomized controlled trials reported data on withdrawals for any reason in patients with chronic epilepsy when felbamate, lamotrigine, topiramate, or vigabatrin were compared versus valproic acid and were amenable for pooling.^{50,61,73,76} The risk of withdrawal was nonsignificantly decreased by 18 percent when the newer agents were compared versus valproic acid in patients with chronic epilepsy (RR 0.82 [0.59 to 1.13]) (Appendix J Figure 13). No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's: $p=0.406$) was detected.

Two randomized controlled trials reported data on withdrawals due to lack of efficacy in patients with chronic epilepsy when topiramate or vigabatrin was compared versus valproic acid and were amenable for pooling.^{61,65} The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 44 percent when either newer agent was compared versus valproic acid in chronic epilepsy (RR 0.56 [0.28 to 1.10]) (Appendix J Figure 19).

One trial comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration in patients with chronic epilepsy.⁷⁶ The risk of remaining seizure free for study duration is nonsignificantly increased by 3.3-fold when newer antiepileptic medications are used versus valproic acid (RR 3.29 [0.99 to 12.40]) (Appendix J Figure 30).

Safety.

New Onset Epilepsy. Six randomized controlled trials reported data on withdrawals due to adverse events in patients with new onset epilepsy when lamotrigine, oxcarbazepine, or topiramate were compared versus valproic acid and were amenable for pooling.^{58,75,77,80,87,89} The risk of withdrawal was significantly decreased by 28 percent when the newer agents were compared versus valproic acid in patients with new onset epilepsy (RR 0.72 [0.53 to 0.97]) (Appendix J Figure 41). Given the RD (RD -0.03 [-0.09 to 0.03]), for every 33 patients treated

with either newer agent, 1 less patient would withdraw compared with those treated with valproic acid. No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.839$).

Two observational studies reported withdrawals due to adverse events in patients with new onset epilepsy when lamotrigine was compared versus valproic acid and were amenable for pooling.^{99,101} The risk of withdrawal was nonsignificantly decreased by 17 percent when lamotrigine was compared versus valproic acid in patients with new onset epilepsy (RR 0.83 [0.37 to 1.86]) (Appendix J Figure 42).

Five trials comparing newer antiepileptic medications to valproic acid reported data on headache in patients with new onset epilepsy.^{58,75,77,82,89} Risk of headache is nonsignificantly decreased by 20 percent when newer antiepileptic medications are used versus valproic acid (RR 0.80 [0.50 to 1.27]) (Appendix J Figure 48). A low level of statistical heterogeneity was detected (I^2 : 15.2 percent), but no publication bias was detected (Egger's $p=0.135$).

Two observational studies comparing newer antiepileptic medications to valproic acid reported data on headache in patients with new onset epilepsy.^{99,105} Risk of headache is nonsignificantly decreased by 23 percent when newer antiepileptic medications are used versus valproic acid (RR 0.77 [0.28 to 2.13]) (Appendix J Figure 49).

Four trials comparing newer antiepileptic medications to valproic acid reported data on fatigue in patients with new onset epilepsy.^{77,80,82,89} Risk of fatigue is nonsignificantly decreased by 18 percent when newer antiepileptic medications are used versus valproic acid (RR 0.82 [0.50 to 1.33]) (Appendix J Figure 51). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.412$).

Three trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with new onset epilepsy.^{58,77,89} Risk of somnolence is significantly decreased by 42 percent when newer antiepileptic medications are used versus valproic acid (RR 0.58 [0.33 to 1.00]) (Appendix J Figure 55). Given the RD (RD -0.060 [-0.160 to 0.040]), for every 17 patients treated, 1 less patient would develop somnolence from treatment with newer antiepileptic medications than with valproic acid. A low level of statistical heterogeneity was detected (I^2 : 13.5 percent), but publication bias was not detected (Egger's $p=0.257$).

Four trials comparing newer antiepileptic medications to valproic acid reported data on dizziness in patients with new onset epilepsy.^{58,77,82,89} Risk of dizziness is nonsignificantly increased by 15 percent when newer antiepileptic medications are used versus valproic acid (RR 1.15 [0.62 to 2.12]) (Appendix J Figure 61). No statistical heterogeneity was detected (I^2 : 0 percent), but significant publication bias was detected (Egger's $p=0.014$).

Two observational studies comparing newer antiepileptic medications to valproic acid reported data on dizziness in patients with new onset epilepsy.^{99,105} Risk of dizziness is nonsignificantly decreased by 50 percent when newer antiepileptic medications are used versus valproic acid (RR 0.50 [0.08 to 3.18]) (Appendix J Figure 62).

Three trials comparing newer antiepileptic medications to valproic acid reported data on nausea in patients with new onset epilepsy.^{58,77,89} Risk of nausea is nonsignificantly decreased by 44 percent when newer antiepileptic medications are used versus valproic acid (RR 0.56 [0.30 to 1.04]) (Appendix J Figure 65). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.421$).

One trial comparing newer antiepileptic medications to valproic acid reported data on vomiting in patients with new onset epilepsy.⁷⁷ Risk of vomiting is nonsignificantly increased by

65 percent when topiramate is used versus valproic acid (RR 1.65 [0.21 to 12.79]) (Appendix J Figure 68).

Two observational study comparing newer antiepileptic medications to valproic acid reported data on skin rash in patients with new onset epilepsy.^{99,105} Risk of skin rash is nonsignificantly increased by over 2.3-fold when newer antiepileptic medications are used versus valproic acid (RR 2.33 [0.22 to 25.11]) (Appendix J Figure 74).

Three trials comparing newer antiepileptic medications to valproic acid reported data on skin rash in patients with new onset epilepsy.^{75,80,82} Risk of skin rash is nonsignificantly increased by 5-fold when newer antiepileptic medications are used versus valproic acid (RR 5.04 [0.91 to 27.84]) (Appendix J Figure 73). No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to valproic acid reported data on alopecia in patients with new onset epilepsy.^{58,77,82} Risk of alopecia is significantly decreased by 70 percent when newer antiepileptic medications are used versus valproic acid (RR 0.30 [0.11 to 0.79]) (Appendix J Figure 77). Given the RD (RD -0.101 [-0.164 to -0.039]), for every 10 patients treated, 1 less patient would develop alopecia from treatment with newer antiepileptic medications than with valproic acid. A low level of statistical heterogeneity was detected (I^2 : 14.4 percent) and significant publication bias was also detected (Egger's $p=0.003$).

Chronic Epilepsy. Three randomized controlled trials reported data on withdrawals due to adverse events in patients with chronic epilepsy when lamotrigine, topiramate, or vigabatrin was compared versus valproic acid and were amenable for pooling.^{61,73,76} The risk of withdrawal was nonsignificantly decreased by 7 percent when the newer agents were compared versus valproic acid in patients with chronic epilepsy (RR 0.93 [0.51 to 1.71]) (Appendix J Figure 41). A lower level of statistical heterogeneity was detected (I^2 : 27.3 percent), but tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to valproic acid reported data on headache in patients with chronic epilepsy.^{50,51,76} Risk of headache is nonsignificantly increased by 1 percent when newer antiepileptic medications are used versus valproic acid (RR 1.01 [0.39 to 2.65]) (Appendix J Figure 48). A high level of statistical heterogeneity was detected (I^2 : 58.5 percent) and tests for publication bias could not be performed.

Two trials comparing newer antiepileptic medications to valproic acid reported data on fatigue in patients with chronic epilepsy.^{50,51} Risk of fatigue is nonsignificantly decreased by 18 percent when newer antiepileptic medications are used versus valproic acid (RR 0.82 [0.13 to 5.10]) (Appendix J Figure 51).

Two trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with chronic epilepsy.^{50,51} Risk of somnolence is nonsignificantly increased by 10 percent when newer antiepileptic medications are used versus valproic acid (RR 1.10 [0.55 to 2.21]) (Appendix J Figure 55). A low level of statistical heterogeneity was detected (I^2 : 8.5 percent) and tests for publication bias could not be performed.

Two trials comparing newer antiepileptic medications to valproic acid reported data on dizziness in patients with chronic epilepsy.^{51,76} Risk of dizziness is nonsignificantly increased by 20 percent when newer antiepileptic medications are used versus valproic acid (RR 1.20 [0.53 to 2.73]) (Appendix J Figure 61).

Two trials comparing newer antiepileptic medications to valproic acid reported data on nausea in patients with chronic epilepsy.^{51,76} Risk of nausea is nonsignificantly decreased by 58

percent when newer antiepileptic medications are used versus valproic acid (RR 0.42 [0.16 to 1.14]) (Appendix J Figure 65).

One trial comparing newer antiepileptic medications to valproic acid reported data on vomiting in patients with chronic epilepsy.⁵¹ Risk of vomiting is nonsignificantly increased by 3 percent when felbamate is used versus valproic acid (RR 1.03 [0.19 to 5.61]) (Appendix J Figure 68).

One trial comparing newer antiepileptic medications to valproic acid reported data on alopecia in patients with chronic epilepsy.⁷⁶ Risk of alopecia is significantly decreased by 92 percent when newer antiepileptic medications are used versus valproic acid (RR 0.08 [0.01 to 0.52]) (Appendix J Figure 77). Given the RD (RD -0.104 [-0.191 to -0.016]), for every 10 patients treated, 1 less patient would develop alopecia from treatment with newer antiepileptic medications than with valproic acid.

Ethosuximide Versus Newer Efficacy.

Generalized Epilepsy. One randomized controlled trial reported withdrawals for any reason while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ This trial included patients with new onset, generalized epilepsy, or childhood absence epilepsy in children ≤ 18 years of age.⁸⁹ The risk of overall withdrawal was nonsignificantly decreased by 5 percent when lamotrigine was compared versus ethosuximide (RR 0.95 [0.53 to 1.71]). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed. This same trial found the risk of overall withdrawal was nonsignificantly decreased by 29 percent when lamotrigine was compared versus ethosuximide (RR 0.71 [0.45 to 1.12]).

Safety.

Generalized Epilepsy. One randomized controlled trial reported data on headache while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤ 18 years of age.⁸⁹ The risk of headache was nonsignificantly decreased by 34 percent when lamotrigine was compared versus ethosuximide (RR 0.66 [0.33 to 1.29]). This same trial found the risk of fatigue was nonsignificantly decreased by 10 percent when lamotrigine was compared versus ethosuximide (RR 0.90 [0.45 to 1.80]). In this trial, the risk of somnolence was significantly decreased by 78 percent when lamotrigine was compared versus ethosuximide (RR 0.22 [0.07 to 0.70]). Given the RD (RD -0.04 [-0.11 to 0.03]), for every 25 patients treated with lamotrigine, 1 less patients would experience headache. In this trial, the risk of dizziness was nonsignificantly decreased by 54 percent when lamotrigine was compared versus ethosuximide (RR 0.46 [0.15 to 1.38]).

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on seizure type.

Gender

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer Efficacy.

Male. One randomized controlled trial reported the number of patients who died in a patient population of >90 percent men (96 percent of the patients enrolled were male) and compared gabapentin or lamotrigine versus carbamazepine.⁷⁸ While the impact was not broken out in males alone, the risk of death was nonsignificantly decreased by 36 percent when gabapentin or lamotrigine was used versus carbamazepine in the mixed population comprising 96 percent men (RR 0.64 [0.33 to 1.23]) (Appendix J Figure 1). In this trial, the risk of withdrawal was significantly decreased by 26 percent when gabapentin or lamotrigine was used versus carbamazepine in the mixed population comprising 96 percent men (RR 0.74 [0.64 to 0.86]) (Appendix J Figure 9). Given the RD (RD -0.17 [-0.25 to -0.08]), for every six patients treated with gabapentin or lamotrigine, one less patient would withdraw compared with those treated with carbamazepine. The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 89 percent when newer agents were compared versus carbamazepine in this population comprising >90 percent men (RR 1.89 [0.72 to 5.00]) (Appendix J Figure 16).

Safety.

Male. One randomized controlled trial reported withdrawals due to adverse events in a patient population comprising more than 90 percent men (96 percent of the patients enrolled in the trial were male) and compared gabapentin or lamotrigine to carbamazepine.⁷⁸ While the impact was not broken out into males alone, the risk of withdrawal due to adverse events was significantly decreased by 47 percent when newer agents were compared with carbamazepine in this mixed population (RR 0.53 [0.30 to 0.94]) (Appendix J Figure 37). Given the RD (RD -0.143 [-0.237 to -0.049]), for every seven patients treated with a newer agent, one less patient would withdraw due to an adverse event compared with carbamazepine. In this trial, risk of headache is nonsignificantly decreased by 2 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.98 [0.66 to 1.46]) (Appendix J Figure 44). The risk of dizziness is nonsignificantly decreased by 14 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.86 [0.66 to 1.14]) in this population (Appendix J Figure 57). The risk of skin rash is significantly decreased by 88 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.12 [0.02 to 0.69]) in this trial (Appendix J Figure 69). Given the RD (RD -0.034 [-0.063 to -0.004]), for every 30 patients treated, 1 less patient would develop skin rash from treatment with newer AED than with carbamazepine.

Valproic Acid Versus Newer

Efficacy.

Female. One randomized controlled trial reported data on withdrawals for any reason when lamotrigine was compared versus valproic acid in a patient population comprised of more than 90 percent women (100 percent of the patients enrolled in the study were women).⁸⁸ The risk of withdrawal was nonsignificantly decreased by 4 percent when lamotrigine was used versus valproic acid in this mixed population (RR 0.96 [0.69 to 1.33]) (Appendix J Figure 13).

In this trial, the risk of withdrawal due to lack of efficacy was nonsignificantly increased by 2.0-fold when lamotrigine was compared with valproic acid in this population (RR 2.03 [0.27 to 15.41]). The risk of remaining seizure free for study duration is nonsignificantly decreased by 20 percent when newer antiepileptic medications are used versus valproic acid (RR 0.80 [0.63 to 1.01]) (Appendix J Figure 30).

Safety.

Female. One randomized controlled trial reported data on withdrawals due to adverse events in a patient population comprising more than 90 percent women (100 percent of the patients enrolled in the trial were women) and compared lamotrigine to valproic acid.⁸⁸ The risk of withdrawal

was nonsignificantly increased by 1 percent when lamotrigine was used versus valproic acid in this population (RR 1.01 [0.42 to 2.44]) (Appendix J Figure 41). The risk of headache is nonsignificantly decreased by 25 percent when newer antiepileptic medications are used versus valproic acid (RR 0.75 [0.48 to 1.17]) (Appendix J Figure 48). The risk of dizziness is nonsignificantly increased by 12 percent when newer antiepileptic medications are used versus valproic acid (RR 1.12 [0.49 to 2.52]) (Appendix J Figure 61). The risk of nausea is significantly decreased by 81 percent when newer antiepileptic medications are used versus valproic acid (RR 0.19 [0.06 to 0.60]) (Appendix J Figure 65). Given the RD (RD -0.058 [-0.096 to -0.021]), for every 18 patients treated, 1 less patient would develop nausea from treatment with newer AED than with valproic acid. The risk of vomiting is significantly decreased by 62 percent when newer antiepileptic medications are used versus valproic acid (RR 0.38 [0.16 to 0.92]) (Appendix J Figure 68). Given the RD (RD -0.045 [-0.085 to -0.004]), for every 23 patients treated, 1 less patient would develop vomiting from treatment with newer AED than with valproic acid. The risk of skin rash is nonsignificantly increased by 13 percent when newer antiepileptic medications are used versus valproic acid (RR 1.13 [0.48 to 2.65]) (Appendix J Figure 73).

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled clinical trial and one observational trial reported data on gender differences.³³ Results showed that women compared with men were more likely to switch from innovator to generic (HR 0.95 [95 percent CI 0.91 to 0.99]; $p=0.0057$), and there was no statistically significant difference in women compared with men when switching back to innovator from generic (HR 1.10 [0.97 to 1.24]; $p=0.130$).

Ethnicity

Older Versus Newer Antiepileptic Drug Evaluation

No controlled clinical trials or observational studies comparing newer versus older antiepileptic medications reported data on ethnicity.

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on ethnicity.

Patient Age

Older Versus Newer Antiepileptic Drug Evaluation

Carbamazepine Versus Newer Efficacy.

Children ≤ 18 Years of Age. Three randomized controlled trials reported data on withdrawals for any reason in patients who were ≤ 18 years of age when lamotrigine or topiramate were compared versus carbamazepine.^{70,79,83} The risk of withdrawal was nonsignificantly increased by 9 percent when newer antiepileptics were compared versus carbamazepine (RR 1.09 [0.60 to 1.99]) (Appendix J Figure 9). A low level of statistical heterogeneity was detected (I^2 : 22.9 percent), and publication bias could not be calculated.

Three observational studies reported withdrawals for any reason when levetiracetam, topiramate, or vigabatrin were compared with carbamazepine in children ≤ 18 years of age.^{98,103,104} The risk of withdrawal was nonsignificantly increased by 82 percent when the aforementioned newer agents were compared versus carbamazepine (RR 1.82 [0.48 to 6.91]) (Appendix J Figure 10). A high level of significant statistical heterogeneity (I^2 : 82 percent) was detected, but tests for publication bias could not be performed.

Three observational studies reported withdrawals due to lack of efficacy when topiramate or vigabatrin were compared with carbamazepine in children ≤ 18 years of age.^{98,104,105} The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 8 percent when newer agents were compared versus carbamazepine in children ≤ 18 years of age (RR 1.08 [0.37 to 3.15]) (Appendix J Figure 17). A high level of statistical heterogeneity was detected (I^2 : 67.9 percent), but tests for publication bias could not be performed.

Five randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in children ≤ 18 years of age.^{56,70,77,82,83} The risk of remaining seizure free for duration of study is nonsignificantly decreased by 1 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.99 [0.84 to 1.17]) (Appendix J Figure 23). No statistical heterogeneity (I^2 : 15.3 percent) or significant publication bias was detected (Egger's $p=0.070$).

Three observational trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in children ≤ 18 years of age.^{98,103,105} The risk of remaining seizure free for duration of study is nonsignificantly decreased by 1 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.99 [0.84 to 1.17]) (Appendix J Figure 27). No statistical heterogeneity was detected (I^2 : 0 percent) but tests for publication bias could not be performed.

Adults 18–65 Years of Age. One randomized controlled trial comparing a newer antiepileptic medication to carbamazepine reported data on seizure freedom for study duration in patients 18–65 years of age.⁵⁶ The risk of remaining seizure free for duration of study is nonsignificantly decreased by 18 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.82 [0.47 to 1.42]) (Appendix J Figure 23).

Adults ≥ 65 Years of Age. One randomized controlled trial reported the number of patients who were ≥ 65 years of age and died when lamotrigine was compared versus carbamazepine.⁶¹ The risk of death was nonsignificantly decreased by 91 percent when lamotrigine was used versus carbamazepine in adults ≥ 65 years of age (RR 0.09 [0.01 to 1.04]) (Appendix J Figure 1).

Two randomized controlled trials reported data on withdrawals for any reason in patients who were ≥ 65 years of age when lamotrigine was compared versus carbamazepine.^{62,70} The risk of withdrawal was nonsignificantly decreased by 49 percent when lamotrigine was used versus carbamazepine (RR 0.51 [0.37 to 0.71]) (Appendix J Figure 9).

One randomized controlled trial reported data on withdrawals due to lack of efficacy among patients who were ≥ 65 years of age. In this trial, lamotrigine was compared versus carbamazepine.⁶² The risk of withdrawal due to ineffective treatment was nonsignificantly decreased by 53 percent when newer agents were compared versus carbamazepine in a population comprising ≥ 65 years of age (RR 0.47 [0.01 to 23.49]) (Appendix J Figure 16).

One randomized controlled trial comparing lamotrigine to carbamazepine reported data on seizure freedom for study duration in patients ≥ 65 years of age.⁶² The risk of remaining seizure free for duration of study is nonsignificantly increased by 88 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.88 [1.07 to 3.49]) (Appendix J Figure 26).

One randomized controlled trial reported withdrawals for any reason when lamotrigine was compared with sustained-release carbamazepine in patients ≥ 65 years of age.⁸⁶ The risk of withdrawal was nonsignificantly decreased by 18 percent when lamotrigine was compared versus sustained-release carbamazepine in patients ≥ 65 years of age (RR 0.82 [0.52 to 1.27]) (Appendix J Figure 11).

One randomized controlled trial reported data on seizure freedom for study duration when lamotrigine was compared with sustained-release carbamazepine in patients ≥ 65 years of age.⁸⁶ The risk of remaining seizure free for study duration was nonsignificantly decreased by 18 percent when lamotrigine was used versus sustained-release carbamazepine (RR 0.82 [0.64 to 1.03]) (Appendix J Figure 28).

Safety.

Children ≤ 18 Years of Age. Three randomized controlled trials reported data on withdrawals due to adverse events in patients who were ≤ 18 years of age when lamotrigine or topiramate were compared versus carbamazepine and were amenable for pooling.^{70,77,83} The risk of withdrawal was nonsignificantly increased by 8 percent when newer antiepileptics were compared versus carbamazepine (RR 1.08 [0.52 to 2.23]) (Appendix J Figure 37). No significant statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's: $p=0.091$) was detected.

Three nonrandomized trials reported withdrawals due to adverse events when levetiracetam, topiramate, and vigabatrin were compared with carbamazepine in patients ≤ 18 years of age and were amenable for pooling.^{98,103,104} The risk of withdrawal was nonsignificantly decreased by 2 percent when either newer agent was compared versus carbamazepine (RR 0.98 [0.25 to 3.77]) (Appendix J Figure 38).

Three trials comparing newer antiepileptic medications to carbamazepine reported data on headache in children ≤ 18 years of age.^{70,77,82} Risk of headache is nonsignificantly decreased by 17 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.83 [0.43 to 1.61]) (Appendix J Figure 44). A low level of statistical heterogeneity was detected (I^2 : 27.3 percent), but no publication bias was detected (Egger's $p=0.211$).

One observational study comparing newer antiepileptic medications to carbamazepine reported data on headache in children ≤ 18 years of age.¹⁰⁵ Risk of headache is nonsignificantly decreased by 58 percent when topiramate is used versus carbamazepine (RR 0.42 [0.12 to 1.50]) (Appendix J Figure 45).

Two trials comparing newer antiepileptic medications to carbamazepine reported data on fatigue in children ≤ 18 years of age.^{77,82} Risk of fatigue is nonsignificantly increased by 3 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.03 [0.47 to 2.28]) (Appendix J Figure 50). No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Three trials comparing newer antiepileptic medications to carbamazepine reported data on somnolence in children ≤ 18 years of age.^{70,77,83} Risk of somnolence is nonsignificantly decreased by 32 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.68 [0.33 to 1.39]) (Appendix J Figure 52).

Three observational studies comparing newer antiepileptic medications to carbamazepine reported data on somnolence in children ≤ 18 years of age.^{79,103,105} Risk of somnolence is significantly decreased by 72 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.28 [0.13 to 0.62]) (Appendix J Figure 53). Given the RD (RD -0.119 [-0.425 to 0.186]), for every nine patients treated, one less patient would develop somnolence from

treatment with newer AED than with carbamazepine. No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

One trial comparing newer antiepileptic medications to carbamazepine reported data on nausea in children ≤ 18 years of age.⁷⁷ Risk of nausea is nonsignificantly decreased by 70 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.30 [0.08 to 1.10]) (Appendix J Figure 63).

One trial comparing newer antiepileptic medications to carbamazepine reported data on vomiting in children ≤ 18 years of age.⁷⁷ Risk of vomiting is nonsignificantly decreased by 12 percent when topiramate is used versus carbamazepine (RR 0.88 [0.19 to 4.12]) (Appendix J Figure 66).

Three randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on skin rash in children ≤ 18 years of age.^{70,82,83} Risk of skin rash is nonsignificantly decreased by 46 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.54 [0.19 to 1.52]) (Appendix J Figure 69). A low level of statistical heterogeneity was detected (I^2 : 38.9 percent) and tests on publication bias could not be performed.

Three observational studies comparing newer antiepileptic medications to carbamazepine reported data on skin rash in children ≤ 18 years of age.¹⁰³⁻¹⁰⁵ Risk of skin rash is significantly decreased by 83 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.17 [0.03 to 0.91]) (Appendix J Figure 70). Given the RD (RD -0.051 [-0.127 to 0.024]), for every 20 patients treated, 1 less patient would develop skin rash from treatment with new AED than with carbamazepine. A low level of statistical heterogeneity was detected (I^2 : 19.9 percent) and tests on publication bias could not be performed.

Two trials comparing newer antiepileptic medications to carbamazepine reported data on alopecia in children ≤ 18 years of age.^{77,82} Risk of alopecia is nonsignificantly decreased by 84 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.16 [0.02 to 1.06]) (Appendix J Figure 75). No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Adults 18–65 Years of Age. One randomized controlled trial reported data on withdrawals due to adverse events in patients who were 18 to 65 years of age when vigabatrin was compared versus carbamazepine.⁵⁶ The risk of withdrawal was nonsignificantly decreased by 68 percent when lamotrigine was used versus carbamazepine (RR 0.32 [0.03 to 3.74]) (Appendix J Figure 37).

One trial comparing newer antiepileptic medications to carbamazepine reported data on headache in patients 18 to 65 years of age.⁵⁶ Risk of headache is nonsignificantly increased by over 8.5-fold when newer antiepileptic medications are used versus carbamazepine (RR 8.66 [0.90 to 88.91]) (Appendix J Figure 44).

One trial comparing newer antiepileptic medications to carbamazepine reported data on fatigue in patients 18 to 65 years of age.⁵⁶ Risk of fatigue is nonsignificantly increased by 92 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.92 [0.59 to 6.51]) (Appendix J Figure 50).

One trial comparing newer antiepileptic medications to carbamazepine reported data on nausea in patients 18 to 65 years of age.⁵⁶ Risk of nausea is nonsignificantly decreased by 76 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.24 [0.04 to 1.47]) (Appendix J Figure 63).

One randomized controlled trial comparing newer antiepileptic medications to carbamazepine reported data on skin rash in patients 18 to 65 years of age.⁵⁶ Risk of skin rash is

nonsignificantly decreased by 68 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.32 [0.03 to 3.74]) (Appendix J Figure 69).

Adults ≥ 65 Years of Age. Three randomized controlled trials reported data on withdrawals due to adverse events in patients who were ≥ 65 years of age when lamotrigine was compared versus carbamazepine and were amenable for pooling.^{60,62,70} The risk of withdrawal was nonsignificantly decreased by 58 percent when lamotrigine was used versus carbamazepine (RR 0.42 [0.26 to 0.66]) (Appendix J Figure 37).

Two trials comparing newer antiepileptic medications to carbamazepine reported data on headache in patients ≥ 65 years of age.^{62,70} Risk of headache is nonsignificantly decreased by 41 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.59 [0.25 to 1.39]) (Appendix J Figure 44).

One trial comparing newer antiepileptic medications to carbamazepine reported data on vomiting in patients ≥ 65 years of age.⁶² Risk of vomiting is nonsignificantly increased by 41 percent when newer antiepileptic medications are used versus carbamazepine (RR 1.41 [0.44 to 4.71]) (Appendix J Figure 66).

Two randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on skin rash in patients ≥ 65 years of age.^{62,70} Risk of skin rash is nonsignificantly decreased by 33 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.67 [0.15 to 2.90]) (Appendix J Figure 69).

One randomized controlled trial reported data on skin rash when lamotrigine was compared with sustained-release carbamazepine in patients ≥ 65 years of age.⁸⁶ The risk of skin rash was nonsignificantly decreased by 59 percent when lamotrigine was used versus sustained release carbamazepine (RR 0.41 [0.16 to 1.07]) (Appendix J Figure 71). In this trial, the risk of withdrawal was nonsignificantly decreased by 45 percent when lamotrigine was compared versus sustained-release carbamazepine in adults patients ≥ 65 years of age (RR 0.55 [0.30 to 1.02]) (Appendix J Figure 39). The risk of dizziness was nonsignificantly increased by 43 percent when lamotrigine was used versus sustained-release carbamazepine in adults ≥ 65 years of age (RR 1.43 [0.66 to 3.13]) (Appendix J Figure 59).

Phenytoin Versus Newer Efficacy.

Children ≤ 18 Years of Age. One randomized controlled trial reported data on withdrawals for any reason when oxcarbazepine was compared with phenytoin in children ≤ 18 years of age.⁵⁹ The risk of withdrawal was nonsignificantly decreased by 30 percent when oxcarbazepine was compared versus phenytoin in children ≤ 18 years of age (RR 0.70 [0.45 to 1.08]) (Appendix J Figure 12). This trial found the risk of remaining seizure free for study duration is nonsignificantly increased by 1 percent when newer antiepileptic drugs are used versus phenytoin (RR 1.01 [0.79 to 1.31]) (Appendix J Figure 29).

Safety.

Children ≤ 18 Years of Age. One randomized controlled trial reported data on withdrawals due to adverse events when oxcarbazepine was compared with phenytoin in children ≤ 18 years of age.⁵⁹ The risk of withdrawal was significantly decreased by 86 percent when oxcarbazepine was compared versus phenytoin (RR 0.14 [0.04 to 0.54]) (Appendix J Figure 40). Given the RD (RD -0.13 [-0.20 to -0.05]), for every eight patients treated with oxcarbazepine, one less would withdraw due to adverse events compared with those treated with phenytoin. In this trial the risk of headache is nonsignificantly decreased by 9 percent when newer antiepileptic medications are used versus phenytoin (RR 0.91 [0.46 to 1.81]) (Appendix J Figure 47). In addition, the risk of

somnolence is nonsignificantly decreased by 16 percent when newer antiepileptic medications are used versus phenytoin (RR 0.84 [0.53 to 1.33]) (Appendix J Figure 54).

Four trials comparing newer antiepileptic medications to carbamazepine reported data on dizziness in children ≤ 18 years of age.^{70,77,82,83} Risk of dizziness is nonsignificantly decreased by 65 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.35 [0.09 to 1.36]) (Appendix J Figure 57). A low level of statistical heterogeneity was detected (I^2 : 47.5 percent), but no publication bias was detected (Egger's $p=0.212$).

Two observational studies comparing newer antiepileptic medications to carbamazepine reported data on dizziness in children ≤ 18 years of age.^{103,105} Risk of dizziness is nonsignificantly decreased by 75 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.25 [0.05 to 1.33]) (Appendix J Figure 58).

Only one randomized controlled trial reported data on vomiting while patients were receiving a newer antiepileptic medication (oxcarbazepine) compared with phenytoin.⁵⁹ This trial was in children ≤ 18 years of age. Risk of vomiting is significantly decreased by 91 percent when oxcarbazepine is used versus phenytoin (RR 0.09 [0.01 to 0.89]) (Appendix J Figure 67). Given the RD (RD -0.053 [-0.102 to -0.004]), for every 19 patients treated, 1 less patient would develop vomiting from treatment with oxcarbazepine than with phenytoin. In this trial, the risk of skin rash is nonsignificantly decreased by 22 percent when newer antiepileptic medications are used versus phenytoin (RR 0.78 [0.23 to 2.62]) (Appendix J Figure 72). The risk of gum hyperplasia is significantly decreased by 92 percent when oxcarbazepine is used versus phenytoin (RR 0.08 [0.02 to 0.30]) (Appendix J Figure 76).

Adults 18–65 Years of Age. One trial comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients 18 to 65 years of age.⁵⁶ Risk of dizziness is significantly decreased by 89 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.11 [0.02 to 0.58]) (Appendix J Figure 57). Given the RD (RD -0.322 [-0.524 to -0.119]), for every four patients treated, one less patient would develop dizziness from treatment with newer antiepileptic medications than with carbamazepine.

Adults ≥ 65 Years of Age. Two trials comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients ≥ 65 years of age.^{62,70} Risk of dizziness is nonsignificantly decreased by 1 percent when newer antiepileptic medications are used versus carbamazepine (RR 0.99 [0.23 to 4.31]) (Appendix J Figure 57).

Valproic Acid Versus Newer Efficacy.

Children ≤ 18 Years of Age. Two randomized controlled trials reported data on withdrawals for any reason in children ≤ 18 years of age when lamotrigine was compared versus valproic acid and were amenable for pooling.^{75,89} The risk of withdrawal was nonsignificantly increased by 34 percent when lamotrigine was compared versus valproic acid in children ≤ 18 years of age (RR 1.34 [0.76 to 2.37]) (Appendix J Figure 13).

One randomized controlled trial reported data on withdrawals due to lack of efficacy in children ≤ 18 years of age when lamotrigine was compared versus valproic acid.⁷⁵ The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 2.0-fold when lamotrigine was compared versus valproic acid in children ≤ 18 years of age (RR 2.00 [0.64 to 6.60]) (Appendix J Figure 19).

One observational study reported data on withdrawals due to lack of efficacy in children ≤ 18 years of age when topiramate was compared versus valproic acid.¹⁰⁵ The risk of withdrawal due

to lack of efficacy was nonsignificantly increased by 2 percent when topiramate was compared versus valproic acid (RR 1.02 [0.65 to 1.60]) (Appendix J Figure 20).

Two trials comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration in children ≤ 18 years of age.^{77,82} The risk of remaining seizure free for study duration is nonsignificantly increased by 10 percent when newer antiepileptic medications are used versus valproic acid (RR 1.10 [0.81 to 1.48]) (Appendix J Figure 30). No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

One observational study comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in children ≤ 18 years of age.¹⁰⁵ The risk of remaining seizure free for study duration is significantly decreased by 20 percent when topiramate is used versus valproic acid (RR 0.80 [0.68 to 0.92]) (Appendix J Figure 31).

Safety.

Children ≤ 18 Years of Age. Three randomized controlled trials reported data on withdrawals due to adverse events in children ≤ 18 years of age when lamotrigine was compared versus valproic acid and were amenable for pooling.^{77,89} The risk of withdrawal was significantly decreased by 35 percent when lamotrigine was compared versus valproic acid in children less than or equal to 18 years of age (RR 0.65 [0.43 to 0.97]) (Appendix J Figure 41). Given the RD (RD -0.50 [-0.12 to 0.02]), for every two patients treated with either newer agent, one less patient would withdraw compared with those treated with valproic acid. No statistical heterogeneity (I^2 : 0 percent) or publication bias (Egger's $p=0.540$) was detected.

Four trials comparing newer AEDs to valproic acid reported data on headache in children ≤ 18 years of age.^{75,77,82,89} Risk of headache is nonsignificantly decreased by 5 percent when newer AEDs are used versus valproic acid (RR 0.95 [0.52 to 1.75]) (Appendix J Figure 48). A low level of statistical heterogeneity was detected (I^2 : 16.1 percent), but no publication bias was detected (Egger's $p=0.292$).

One observational study comparing newer AEDs to valproic acid reported data on headache in children ≤ 18 years of age.¹⁰⁵ Risk of headache is nonsignificantly decreased by 45 percent when topiramate is used versus valproic acid (RR 0.55 [0.16 to 1.82]) (Appendix J Figure 49).

Three trials comparing newer antiepileptic medications to valproic acid reported data on fatigue in children ≤ 18 years of age.^{77,82,89} Risk of fatigue is nonsignificantly decreased by 13 percent when newer antiepileptic medications are used versus valproic acid (RR 0.87 [0.52 to 1.47]) (Appendix J Figure 51). No statistical heterogeneity (I^2 : 0 percent) or publication bias was detected (Egger's $p=0.242$).

Two trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in children ≤ 18 years of age.^{77,89} Risk of somnolence is significantly decreased by 61 percent when newer antiepileptic medications are used versus valproic acid (RR 0.39 [0.17 to 0.89]) (Appendix J Figure 55). Given the RD (RD -0.124 [-0.367 to 0.120]), for every nine patients treated, one less patient would develop somnolence from treatment with newer antiepileptic medications than with valproic acid. No statistical heterogeneity was detected (I^2 : 0 percent), but tests for publication bias could not be performed.

One observational study comparing newer antiepileptic medications to valproic acid reported data on somnolence in children ≤ 18 years of age.¹⁰⁵ Risk of somnolence is nonsignificantly decreased by 77 percent when topiramate is used versus valproic acid (RR 0.23 [0.02 to 2.46]) (Appendix J Figure 56). Tests for statistical heterogeneity or publication bias could not be performed.

Two trials comparing newer antiepileptic medications to valproic acid reported data on dizziness in children ≤ 18 years of age.^{77,82} Risk of dizziness is nonsignificantly increased by 95 percent when newer antiepileptic medications are used versus valproic acid (RR 1.95 [0.36 to 10.58]) in this population (Appendix J Figure 61).

One observational study comparing newer antiepileptic medications to valproic acid reported data on dizziness in children ≤ 18 years of age.¹⁰⁵ Risk of dizziness is nonsignificantly decreased by 45 percent when topiramate is used versus valproic acid (RR 0.55 [0.08 to 3.76]) (Appendix J Figure 62).

Three trials comparing newer antiepileptic medications to valproic acid reported data on nausea in children ≤ 18 years of age.^{72,77,89} Risk of nausea is nonsignificantly decreased by 45 percent when newer antiepileptic medications are used versus valproic acid (RR 0.55 [0.20 to 1.52]) (Appendix J Figure 65). A low level of statistical heterogeneity was detected (I^2 : 25 percent), but no publication bias was detected (Egger's $p=0.744$).

One trial comparing newer antiepileptic medications to valproic acid reported data on vomiting in children ≤ 18 years of age.⁷⁷ Risk of vomiting is nonsignificantly increased by 65 percent when topiramate is used versus valproic acid (RR 1.65 [0.21 to 12.79]) (Appendix J Figure 68).

Two trials comparing newer antiepileptic medications to valproic acid reported data on skin rash in children ≤ 18 years of age.^{75,82} Risk of skin rash is nonsignificantly increased by 3.9-fold when newer antiepileptic medications are used versus valproic acid (RR 3.86 [0.46 to 32.34]) (Appendix J Figure 73).

One observational study comparing newer antiepileptic medications to carbamazepine reported data on skin rash in children ≤ 18 years of age.¹⁰⁵ Risk of skin rash is nonsignificantly decreased by 18 percent when topiramate is used versus valproic acid (RR 0.82 [0.11 to 6.19]) (Appendix J Figure 74).

Two trials comparing newer antiepileptic medications to valproic acid reported data on alopecia in children ≤ 18 years of age.^{77,82} Risk of alopecia is significantly decreased by 92 percent when newer antiepileptic medications are used versus valproic acid (RR 0.08 [0.01 to 0.48]) (Appendix J Figure 77). Given the RD (RD -0.120 [-0.215 to -0.024]), for every nine patients treated, one less patient would develop alopecia from treatment with newer AEDs than with valproic acid. No statistical heterogeneity was detected (I^2 : 0 percent) and tests for publication bias could not be performed.

Ethosuximide Versus Newer Efficacy.

Children ≤ 18 Years of Age. One randomized controlled trial reported withdrawals for any reason while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤ 18 years of age.⁸⁹ The risk of overall withdrawal was nonsignificantly decreased by 5 percent when lamotrigine was compared versus ethosuximide (RR 0.95 [0.53 to 1.71]). Since only one trial was available, tests for statistical heterogeneity and publication bias could not be performed.

In this trial, the risk of overall withdrawal was nonsignificantly decreased by 29 percent when lamotrigine was compared versus ethosuximide (RR 0.71 [0.45 to 1.12]).

Safety.

Children ≤ 18 Years of Age. One randomized controlled trial reported data on headache while patients were receiving lamotrigine compared with ethosuximide.⁸⁹ This trial included patients with new onset, generalized epilepsy, or childhood absence epilepsy in children ≤ 18 years of

age.⁸⁹ The risk of headache was nonsignificantly decreased by 34 percent when lamotrigine was compared versus ethosuximide (RR 0.66 [0.33 to 1.29]). The risk of fatigue was nonsignificantly decreased by 10 percent when lamotrigine was compared versus ethosuximide (RR 0.90 [0.45 to 1.80]). The risk of somnolence was significantly decreased by 78 percent when lamotrigine was compared versus ethosuximide (RR 0.22 [0.07 to 0.70]). In this trial, the risk of dizziness was nonsignificantly decreased by 54 percent when lamotrigine was compared versus ethosuximide (RR 0.46 [0.15 to 1.38]).

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled clinical trial and one observation trial reported data on age differences.³³ Results showed that younger patients were more likely to require a switchback to innovator medication compared with older patients (HR 0.993 [0.988 to 0.997]; $p=0.002$). The study also showed that patients treated with antiepileptic medications were younger (mean age of 38 to 49 years) than those treated with other chronically used drugs (mean age of 71 to 73 years).

Pharmacogenetic Profile

Older Versus Newer Antiepileptic Drug Evaluation

No controlled clinical trials or observational studies comparing newer versus older antiepileptic medications reported data on pharmacogenetic profile.

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled clinical trials or observational studies comparing innovator versus generic antiepileptic medications reported data on pharmacogenetic profile.

Types of Medications

Older Versus Newer Antiepileptic Drug Evaluation

No controlled clinical trials or observational studies comparing newer versus older antiepileptic medications reported data on types of medications.

Innovator Versus Generic Antiepileptic Drug Evaluation

No controlled clinical trial and one observational trial reported data on differences in medication use.³³ Results showed that patients treated with antiepileptic medications (all combined) were less likely to switch from innovator to generic than those treated with non-antiepileptic drugs (HR 0.74 [0.67 to 0.82]; $p=0.0001$). Among patients switching to generic, those receiving antiepileptic medications were nearly two and a half times more likely to revert back to the innovated medication than non-antiepileptic medication users than non-antiepileptic medication users (HR 2.46 [1.93 to 3.14]; $p=0.0001$). Patients receiving polytherapy were less likely to switch to generic [(HR 0.76 [0.69 to 0.83]; $p=0.056$], but no more or less likely to switch back to innovator (HR 1.23 [0.995 to 1.515]; $p=0.056$).

Discussion

The results of these a priori subgroup analyses are not very informative. By splitting our newer antiepileptic medication versus carbamazepine, phenytoin, valproic acid, or ethosuximide by seizure etiology, 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, for an outcome, one subpopulation was evaluated but the other subpopulation was not. We cannot identify a subpopulation for which differential effects on an outcome might have occurred based on a subgroup. The results generally followed those in the base case evaluations although were much less likely to be significantly different. Data were limited mostly to partial, new onset epilepsy and was generally in patients 18 years or younger. Gender, genetic profile, and polypharmacy's impact on results could not be determined.

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.³³ There was no statistically significant difference in women compared with men when switching back to innovator from generic (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]; $p=0.056$).

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.

Summary and Discussion

Our general results with strength of evidence rating are given in Table 10. Only one outcome, the risk of gum hyperplasia with phenytoin versus newer antiepileptic medications, had a high strength of evidence. For the outcomes reported in the discussion above, the strength of evidence was predominantly moderate to low for the newer versus older antiepileptic medication evaluation and low to insufficient for the innovator versus generic evaluation. In many cases, strength of evidence was reduced for issues of inconsistency and imprecision. Pooling multiple newer antiepileptic medication comparisons versus a single older antiepileptic medication enhanced power to detect differences but reduced consistency. Precision was frequently impacted negatively by having only a few small trials for an analysis. Analyses with only observational studies had a greater risk of bias which negatively impacted strength of evidence.

Applicability of evidence for both the newer versus older antiepileptic medication evaluation and the innovator versus generic evaluation was more evenly dispersed between insufficient, low, and moderate with no areas of high applicability. 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.

Older Versus Newer Evaluation

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. The risk of being seizure free for either 12 or 24 months was significantly lower for newer antiepileptic agents versus carbamazepine. No differences in 12- or 24-month seizure freedom were seen for newer antiepileptic medications versus valproic acid although this was based on a single controlled clinical trial. There was a significant increase in the time to first seizure when newer antiepileptic medications were compared versus phenytoin. No difference in the time to first seizure was seen between newer antiepileptic medications versus carbamazepine or valproic acid.

Withdrawals can be due to lack of efficacy, adverse events, or other factors. We could not find any significant difference in the risk of withdrawing for any reason when newer antiepileptic medications were compared with carbamazepine, controlled/sustained release carbamazepine, ethosuximide, phenytoin, or valproic acid. However, in the case of carbamazepine and controlled/sustained release carbamazepine, this was due to an offsetting significant increase in the risk of withdrawals due to lack of efficacy and a significant decrease in withdrawals due to adverse events.

In this analysis we compared newer antiepileptic medications to older epileptic medications for dizziness, fatigue, headache, nausea, skin rash, and somnolence. Taken together, patients taking newer antiepileptic medications had a significantly lower risk of developing dizziness, fatigue, skin rash, and somnolence versus those taking carbamazepine. Patients taking newer antiepileptic medications had a significantly lower risk of developing fatigue, nausea, and somnolence versus those patients taking valproic acid. In many cases, the controlled/sustained release carbamazepine and phenytoin analyses were based on limited data. However, the risk of skin rash was significantly lower with newer antiepileptic medications versus controlled/sustained release carbamazepine. The risk of vomiting was significantly reduced when newer antiepileptic medications were compared versus phenytoin. For cosmetic adverse events, newer antiepileptic medications had a lower risk of alopecia than valproic acid but not versus

carbamazepine. Newer antiepileptic medications also had a lower risk of causing gum hyperplasia versus phenytoin.

In total, carbamazepine or controlled/sustained-release carbamazepine have some efficacy advantages over newer antiepileptic medications but have more adverse events and adverse events causing withdrawal. The other older antiepileptic medications agents have similar efficacy versus newer antiepileptic medications and have more adverse events although the adverse events do not lead to a higher rate of withdrawal.

Innovator Versus Generic Evaluation

For the comparison of innovator antiepileptic medications to their respective generic versions, we found that seizure occurrence and frequency was similar between groups in controlled clinical trials. In addition, there were no 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 study had marked differences in several demographic variables (age, insurance type, and concomitant migraine headache and cerebral palsy), but the study investigators did not conduct adjusted analyses. When viewed together, the data suggests that generic antiepileptic medication use, predominantly with carbamazepine, phenytoin, and valproic acid provides a similar level of efficacy to a population of people with epilepsy as their respective innovator products. While the source of the innovator and the generic (internationally versus domestically) may impact the variability in blood concentrations, the pharmacokinetic and final health outcomes results for initiating innovator versus generic medications seem congruent.

Data on withdrawal rates due to adverse events were only available for innovator versus generic carbamazepine and phenytoin limiting the ability to extrapolate findings to other antiepileptic medications. The withdrawals due to adverse events were similar between the innovator and generic versions of antiepileptic medications. These results are in agreement with the overall withdrawal rates reported in Key Question 1. While our data suggests that tolerability is similar in a population of patients receiving an innovator versus generic version of antiepileptic medication, we cannot say that an individual patient would not have changes in tolerability upon switching either due to changes in pharmacokinetics or as a result of the anxiety that they feel from switching. Data on combined neurological adverse events was only available for carbamazepine limiting the ability to extrapolate findings to other antiepileptic medications. There was no statistically significant difference in the combined neurological adverse events between the innovator and generic carbamazepine. However, in the single controlled trial and single observational study, the occurrence of neurological adverse events was qualitatively greater. For individual neurological adverse events, data on headache was only reported for carbamazepine and phenytoin, which showed no statistically significant difference between the innovator and generic versions. Data on dizziness, somnolence, and diplopia was only reported for carbamazepine, which also showed no statistically significant difference between the innovator and generic versions carbamazepine. Data on incidence of rash or the impact on cognition was only available for carbamazepine and in both cases showed no statistically significant difference between innovator and generic versions.

Many of the 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 form of the medication, whether

an innovator or generic, would increase the loss of seizure control or adverse events versus maintaining therapy with the same version. Unfortunately this has not been directly assessed in any controlled clinical trial or controlled observational trial.

Four controlled observational trials evaluated the impact of switching from one version of an antiepileptic medication (either an innovator or generic) to another version of the medication on outpatient resource utilization, hospitalization, and hospital stay duration. Two controlled observational trials (one evaluating several antiepileptic medications together as one group and another focusing on lamotrigine) found an increased incidence of utilizing outpatient resources^{33,129} but two other trials did not.^{133,162} Of the six analyses evaluating hospitalization rate within these four trials, four analyses found significant increases in hospitalization rates and two found trends toward increases. All four controlled observational studies found a significant increase in hospital length of stay. These observational studies have important limitations. They were evaluating patients who were likely stabilized on the innovator therapy, were switched to the generic medication and were switched back. They cannot be used to assess where the initial use of an innovator or generic antiepileptic medication makes a difference. It is not specified that the generic medications were all “A” rated and if not, the differences noted might not be translatable to “A” rated versions. Since the switch was not blinded, patients and clinicians may have been aware the switch had occurred and emotional or anxiety related triggers for medical service utilization not related to the comparability of the innovator and generic products could have occurred.

Three well conducted controlled observational studies assessed a composite endpoint of medical service utilization. Two of the studies 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 and limited the analyses to “A” rated products but could not control for comorbidities or changes in other medications. In a third important case control study, no significant difference was found after adjusting for confounders. Unlike the other two trials,^{126,127} this study authors controlled for person’s risk of epilepsy exacerbation, change in disease severity, drug interactions, poor adherence, and change in patient diagnosis.¹²⁸ 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.

As such, the data suggests that for initial drug selection, choosing an innovator or generic version of an antiepileptic medication would result in similar efficacy and safety. Preliminary and limited data suggests that switching may have resulted in additional adverse events although the differences could be attributable to confounders which were not well accounted for.

Table 10. Summary of results and strength of evidence

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
KEY QUESTION 1 ENDPOINTS				
MORTALITY: Newer vs. Carbamazepine	6 RCTs	Yes	No effect, RR 0.75 (0.51, 1.12)	SOE: L
Newer vs. Phenytoin	3 RCTs	Yes	No effect, RR 0.30 (0.05, 1.95)	SOE: L
Newer vs. Valproic Acid	3 RCTs	Yes	No effect, RR 0.94 (0.31, 2.80)	SOE: L
OUTPATIENT SERVICE UTILIZATION: Innovator vs. Generic	4 OBS	No	Similar utilization of outpatient services during generic medication periods.	SOE: L
HOSPITALIZATIONS: Newer vs. Carbamazepine	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared with carbamazepine.	SOE: I
Newer vs. Valproic Acid	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared with valproic acid.	SOE: I
Newer vs. Ethosuximide	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared with ethosuximide.	SOE: I
Innovator vs. Generic	4 OBS	No	Increased risk of hospitalizations during generic medication periods.	SOE: L
HOSPITAL STAY DURATION: Innovator vs. Generic	4 OBS	No	Increased hospital stay during generic medication periods.	SOE: L

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
COMPOSITE OF MEDICAL SERVICE UTILIZATION (Ambulance service, hospitalization, or emergency department visit for epilepsy): Innovator vs. Generic	3 OBS	No	Increase in medical service utilization during periods when a patient's antiepileptic medication is switched to an "A" rated version of the product (innovator to generic, generic to generic, generic to innovator).	SOE: I
HEALTH-RELATED QUALITY OF LIFE: Newer vs. Carbamazepine Newer vs. Carmabazepine CR/SR Newer vs. Phenytoin Newer vs. Valproic Acid	3 RCTs 1 RCT 2 RCTs 3 RCTs	No No No No	Different scales and subscales, data inconclusive Different scales and subscales, data inconclusive Different scales and subscales, data inconclusive Different scales and subscales, data inconclusive	SOE: I SOE: I SOE: I SOE: I
TIME TO FIRST SEIZURE: Newer vs. Carbamazepine Newer vs. Phenytoin Newer vs. Valproic Acid	4 RCTs 2 RCTs 1 RCT	Yes Yes Yes	No effect, (HR 1.14 [0.98, 1.33]) Time to seizure increased for newer vs. phenytoin. (HR 1.59 [1.04, 2.43]) No effect, (HR 0.8 [0.63, 1.02])	SOE: L SOE: L SOE: L
SEIZURE OCCURRENCE: Innovator vs. Generic	7 RCTs	Yes	No effect, (0.87 [0.64, 1.18])	SOE: L
SEIZURE FREEDOM FOR STUDY DURATION: Newer vs. Carbamazepine Newer vs. Carbamazepine CR/SR Newer vs. Phenytoin Newer vs. Valproic Acid	15 RCTs 2 RCTs 4 RCTs 12 RCTs	Yes Yes Yes Yes	No effect, (RR 0.94 [0.87, 1.03]) No effect, (RR, 0.90 [0.79, 1.02]) No effect, (RR 0.92 [0.85, 1.00]) No effect, (RR 0.97 [0.87, 1.08])	SOE: L SOE: M SOE: M SOE: M

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
SEIZURE FREQUENCY: Newer vs. Carbamazepine Newer vs. Phenytoin Newer vs. Valproic Acid Innovator vs. Generic	1 RCT 2 RCTs 1 RCT 3 RCTs	No No No Yes	No effect, (MD -3 [-6.32, 0.32]) Not enough data to evaluate effect Not enough data to evaluate effect No effect, (SMD 0.03 [-0.08, 0.14])	SOE: I SOE: I SOE: I SOE: L
SEIZURE REMISSION 6- to 12-Month: Newer vs. Carbamazepine	2 RCTs	Yes	Patients on newer antiepileptic medications were less likely to have seizure remission vs. carbamazepine. (RR 0.81 [0.67, 0.99], NNT 9)	SOE: L
Newer vs. Valproic Acid	1 RCT	Yes	No effect, (RR 0.97 [0.89, 1.06])	SOE: M
24-Month: Newer vs. Carbamazepine	1 RCT	Yes	Patients on newer antiepileptic medication were less likely to have seizure remission vs. carbamazepine. (RR 0.82 [0.72, 0.94], NNT 13)	SOE: M
Newer vs. Valproic Acid	1 RCT	Yes	No effect, (RR 0.85 [0.73, 1.00])	SOE: M
STATUS EPILEPTICUS, SECONDARY INJURY FROM SEIZURES, LOSS OF DRIVER'S LICENSE/EMPLOYMENT: Innovator vs. Generic	No data	No	No data	SOE: I
TOTAL WITHDRAWALS: Newer vs. Carbamazepine Newer vs. Carbamazepine CR/SR Newer vs. Phenytoin Newer vs. Valproic Acid Newer vs. Ethosuximide Innovator vs. Generic	14 RCTs 2 RCTs 3 RCTs 16 RCTs 1 RCT 9 RCTs + 1 NRCT	Yes Yes Yes Yes No Yes	No effect, (RR 0.90 [0.82, 1.00]) No effect, (RR 0.96 [0.78, 1.18]) No effect, (RR 0.91 [0.76, 1.09]) No effect, (RR 0.96 [0.85, 1.09]) No effect, (RR 0.95 [0.53, 1.71]) No effect, (RR 0.90 [0.39, 2.08])	SOE: L SOE: L SOE: L SOE: L SOE: I SOE: L

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
WITHDRAWALS DUE TO LACK OF EFFICACY: Newer vs. Carbamazepine	10 RCTs	Yes	Withdrawals due to lack of efficacy increased with newer agents vs. carbamazepine. (RR 1.59 [1.25, 2.02], NNT 50)	SOE: L
Newer vs. Carbamazepine CR/SR	1 RCT	No	Withdrawals due to lack of efficacy increased with newer agents vs. carbamazepine CR/SR. (RR 2.43 [1.32, 4.52], NNT 16)	SOE: I
Newer vs. Phenytoin	3 RCTs	Yes	No effect, (RR 1.03 [0.33, 3.23])	SOE: L
Newer vs. Valproic Acid	11 RCTs	Yes	No effect, (RR 1.10 [0.77, 1.56])	SOE: L
Innovator vs. Generic	9 RCTs + 1 NRCT	Yes	No effect, (RR 1.02 [0.41, 2.54])	SOE: L
KEY QUESTION 2 ENDPOINTS				
Maximum Concentration: Innovator vs. Generic	7 RCTs + 1 NRCT	Yes	No effect, (SMD 0.10 [-0.13, 0.32])	SOE: L
Minimum Concentration: Innovator vs. Generic	5 RCTs + 1 NRCT	Yes	No effect, (SMD 0.05 [-0.21, 0.31])	SOE: L
Steady State Concentration: Innovator vs. Generic	7 RCTs	Yes	No effect, (SMD 0.18 [-0.09, 0.45])	SOE: L
Time to Maximal Concentration: Innovator vs. Generic	5 RCTs	Yes	No effect, (WMD 0.00 [-0.43, 0.43]) (Note: a WMD was calculated vs. an SMD for T _{max} because only carbamazepine trials made up this evaluation).	SOE: I
AREA UNDER THE CURVE: Innovator vs. Generic	7 RCTs + 1 NRCT	Yes	No effect, (SMD 0.05 [-0.18, 0.28])	SOE: L

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
DOSE REQUIREMENTS FOR SEIZURE CONTROL: Innovator vs. Generic	No data	No	No data	SOE: I
SWITCHBACK RATES: Innovator vs. Generic	4 OBS	No	Switchback rates from a generic back to an innovator antiepileptic medication varied from 12.4% to 44.1%	SOE: L
KEY QUESTION 3 ENDPOINTS				
WITHDRAWALS DUE TO ADVERSE EVENTS: Newer vs. Carbamazepine	18 RCTs	Yes	Withdrawals due to adverse events were reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.62 [0.53, 0.73], NNT 13)	SOE: M
Newer vs. Carbamazepine CR/SR	2 RCTs	Yes	Withdrawals due to adverse events were reduced with newer antiepileptic medications vs. carbamazepine CR/SR. (RR 0.69 [0.50, 0.95], NNT 16)	SOE: M
Newer vs. Phenytoin	3 RCTs	Yes	No effect, (0.38 [0.14, 1.03])	SOE: I
Newer vs. Valproic Acid	16 RCTs	Yes	No effect, (RR 0.90 [0.75, 1.08])	SOE: L
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.71 [0.45, 1.12])	SOE: I
Innovator vs. Generic	9 RCTs + 1 NRCT	Yes	No effect, (RR 0.79 [0.28, 2.20])	SOE: L
HEADACHE: Newer vs. Carbamazepine	15 RCTs	Yes	No effect, (RR 0.92 [0.78, 1.08])	SOE: L
Newer vs. Carbamazepine SR/CR	2 RCTs	Yes	No effect, (RR 0.83 [0.63, 1.10])	SOE: L
Newer vs. Phenytoin	4 RCTs	Yes	No effect, (RR 0.74[0.53, 1.02])	SOE: L
Newer vs. Valproic Acid	15 RCTs	Yes	No effect, (RR 0.90 [0.70, 1.16])	SOE: L
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.66 [0.33, 1.29])	SOE: I
Innovator vs. Generic	3 RCTs	Yes	No effect, (RR 0.95 [0.55, 1.64])	SOE: I

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
FATIGUE:				
Newer vs. Carbamazepine	7 RCTs	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.57 [0.41, 0.80], NNT 11)	SOE: L
Newer vs. Carbamazepine SR/CR	1 RCT	Yes	No effect, (RR 1.17 [0.80, 1.72])	SOE: I
Newer vs. Phenytoin	1 RCT	No	No effect, (RR 1.05 [0.49, 2.25])	SOE: I
Newer vs. Valproic Acid	8 RCTs	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. valproic acid. (RR 0.61 [0.44, 0.85], NNT 23)	SOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.90 [0.45, 1.80])	SOE: I
Innovator vs. Generic	No data	No	No data	SOE: I
SOMNOLENCE:				
Newer vs. Carbamazepine	8 RCTs	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.47 [0.36, 0.61], NNT 14)	SOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	No	No effect, (RR 1.21 [0.75, 1.96])	SOE: I
Newer vs. Phenytoin	4 RCTs	Yes	No effect, (RR 0.72 [0.44, 1.18])	SOE: I
Newer vs. Valproic Acid	9 RCTs	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. valproic acid. (RR 0.65 [0.43, 0.98], NNT 25)	SOE: M
Newer vs. Ethosuximide	1 RCT	No	Risk of somnolence reduced with newer antiepileptic medications vs. ethosuximide. (RR 0.22 [0.07, 0.70], NNT 15)	SOE: I
Innovator vs. Generic	2 RCTs	Yes	No effect, (RR 0.90 [0.48, 1.70])	SOE: L
DIZZINESS:				
Newer vs. Carbamazepine	16 RCTs	Yes	Risk of dizziness reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.78 [0.67, 0.91], NNT 50)	SOE: M
Newer vs. Carbamazepine SR/CR	2 RCTs	Yes	No effect, (RR 0.96 [0.56, 1.66])	SOE: L
Newer vs. Phenytoin	3 RCTs	Yes	No effect, (RR 0.67 [0.43, 1.05])	SOE: L
Newer vs. Valproic Acid	12 RCTs	Yes	No effect, (RR 0.98 [0.71, 1.35])	SOE: L
Newer vs. Ethosuximide	1 RCT	No	No effect, (RR 0.46 [0.15, 1.38])	SOE: I
Innovator vs. Generic	No data	No	No data	SOE: I

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
COMBINED NEUROLOGICAL ADVERSE EVENTS: Innovator vs. Generic	1 RCT + 1 OBS	No	No effect, RCT: 4.3% vs 21.7%, p=0.189; OBS: 75.7 events per 1,000 person years, 75.7 events per 1,000 person years, p=NS	SOE: L
DIPLOPIA: Innovator vs. Generic	2 RCT	Yes	No effect, (1.28 [0.38, 4.31])	SOE: L
HYPOTENSION, ASTHENIA, ATAXIA, NYSTAGMUS, TREMOR: Innovator vs. Generic	No data	No	No data	SOE: I
NAUSEA: Newer vs. Carbamazepine	8 RCTs	Yes	No effect, (RR 0.69 [0.46, 1.02])	SOE: L
Newer vs. Carbamazepine SR/CR	1 RCT	No	No effect, (RR 0.66 [0.39, 1.12])	SOE: I
Newer vs. Phenytoin	4 RCTs	Yes	No effect, (RR 0.88 [0.56, 1.37])	SOE: L
Newer vs. Valproic Acid	11 RCTs	Yes	Risk of nausea reduced with newer antiepileptic medications vs. valproic acid. (RR 0.56 [0.41, 0.77], NNT 31)	SOE: M
Innovator vs. Generic	No data	No	No data	SOE: I
VOMITING: Newer vs. Carbamazepine	3 RCTs	Yes	No effect, (RR 1.25 [0.66, 2.35])	SOE: L
Newer vs. Phenytoin	1 RCT	No	Risk of vomiting was reduced with newer antiepileptic medications vs. phenytoin. (RR 0.09 [0.01, 0.89], NNT 19)	SOE: I
Newer vs. Valproic Acid	5 RCTs	Yes	No effect, (RR 0.69 [0.34, 1.42])	SOE: L
Innovator vs. Generic	No data	No	No data	SOE: I

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
SKIN RASH: Newer vs. Carbamazepine	13 RCTs	Yes	Risk of skin rash was reduced with newer antiepileptic medications vs. carbamazepine. (RR 0.52 [0.39, 0.69], NNT 24)	SOE: M
Newer vs. Carbamazepine SR/CR	2 RCTs	Yes	Risk of skin rash was reduced with newer antiepileptic medications vs. carbamazepine SR/CR. (RR 0.47 [0.25, 0.89], NNT 27)	SOE: L
Newer vs. Phenytoin	4 RCTs	Yes	No effect, (RR 0.76 [0.34, 1.66])	SOE: I
Newer vs. Valproic Acid	10 RCTs	Yes	No effect, (RR 1.17 [0.55, 2.48])	SOE: L
Innovator vs. Generic	2 RCTs	Yes	No effect, (RR 0.77 [0.17, 3.57])	SOE: I
SUICIDAL IDEATION: Newer vs. Carbamazepine	1 Obs	No	Risk of attempted suicide was increased with gabapentin vs. carbamazepine. (RR 13.92 [1.82, 106.38])	SOE: I
Innovator vs. Generic	No data	No	No data	SOE: I
MOOD AND COGNITION: Newer vs. Carbamazepine	4 RCTs	No	Different scales and subscales, data inconclusive	SOE: I
Newer vs. Phenytoin	1 RCT	No	No effect	SOE: I
Newer vs. Valproic Acid	5 RCTs	No	Different scales and subscales, data inconclusive	SOE: I
Innovator vs. Generic	1 RCT	No	Only cognition evaluated. No significant differences between innovator of generic but 4 of 5 cognitive test measures showed better scores for innovator than generic.	SOE: I
BONE DENSITY: Newer vs. Older	No data	No	No data	SOE: I
Innovator vs. Generic	No data	No	No data	SOE: I
ALOPECIA: Newer vs. Carbamazepine	6 RCTs	Yes	No effect, (RR 0.60 [0.23, 1.58])	SOE: L
Newer vs. Valproic Acid	8 RCTs	Yes	Risk of alopecia was reduced with newer antiepileptic medications vs. valproic acid. (RR 0.18 [0.10, 0.31], NNT 10)	SOE: M
ACNE: Newer vs. Phenytoin	1 RCT	No	No effect, (RR 2.78 [0.82, 9.53])	SOE: I

Table 10. Summary of results and strength of evidence (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence
GUM HYPERPLASIA: Newer vs. Phenytoin	2 RCTs	Yes	Risk of gum hyperplasia was reduced with newer antiepileptic medications vs. phenytoin. (RR 0.10 [0.04, 0.27], NNT 6)	SOE: H

Legend: CR = controlled release; H = high; I = insufficient; L = low; M = moderate; MD = mean difference; SMD = standardized mean difference; NRCT = nonrandomized controlled trial; NNT = number needed to treat; OBS = observational study; RCT = randomized controlled trial; RR = relative risk; SOE = strength of evidence; SR = sustained release; WMD = weighted mean difference

Future Research

Limitations of Current Research

This comparative effectiveness review (CER) is limited by heterogeneity. A heterogeneous group of antiepileptic medications was placed into groups based on whether they were older, newer, innovator, or generic. A heterogeneous group of epilepsy types was also lumped together, and the diagnosis and detection of these different types have changed over time, making clear subgroup evaluations using these trials difficult. Patients with different pharmacodynamic and pharmacokinetic genetic polymorphisms were not elucidated in virtually all the trials, but these factors could lead some medications to be more or less preferable. The use of studies from different countries, different time periods, utilizing differing study durations, mixing of patients with different baseline seizure frequency rates and different environmental triggers, and the use of “A” rated and non-“A” rated products in some analyses may have also introduced heterogeneity.

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, and 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 evaluate some of the major potential sources of heterogeneity in subgroup analyses. Other sources of heterogeneity, such as genomic differences, durations of therapy, and mixing of patients with differing seizure frequencies should have been attenuated within a trial due to randomization. We are transparent in our presentation of the results since in the full report we provide individual agent comparisons and subgroup analyses for other potential sources of heterogeneity but could not report the results in the executive summary given wording limitations.

We did not include every possible endpoint of interest. We had to make some choices as to what endpoints would be included and which would not, and we wanted to make those decisions a priori. We included myriad endpoints that while not exhaustive, are very broad but may not contain a specific endpoint that a particular practitioner may wish to see. For instance, we included loss of job or driving privileges but did not include school performance.

While we sought to evaluate the impact of newer versus older antiepileptic medications, only a few older antiepileptic medications were substantively evaluated and were compared to a greater or lesser extent with newer antiepileptic medications. In the full report, we provide the data for each individual newer antiepileptic medication versus each individual older antiepileptic medication. This data is more specific than the aggregate pooled data of all newer antiepileptic medication versus each older antiepileptic medication and decreases the clinical and methodological heterogeneity in the data. However, the power to detect differences in these individual analyses is substantially compromised.

For the older versus newer antiepileptic medication evaluation, no controlled trials or observational studies evaluated the impact of older or newer antiepileptic medications on the use of medical services including office or emergency room visits, ambulance services, outpatient medical care, or hospitalization.

Our evaluation of newer versus older antiepileptic medications provide populationwide insight into comparative benefits and harms but cannot account for individual patient factors that may make the use of a certain antiepileptic medication more or less desirable. Factors such as

pregnancy or desire 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 need more information on the benefits and harms associated with older and newer antiepileptic medications in different seizure types and it needs to be understood that the classification of epilepsy types is an evolving science.

For the innovator versus generic medication evaluation, seizure occurrence and frequency, pharmacokinetics, and tolerability of innovator antiepileptic medications are similar to that of their generic counterparts. Since these trials were predominantly crossover or parallel design trials, they can only provide information on the innate comparability of the products when used in a population of patients with epilepsy. They cannot be used to say that switching from one version to another would or would not result in a loss of efficacy or an increase in patient harm.

Controlled observational studies show that switchback rates from generic to innovator products are high and that there may be an increased use of medical services associated with switching from one version (either an innovator or generic) of an antiepileptic medication to another version (either an innovator or generic). Unfortunately, these observational studies, while well conducted, have inherent biases and limitations that reduce their internal validity.

Our subgroup analyses could have been very important in helping identify which populations have an accentuated or attenuated effect versus the average, but due to a lack of power and methodological limitations, we were unable to generate data that could guide therapy in this manner.

For the innovator versus generic medication evaluation, no controlled clinical trials or observational studies evaluated the impact on mortality, health-related quality of life, loss of driver's license or employment, time to first seizure, seizure remission, seizure freedom for the duration of the study, secondary seizure injury, status epilepticus or the dose requirements required for seizure control.

Future Avenues for Research

For the newer versus older comparison, future direct comparative clinical trials of the same size and duration can continue to increase power to detect differences, if they truly exist. This is especially true for individual newer versus individual older antiepileptic medication comparisons. More extensive determination of harms and more clearly delineating the population being studied would also be beneficial. More extensive evaluations of medical service utilization in controlled clinical trials and observational studies are also warranted.

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. If so, the reasons (pharmacokinetic, psychological, other) for differential effects need to be researched. A proposed methodology would be to take a population of patients receiving either innovator or an “A” rated generic version of a medication and then randomize some patients to be switched and other patients to be maintained on initial therapy in a double blind manner. This would eliminate the impact of clinician or patient apprehension about the switch to impact resource utilization or to increase the risk of experiencing a seizure or an adverse event either directly or indirectly through noncompliance or dose alteration. Followup could be relatively brief (3 months) and

should include a pharmacokinetic (using Bayesian population pharmacokinetics whereby only one or two samples from each patient would suffice) and final health outcome component (assessing for seizure occurrence, seizure frequency, health care utilization, and adverse events). Without randomization, blinding, and exclusive use of “A” rated products, future studies would share the substantial flaws of the current body of literature.

Future research for the brand versus generic evaluation should include controlled clinical trials and observational studies of increased duration to capture endpoints such as seizure remission, seizure freedom for the duration of the study and mortality. Additionally, future research should be designed to capture and report outcomes such as loss of driver’s license or employment, secondary seizure injury, status epilepticus and health-related quality of life.

Future newer versus older and innovator versus generic antiepileptic medication trials should report on their benefits and harms in these subpopulations even in the absence of power to judge significance because it will allow subsequent systematic reviewer to pool the results together.

Endpoints such as bone fracture and concussion should be assessed in everyone, loss of job or driving privileges should be assessed in adults, and school performance should be evaluated in children.

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Appendix A. Search Strategies

Search Strategy for Innovator versus Generic Antiepileptic Drug Evaluation for MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (each in OVID starting in 1950), Web of Science (limited to meeting abstracts only)

1. generic.mp.
2. innovator.mp.
3. nonproprietary.mp.
4. drugs, generic/
5. therapeutic equivalency/
6. (brand adj name).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Epilepsy/ or epilepsy.mp.
9. epilep\$.mp.
10. seiz\$.mp.
11. convuls\$.mp.
12. 8 or 9 or 10 or 11
13. 7 and 12

Search Strategy for Older versus Newer Antiepileptic Drug Evaluation for MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (each in OVID starting in 1950), Web of Science (limited to meeting abstracts only)

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/12-23
24. 11 or 24
25. Epilepsy/ or epilepsy.mp.
26. epilep\$.mp.
27. seiz\$.mp.
28. convuls\$.mp.
29. 26 or 27 or 28 or 29
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. 31 or 32 or 33 or 34 or 35 of 36 or 37 of 38 or 39 or 40 or 41 or 42
43. 30 and 43
44. 44 and (11 or 24)

Appendix B. Data Extraction Forms

Study Identification for Innovator versus Generic Antiepileptic Drug Evaluation

First Author:	Year:	RefID #:
Funding Source Specify: <input type="checkbox"/> Industry <input type="checkbox"/> Government/Foundation <input type="checkbox"/> Academia <input type="checkbox"/> Other/Unknown		Countries:

Design Characteristics for Innovator versus Generic Antiepileptic Drug Evaluation

Study Design <input type="checkbox"/> RCT – Parallel <input type="checkbox"/> Case Report <input type="checkbox"/> RCT – Crossover <input type="checkbox"/> Other <input type="checkbox"/> Obs – Cohort <input type="checkbox"/> Obs – Case Control <input type="checkbox"/> Obs – Cross-Sectional <input type="checkbox"/> Obs – Registry	Randomization Adequate? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Double Blinded? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Single	Blinding Adequate? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Allocation Concealment? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Concealment Adequate? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Description of Withdrawals? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Intent-to-Treat? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
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Study Protocol for Innovator versus Generic Antiepileptic Drug Evaluation

Innovator AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Generic #1 AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Generic #2 AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Generic #3 AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Run-in period? <input type="checkbox"/> Yes <input type="checkbox"/> No	Describe Run-in:	Patients removed from run-in, why:	

Overall #enrolled:	Overall #analyzed:
Duration of Treatment:	Duration of follow-up:

Study Population for Innovator versus Generic Antiepileptic Drug Evaluation

<p>Inclusion Criteria</p> <p>Age (range):</p> <p>Gender (if applicable):</p> <p>Seizure Etiology:</p> <p><input type="checkbox"/> Any</p> <p><input type="checkbox"/> Partial: specify</p> <p><input type="checkbox"/> Generalized: specify</p> <p><input type="checkbox"/> Other: specify</p> <p>Seizure Onset:</p> <p><input type="checkbox"/> New Onset</p> <p><input type="checkbox"/> Chronic</p> <p><input type="checkbox"/> Other: specify</p> <p>Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)</p> <p>Prior AED use:</p> <p><input type="checkbox"/> None</p> <p><input type="checkbox"/> Other: specify</p> <p>Other relevant criteria:</p>	<p>Exclusion Criteria</p> <p>Age (range):</p> <p>Gender (if applicable):</p> <p>Seizure Etiology:</p> <p><input type="checkbox"/> Partial: specify</p> <p><input type="checkbox"/> Generalized: specify</p> <p><input type="checkbox"/> Other: specify</p> <p>Seizure Onset:</p> <p><input type="checkbox"/> New Onset</p> <p><input type="checkbox"/> Chronic</p> <p><input type="checkbox"/> Other: specify</p> <p>Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)</p> <p><input type="checkbox"/> Prior AED use/Timing: (e.g. No AEDs within 2 months)</p> <p><input type="checkbox"/> Pregnancy Risk</p> <p><input type="checkbox"/> Pregnancy</p> <p><input type="checkbox"/> Lactation</p> <p><input type="checkbox"/> History of Status Epilepticus</p> <p><input type="checkbox"/> Mental Retardation</p>
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	<ul style="list-style-type: none"><input type="checkbox"/> Psychiatric Disorder: specify <input type="checkbox"/> Neurologic Disorder: specify <input type="checkbox"/> Alcoholism / Drug Abuse: frequency?
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Baseline Characteristics for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED	Generic AED #1	Generic AED #2	Generic AED #3
Sample size (n)				
Age (years) [Mean \pm SD]				
Percent Males (%)				
Body Weight (kg) [Mean \pm SD]				
Race, (n) %				
Caucasian				
Black				
Asian				
Hispanic				
Other-specify:				
Epilepsy History				
New Onset, n (%)				
Chronic Epilepsy, n (%)				
Age at Onset of Epilepsy, years				
Epilepsy duration, years				
No. Seizures in Past [Time-specify] [Mean \pm SD]				
Seizure type				

	Innovator AED	Generic AED #1	Generic AED #2	Generic AED #3
Partial Seizures (no further definition), n (%)				
Simple Partial, n (%)				
Complex Partial, n (%)				
With Secondary Generalization, n (%)				
Generalized (no further definition), n (%)				
Tonic-Clonic, n (%)				
Myoclonic, n (%)				
Absence, n (%)				
Atonic, n (%)				
Unclassified, n (%)				
Prior/Concurrent AED Use				
Untreated, n (%)				
Carbamazepine, n (%) / mean dose \pm SD				
Phenytoin, n (%) / mean dose \pm SD				
Valproic Acid, n (%) / mean dose \pm SD				
Other, n (%) / mean dose \pm SD – specify:				

Pharmacokinetic Outcomes (Continuous) – Means (Standard Deviations or Standard Errors; please specify) for Innovator versus Generic Antiepileptic Drug Evaluation

Generic Antiplatelet Drug Evaluation										
Sample size (n)	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3		Specify comparison:	
	End of study Mean (SD)*	P-value	End of study Mean (SD)	P-value	End of study Mean (SD)	P-value	End of study Mean (SD)	P-value	Mean Difference between groups (SD)	P-value for Difference Between Groups
C _{max}										
C _{min}										
C _{ss}										
AUC										
T _{max}										
Range										
Total Serum AED conc (mg/l)										
Free Serum AED conc (mg/l)										

*If not reported as mean and SD, please specify

Withdrawals and Discontinuations (Categorical) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Overall withdrawals								
Withdrawal due to ineffective treatment								
Withdrawal due to ADRs								
ADRs causing study withdrawal								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								

Seizure Outcomes – Means (Standard Deviations or Standard Errors; please specify) for Innovator versus Generic Antiepileptic Drug Evaluation

Evaluation	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
Sample size (n)								
Continuous Outcomes below:								
	Mean Change from Baseline (SD)	P- value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value
Seizure Frequency (per month)								
	End of Study Mean (SD)		End of Study Mean (SD)		End of Study Mean (SD)		End of Study Mean (SD)	
Dose needed for seizure control (mg/day)								
Breakthrough Seizures (mean, SD)								
Categorical Outcomes below:								
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Breakthrough Seizures (number of events total)								
Status Epilepticus								
Switchback rate Specify starting/final drugs:								

*If not reported as mean and SD, please specify

Comparative Tolerance and Harm (Categorical) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Mortality								
Medical service utilization:								
Office/ER visits (number of events)								
Hospitalizations (number of events)								
Hospital stay duration (mean±SD)								
Composite of Ambulance/ ER/ Hospitalizations								
Other:								
Loss of Driver's License								
Loss of employment								

Comparative Tolerance and Harm (Categorical) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Overall ADRs with/without withdrawal from study								
Overall ADRs reported								
ADRs <u>without</u> withdrawal from study								
Skin Rash								
Suicidal Ideation								
Hypotension								
Neurological Adverse Events								
Asthenia								
Ataxia								
Diplopia								
Dizziness								
Headache								
Nystagmus								
Somnolence								
Tremor								
Mood or Cognition-related Adverse Events								
Aggression								
Anxiety								

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Depression								
Impaired Cognition								
Emotional Lability								
Nervousness								
Harms specific to AED								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								
Secondary seizure injury; specify type:								
Secondary Seizure Injury Rate								

Tolerance and Harms (Continuous) – Means (Standard Deviations or Standard Errors; please specify)

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
Sample size (n)								
	Mean Change from Baseline (SD)	P- value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value
HRQOL – Scale used:								
HRQOL Overall score								
HRQOL Sub-score 1 Please specify								
HRQOL Sub-score 2 Please specify								
HRQOL Sub-score 3 Please specify								

Quality Rating for Innovator versus Generic Antiepileptic Drug Evaluation

<input type="checkbox"/>	<p>Good (low risk of bias)</p> <ul style="list-style-type: none">• Good studies have the least bias and are considered valid.• A study is considered good if it is randomized and controlled and provides a clear description of the population, setting, interventions, and comparison groups.• A good study performs the appropriate measurement of outcomes, statistical and analytical methods and reporting.• A good study does not have reporting errors.• Good studies have less than 20% dropout and clearly report dropouts.
<input type="checkbox"/>	<p>Fair</p> <ul style="list-style-type: none">• Fair studies may be susceptible to some bias, but the bias is not sufficient to invalidate the results.• Fair studies do not meet all of the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias.• A fair study may be missing information, making it difficult to assess limitations and potential problems.
<input type="checkbox"/>	<p>Poor (high risk of bias)</p> <ul style="list-style-type: none">• Poor studies have significant flaws of various types that may invalidate the results.• Poor studies have serious errors in design, analysis or reporting.• Poor studies may be missing large amounts of information or have discrepancies in reporting.

Study Identification for Older versus Newer Antiepileptic Drug Evaluation

First Author:	Year:	RefID #:
Funding Source Specify: <input type="checkbox"/> Industry <input type="checkbox"/> Government/Foundation <input type="checkbox"/> Academia <input type="checkbox"/> Other/Unknown	Countries:	

Study Design for Older versus Newer Antiepileptic Drug Evaluation

Study Design <input type="checkbox"/> RCT – Parallel <input type="checkbox"/> Case Report <input type="checkbox"/> RCT – Crossover <input type="checkbox"/> Other <input type="checkbox"/> Obs – Cohort <input type="checkbox"/> Obs – Case Control <input type="checkbox"/> Obs – Cross-Sectional <input type="checkbox"/> Obs – Registry	Randomization Adequate? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Double Blinded? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Single	Blinding Adequate? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Allocation Concealment? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Concealment Adequate? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Description of Withdrawals? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Intent-to-Treat? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
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Stratification of Randomization

- ☐ None
- ☐ Seizure Etiology – Specify Etiology :
- ☐ Seizure Onset – New Onset / Chronic Epilepsy
- ☐ Patient Age – Specify age:
- ☐ Study Center – Specify:
- ☐ Gender
- ☐ Other – Specify:

Patient Characteristics for Older versus Newer Antiepileptic Drug Evaluation

Inclusion Criteria

Age (range):

Gender (if applicable):

Seizure Etiology:

☐ Any

☐ Partial: specify

☐ Generalized: specify

☐ Other: specify

Seizure Onset:

☐ New Onset

☐ Chronic

☐ Other: specify

Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)

Prior AED use:

☐ None

☐ Other: specify

Other relevant criteria:

Exclusion Criteria

Age (range):

Gender (if applicable):

Seizure Etiology:

☐ Partial: specify

☐ Generalized: specify

☐ Other: specify

Seizure Onset:

☐ New Onset

☐ Chronic

☐ Other: specify

Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)

☐ Prior AED use/Timing: (e.g. No AEDs within 2 months)

☐ Pregnancy Risk

☐ Pregnancy

☐ Lactation

☐ History of Status Epilepticus

☐ Mental Retardation

☐ Psychiatric Disorder: specify

☐ Neurologic Disorder: specify

☐ Alcoholism / Drug Abuse: frequency?

Study Protocol for Older versus Newer Antiepileptic Drug Evaluation

Retrospective Phase <input type="checkbox"/> Yes <input type="checkbox"/> No Time (weeks):	Describe Retrospective Phase:	
Intervention 1 Drug:		
Titration <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Maintenance <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Additional Follow-up Phase <input type="checkbox"/> Yes <input type="checkbox"/> No Specify: Duration: Dose N:
Intervention 2 Drug:		
Titration <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Maintenance <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Additional Follow-up Phase <input type="checkbox"/> Yes <input type="checkbox"/> No Specify: Duration: Dose N:
Intervention 3 Drug:		
Titration <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Maintenance <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Additional Follow-up Phase <input type="checkbox"/> Yes <input type="checkbox"/> No Specify: Duration: Dose N:

Intervention 4 Drug:		
Titration <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Maintenance <input type="checkbox"/> Yes <input type="checkbox"/> No Duration: Dose N:	Additional Follow-up Phase <input type="checkbox"/> Yes <input type="checkbox"/> No Specify: Duration: Dose N:

Baseline Characteristics for Older versus Newer Antiepileptic Drug Evaluation

	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Sample size (n)				
Age (years) [Mean \pm SD]				
Percent Males (%)				
Body Weight (kg) [Mean \pm SD]				
Race, (n) %				
Caucasian				
Black				
Asian				
Hispanic				
Other-specify:				
Epilepsy History				
New Onset, n (%)				
Chronic Epilepsy, n (%)				
Age at Onset of Epilepsy, years				
Epilepsy duration, years				
No. Seizures in Past [Time-specify] [Mean \pm SD]				
Seizure type				
Partial Seizures (no further definition), n (%)				
Simple Partial, n (%)				

	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Complex Partial, n (%)				
With Secondary Generalization, n (%)				
Generalized (no further definition), n (%)				
Tonic-Clonic, n (%)				
Myoclonic, n (%)				
Absence, n (%)				
Atonic, n (%)				
Unclassified, n (%)				
Prior/Concurrent AED Use				
Untreated, n (%)				
Carbamazepine, n (%) / mean dose \pm SD				
Phenytoin, n (%) / mean dose \pm SD				
Valproic Acid, n (%) / mean dose \pm SD				
Other, n (%) / mean dose \pm SD – specify:				

Withdrawals and Discontinuations for Older versus Newer Antiepileptic Drug Evaluation (Categorical)

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Overall withdrawals								
Completed Study								
Withdrawal due to ineffective treatment								
Time to withdrawal due to ineffective treatment [Mean±SD]								
Withdrawal due to ADRs								
ADRs causing study withdrawal								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								

Seizure Outcomes for Older versus Newer Antiepileptic Drug Evaluation

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
Sample size (n)								
Continuous Outcomes below:								
	Mean Change from Baseline (SD)	P- value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value
Seizure Frequency Specify unit of time:								
	End of Study Mean (SD)		End of Study Mean (SD)		End of Study Mean (SD)		End of Study Mean (SD)	
Time to first seizure Specify units:								
Categorical Outcomes below:								
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Seizure free for duration of study								
Seizure remission for 12-month period								
Seizure remission for 24-month period								
Seizure frequency reduction by 25%								
Seizure frequency reduction by 50%								
Seizure frequency reduction by 75%								

Final Health Outcomes for Older versus Newer Antiepileptic Drug Evaluation (Categorical)

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Mortality								
Medical service utilization:								
Office/ER visits (number of events)								
Hospitalizations (number of events)								
Hospital stay duration (mean±SD)								
Composite of Ambulance/ ER/ Hospitalizations								
Other:								
Loss of Driver's License								
Loss of employment								

Adverse Events for Older versus Newer Antiepileptic Drug Evaluation (Categorical)

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Overall ADRs with/without withdrawal from study								
Overall ADRs reported								
ADRs <u>without</u> withdrawal from study								
Skin Rash								
Suicidal Ideation								
Hypotension								
Neurological Adverse Events								
Asthenia								
Ataxia								
Diplopia								
Dizziness								
Headache								
Nystagmus								
Somnolence								
Tremor								
Mood or Cognition-related Adverse Events								
Aggression								
Anxiety								

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Depression								
Impaired Cognition								
Emotional Lability								
Nervousness								
Cosmetic Adverse Effects								
Acne								
Alopecia								
Hirsutism								
Gum Hyperplasia								
Harms specific to AED								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								

Other Outcomes for Older versus Newer Antiepileptic Drug Evaluation (Continuous)

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
Sample size (n)								
	Mean Change from Baseline (SD)	P- value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value	Mean Change from Baseline (SD)	P-value
Bone density								
HRQOL – Scale used:								
HRQOL Overall score								
HRQOL Sub-score 1 Please specify								
HRQOL Sub-score 2 Please specify								
HRQOL Sub-score 3 Please specify								

Quality Rating for Older versus Newer Antiepileptic Drug Evaluation

<input type="checkbox"/>	<p>Good (low risk of bias)</p> <ul style="list-style-type: none">• Good studies have the least bias and are considered valid.• A study is considered good if it is randomized and controlled and provides a clear description of the population, setting, interventions, and comparison groups.• A good study performs the appropriate measurement of outcomes, statistical and analytical methods and reporting.• A good study does not have reporting errors.• Good studies have less than 20% dropout and clearly report dropouts.
<input type="checkbox"/>	<p>Fair</p> <ul style="list-style-type: none">• Fair studies may be susceptible to some bias, but the bias is not sufficient to invalidate the results.• Fair studies do not meet all of the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias.• A fair study may be missing information, making it difficult to assess limitations and potential problems.
<input type="checkbox"/>	<p>Poor (high risk of bias)</p> <ul style="list-style-type: none">• Poor studies have significant flaws of various types that may invalidate the results.• Poor studies have serious errors in design, analysis or reporting.• Poor studies may be missing large amounts of information or have discrepancies in reporting.

Appendix C. Excluded Studies From Full-Text Review

Excluded Studies From Full-Text Review for Innovator Versus Generic Antiepileptic Drug Evaluation

Reference	Reason for Exclusion
Aita JF. Generic vs. branded carbamazepine. Nebraska Medical Journal. 1998; 73(11): 322-3.	Not a report of new discovery in humans
Argumosa A, Herranz JL. The clinical and economic impact of generic drugs in the treatment of epilepsy. Revista de neurologia. 2005; 41(1):45-9.	Not a report of new discovery in humans
Contillo C. Lessons Learned in reno. American Journal of Nursing 2011;111(1): 11.	Not a report of a new discovery in humans
Gagne JJ, Avorn J, Shrank WH, et al. Refilling and switching of antiepileptic drugs and seizure-related events. Clinical pharmacology and therapeutics. 2010; 88 (3): 347-53.	Unable to determine methodology employed in evaluating cases and controls.
Girolineto BM, Alexandre V, Queiroz RH, et al. Interchangeability among therapeutics equivalents of lamotrigine in the treatment of refractory epilepsy patients: risks and benefits. Revista de neurology. 2010; 51 (6): 330-6.	Not in English language
Helmers SL, Paradis PE, Manjunath R, et al. Economic burden associated with the use of generic antiepileptic drugs in the united states. Epilepsy and behavior. 2010; 18 (4): 437-44.	Not evaluating outcomes of interest
Jefferys R. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Klingler D, Nitsche V, Schmidbauer H. Diphenylhydantoin intoxication following the exchange of seemingly equal DPH-preparations. Wiener Medizinische Wochenschrift 1981;131(11):295-300.	Not in patients with epilepsy
Moore N, Berdaï D, Bégaud B. Are generic drugs really inferior medicines? Nature. 2010; 88 (3): 302-4.	Not a report of a new discovery in humans
Oles KS, Gal P. Bioequivalency revisited: epitol versus tegretol. Neurology 1993;43(12):2435-6.	Not a report of new discovery in humans
Perron,R. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;64(8):1485-6.	Not a report of new discovery in humans
Rackley,R. J. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Sander JW, Ryvlin P, Stefan H, et al. Generic substitution of antiepileptic drugs. Expert reviews in neurotherapeutics. 2010; 10 (12): 1887-98.	Not a report of a new discovery in humans.
Sherry JH, Bechtel T. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Simpson GM, Varga E, Reiss M, Cooper TB, Bergner PE, Lee JH. Bioequivalency of generic and brand-named chlorpromazine. Clinical Pharmacology & Therapeutics 1974;15(6):631-41.	Not in patients with epilepsy
Stetz SA. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;64(8):1485-6.	Not a report of new discovery in humans

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation

Reference	Reason for Exclusion
Aberg, L. E.; Backman, M.; Kirveskari, E.; Santavuori, P. Epilepsy and antiepileptic drug therapy in juvenile neuronal ceroid lipofuscinosis. <i>Epilepsia</i> 2000; 41(10):1296-1302	Not conducted in an epilepsy population
Andermann, F.; Duh, M. S.; Gosselin, A.; Paradis, P. E. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. <i>Epilepsia</i> 2007; 48(3):464-469	Not reporting outcomes of interest
Antoniuk A, Bruck I, Spessatto A, et al. West syndrome: clinical and electroencephalographic follow up of 70 patients and response to its treatment with adrenocorticotrophic hormone, prednisone, vigabatrin, nitrazepam and valproate. <i>Arq Neuropsiquiatr</i> 2000; 58(3-A):683-690	Not conducted in an epilepsy population
Bauer, J.; Buchmuller, L.; Reuber, M.; Burr, W. Which patients become seizure free with antiepileptic drugs? An observational study in 821 patients with epilepsy. <i>Acta Neurol Scand</i> 2008; 117:55-59	Not a comparison of older versus newer antiepileptic drugs
Ben-Menachem E, Brodie M, Perucca E. Efficacy of levetiracetam monotherapy; Randomized double-blind head-to-head comparison with carbamazepine-CR in newly diagnosed epilepsy patients with partial onset or generalized tonic-clonic seizures[abstract]. <i>European Journal of Neurology</i> 2006; 13(Suppl. 2):12	No response from author
Ben-Menachem E, Privitera M, Neto W, et al. Response to topiramate (TPM), carbamazepine (CBZ) or valproate (VPA) by seizure type in newly, diagnosed epilepsy[abstract]. <i>Epilepsia</i> 2005; 46(Suppl.6):274	No response from author
Ben-Menachem E, Privitera M, Wang S, et al. Topiramate, carbamazepine or valproate in newly diagnosed epilepsy: Response by seizure type[abstract]. <i>European Journal of Neurology</i> 2005; 12(Suppl. 2):119	No response from author
Berlowitz, D. R.; Pugh, M. J. Pharmacoepidemiology in community-dwelling elderly taking antiepileptic drugs. <i>International Review of Neurology</i> 2007; 81:153-63	Not a comparison of older versus newer antiepileptic drugs
Boldyreva SR, Ermakov AY. Comparative efficacy of carbamazepine, valproic acid and topiramate in symptomatic and cryptogenic frontal lobe epilepsy in children. <i>Zhurnal Nevrologii i Psikiatrii Imeni S.S.Korsakova</i> . 2010; 110(6): 58-65.	Not in English language
Boldyreva SR, Ermakov AY. Efficacy of carbamazepine, valproate and topiramate in the treatment of medical temporal epilepsy in children. <i>Zhurnal Nevrologii i Psikiatrii Imeni S.S. Korsakova</i> . 2010; 110 (4):41-7.	Not in English language
Bondarnek II. Experience in the use of the anticonvulsant pregabalin as an add-on therapy in patients with partial epilepsy with polymorphic seizures. <i>Neuroscience and Behavioral Physiology</i> . 2010; 40 (2): 163-4.	Not a comparison of older versus newer antiepileptic drugs
Brodie M, Ben-Menachem E, Perucca E. Efficacy of levetiracetam monotherapy; Randomised double-blind head-to-head comparison with carbamazepine-CR in newly diagnosed epilepsy patients with partial onset or generalised tonic-clonic seizures[abstract]. <i>European Journal of Neurology</i> 2006; 13(Suppl. 2):112	No response from author
Brodie, M. J.; Yuen, A. W. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. <i>Epilepsy Res</i> 1997; 26(3):423-32.	Not a comparison of older versus newer antiepileptic drugs
Bryant-Comstock, L.; Moorat, A. Improvement in quality of life and severity of side effects in patients with epilepsy receiving lamotrigine or valproate [abstract]. <i>Epilepsia</i> 1999; 40(Suppl. 7):1999	No response from the author

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Buchanan,N. The use of lamotrigine in juvenile myoclonic epilepsy. <i>Seizure</i> 1996;5:149-151.	Not reporting outcomes of interest
Calloway,M. O.;Blum,D.;Hammer,A. E.;Kustra,R. P. Quality of life in treatment of epilepsy: Lamotrigine versus conventional anti-epileptic drug therapy [abstract]. <i>Epilepsia</i> 2003;44(Suppl. 8):173.	Not a report of a new discovery
Cansu A, Serdaroglu A, Camurdan O, et al. The evaluation of thyroid functions, thyroid antibodies, and thyroid volumes in children with epilepsy during short-term administration of oxcarbazepine and valproate. <i>Epilepsia</i> 2006;47(11):1855–9.	Not reporting outcomes of interest
Cansu A, Serdaroolu A, Yesilkaya E et al. The Effect of Oxcarbazepine and Valproate Therapy on Growth in Children with Epilepsy[abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):223.	Does not report outcomes of interest
Carius A, Schreiner A, Schauble B. Effectiveness of topiramate in patients with epilepsy transitioning from valproic acid - Results of an open-label, non-interventional trial [abstract]. <i>European Journal of Neurology</i> 2007;14(Suppl. 1):91.	No response from the author
Chung S, Cho E. Age- and dose-related hyponatremia during carbamazepine and oxcarbazepine therapy in children with epilepsy [abstract]. <i>Epilepsia</i> 2006;47(Suppl. 3);172.	Not reporting outcomes of interest
Clemens B, Menes A, Piros P, et al. Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings. <i>Epilepsy Research</i> 2006;70:190-9.	Not reporting outcomes of interest
Contin M, Riva R, Albani F, et al. Effect of felbamate on clobazam and its metabolite kinetics in patients with epilepsy. <i>Therapeutic Drug Monitoring</i> 1999;21:604-8	Not reporting outcomes of interest
De Romanis F, Sopranzi N. Lamotrigine: monotherapy in refractory epilepsy. <i>Clinica Terapeutica</i> 1997;148:153-8	Not a comparison of older versus newer antiepileptic drugs
De Romanis F, Sopranzi N. Felbamate: a long-term study in subjects with refractory epilepsy. <i>Clinica Terapeutica</i> 1997;148:83-7	Not a comparison of older versus newer antiepileptic drugs
DeToledo J, Ramsay R, Lowe M, et al. Increased seizures after discontinuing carbamazepine: results from the gabapentin monotherapy trial. <i>Therapeutic Drug Monitoring</i> 2000;22:753-6	Not reporting outcomes of interest
Ding YX, Zou LP, Ma MS, et al. Retorspective analysis of the effectiveness of first-line antiepileptic drugs for generalized onset and unclassified epileptic seizures in Chinese children. <i>Childs Nervous System</i> . 2011; 27(2): 279-284.	Not a comparison of older versus newer antiepileptic drugs
Dong X, Leppik I, White J, et al. Hyponatremia from oxcarbazepine and carbamazepine. <i>Neurology</i> 2005;65:1976-8	Not reporting outcomes of interest
Ehtisham A, Taylor S, Klein M, et al. Cognitive outcomes following seizure prophylaxis for intracranial hemorrhages of different subtypes with levetiracetam versus phenytoin [abstract]. <i>Annals of Neurology</i> 2008;64(Suppl. 12):S30	Not conducted in an epilepsy population

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Ermakov A, Boldyreva S, Litvinovich, The comparative study of effectiveness of lamotrigine and other antiepileptic drugs in cryptogenic and symptomatic focal epilepsy. Zh Neurol Psikhiatr Im SS Korsahova 2007;107(12):94-7	Not in English language
Eun So-Hee, Eun B, Lee J, et al. The Effects on Cognition and Behavior of Lamotrigine Compared to Carbamazepine as Monotherapy for Children with Partial Epilepsy [abstract]. Epilepsia 2008;49(suppl. 7):88	No response from the author
Feucht M, Brantner-Inthaler S. Gamma-vinyl-GABA (vigabatrin) in the therapy of Lennox-Gastaut syndrome: an open study. Epilepsia 1994;35(5):993-8	Not a comparison of older versus newer antiepileptic drugs
Fife D, Blum D, Fisher S. Measuring the effects of antiepileptic medications on balance in older people. Epilepsy Research 2006;70:103-9	Not reporting outcomes of interest
Filho, G. M. A.; Sousa, P. S.; Garzon, E.; Sakamoto, A. C.; Yacubian, E. M. T. Psychiatric disorders in juvenile myoclonic epilepsy: A study comparing patients treated with valproate and topiramate [abstract]. Epilepsia 2005;46(Suppl. 6):180	No response from the author
Freidel M, Krause E, Kuhn K, et al. Oxcarbazepine in the treatment of epilepsy. Fortschr Neurol Pshchiat 2007;75:100-6	Not a comparison of older versus newer antiepileptic drugs
Garg K, Kar M, Singh K. Carbamazepine versus topiramate monotherapy: A prospective comparative study on Indian patients with single small enhancing CT lesions (SSECTLS) and seizures [abstract]. Epilepsia 2003;44 (Suppl. 8):81	No response from the author
Gates J, McCague K, D'Souza J. Oxcarbazepine is efficacious in patients with partial seizures when switching from carbamazepine phenytoin or valproate [abstract]. Epilepsia 2004;45(Suppl. 7):133	No response from the author
Gaus V, Coban I, Kretz R, et al. EURAP Germany: Seizure control and dose modifications during pregnancy under treatment with valproate, carbamazepine, and lamotrigine in monotherapy [abstract]. Epilepsia 2006;47(Suppl. S3):125	Not reporting outcomes of interest
Gaus V, Coban I, Kretz R, et al. Seizure control in the course of pregnancy under treatment with lamotrigine, carbamazepine and valproic acid in monotherapy: Observations from the German EURAP project [abstract]. Epilepsia 2005;46(Suppl. 6):261	Not reporting outcomes of interest
Gaus V, Cohan I, Dennig D, et al. EURAP Germany: Seizure control and dose modifications during pregnancy under treatment with valproate, carbamazepine and lamotrigine in monotherapy - Update 2007 [abstract]. Epilepsia 2007;48(Suppl. 6):340	Not reporting outcomes of interest
Gidal E, Tamura T, Hammer A, et al. Blood homocysteine, folate and vitamin B-12 concentrations in patients with epilepsy receiving lamotrigine or sodium valproate for initial monotherapy. Epilepsy Research 2005;64:161-6	Not reporting outcomes of interest
Gilad R, Sadeh M, Rapoport A, et al. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol 2007;30:189-95	Not conducted in an epilepsy population
Giorgi L, Gomez G, O'Neill F, et al. The tolerability of lamotrigine in elderly patients with epilepsy. Drugs & Aging 2001;18(8):621-30	Not a report of a new discovery

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Glauser A, Privitera M, Neto W et al. Response of partial-onset or generalized seizures to topiramate, carbamazepine or valproate in newly diagnosed epilepsy [abstract]. <i>Neurology</i> 2005;64(Suppl. 1);A116	No response from the author
Guido M, de Tommaso M, La Neve A, et al. Event-related potentials in the evaluation of the effect of levetiracetam and carbamazepine on cognitive functions in newly diagnosed epilepsy patients: Preliminary results of a randomised trial [abstract]. <i>Epilepsia</i> 2007;48(Suppl. 8):107	No response from the author
Guido MT, Goffredo R, Castriota O, et al. Event-related potentials (ERPs) in the evaluation of the effect of levetiracetam and carbamazepine on cognitive functions in adult patients with newly diagnosed epilepsy [abstract]. <i>European Journal of Neurology</i> 2008;15(Suppl. 3):305	No response from the author
Guo C, Ronen G, Atkinson A. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. <i>Epilepsia</i> 2001;42(9):1141-7.	Not reporting outcomes of interest
Hallioğlu O, Okuyaz C, Mert E, et al. Effects of antiepileptic drug therapy on heart rate variability in children with epilepsy. <i>Epilepsy Research</i> 2008;79:49-54	Not reporting outcomes of interest
Hamed A, Fida N, Hamed E. States of serum leptin and insulin in children with epilepsy: risk predictors of weight gain. <i>European Journal of Paediatric Neurology</i> 2009;13:261-8	Not reporting outcomes of interest
Hasan SS, Bahari MB, Babar ZU, et al. Antiepileptic drug utilization and seizure outcome among paediatric patients in a Malaysian public hospital. <i>Singapore Medical Journal</i> . 2010; 51(1): 21-1.	Not reporting outcomes of interest
Hayes F, Caldwell P, Sluss P, et al. Body weight and serum lipid levels in young women with epilepsy treated with valproate versus lamotrigine[abstract]. <i>Epilepsia</i> 2005;46(Suppl. 8):207	Not reporting outcomes of interest
Heller A, Wright W, LaRoche S, et al. A comparison of levetiracetam and phenytoin as seizure prophylaxis for aneurysmal subarachnoid hemorrhage [abstract]. <i>Epilepsia</i> 2007;48(Suppl. 6):331	Not conducted in an epilepsy population
Herranz J, Argumosa A, Rejas J, et al. Model-based evaluation of the cost-effectiveness of pregabalin, levetiracetam and generic gabapentin versus standard therapy as an add-on anti-epileptic therapy in patients with refractory epilepsy: A Spanish perspective [abstract]. <i>Epilepsia</i> 2005;46(Suppl. 6):115	Not a comparison of older versus newer antiepileptic drugs
Hirfanoglu T, Serdaroglu A, Camurdan O, et al. Evaluation of thyroid functions and thyroid volumes in children with epilepsy in long term administration of carbamazepine, oxcarbazepine and valproic acid [abstract]. <i>Epilepsia</i> 2005;46(Suppl. 6):241	Not reporting outcomes of interest
Hirfanoglu T, Serdaroglu A, Camurdan O, et al. Thyroid function and volume in epileptic children using carbamazepine, oxcarbazepine and valproate. <i>Pediatrics International</i> 2007;49:822-6	Not reporting outcomes of interest
Hirsch L, Arif H, Nahm E, et al. Cross-sensitivity of skin rashes with antiepileptic drug use. <i>Neurology</i> 2008;71:1527-34	Not a comparison of older versus newer antiepileptic drugs
Hogan R, Bertrand M, Deaton R, et al. Total percentage body weight changes during add-on therapy with tiagabine, carbamazepine and phenytoin. <i>Epilepsy Research</i> 2000;41:23-8	Not reporting outcomes of interest

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Houtkooper M, Lammertsma A, Meyer J, et al. Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine?. <i>Epilepsia</i> 1987;28(6):693-8	Not a comparison of older versus newer antiepileptic drugs
Hufnagel A, Limburg S, Evers S, et al. Safety and efficacy of rapidly i.v. titrated levetiracetam versus valproate in patients with partial epilepsy [abstract]. <i>European Journal of Neurology</i> 2009;16(Suppl. 6):473	No response from the author
Hyson C, Sadler M. Cross sensitivity of skin rashes with antiepileptic drugs. <i>Canadian Journal of Neurological Sciences</i> 1997;24:245-9	Not reporting outcomes of interest
Inesta I. Carmabazepine in pregnancy: Levetiracetam and lamtrigine are better options. <i>British Medical Journal</i> . 2011; 342: 279.	Not a report of a new discovery in humans
Ishihara L, Webb DJ, Irizarry M, et al. Exploring differential prescribing between anti-epileptic drugs in epilepsy patients with a history of mood disorders. <i>Pharmacoepidemiology and Drug Safety</i> . 2010; 19: 289-295.	Not a comparison of older versus newer antiepileptic drugs
Isojarvi J, Lofgren E, Juntunen K, et al. Effect of epilepsy and antiepileptic drugs on male reproductive health. <i>Neurology</i> 2004;64:247-53	Not reporting outcomes of interest
Isojarvi J, Turkka J, Pakarinen A, et al. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. <i>Epilepsia</i> 2001;42(7):930-4.	Not reporting outcomes of interest
Isojarvi J, Tapanainen J, Rattya J, et al. Changes in Body-Weight, Fasting Serum-Insulin and Testosterone Levels and Ovarian Structure in Women with Epilepsy After Substituting Lamotrigine for Valproate [abstract]. <i>Epilepsia</i> 1995;36:290	Not reporting outcomes of interest
Isojarvi J, Tapanainen J, Rattya J, et al. Body-Weight, Serum Testosterone Levels, and Ovarian Structure in Women with Epilepsy After Replacement of Valproate with Lamotrigine [abstract]. <i>Epilepsia</i> 1995;36(Suppl. 3):S117	Not reporting outcomes of interest
Kalviainen R, Aikia M, Mervaala E, et al. Prognosis of Newly-Diagnosed Epilepsy and Effects of Initial Vigabatrin Monotherapy Compared with Carbamazepine Monotherapy [abstract]. <i>Neurology</i> 1994;44(Suppl. 2):A204	No response from the author
Kalviainen R, Aikia M, Partanen J, et al. Randomized controlled pilot study of vigabatrin versus carbamazepine monotherapy in newly diagnosed patients with epilepsy: an interim report. <i>Journal of Child Neurology</i> 1991;6(Suppl. 2):2S60-9	Interim report of final analysis Final analysis included in review
Kalviainen R, Halonen T, Pitkanen A, et al. Amino acid levels in the cerebrospinal fluid of newly diagnosed epileptic patients: effect of vigabatrin and carbamazepine monotherapies. <i>Journal of Neurochemistry</i> 1993;60(4):1244-50	Not reporting outcomes of interest
Kang H, Eun B, Lee C, et al. A multicenter, randomized, open-labeled, clinical study to evaluate the effect on cognitive and behavioral function of topiramate compared with carbamazepine as monotherapy in children with benign rolandic epilepsy [abstract]. <i>Epilepsia</i> 2006;47(Suppl. 4):138	Meeting abstract for analysis included in review
Kim J, Lee W. Metabolic and hormonal disturbances in women with epilepsy on antiepileptic drug monotherapy. <i>Epilepsia</i> 2007;48(7):1366-70	Not reporting outcomes of interest
Korabathina K, Benbadis S. Levetiracetam is as effective as carbamazepine in newly diagnosed epilepsy. <i>Expert Review of Neurotherapeutics</i> 2007;7(6):599-601	Not a report of a new discovery in humans

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Kurul S, Dirik E, Iscan A. Serum carnitine levels during oxcarbazepine and carbamazepine monotherapies in children with epilepsy. <i>Journal of Child Neurology</i> 2003;18:552-4	Not reporting outcomes of interest
Kustra R, Morrell M, Hayes F, et al. The incidence of components of polycystic ovary syndrome is higher in young women with epilepsy treated with valproate versus lamotrigine [abstract]. <i>Epilepsia</i> 2006;47(Suppl. S3):124	Not reporting outcomes of interest
Kuzmanovski I, Nikodijevic-Kedeva D, Petrovska D, et al. Tegretol versus lamotrigine in patients with partial refractory epilepsy: a 6 month clinical study [abstract]. <i>Epilepsia</i> 2004;45(Suppl. 3):134	No response from the author
Kwon S, Lee S, Hyun M, et al. The potential for QT prolongation by antiepileptic drugs in children. <i>Pediatric Neurology</i> 2004;30(2):99-101	Not reporting outcomes of interest
Labar R. Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy: a registry study. <i>Neurology</i> 2002;59(6)	Not a comparison of older versus newer antiepileptic drugs
Leach J, Brodie M, Sills G, et al. Randomised comparison of lamotrigine and valproate in newly diagnosed epilepsy - Efficacy, tolerability, and endocrine effects[abstract]. <i>Epilepsia</i> 2006;47(Suppl. 4):164	No response from the author
Lee SA, Heo K, Kim WJ, et al. Clinical feasibility of immediate overnight switching from slow-release carbamazepine to oxcarbazepine in Korean patients with refractory partial epilepsy. <i>Seizure</i> . 2010; 19(6): 356-8.	Not a comparison of older versus newer antiepileptic drugs
Legros B, Bazil C. Effects of antiepileptic drugs on sleep architecture: a pilot study. <i>Sleep Medicine</i> 2003;4:51-5	Not reporting outcomes of interest
Levisohn P, Holland K, Hulihan J, et al. Topiramate or valproate in juvenile myoclonic epilepsy[abstract]. <i>Child Neurology Society</i> 2004;56:S117	No response from the author Duplicate of full text article included in evaluation
Levisohn P, Holland K, Hulihan J, et al. Topiramate versus valproate in patients with juvenile myoclonic epilepsy [abstract]. <i>Epilepsia</i> 2003;44,(Suppl. 9):267	No response from the author Duplicate of full text article included in evaluation
Lim D, Tarapore P, Chang E, et al. Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: a randomized phase II pilot study. <i>Journal of Neurooncology</i> 2009;93:349-354	Not conducted in an epilepsy population
Lim D, Tarapore P, Chang E, et al. Comparison of levetiracetam monotherapy with continued phenytoin therapy after supratentorial craniotomies in patients with a history of tumor-related seizures: A phase II, pilot study[abstract]. <i>Epilepsia</i> 2007;48(S6):343	Not conducted in an epilepsy population
Lim K, Kim H. Low-dose topiramate compared with carbamazepine in treating benign rolandic epilepsy [abstract]. <i>Epilepsia</i> 2004;45(Suppl. 7):322	Not conducted in an epilepsy population
Lofgren E, Tapanainen J, Koivunen R, et al. Effects of carbamazepine and oxcarbazepine on reproductive endocrine function in women with epilepsy [abstract]. <i>Epilepsia</i> 2005;46(Suppl. 8):87	Not reporting outcomes of interest

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Lofgren E, Tapanainen J, Koivunen R, et al. Effects of carbamazepine and oxcarbazepine on the reproductive endocrine function in women with epilepsy. <i>Epilepsia</i> 2006;47(9):1441-6	Not reporting outcomes of interest
Loring D, Kamin M, Karim R. Topiramate and valproate added to carbamazepine: Effect on cognitive function in adults with epilepsy [abstract]. <i>Neurology</i> 2001;56(Suppl 3):A334.	No response from the author
Luef G, Rauchenzauner M, Waldmann M, et al. Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug treatment. <i>Epilepsy Research</i> 2009;86:42-7	Not reporting outcomes of interest
Lukic S, Spasic M. Treatment of newly diagnosed epilepsy with valproate and lamotrigine [abstract]. <i>European Journal of Neurology</i> 2004;11(Suppl. 2):227	No response from author
Lukic S, Spasic M, Lukic N. Comparison of valproate and lamotrigine for treatment of newly diagnosed epilepsy - interim report [abstract]. <i>European Journal of Neurology</i> 2005;12(Suppl. 2):237	No response from author
Majkowska-Zwolinska B, Jedrzejczak J, Zwolinski P, et al. The Effectiveness of Oxcarbazepine After Switch from Carbamazepine in the Treatment of Partial Epilepsy Evaluated in Daily Routine Medical Practice in Poland. Results of a National, Observational 'E-Pill Study' [abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):198-9	No response from author
Martsenkovsky I, Bikshaeva J, Martsenkovska I, et al. Efficacy of monotherapy and polytherapy by topiramate and valproate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome) [abstract]. <i>Epilepsia</i> 2006;47(Suppl. 3):141	No response from author
Martyniuk V, Kharytonov V, Yarmolyuk T. Efficacy and Safety of Topiramate Monotherapy Comparing with Carbamazepine and Lamotrigine in Treatment of Recently Diagnosed Epilepsies with Partial Seizures [abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):230	No response from author
Mazurkiewicz-Beldzinska M, Matheisel A, Szmuda M. Long Term Retention Rates of Valproate Versus Lamotrigine in Idiopathic Generalized Epilepsies [abstract]. <i>Epilepsia</i> 2009;50(Suppl. 10):102	Not reporting outcomes of interest
Mazurkiewicz-Beldzinska M, Matheisel A, Szmuda M. Long term efficacy of valproate versus lamotrigine in treatment of idiopathic generalized epilepsies [abstract]. <i>European Journal of Neurology</i> 2009;16(Suppl. 3):140	Not reporting outcomes of interest
Mazurkiewicz-Beldzinska M, Marta S, Matheisel A. Long-term efficacy of valproate versus lamotrigine in treatment of idiopathic generalized epilepsies in children and adolescents. <i>Seizure</i> 2010;19:195-7	Not reporting outcomes of interest
McCrindle S, Parker P, Stephen L, et al. Randomised comparison of sodium valproate and lamotrigine in newly diagnosed epilepsy [abstract]. <i>Epilepsia</i> 2003;44(Suppl. 8):133	No response from author
McVearry K, Gaillard W, VanMeter J, et al. A prospective study of cognitive fluency and originality in children exposed in utero to carbamazepine, lamotrigine, or valproate monotherapy[abstract]. <i>Epilepsy & Behavior</i> 2009;16:609-16	Not reporting outcomes of interest
Meador KJ, Gevins A, Leese PT, et al. Neurocognitive effects of brivaracetam, levetiracetam, and lorazepam. <i>Epilepsia</i> . 2011; 52(2): 264-272.	Not a comparison of older versus newer antiepileptic drugs

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Meador K, Baker G, Finnell R, et al. In utero antiepileptic drug exposure: fetal death and malformations. <i>Neurology</i> 2006;67:407–12	Not reporting outcomes of interest
Meischenguiser R, D'Giano C, Ferraro S. Oxcarbazepine in pregnancy: clinical experience in Argentina. <i>Epilepsy & Behavior</i> 2004;5:163-7	Not reporting outcomes of interest
Mervaala E, Partanen J, Nousianinen U, et al. Electrophysiologic effects of gamma-vinyl GABA and carbamazepine. <i>Epilepsia</i> 1989;30(2):189-93	Not reporting outcomes of interest
Mikkonen K, Knip M, Pakarinen A, et al. Growth and lipid metabolism in girls and young women with epilepsy during pubertal maturation. <i>Epilepsia</i> 2005;46(7):1114–1120	Not reporting outcomes of interest
Mikkonen K, Tapanainen P, Pakarinen A, et al. Serum androgen levels and testicular structure during pubertal maturation in male subjects with epilepsy. <i>Epilepsia</i> 2004;45(7):769-76	Not reporting outcomes of interest
Mikkonen K, Vainionpaa L, Pakarinen A, et al. Long-term reproductive endocrine health in young women with epilepsy during puberty. <i>Neurology</i> 2004;62:445-50	Not reporting outcomes of interest
Mintzer S, Boppana P, Toguri J, et al. Vitamin D levels and bone turnover in epilepsy patients taking carbamazepine or oxcarbazepine. <i>Epilepsia</i> 2006;47(3):510-15	Not reporting outcomes of interest
Mintzer S, Toguri J, Boppana P, et al. Vitamin D levels and bone turnover in epilepsy patients taking oxcarbazepine or carbamazepine. <i>Epilepsia</i> 2005;46(Suppl. 8):214	Not reporting outcomes of interest
Mirza W, Biton V, Barrett P, et al. Weight gain associated with valproate monotherapy in patients with epilepsy: An interim analysis of a randomized, double-blinded comparative clinical trial with lamotrigine[abstract]. <i>Epilepsia</i> 1999;40(Suppl. 2):282	No response from author
Mockenhaupt M, Messenheimer J, Tennis P, et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. <i>Neurology</i> 2004;65:1134-8	Not reporting outcomes of interest
Mohanraj R, Brodie M. Outcomes of newly diagnosed idiopathic generalized epilepsy syndromes in a non-pediatric setting. <i>Acta Neurol Scand</i> 2007;115:204-8	Not reporting outcomes of interest
Mohanraj R, Brodie M. Pharmacological outcomes in newly diagnosed epilepsy. <i>Epilepsy & Behavior</i> 2005;6:382-7	Not reporting outcomes of interest
Moreno M, Giagante B, Saidon P, et al. Visual defects associated with vigabatrin: a study of epileptic argentine patients. <i>Canadian Journal of Neurological Sciences</i> 2005;32:459-64	Not reporting outcomes of interest
Morrell M, Hayes F, Sluss P, et al. Reproductive endocrine function in women with epilepsy treated with lamotrigine versus valproate [abstract]. <i>Neurology</i> 2006;66(5):A72	Not reporting outcomes of interest
Morrell M, Hayes F, Sluss P et al. Higher incidence of components of polycystic ovary syndrome in young women with epilepsy treated with valproate versus lamotrigine[abstract]. <i>Epilepsia</i> , 2005;46(Suppl. 8):88	Not reporting outcomes of interest
Morrell M, Isojarvi J, Taylor A, et al. Higher androgens and weight gain with valproate compared with lamotrigine for epilepsy. <i>Epilepsy Research</i> 2003;54:189-99	Not reporting outcomes of interest

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Morrell M, Isojarvi J, Gomez G, et al. Cross-sectional study comparing weight gain and androgen levels in women with epilepsy taking lamotrigine compared to valproate monotherapy[abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):192	No response from author
Nicolson A, Appleton R, Chadwick D, et al. The relationship between treatment with valproate, lamotrigine, and topiramate and the prognosis of the idiopathic generalised epilepsies. <i>Journal of Neurology Neurosurgery and Psychiatry</i> 2004;75:75-9	Not reporting outcomes of interest
Nikodijevic-Kedeva D, Nikolovski G, Petrovska-Cvetkovska D, et al. Quality of life in treatment of epilepsy: Topiramate compared to conventional AEDs-carbamazepine and valproic acid [abstract]. <i>Epilepsia</i> 2005;46(Suppl.6):114	No response from author
Nikoloski G. Etotol Antioxidant Status (Tas) in Patients with Epilepsy on Monotherapy with Carbamazepine (Cbz) and Lamotrigine (Ltg)[abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):192	Not reporting outcomes of interest
Nolt D, Mott J, Lopez W. Assessment of anticonvulsant effectiveness and safety in patients with Angelman's syndrome using an Internet questionnaire. <i>American Journal of Health-Systems Pharmacists</i> 2003;60:2583-7	Not reporting outcomes of interest
Nousiainen I, Kalviainen R, Mantyjarvi M. Contrast and glare sensitivity in epilepsy patients treated with vigabatrin or carbamazepine monotherapy compared with healthy volunteers. <i>British Journal of Ophthalmology</i> 2000;84:622-5	Not reporting outcomes of interest
Nousiainen I, Kalviainen R, Mantyjarvi M. Color vision in epilepsy patients treated with vigabatrin or carbamazepine monotherapy. <i>Ophthalmology</i> 2000;107:884-8	Not reporting outcomes of interest
Pace A, Bove L, Innocenti P, et al. Epilepsy and gliomas: incidence and treatment in 119 patients. <i>Journal of Experimental Clinical Cancer Research</i> 1998;17(4):479-82	Not reporting outcomes of interest
Paciello N, Marchi P, Chiumminto M, et al. Levetiracetam vs carbamazepine in epileptic elderly patients[abstract]. <i>Epilepsia</i> 2006;47(S4):168	No response from author
Pack A, Morrell M, Marcus R, et al. Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. <i>Annals of Neurology</i> 2005;57:252-7	Interim report for trial included in evaluation
Papacostas S. Oxcarbazepine versus carbamazepine treatment and induction of serum lipid abnormalities. <i>Journal of Child Neurology</i> 2000;15:138-40	Not reporting outcomes of interest
Perry M, Holt P, Olson L, et al. Comparison of levetiracetam and carbamazepine monotherapy for partial seizures in children less than 16 years of age: A retrospective review [abstract]. <i>Annals of Neurology</i> 2007;62(Suppl 11):S138	No response from author
Perry M, Holt P, Olson L, et al. Comparison of levetiracetam and carbamazepine as initial monotherapy for newly diagnosed epilepsy in children < 16 years old: A retrospective review[abstract]. <i>Epilepsia</i> 2007;48:351	No response from author
Petroff O, Hyder F, Rothman D, et al. Homocarnosine and seizure control in juvenile myoclonic epilepsy and complex partial seizures. <i>Neurology</i> 2001;56:709-15	Not evaluating endpoints of interest

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Petroff O, Hyder F, Rothman D, et al. Brain GABA levels are below normal in epilepsy patients treated with valproate and lamotrigine[abstract]. <i>Annals of Neurology</i> 1999;46(3):455	Not evaluating endpoints of interest
Petrovska-Cvetkovska D, Nikodijevic D, Dzonov I. Quality of Life in Treatment of Elderly Patients with Epilepsy: Lamotrigine and Topiramate Versus Conventional Aeds-Carbamazepine and Valproic Acid [abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):163	No response from author
Piattella L, Zamponi N, Cardinali C. Vigabatrin Versus Carbamazepine in Newly-Diagnosed Partial Epilepsy in Childhood [abstract]. <i>Epilepsia</i> 1995;36(Suppl. 3):S103	No response from author
Pienimäki P, Lampela E, Hakkola J, et al. Pharmacokinetics of oxcarbazepine and carbamazepine in human placenta. <i>Epilepsia</i> 1997;38(3):309-16	No evaluating endpoints of interest
Pisani F, Oteri G, Russo M, et al. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. <i>Epilepsia</i> 1999;40(8):1141-6	No evaluating endpoints of interest
Pohlmann-Eden B, Van Paesschen W, Hallstrom Y, et al. The Komet Study: an Open-Label, Randomized, Parallel-Group Trial Comparing the Efficacy and Safety of Levetiracetam with Sodium Valproate and Carbamazepine as Monotherapy in Subjects with Newly Diagnosed Epilepsy [abstract]. <i>Epilepsia</i> , 2008;49(suppl. 7):448-9	No response from author
Prasad A, Kuzniecky R, Knowlton R, et al. Evolving antiepileptic drug treatment in juvenile myoclonic epilepsy. <i>Archives of Neurology</i> 2003;60:1100-5	No evaluating endpoints of interest
Privitera M, Brodie M, Neto W, et al. Topiramate, carbamazepine, and valproate in the spectrum of newly diagnosed epilepsy [abstract]. <i>Neurology</i> 2001;56(8):332	Duplicate of full text included in the analysis
Pylvanen V, Knip M, Pakarinen J, et al. Fasting serum insulin and lipid levels in men with epilepsy. <i>Neurology</i> 2003;60:571-4	No evaluating endpoints of interest
Ramsay E, Faught E, Krumholz A, et al. Efficacy, Tolerability and Safety of Initial Monotherapy Topiramate Vs Phenytoin in Patients with New-Onset Epilepsy [abstract]. <i>Epilepsia</i> 2008;49(Suppl. 7):115-6	No response from author
Ramsay E, Pryor F, Collins J. Comparative efficacy of carbamazepine, gabapentin, and lamotrigine in new onset geriatric epilepsy stratified by decade[abstract]. <i>Neurology</i> 2007;68(12):A97	No response from author
Ramsay T, Bainbridge J, Fredricks T, et al. Results of a randomized double-blind comparison of levetiracetam & carbamazepine in new onset seizures in a geriatric population [abstract]. <i>Epilepsia</i> 2007;48(Suppl. 6):36-7	No response from author
Rattya J, Turkka J, Pakarinen A, et al. Reproductive effects of valproate, carbamazepine, and oxcarbazepine in men with epilepsy. <i>Neurology</i> 2001;56:31-6	No evaluating endpoints of interest
Rattya J, Turkka J, Paskarinen A, et al. Reproductive endocrine effects of valproate, carbamazepine and oxcarbazepine in men with epilepsy[abstract]. <i>Epilepsia</i> 1999;40(Suppl. 2):194-5	No evaluating endpoints of interest
Rattya J, Vainionpää L, Knip M, et al. The effects of valproate, carbamazepine, and oxcarbazepine on growth and sexual maturation in girls with epilepsy. <i>Pediatrics</i> 1999;130(3):588-93	No evaluating endpoints of interest

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Resendiz-Aparicio J, Rodriguez-Rodriguez E, Contreras-Bernal J, et al. A randomised open trial comparing monotherapy with topiramate versus carbamazepine in the treatment of paediatric patients with recently diagnosed epilepsy. <i>Revista de Neurology</i> 2004;39(3):201-4	Not in English language
Rimmer E, Milligan N, Richens A. A comparison of the acute effect of single doses of vigabatrin and sodium valproate on photosensitivity in epileptic patients. <i>Epilepsy Research</i> 1987;1(6):339-46	No evaluating endpoints of interest
Ronga B, Andreone V, Pagliuca M. Lamotrigine versus valproate as monotherapy in adult patients with idiopathic generalized epilepsy[abstract]. <i>Epilepsia</i> 1999;40(Suppl. 2):284	No response from author
Rudakova G, Morozova O, Kotov A. Impact of the current antiepileptic drugs on quality of life of epileptic patients. <i>Zhurnal Nevrologii i Psikiatrii Imeni S.S.Korsakova</i> 2008;3:36-40	Not in English language
Rufo Campos M, Carreno,M. Utilization of carbamazepine and oxcarbazepine in pediatric patients with partial epilepsy in Spain. An observational study. <i>Neurologia</i> 2009;24(1):30-9	Not a comparison of older versus newer antiepileptic drugs
Sabers A, Dam M, A-Rogvi-Hansen B et al. Epilepsy and pregnancy: lamotrigine as main drug used. <i>Acta Neurologica Scandinavica</i> 2004;109:9-13	No evaluating endpoints of interest
Sackellares C, Vuong A, Hammer A. Lamotrigine monotherapy improves mood in adolescents with epilepsy: A randomized, double-blind comparison with valproate [abstract]. <i>Epilepsia</i> 2004;45(Suppl. 70):356	No response from author
Saetre E, Abdelnoor M, Amlie J, et al. Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine. <i>Epilepsia</i> 2009;50(8):1841-9	No evaluating endpoints of interest
Saetre E, Ansteensen G, Perucca E et al. Randomised double-blind trial of lamotrigine versus sustained-release carbamazepine in newly diagnosed elderly epilepsy patients: A preliminary analysis [abstract]. <i>Epilepsia</i> 2005;46(Suppl. 6):278	No response from author
Saetre E, Ansteensen G, Perucca E, et al. Safety of Antiepileptic drug treatment in old age. experiences from the European multi-center double-blind comparative study of lamotrigine and slow-release carbamazepine in newly diagnosed elderly epilepsy patients (LAM 40089 trial) [abstract]. <i>Neurology</i> 2005;64(Suppl. 10):A190	No response from author
Saetre E, Perucca E, Gjerstad L, et al. An international multi-centre double-blind randomised comparative trial of lamotrigine and slow release carbamazepine in elderly patients with newly diagnosed epilepsy: a preliminary analysis [abstract]. <i>Epilepsia</i> 2004;45(Suppl. 3):135	No response from author
Saetre E, Perucca E, Isojarvi J, et al. An international multicenter double-blind double-dummy randomised trial comparing lamotrigine and slow-release carbamazepine for treating newly diagnosed epilepsy in the elderly[abstract]. <i>Epilepsia</i> 2006;47(S3):1	No response from author
Saetre E, Perucca E, Isojarvi J, et al. An international multicenter double-blind randomised comparative trial of lamotrigine and slow release carbamazepine in elderly patients with newly diagnosed epilepsy [abstract]. <i>Epilepsia</i> , 2005;46(Suppl. 8):216	No response from author
Schmidt T, Schmitz B, Jokiel B, et al. Constriction of the visual field in epilepsy patients taking vigabatrin and other antiepileptic drugs: A longitudinal study[abstract]. <i>Epilepsia</i> 1999;40(Suppl. 2):256	No evaluating endpoints of interest

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Schumacher T, Beck H, Steinhauser C, et al. Effects of phenytoin, carbamazepine, and gabapentin on calcium channels in hippocampal granule cells from patients with temporal lobe epilepsy. <i>Epilepsia</i> 1998;39(4):355-63	No evaluating endpoints of interest
Selai C, Trimble M. Adjunctive therapy in epilepsy with new antiepileptic drugs: is it of any value?. <i>Seizure</i> 1998;7:417-8	No evaluating endpoints of interest
Serdaroglu A, Cansu A, Camurdan O, et al. Short-term evaluation of thyroid functions and volumes in children with epilepsy treated with oxcarbazepine and valproic acid [abstract]. <i>Epilepsia</i> 2005;46(Suppl.6):282	No evaluating endpoints of interest
Shakespeare A, Simeon G. Economic analysis of epilepsy treatment: a cost minimization analysis comparing carbamazepine and lamotrigine in the UK. <i>Seizure</i> 1998;7:119-25	No evaluating endpoints of interest
Sillanpaa M, Pihlaja T. Oxcarbazepine (GP 47 680) in the treatment of intractable seizures. <i>Acta Paediatrica Hungarica</i> 1989-99;29(3-4):359-64	No evaluating endpoints of interest
Sills G, Stephen L, Butler E, et al. A randomised open-label comparison of the efficacy, tolerability, and hormonal effects of sodium valproate and lamotrigine monotherapy in newly-diagnosed epilepsy [abstract]. <i>Epilepsia</i> 2006;47(S3):1	No response from author
Smith D, Marson A, Smith C, et al. Valproate versus lamotrigine and topiramate for epilepsy: Results from arm B of the sanad trial [abstract]. <i>Epilepsia</i> 2006;47(Suppl. 4):247	Duplicate of full text included in the evaluation
Sokolova L, Kalinin V, Zheleznova E, et al. Comparison of efficacy of trileptal (oxcarbazepine) and carbamazepine in the treatment of temporal epilepsy. <i>Zhurnal Nevrologii i Psikiatrii Imeni S.S.Korsakova</i> 2008;(Suppl. 2):63-7	Not in English language
Sorokina N, Selitsky G. Cognitive effects of topiramate and depakine for frontal lobe epilepsy[abstract]. <i>Epilepsia</i> 2005;6(Suppl.6):311	No response from author
Specchio L, Goffredo R, Castriota O, et al. Event-Related Potentials (Erps) in the Evaluation of the Effect of Levetiracetam and Carbamazepine on Cognitive Functions in Adult Newly Diagnosed Epileptic Patients. Preliminary Results of a Randomized Open Trial[abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):98	No response from author
Steinhoff B, Freudenthaler N, Paulus W. The influence of established and new antiepileptic drugs on visual perception. II. A controlled study in patients with epilepsy under long-term antiepileptic medication. <i>Epilepsy Research</i> 1997;29:49-58	No evaluating endpoints of interest
Steinhoff B, Ueberall M, Siemes H, et al. The lam-safe study: lamotrigine versus carbamazepine and valproic acid in newly diagnosed focal and generalised epilepsies in adolescents and adults [abstract]. <i>Epilepsia</i> 2004;45(Suppl. 3):68	No response from author
Stephen L, Kwan P, Shapiro D, et al. Hormone profiles in young adults with epilepsy treated with sodium valproate or lamotrigine monotherapy. <i>Epilepsia</i> 2001;42(8):1002-6	No evaluating endpoints of interest
Sturm Y, Miller M. Long-term oxcarbazepine therapy in children is at least as effective as and better tolerated than phenytoin[abstract]. <i>Epilepsia</i> 2003;44(Suppl. 9):272	No response from author

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Svalheim S, Tauboll E, Luef G, et al. Differential effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults. <i>Epilepsy & Behavior</i> 2009;16:281-7	No evaluating endpoints of interest
Svalheim S, Tauboll E, Rauchenzauner M, et al. Levetiracetam, Lamotrigine and Carbamazepine Differentially Influence Sex Steroid Hormones in Patients with Epilepsy [abstract]. <i>Epilepsia</i> 2008;49(suppl. 7):458	No evaluating endpoints of interest
Tanabe T, Awaya Y, Matsuishi T, et al. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome)--a nationwide questionnaire survey in Japan. <i>Brain & Development</i> 2008;30:629-35	No evaluating endpoints of interest
Tanganelli P, Regesta G. Vigabatrin Versus Carbamazepine in Newly-Diagnosed Epileptic Patients - a Randomized-Response Conditional Cross-Over Study[abstract]. <i>Epilepsia</i> 1999;36(Suppl. 3):S104	No response from author
Tonekaboni SH, Ghazavi, Karimzadeh P, et al. Efficacy of levetiracetam in children with refractory epilepsy as an add-on trial. <i>Epilepsy Research</i> . 2010; 90(3): 273-7.	Not a comparison of older versus newer antiepileptic drugs
Trinka E, VanPaesschen W, Hallstrom Y, et al. The Komet Study: an Open-Label, Randomized, Parallel-Group Trial Comparing the Efficacy and Safety of Levetiracetam with Sodium Valproate and Carbamazepine as Monotherapy in Subjects with Newly Diagnosed Epilepsy[abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):45	No response from author
Tripathi M, Vibha D, Choudhary N, et al. Management of refractory status epilepticus at a tertiary care center in a developing country. <i>Seizure</i> . 2010; 19(2): 109-11.	Not a comparison of older versus newer antiepileptic drugs
Trudeau V, Dimond K, Smith F et al. Gabapentin (Gbp Neurontin(r)) Monotherapy Compared with Carbamazepine (Cbz) Monotherapy and Combination Gbp Plus Cbz (Gbp/cbz) Therapy in Patients with Medically Refractory Partial Seizures - a 3-Way Cross-Over Trial (94536)[abstract]. <i>Epilepsia</i> 1995;36(Suppl. 4):68	No response from author
Tutor-Crespo M, Hermida J, Tutor J. Relation of blood platelet count during carbamazepine and oxcarbazepine treatment with daily dose, and serum concentrations of carbamazepine, carbamazepine-10, 11-epoxide, and 10-hydroxycarbamazepine. <i>Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic</i> 2007;151(1):91-4	No evaluating endpoints of interest
Vainionpaa L, Mikkonen,K.;Rattya,J, et al. Thyroid function in girls with epilepsy with carbamazepine, oxcarbazepine, or valproate monotherapy and after withdrawal of medication. <i>Epilepsia</i> 2004;45(3):197-203	No evaluating endpoints of interest
Vajda FJ, Graham JE, Hitchcock AA, et al. Is lamotrigine a significant human teratogen? Observations from the Australian pregnancy register. <i>Seizure</i> 2010; 19(9): 558-61.	No evaluating endpoints of interest
Vajda FJ, Hollingworth S, Graham J, et al. Changing patterns of antiepileptic drug use in pregnant Australian women. 2010; 121(2): 89-93.	No evaluating endpoints of interest
Vajda F, Hitchcock A, Graham J, et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. <i>European Journal of Neurology</i> 2006;13:645-54	No evaluating endpoints of interest
Vajda F, O'Brien T, Hitchcock A, et al. The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. <i>Journal of Clinical Neuroscience</i> 2003;10(5):543-9	No evaluating endpoints of interest

Excluded Studies From Full-Text Review for Older Versus Newer Antiepileptic Drug Evaluation (continued)

Reference	Reason for Exclusion
Van Paesschen W, Duncan J, Connelly A. A comparison of the neuropathological effects of vigabatrin and carbamazepine in patients with newly diagnosed localization-related epilepsy using MR-based cerebral T2 relaxation time measurements. <i>Epilepsy Research</i> 1998;29:155-60	No evaluating endpoints of interest
Vasquez B, Sachdeo R, Chang G, et al. Tiagabine or phenytoin as first add-on therapy for complex partial seizures[abstract]. <i>Neurology</i> 1998;50:A199	No response from author
Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. <i>Epilepsia</i> 2004;45(11):1330-7	Not evaluating endpoints of interest
Viteri C, Codina M, Cobaleda S, et al. Quality of life and treatment satisfaction in Spanish epilepsy patients on monotherapy with lamotrigine or valproic acid. <i>Seizure</i> 2010; 19(7): 432-8.	Not evaluating endpoints of interest
Viteri C, Codina M, Cobaleda S, et al. Validacion de la version espanola del cuestionario de calidad de vida en epilepsia QOLIE-10. <i>Neurologia</i> 2008;23(3):157-67	Not in English language
Wheless J, Neto W, Twyman R. Topiramate, carbamazepine, and valproate as first-line monotherapy in children/adolescents with newly diagnosed epilepsy[abstract]. <i>Annals of Neurology</i> 2003;54:S135-6	No response from author
Wheless J, Neto W, Wang S. Topiramate, carbamazepine, and valproate in children with newly diagnosed epilepsy: A unique trial design[abstract]. <i>Neurology</i> 2001;56(8):A234-5	No response from author
Wilensky A, Friel P, Ojemann L, et al. Zonisamide in epilepsy: a pilot study. <i>Epilepsia</i> 1985;26(3):212-20	No evaluating endpoints of interest
Williamson P, Kolamunnage-Dona R, Philipson P, et al. Joint modelling of longitudinal and competing risks data. <i>Statistics in Medicine</i> 2008; 27:6426-38	No evaluating endpoints of interest
Yu L, Huang Y, Sun H, et al. Effects of topiramate and carbamazepine on thyroid hormone level in adults with epilepsy. <i>Neural Regeneration Research</i> 2006;1(8):706-9	No evaluating endpoints of interest
Yu P, Zhu G, Xu Y, et al. Cognitive Function and Quality of Life Effect of Valproate, Carbamazepine, and Lamotrigine in Patients with Newly Diagnosed Epilepsy After 2-Year Follow-Up [abstract]. <i>Epilepsia</i> 2009;50(Suppl. 10):139	No response from author
Zamponi N, Cardinali C. Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children. <i>Archives of Neurology</i> 1999;56:605-7	No evaluating endpoints of interest
Zarubova J, Hill M. The Effect of Lamotrigine, Carbamazepine and Valproate on the Levels of Free and Conjugated Steroids in the Serum of Premenopausal Women with Epilepsy[abstract]. <i>Epilepsia</i> 2009;50(Suppl. 4):84	No response from author
Zeber JE, Copeland LA, Pugh MJV. Variation in Antiepileptic drug adherence among older patients with new-onset epilepsy. <i>Neurology</i> 2010; 44(12): 1896-1904.	No evaluating endpoints of interest
Zelnik,N.;Isler,N.;Goez,H, et al. Vigabatrin, lamotrigine, topiramate and serum carnitine levels. <i>Pediatric Neurology</i> 2008;39:18-21	No evaluating endpoints of interest

Appendix D. Glossary

Area Under the Curve (AUC): The area under the concentration versus time curve derived when an antiepileptic medication is dosed. Also referred to as the total systemic exposure to the drug over time.

“A” Rated Drug Products: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products. “A” products are those for which actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence.

Bioequivalent Drug Products: Pharmaceutical equivalent or alternative products that display comparable bioavailability when studied under similar experimental conditions.

Benign Rolandic Epilepsy: An epilepsy syndrome that occurs in childhood and usually resolves by adolescence or early adulthood. It is characterized by simple partial seizures involving the mouth and face or generalized tonic clonic seizures.

Biopharmaceutics Classification System (BCS): Classification of antiepileptic medications based on properties and relegated into 4 classes; high solubility/high permeability (Class I, optimal class with lowest risk of absorption variability), low solubility/high permeability (Class II), high solubility/low permeability (Class III) and low solubility/low permeability (Class IV).

Bone Mineral Density (BMD): A measurement of the amount of bone matter per square centimeter, expresses as grams/centimeter² or Z-score.

C_{max}: The maximal concentration of antiepileptic medication obtained after dosing.

Confidence Intervals (CIs): A range that is likely to include the given value. Usually presented as a percent (%). For example, a value with 95% confidence interval implies that when a measurement is made 100 times, it will fall within the given range 95% of the time.

Correlation Coefficient: A value (which usually ranges from zero to one) that indicates the degree of relationship between two variables. For example, a correlation coefficient of one would indicate a strong relationship.

C_{ss}: The concentration of antiepileptic medication obtained at steady state.

DerSimonian and Laird Random-Effects Model: A statistical method based on the assumption that the effects observed in different studies (in a meta-analysis) are truly different.

Health-Related Quality of Life (HRQoL): Assessment of the overall well-being of a patient. Usually in the form of questionnaires that can be tailored to specific disease states such as cystic fibrosis.

Egger's Weighted Regression Statistics: A method of identifying and measuring publication bias.

Epilepsy: A clinical phenomenon in which a person has recurrent seizures due to a chronic underlying process. The main types of seizures include partial (simple partial, complex partial, partial with secondary generalization) and generalized (absence, tonic-clonic, tonic, atonic, myoclonic).

Generalized Epilepsy: A type of epilepsy characterized by seizure activity that occurs in diffuse regions of the brain simultaneously.

I²: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to 100.

Juvenile Myoclonic Epilepsy: An epilepsy syndrome associated with central nervous system delays or dysfunction from a variety of causes, including developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions.

Lennox-Gastaut Epilepsy Syndrome: An epilepsy syndrome that occurs in children and is defined by the following triad: multiple seizure types (generalized tonic-clonic, atonic, and atypical absence), specific electroencephalographic findings (<3 Hz spike-and-wave discharges), and impaired cognitive function.

Mesial Temporal Lobe Epilepsy Syndrome: An epilepsy syndrome associated with complex partial epilepsy and hippocampal sclerosis.

Meta-analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.

Partial Epilepsy: A type of epilepsy characterized by seizure activity in discrete areas of the cerebral cortex.

Publication Bias: The possibility that published studies may not represent all the studies that have been conducted, and therefore, create bias by being left out of a meta-analysis.

Q Statistic: A test to assess the presence of statistical heterogeneity among several studies.

Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a non-exposed group in a given population. A ratio of one indicates no difference in the risk between the two groups.

Risk Difference: The absolute difference in the event rate between two comparison groups. A risk difference of zero indicates no difference between comparison groups.

Sensitivity Analysis: A “what if” analysis that helps determine the robustness of a study. Helps determine the degree of importance of each variable for a given outcome.

Standard Deviations (SDs): A measure of the variability of a data set. For a simple data set with numbers, can be calculated using the following formula:

$$\sigma = ((\sum(x-x_m))^2/N)^{0.5}$$

σ is standard deviation.

x_m is the average.

$\sum(x-x_m)$ is the sum of x_m subtracted from each individual number x .

N is the total number of values.

Note: Other formulas also exist.

Statistical Heterogeneity: Variability in the observed effects among studies in a meta-analysis.

Therapeutic Equivalence: Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

T_{max}: The time from administration until the C_{max} (see C_{max} above) is obtained.

Z-Score: The number of standard deviations above or below the mean for the patient's age, sex, and ethnicity.

Appendix E. Abbreviations

Abbreviation	Definition
“A” Rated generic	Generic drug that is equivalent to the brand name product in safety and effectiveness as determined by FDA
AED	Antiepileptic drug(s)
AOE	Applicability of Evidence
AUC	Area Under the Curve
AV defect	Atrioventricular defect
BCS	Biopharmaceutics Classification System
BMI	Body Mass Index
Ca ²⁺	Calcium ion
CI	Confidence Interval
C _{max}	Maximum plasma concentration
C _{min}	Minimum plasma concentration
C _{ss}	Average Steady-state Concentration
CNS	Central Nervous System
CP	Complex Partial Seizures
CR	Controlled Release
CT	X-ray Computed Tomography
CYP	Cytochrome P enzyme
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EQ-5D	Descriptive Health Related Quality of Life States
ER	Emergency Room
FDA	Food and Drug Administration
GABA	Gamma Amino Butyric Acid
GTCS	Generalized Tonic Clonic Seizures
H	High
HR	Hazard Ratio
I	Insufficient
IBW	Ideal Body Weight
ICS	International Classification of Epileptic Seizures
ILAE	International League Against Epilepsy
IQ	Intelligence Quotient
JME	Juvenile Myoclonic Epilepsy
L	Low
M	Moderate
MRI	Magnetic Resonance Imaging
Na ⁺	Sodium ion
NEWQOL	Newly Diagnosed Epilepsy Quality of Life
NMDA	N-methyl D-aspartic acid
NNT	Number Needed to Treat
NRCT	Non Randomized Controlled Trial
OBS	Observational Study
PCOS	Polycystic Ovary Disease
PE	Partial Epilepsy
QOLIE-89	Quality of Life in Epilepsy-89
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation
SMD	Standardized Mean Difference

Abbreviation	Definition
SOE	Strength of Evidence
SR	Sustained Release
SANAD	Standard And New Antiepileptic Drugs
SEALS Inventory	Side Effect and Life Satisfaction Inventory
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
T _{max}	Time to Maximum Concentration
WMD	Weighted Mean Difference

Appendix F. Baseline Characteristics for Included Studies and Trials

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Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>									
Zachry, 2009 (N=1664)	Retrospective Observational (Case-control)	United States	Abbott Laboratories sponsored the study and three authors were employees	Fair – Retrospective, uses case-control methodology which has more inherent limitations, did not control for factors other than epilepsy diagnosis code and age. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported	Innovator antiepileptic	“A” rated generic antiepileptic	Six months before the index date	Cases : Received ambulance transport, emergency department visitation, or inpatient hospitalization for epilepsy occurred between July 1 and December 31, 2006 (the index date). Controls: Ambulatory office visit for with a primary diagnosis of epilepsy between July 1 and December 31, 2006 (the index date)	ICD-9 code for infantile spasms, aged below 12 or over 64 years of age, or did not have continuous insurance coverage for 6 months before the index date. Cases were matched 3:1 for age and ICD-9 codes to controls, other controls were excluded

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Rascati, 2009 (N=3964)	Retrospective Observational (Case-control)	United States	Unrestricted educational grant from Abbott Laboratories	Fair – Retrospective, uses case-control methodology which has more inherent limitations, did not control for factors other than epilepsy diagnosis code and age. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported	Various	Various Only “A” rated generics were evaluated	-	Patients with and ICD-9 code for epilepsy (excluding infantile spasm) in the PharMetrics database (a database accounting for 55 million patients from across the United States) between 12 and 64 years of age, continuous insurance coverage and a prescription for antiepileptic drugs for 145 days. Cases were identified if they had an epilepsy related acute event (ambulance service, emergency department visit, or	Patients with an ICD-9 code for infantile spasms Cases were matched 3:1 for age (within 5 years), gender, and ICD-9 codes to controls, other controls were excluded

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
								hospitalization) between Oct. 1, 2005 and Dec. 31, 2006 and no acute event 6 months prior. Controls were identified if they had epilepsy and visited a doctor' s office during the same time period but did not have an acute event.	
Devine, 2010 (N=11796) ESI Study	Retrospective Observational Cohort study	United States	Express Scripts, Inc.	Fair – Retrospective, uses case-control methodology which has more inherent limitations, controlled for factors such as epilepsy diagnosis code, age, gender, geographical location, co-morbidities, disease severity, interacting	Various	Various Only “A” rated generics were evaluated	90 days before the index date	The study population was made up of individuals with stable epilepsy and AED use during the last 6 months of 2005. Patients were included in the study if they: (1) had a primary or secondary diagnosis of epilepsy, (2) had a prescription	Patients younger than 18 years old were not included in the study due to unstable hormone levels increasing their risk for epilepsy exacerbations . Patients 65 years and older were not included because they are not

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
				medication, non-adherence, patient diagnosis, baseline disease state, and time. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported				claim for an AED with a days' supply carrying over through January 1, 2006, (3) had eligibility for medical and prescription benefit coverage as of July 1, 2005 through June 30, 2006, and (4) were between the ages of 18 and 64 (inclusive) as of January 1, 2006	represented in the MarketScan commercial database. Patients were excluded when there was one or more inpatient or emergency room claim with a primary diagnosis of epilepsy between July 1 and December 31, 2005, as patients with a recent history of exacerbation of epilepsy may be at high risk for repeat seizures
Labiner, 2010a (N=18125)	Retrospective Observational Cohort study	United States	GlaxoSmithKline One author is an employee of GlaxoSmithKline	Poor – Not limited to “A” rated generics, dosing may or may not have been similar, administrative claims data does not have	Branded carbamazepine, phenytoin, primidone, zonisamide (if limited to innovator or branded generics is not	Carbamazepine gabapentin, phenytoin, primidone, zonisamide (Manufacturers not reported)	From target medication dispensing until 30 days after the last drug supply was obtained,	Patients 18 years or older with 2 or more years of continuous health plan enrollment, an ICD-9 code for nonfebrile	For gabapentin, only monotherapy use was permitted to reduce the risk of use in nonepilepsy

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
				several potentially relevant confounders (including disease severity), there may be inaccuracies in coding of diagnoses and procedures, whether drugs dispensed were consumed and how were consumed is not known, if limited to innovator or branded generics is not known, exact brand names and forms included not reported	known, exact brand names and forms included not reported)		health coverage ended, or the end of data availability, whichever occurred first. Mean observation period ~ 4 years	convulsions (ICD-9: 780.3 or 780.39), dispensing of target drugs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) at least twice, and at least 60 days worth of drugs dispensed during the first 90 days of treatment. Stable patients only	indications
Labiner, 2010b (N=15500)	Retrospective Observational Cohort study	United States	GlaxoSmithKline One author is an employee of GlaxoSmithKline	Poor – Not limited to “A” rated generics, dosing may or may not have been similar, administrative claims data does not have several	Branded carbamazepine, phenytoin, primidone, zonisamide (if limited to innovator or branded generics is not known, exact	Carbamazepine gabapentin, phenytoin, primidone, zonisamide	From target medication dispensing until 30 days after the last drug supply was obtained, health	Patients 18 years or older with 2 or more years of continuous health plan enrollment, an ICD-9 code for nonfebrile convulsions	For gabapentin, only monotherapy use was permitted to reduce the risk of use in nonepilepsy indications

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
				potentially relevant confounders (including disease severity), there may be inaccuracies in coding of diagnoses and procedures, whether drugs dispensed were consumed and how were consumed is not known, if limited to innovator or branded generics is not known, exact brand names and forms included not reported	brand names and forms included not reported)		coverage ended, or the end of data availability, whichever occurred first. Mean observation period ~ 4 years	(ICD-9: 780.3 or 780.39), dispensing of target drugs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) at least twice, and at least 60 days worth of drugs dispensed during the first 90 days of treatment. Unstable patients only	
Carbamazepine									
Kauko, 1974 (N=20)	Two Concurrently run unblinded “before and after” trials	Finland	Drug provided by Ciba-Geigy	Poor – Before and after evaluations, exclusion criteria and demographics not well described, only pharmacokinetic	Tegretol (Ciba-Geigy) tablets 15.6 mg/kg/day	Carbamazepine (Laake Oy) 15.6 mg/kg/day Not an “A” rated generic in the United States	20 weeks	In the first trial, patients had to be taking generic carbamazepine at baseline. In the second trial, patients had to be taking	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
				c endpoints evaluated, no measure of AUC, not an “A” rated generic in the United States				Tegretol at baseline	
Glende, 1983 (N=5)	Randomized crossover design	Germany	Unknown		Tegretol (Ciba-Geigy) tablets	Carbamazepine (AWD Dresden) Not an “A” rated generic in the United States	4 weeks (2 weeks per phase)	The patients had been receiving carbamazepine for several years	-
Jumao-as, 1989 (N=10)	Randomized Double-blind Crossover	United States	Veterans Administration and University of Pittsburgh	Fair – Demographics not well described, dose of carbamazepine not reported, not an “A” rated generic in the United States	Tegretol (Ciba-Geigy) tablets	Carbamazepine (Parke-Davis) tablets Not currently an “A” rated generic in the United States	10 weeks (5 weeks per phase)	The patients had to be receiving carbamazepine prior to entry and had at least 1 seizure in the past year.	-
Hartley, 1990 (N=23)	Randomized Crossover Blinding not reported	United Kingdom	Ciba-Geigy funded the study and provided carbamazepine tablets. UK Generics provided the generic tablets	Fair – Short duration of followup, not an “A” rated generic in the United States	Tegretol (Ciba-Geigy) Tablets 16.2 mg/kg/day	Carbamazepine (United Kingdom Generics) 16.2 mg/kg/day Not an “A” rated generic in the United States	12 weeks (6 weeks per phase)	Patients needed to experience at least 3 seizures in the past to be included	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Hartley, 1991 (N=12)	Randomized Crossover Blinding not reported	United Kingdom	-	Fair – Blinding not reported, exact dose of carbamazepine not reported, not an “A” rated generic in the United States	Tegretol (Ciba-Geigy) Tablets ~20mg/kg/day	Carbamazepine (Ethical Generics) Tablets ~20mg/kg/day Not an “A” rated generic in the United States	12 weeks (6 weeks per phase)	-	-
Oles, 1992a (N=20)	Randomized Double-blind Crossover	United States	Financial support: Lemmon Co; Drug: Ciba-Geigy	Good –	Tegretol (Ciba-Geigy) Tablets 12.4 (3.5) mg/kg daily	Carbamazepine (Lemmon Co) Tablets 12.4 (3.5) mg/kg daily An “A” rated generic in the United States	6 months (3 months in each phase with pharmacokinetics determined 2 weeks into each phase)	Patients had to be seizure-free for over 5 months	Taking carbamazepine for less than 6 months, and hepatic or renal disease
Oles, 1992b (N=20)	Randomized Double-blind Crossover	United States	Financial support: Lemmon Co; Drug: Ciba-Geigy	Good - Followup was brief	Tegretol (Ciba-Geigy) Tablets 21.9 (6.2) mg/kg daily	Carbamazepine (Lemmon Co) Tablets 21.9 (6.2) mg/kg daily An “A” rated generic in the United States	6 months (3 months in each phase with pharmacokinetics determined 2 weeks into each phase)	Patients had to have refractory seizures.	Taking carbamazepine for less than 6 months, and hepatic or renal disease
Reunanen, 1992 (N=21)	Randomized Single-blind Crossover	Finland	-	Poor – Single-blinded, not an “A” rated generic in the United States, short duration of followup	Tegretol Retard (Ciba-Geigy) Tablets 685 (268) mg/day	Carbamazepine (Laakefarmos) Tablets 685 (268) mg/day Not an “A” rated generic in the United States	4 weeks (2 weeks per phase)	Patients age 18-65 years with epilepsy	Seizure within the past 4 months; severe psychiatric, renal, hepatic, gastrointestinal

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
									al, other disease that impact absorption; drug or alcohol abuse
Silpakit, 1997 (N=18)	Randomized Double-blind Three phase Crossover	Thailand	Srithanya Hospital Fund	Fair – Not an “A” rated generic in the United States, short duration of followup	Tegretol (Ciba-Geigy) Tablets 677.8 (155.5) mg/day	Carbamazepine (Central Poly) 677.8 (155.5) mg/day Carbamazepine (Condrugs) 677.8 (155.5) mg/day Carbamazepine (Pharmaland) 677.8 (155.5) mg/day Not an “A” rated generic in the United States	12 weeks (3 weeks each phase)	Patients had to have epilepsy, epilepsy with psychosis, or temporal lobe psychosis	Seizure free for <5 months, abnormal renal or liver function, electrolyte of blood count abnormalities
Aldenkamp, 1998 (N=12)	Randomized Open-Label Crossover	Netherlands	Unknown	Fair – Not an “A” Rated Generic in the United States, Open Label	Tegretol (Ciba-Geigy) Tablets Average dose for all products: 717 (180)mg	Carbamazepine (Pharmachemie) Tablets Carbamazepine (Pharbita) Tablets Average dose for all products 717 (180)mg Not an “A” rated generic in the United States	9 days total, 3 days per therapy	Outpatients with average intelligence with ages between 18 and 60 years. Epilepsy treated with carbamazepine monotherapy for >2 months	Psychiatric, heart, liver, kidney, thyroid, pulmonary, or hematologic disorders; neurological deficits other than epilepsy; or use of non-antiepileptic agents except modest alcohol intake

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Garnett, 2005 (N=980)	Retrospective Observational (Cohort)	United States	Shire US, Inc	Poor – Retrospective design, data on outcomes not adjusted for confounders, dose not controlled, some changes in CBZ exposure after study entry, not limited to “A” rated generics	Tegretol (Novartis) Tablets	Carbamazepine Tablets Not limited to “A” rated products	-	Patients 18 years or older with ICD-9-CM codes for epilepsy and started on immediate release carbamazepine between 1999 and 2001 in the PharMetrics database	Incomplete data records or a history of pre-existing conditions (aplastic anemia, agranulocytosis, Lyell's or Stevens-Johnson syndrome, psychosis, brain cancer, visual disturbances, ataxia, confusion, diplopia, or vertigo)
LeLorier, 2008d (N=851)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript		Tegretol CR	Carbamazepine Whether they were “A” rated products in the United States is not known. Whether only sustained release generics were allowed in the study is not known	Mean duration of observation 1,117 (307.6) days	Patients with medical and pharmacy claims in Quebec's provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Tegretol CR	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
								for at least sixty days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy	
Clobazam									
Andermann, 2007b (N=1600)	Retrospective Observational Before-and-after	Canada	GlaxoSmithKline	Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only “A” rated generics were used is not known	Frisium	Clobazam (manufacturers not reported) Whether only “A” rated generics were used is not known	The study period ranged from 1 year before generic entry to March 2006	Patients who continuously used Frisium for 3 or more months in the 6 months preceding generic entry.	Patients who were not switched to the generic counterpart
LeLorier, 2008b (N=1060)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in	Poor – Retrospective, whether generics were	Frisium	Clobazam Whether they were “A” rated products in the	Mean duration of observation 1,090	Patients with medical and pharmacy claims in	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
			the design, review, and approval of the manuscript	"A" rated was unknown, no attempts made to correct for baseline differences		United States is not known	(329.4) days	Quebec's provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Frisium for at least 60 days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy	
Gabapentin									
LeLorier, 2008c (N=202)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in the design, review, and approval of the	Poor – Retrospective, whether generics were "A" rated was unknown, no attempts made	Neurontin	Gabapentin Whether they were "A" rated products in the United States is not known	Mean duration of observation 1,019 (351.5) days	Patients with medical and pharmacy claims in Quebec's provincial health plan	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
			manuscript	to correct for baseline differences				from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Neurontin for at least 60 days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy	
Lamotrigine									
Andermann, 2007a (N=1142)	Retrospective Observational Before-and-after	Canada	GlaxoSmithKline	Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist,	Lamictal Group who switched to generic and then switched back: 252.2 mg and 250.7 mg. Group who switched to	Lamotrigine (manufacturers not reported) Group who switched to generic and then switched back: 254.6 mg. Group who	The study period ranged from 1 year before generic entry to March 2006	Patients who continuously used Lamictal for 3 or more months in the 6 months preceding generic entry.	Patients who were not switched to the generic counterpart

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
				whether only "A" rated generics were used is not known	generic but did not switch back: 255.3 mg	switched to generic but did not switch back: 271.1 mg Whether only "A" rated generics were used is not known			
LeLorier, 2008a (N=671)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript	Poor – Retrospective, whether generics were "A" rated was unknown, no attempts made to correct for baseline differences	Lamictal (GlaxoSmithKline) 239.1 mg/day	Lamotrigine (manufacturer(s) not reported) 251.4 mg/day Whether they were "A" rated products in the United States is not known	Mean duration of observation 1,098 (327.9) days	Patients with medical and pharmacy claims in Quebec's provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Lamictal for at least sixty days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
								health plan coverage, and having an ICD-9 code for epilepsy	
Nielsen, 2008a (N=9)	Before-and-after Unblinded	Denmark	Funding for the study was not reported but one author was on the UCB advisory board and another author has received speaker fees and sponsorship from several pharmaceutical companies	Poor – Before and after design, multiple generics being compared to a single innovator product, small sample size, population all had concerns or problems on generic medication in the past, not “A” rated generics in the United States, short duration of followup	Lamictal 755.6 (202) mg	Lamotrigine (Copyform, Hexal, Ratiopharm, Farma, Actavis, Stada) 755.6 (202) mg Generics stated to be bioequivalent with innovator lamotrigine. Not “A” rated generics in the United States	17 days, patients were on Lamictal for 2 weeks and then on a generic for 7-15 days	Patients had to have reported a problem after switching from innovator to generic to be eligible for entry into the trial	-
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>									
Lund, 1974 (N=9)	Prospective Before-and-after	Sweden	Swedish Medical Research Council	Poor Sequential, not randomized	Epanutin (Parke-Davis) capsules, 100 mg Patients continued on same dose from baseline	Phenytoin sodium (Leo) capsules, 100 mg Patients continued on same dose from baseline	Epanutin days 1 to 8, phenytoin sodium days 9-19	Epileptic outpatients	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Chen, 1982 (N=18)	Prospective Crossover	United Kingdom	-	Poor Sequential, not randomized. Different dosage forms compared (tab vs cap)	Epanutin (Parke-Davis) capsules, 100 mg, 50 mg Patients continued on same dose from baseline\	Phenytoin sodium (Boots) tablets, 100 mg, 50 mg Phenytoin sodium (Cox) tablets, 100 mg, 50 mg Phenytoin sodium (Kerfoot) tablets, 100 mg, 50 mg Phenytoin sodium (McCarthy UK) tablets, 100 mg, 50 mg Patients continued on same dose from baseline	3 weeks per product	Aged 26 to 68 years on long-term treatment with phenytoin	-
Hodges, 1986 (N=30)	Randomized Crossover	United Kingdom	Parke-Davis	Fair Not the same dosage form compared	Phenytoin (Parke-Davis) capsules, 50 mg Dose ranged from 5 to 7.5 mg/kg/day	Phenytoin (Boots) tablets, 50 mg Phenytoin (Evans) tablets, 50 mg Dose ranged from 5 to 7.5 mg/kd/day	4 weeks per product	New patients between 3 and 15 years	-
Kishore, 1986 (N=60)	Randomized Parallel	India	-	Fair Blinding uncertain	Dilantin (Parke-Davis, India) capsules, 100 mg In patients weighing <55kg, 200 mg/day In patients ≥55 kg, 300 mg/day	Phenytoin (Epsolin, Cadila) tablets, 100 mg Phenytoin (Eptoin, Boots India) tablets, 100 mg Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules, 100 mg Salt forms not reported In patients	3 months	Newly diagnosed epilepsy patients	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
						weighing <55kg, 200 mg/day In patients ≥55 kg, 300 mg/day			
Mikati, 1992 (N=10)	Randomized Crossover Double-blinded	United States	-	Fair Not all patients with epilepsy. Sample size small	Dilantin (Parke-Davis) capsule, 100 mg	Phenytoin (Phenytek, manufacturer not reported) capsules, 100 mg	3 months per product	Adults aged 18 to 60 years receiving phenytoin monotherapy for seizure prophylaxis. All but one had partial or generalized seizures. One patient was receiving phenytoin prophylaxis after intracranial surgery	Patients judged to have poor compliance or judged to be unreliable in reporting the necessary information, side effects, or seizures
Soryal, 1992 (N=14)	Randomized Crossover Observer-blinded	United Kingdom	-	Fair Different dosage forms	Epanutin (Parke-Davis) capsules, 100 mg, 50 mg Patients continued on same dose from baseline	Phenytoin sodium (Evans) tablets, 100 mg, 50 mg Phenytoin sodium (APS) tablets, 100 mg, 50 mg Phenytoin sodium (Cox) tablets, 100 mg, 50 mg Phenytoin sodium (Kerfoot) tablets, 100 mg, 50 mg Phenytoin sodium (Regent) tablets, 100 mg, 50 mg	4 weeks per product	Patients with epilepsy from the Epilepsy Unit on maintenance treatment with phenytoin	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
						Patients continued on same dose from baseline			
Topiramate									
Duh, 2009 (N=948)	Retrospective Observational Registry database	Canada	Ortho-McNeil Janssen Scientific Affairs	Poor	Topamax (Ortho-McNeil)	Topiramate (Various manufacturers) Also provided switchback rates for: Lamotrigine Gabapentin Divalproex Clobazam Clonazepam Valproate Carbamazepine	Starting 180 days before generic entry or January 2000, through the end of patient eligibility, treatment discontinuation or October 2007	Patients from the RAMQ database with epilepsy with continuous health plan coverage, treated for at least 60 days with the branded version of one of the AED or non-AED study drugs before the generic entry date, and at least one dispensing of the studied drug (brand or generic) following generic entry, and continuous use of the studied drug throughout the study period	-

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Paradis, 2009 ^a (N=1164)	Retrospective Observational Registry database	Canada	Janssen-Cilag EMEA	Poor	Topamax (Ortho-McNeil)	Topiramate (Various manufacturers)	From January 2006 to September 2008	Patients from the RAMQ database with epilepsy with continuous health plan coverage, treated for at least 60 days with the branded version of one of the AED or non-AED study drugs before the generic entry date, and at least one dispensing of the studied drug (brand or generic) following generic entry, and continuous use of the studied drug throughout the study period	-
Valproic Acid									
Vadney, 1997 (N=64)	Randomized Crossover Open-label	United States	Texas Department of Mental Health and Mental Retardation	Fair Not blinded	Depakene (Abbott)	Valproic acid (Solvay)	4 weeks per product	Patients at an Intermediate Care Facility for the Mentally	Individuals who could not be at the facility for consistent

Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
								Retarded who were already receiving either valproic acid or Depakene for primary diagnosis of seizure disorder	observation, those who required any change in an antiepileptic drug or psychotropic medication, or residents who experienced toxicity
Andermann, 2007c (N=2017)	Retrospective Observational Before-and-after	Canada	GlaxoSmithKline	Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only “A” rated generics were used is not known	Depakene	Valproic Acid (manufacturers not reported) Whether only “A” rated generics were used is not known	The study period ranged from 1 year before generic entry to March 2006	Patients who continuously used Depakene for 3 or more months in the 6 months preceding generic entry	Patients who were not switched to the generic counterpart

- = not reported; N = sample size

^aReports on same database as Duh 2009

Table F-2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Mean Age (SD)	Male (%)	Body Weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Unspecified Innovator and Brand Antiepileptic Drug Products										
Rascati, 2009	Cases	991	35.6 (15.1)	49.0	-	-	-	-	-	-
	Controls	2973	35.6 (15.1)	48.6	-	-	-	-	-	-
Zachry, 2009	Cases	416	37.4 (14.8)	45.0	-	-	-	-	-	-
	Controls	1248	37.5 (14.7)	44.2	-	-	-	-	-	-
Devine, 2010	Cases	2949	42	43.9	-	-	-	-	-	-
	Controls	8847	44	44.7	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	52.5 (16.0)	47.6	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)									
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	49.1 (16.1)	49.2	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)									

Table F-2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Body Weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Carbamazepine										
Kauko, 1974	Tegretol (Ciba-Geigy) Tablets	20	20 years (Range: 7 to 34)	70.0	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets									
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	Range: 19-42 years	80	Range: 50-83	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets									
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	Range: 34 – 70 Years	100.0	-	-	-	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets									
Hartley, 1990	Tegretol (Ciba-Geigy)	23	10.7 (2.9)	60.9	35.8 (11.8)	-	-	-	-	-
	Carbamazepine (Ethical Generics)									
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	10.6 (2.8)	75.0	-	-	-	-	-	-
	Generic Carbamazepine (Ethical Generics) Tablets									
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	33.4 (15.4)	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets									
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	36.8 (16.2)	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets									

Table F-2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Body Weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	32.9 (9.1)	50	53.9 (11.9)	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets									
	Carbamazepine (Condrugs) Tablets									
	Carbamazepine (Pharmaland) Tablets									
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	42.7 (12.7)	40	-	-	-	-	-	-
	Carbamazepine Slow Release (Laakefarmos) Tablets									
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	45.1 (10.6)	58.3	-	-	-	-	-	-
	Carbamazepine (Pharmachemie) Tablets									
	Carbamazepine (Pharbita) Tablets									
Garnett, 2005	Tegretol (Novartis) Tablets	275	40.6 (SE 0.8)	41.1	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	43.5 (SE 0.6)	40.0	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	40 (17.3)	50.6	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)									
Clobazam										
Andermann, 2007b	Frisium (manufacturer not reported)	1600	38.5 (20.5)	50.8	-	-	-	-	-	-
	Clobazam (manufacturers not reported)									

Table F-2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Body Weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
LeLorier, 2008b (N=1060)	Frisium (manufacturer not reported)	1060	38 (18.5)	47.4	-	-	-	-	-	-
	Clobazam (manufacturer not reported)									
Gabapentin										
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	49 (18.5)	39.6	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)									
Lamotrigine										
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1445	38.9 (20.8)	46.5	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)									
LeLorier, 2008	Lamictal (GlaxoSmithKline)	671	39 (18.7)	43.8	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)									
Nielsen, 2008	Lamictal (manufacturer not reported)	9	43.8 (10.4)	66.7	-	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)									
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin										
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules									

Table F-2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Body Weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets									
	Phenytoin sodium (Cox) tablets									
	Phenytoin sodium (Kerfoot) tablets									
	Phenytoin sodium (McCarthy UK) tablets									
Hodges, 1986	Phenytoin (Parke-Davis) capsules	30	9.5 years of 30 initially enrolled	60% of 30 initially enrolled	-	-	-	-	-	-
	Phenytoin (Boots) tablets									
	Phenytoin (Evans) tablets									
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	60	30.3 (11.3)	-	55.4 (5.1) ^m 49 (7.5) ^f	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets									
	Phenytoin (Eptoin, Boots India) tablets									
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules									
Mikati, 1992 ^a	Dilantin (Parke-Davis) capsules	10	-	54% of 13 enrolled	-	-	-	-	-	-
	Phenytoin (Phenytext, manufacturer not reported) capsules									

Table F-2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Body Weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Soryal, 1992 ^a	Epanutin (Parke-Davis) capsules	14	Range 18 to 67 years	35%	All within 20% of IBW	-	-	-	-	-
	Phenytoin sodium (Evans) tablets									
	Phenytoin sodium (APS) tablets									
	Phenytoin sodium (Cox) tablets									
	Phenytoin sodium (Kerfoot) tablets									
	Phenytoin sodium (Regent) tablets									
Topiramate										
Duh, 2009 (N=948)	Topamax (Ortho-McNeil)	875	34.5 (17.0)	39.3%	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	37.5 (16.1)	41.4%	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	33.7 (14.7)	32.3%	-	-	-	-	-	-
Paradis, 2009 ^b (N=1164)	Topamax (Ortho-McNeil) Topiramate (Various manufacturers)	1164	39.8 (17.2)	38.3%	-	-	-	-	-	-
Valproic Acid										
Vadney, 1997	Depakene (Abbott)	64	39.6 (Range 17 to 72)	-	59.6 kg (Range 35 to 94)	-	-	-	-	-
	Valproic acid (Solvay)									

Table F-2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Body Weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Andermann, 2007c	Depakene (manufacturer not reported)	2017	44.4 (18.2)	48.0	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)									

- = not reported; IBW = ideal body weight; ^f = value for females; kg = kilograms; N = sample size; ^m = value for males; SD = standard deviation

^aCrossover Study

^bReports on same database as Duh 2009

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Unspecified Innovator and Brand Antiepileptic Drug Products												
Rascati, 2009	Cases	991	-	-	-	-	21.7	-	-	31.7	-	-
	Controls	2973	-	-	-	-	21.7	-	-	31.7	-	-
Zachry, 2009	Cases	416	-	-	-	-	45.6	-	-	39.6	-	-
	Controls	1248	-	-	-	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	20.4	-	-	16.9	-	-
	Controls	8847	-	-	-	-	20.4	-	-	16.9	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-	-

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Carbamazepine												
Kauko, 1974	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets											
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets											
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets											
Hartley, 1990	Tegretol (Ciba-Geigy)	23	56.5%	43.5%	-	-	-	8.7	8.7	-	82.6	-
	Carbamazepine (Ethical Generics)											
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-	-	Patients had experienced 3 complex partial or tonic-clonic seizures in the past	-	Patients had experienced 3 complex partial or tonic-clonic seizures in the past	-
	Carbamazepine (Ethical Generics) Tablets											

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets											
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets											
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	-	-	16.0 (9.6)	-	5.0	15.0	80.0	-	-
	Carbamazepine Slow Release (Laakefarmos) Tablets											
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	7.0 (5.7)	-	-	22.2	-	44.4	-
	Carbamazepine (Central Poly) Tablets											
	Carbamazepine (Condrugs) Tablets											
	Carbamazepine (Pharmaland) Tablets											
Aldenka mp, 1998 (N=12)	Tegretol (Ciba-Geigy) Tablets	12	0	100	-	178.4 (193) mo	75.0	-	16.7	8.3	-	-
	Generic (Pharmachemie) Tablets											
	Generic (Pharbita) Tablets											

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)											
Clobazam												
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-	-	-	-	-
	Clobazam (manufacturers not reported)											
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-	-	-	-	-
	Clobazam (manufacturer not reported)											
Gabapentin												
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)											

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Lamotrigine												
Andermann, 2007	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)											
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)											
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-	-	-	-	-	55.6	11.1	-	22.2
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)											
Levetiracetam, Oxcarbazepine, <i>Phenobarbital or Primidone, Phenytoin</i>												
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules											

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets											
	Phenytoin sodium (Cox) tablets											
	Phenytoin sodium (Kerfoot) tablets											
	Phenytoin sodium (McCarthy UK) tablets											
Hodges, 1986	Phenytoin (Parke-Davis) capsules	30	-	-	-	-	-	-	13%	-	87%	-
	Phenytoin (Boots) tablets											
	Phenytoin (Evans) tablets											
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	60	60	-	-	-	-	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets											
	Phenytoin (Eptoin, Boots India) tablets											
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules											

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Mikati, 1992 ^a	Dilantin (Parke-Davis) capsules	10	-	-	-	-	-	-	-	-	-	-
	Phenytoin (Phenytek, manufacturer not reported) capsules											
Soryal, 1992 ^a	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Evans) tablets											
	Phenytoin sodium (APS) tablets											
	Phenytoin sodium (Cox) tablets											
	Phenytoin sodium (Kerfoot) tablets											
	Phenytoin sodium (Regent) tablets											
Topiramate												
Duh, 2009 (N=948)	Topamax (Ortho-McNeil)	875	-	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-	-	-	-	-

Table F-3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Epilepsy History				Seizure Type					
			New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Paradis, 2009 ^a (N=1164)	Topamax (Ortho-McNeil) Topiramate (Various manufacturers)	1164	-	-	-	-	-	-	-	-	-	-
Valproic Acid												
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-	-	-	-	-	-
	Valproic acid (Solvay)											
Andermann, 2007 ^c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)											

--= not reported; N = sample size; SD = standard deviation

^aCrossover Study

Table F-4. Prior or concurrent AED use in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Combination Therapy (%)
Unspecified Innovator and Brand Antiepileptic Drug Products							
Rascati, 2009	Cases	991	0	-	-	-	-
	Controls	2973	0	-	-	-	-
Zachry, 2009	Cases	416	0	-	-	-	-
	Controls	1248	0	-	-	-	-
Devine, 2010	Cases	2949	0	-	-	-	42.9
	Controls	8847	0	-	-	-	22.4
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	0	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		0	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	0	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		0	-	-	-	-
Carbamazepine							
Kauko, 1974	Tegretol (Ciba-Geigy) Tablets	20	0	100	-	-	80
	Generic Carbamazepine (Laake Oy) Tablets						
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	0	100	-	-	Some were reported as receiving combination therapy
	Carbamazepine (AWD Dresden) Tablets						
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	100	10	-	40
	Generic Carbamazepine (Parke Davis) Tablets						

Table F-4. Prior or Concurrent AED Use in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Combination Therapy (%)
Hartley, 1990	Tegretol (Ciba-Geigy)	23	56.5	43.5	-	-	-
	Carbamazepine (Ethical Generics)						
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets						
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	0	100	0	0	0
	Carbamazepine (Lemmon Co) Tablets						
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	0	100	-	-	-
	Carbamazepine (Lemmon Co) Tablets						
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	0	100	15	25	-
	Carbamazepine Slow Release (Laakefarmos) Tablets						
Silpakit, 1997 (N=18)	Tegretol (Ciba-Geigy) Tablets	18	0	100	0	5.6	38.9
	Carbamazepine (Central Poly) Tablets						
	Carbamazepine (Condrugs) Tablets						
	Carbamazepine (Pharmaland) Tablets						
Aldenkamp, 1998 (N=12)	Tegretol (Ciba-Geigy) Tablets	12	0	100	0	0	0
	Generic (Pharmachemie) Tablets						
	Generic (Pharbita) Tablets						
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	0	12.7	4.4	-
	Generic (Various/Unspecified) Tablets	705	-	0	17.0	8.9	-
LeLorier 2008d	Tegretol CR (manufacturer not reported)	851	0	100	-	-	51.8
	Carbamazepine CR (manufacturer not reported)						
Clobazam							
Andermann, 2007b	Frisium (manufacturer not reported)	1600	0	-	-	-	-
	Clobazam (manufacturers not reported)						
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	0	-	-	-	93.9
	Clobazam (manufacturer not reported)						
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	0	-	-	-	83.2
	Gabapentin (manufacturer not reported)						
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	0	0	0	0	71.1
	Lamotrigine (manufacturers not reported)						

Table F-4. Prior or Concurrent AED Use in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Combination Therapy (%)
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	0	19.2	-	15.2	82.7
	Lamotrigine (manufacturer(s) not reported)						
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	0	-	-	11.1	55.6
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)						
Levetiracetam, Oxcarbazepine, <i>Phenobarbital or Primidone, Phenytoin</i>							
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-
	Phenytoin sodium (Leo) capsules						
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	Concurrent treatment was usually phenobarbital, primidone, or carbamazepine.	100%	-	-
	Phenytoin sodium (Boots) tablets						
	Phenytoin sodium (Cox) tablets						
	Phenytoin sodium (Kerfoot) tablets						
	Phenytoin sodium (McCarthy UK) tablets						
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-
	Phenytoin (Boots) tablets						
	Phenytoin (Evans) tablets						
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15					
	Phenytoin (Eptoin, Boots India) tablets	15					
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15					
Mikati, 1992 ^a	Dilantin (Parke-Davis) capsules	10	0	0	100%	0	0
	Phenytoin (Phenytext, manufacturer not reported) capsules						

Table F-4. Prior or Concurrent AED Use in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Combination Therapy (%)
Soryal, 1992a	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-
	Phenytoin sodium (Evans) tablets						
	Phenytoin sodium (APS) tablets						
	Phenytoin sodium (Cox) tablets						
	Phenytoin sodium (Kerfoot) tablets						
	Phenytoin sodium (Regent) tablets						
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	70%, products not reported
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	71%, products not reported
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	72%, products not reported
Paradis, 2009 ^b	Topamax (Ortho-McNeil)	-	-	-	-	-	78.9%, products not reported
	Topiramate (Various manufacturers)	-					
Valproic Acid							
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-
	Valproic acid (Solvay)						
Andermann, 2007 ^c	Depakene (manufacturer not reported)	2017	0	-	-	100	-
	Valproic Acid (manufacturers not reported)						

- = not reported; N = sample size

^aCrossover Study

^bReports on same database as Duh 2009

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Reinikainen, 1987 (N= 40)	Randomized Double Blind Parallel Group	Finland	Study medication provided by: Ciba-Geigy	Fair	Carbamazepine Increased gradually up to 600-1200 mg/day during the first 2 or 3 weeks according to the clinical condition	Oxcarbazepine Increased gradually up to 400-800 mg/day during the first 2 or 3 weeks according to the clinical condition	48-50 weeks
Danner, 1988 (N=25)	Randomized Double Blind Cross Over	Unknown	Unknown	Fair	Carbamazepine 200 mg twice a day Dosages were increased to 4 tablets daily, if necessary	Oxcarbazepine 300 mg twice a day Dosages were increased to 4 tablets daily, if necessary	24 weeks
Dam, 1989 (N=194)	Randomized Double Blind Parallel Group	Denmark Finland Norway Sweden	Ciba-Geigy Ltd.	Fair	Carbamazepine Starting Dose: 200 mg/day Mean final dose: 684 mg/day Daily dose adjusted from starting dose at weekly intervals to obtain the best possible therapeutic effect associated with satisfactory tolerability The titration phase was between 4 and 8 weeks. Once the optimal dose had been determined, treatment was continued using that dose for 12 weeks (maintenance period I) and for a further 36 weeks (maintenance period II) in patients who were well controlled and willing to continue the study	Oxcarbazepine Starting Dose: 300 mg/day Mean final dose: 1040 mg/day Daily dose adjusted from starting dose at weekly intervals to obtain the best possible therapeutic effect associated with satisfactory tolerability The titration phase was between 4 and 8 weeks. Once the optimal dose had been determined, treatment was continued using that dose for 12 weeks (maintenance period I) and for a further 36 weeks (maintenance period II) in patients who were well controlled and willing to continue the study	56 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Sachdeo, 1992 (N=44)	Randomized Double Blind Parallel Group Active Control	United States	Not specified	Poor	Valproic Acid Initial dose: 15 mg/kg/day to the closest 250 mg	Felbamate Titrated to 3,600 mg/day or the maximum tolerated dose on study day 6	56-day baseline period Study day1 – one-third reduction in dosage of previous AED. Seizure calenders, vitals and clinical lab exams were obtained on days 14, 28, 42, 70, 112. Patients completed study after 112 days of double blind treatment.
Faught, 1993 (N=111)	Randomized Double Blind Active Control Parallel Group	United States	Wallace Laboratories	Fair	Valproic Acid Constant dosage of 15 mg/kg/day or their maximum tolerated dosage throughout the treatment period Mean dose 3600 mg/d	Felbamate Days 1-2: 1200 mg/day Days 3-5: 2400 mg/day Remainder of the treatment period: 3600 mg/day or maximum tolerated dose Mean dose 1081.8 mg/d	16 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Brodie, 1995 (N=260)	Randomized Double Blind Parallel Group	8 Countries in the United Kingdom	Wellcome Foundation	Fair	Carbamazepine Week 1: 200 mg/day Week 2: 200 mg twice a day Week 3-4: 200 mg in the morning and 400 mg in the evening (600 mg/day) Week 6-24: The daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant adverse events had been reported provided that the drug was in the lower half of the target range or lower. Median daily dose of patients who completed the study: 600 mg	Lamotrigine Week 1: 50 mg/day Week 2: 50 mg twice a day Week 3-4: 50 mg in the morning and 100 mg in the evening (150mg/day) Week 6-24: The daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant adverse events had been reported provided that the drug was in the lower half of the target range or lower. Median daily dose of patients who completed the study: 150 mg	52 weeks
Kalviainen, 1995 (N=100)	Randomized Open-Label Parallel Group	Finland	Unknown	Poor	Carbamazepine Titration: Daily dose increased to a plasma level of 35 µmol/L (therapeutic range 20 to 50 µmol/L) or lower in cases of complete seizure control or dose related side effects If clinically necessary, the doses were regularly increased until seizures were controlled or toxic effects developed	Vigabatrin Titration: Daily dose increased to a mean level of 50 mg/kg or lower in cases of complete seizure control or dose related side effects Dosages were not increased beyond 50 mg/kg, even in the cases of inadequate control because doses in excess of 50 mg/kg do not provide additional benefit	12 months

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Sabers, 1995 (N= 52)	Prospective Observational Observer Blinded	Denmark	Ciba Geigy A/S Denmark The Danish Medical Research Council The Jacob and Olga Madsen Foundation Sygekassernes Helsefond	Fair	Carbamazepine Mean dose: 8.4 mg/kg/day Phenobarbital Mean dose: 1.4 mg/kg/day Phenytoin Mean dose: 4.7 mg/kg/day Valproic Acid Mean dose: 18.6 mg/kg/day	Oxcarbazepine Mean dose: 13.3 mg/kg/day	16 weeks
Reunanen, 1996 (N= 343)	Randomized Open Label Parallel Group	Australia Czech Republic Denmark Eire Finland Germany Italy Netherlands Norway	Unknown	Good	Carbamazepine Week 1-2: 200 mg/day in 2 divided doses Week 3-4: 400 mg/day in 2 divided doses Week5-30: 600 mg/day in 2 divided doses	Lamotrigine 100 mg Week 1-2: 25 mg/day Week 3-4: 50 mg/day Week 5-30: 100 mg/day Lamotrigine 200 mg Week 1-2: 25 mg/day Week 3-4: 50 mg/day Week 5-30: 200 mg/day	30 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Tanganelli, 1996 (N= 51)	Randomized Response Conditional Cross-over	Italy	Unknown	Poor	Carbamazepine Starting dose: 0.2 g/day Titration: the dose was progressively increased at weekly intervals by 0.2 g Maximum recommended dose: 1.4 g/day	Vigabatrin Starting dose: 1.0 g/day Titration: the dose was progressively increased at weekly intervals 0.5 g at a time Maximum recommended dose: 3.5 g/day	Run-in: 8 weeks Phase 1: Randomization to vigabatrin or Carbamazepine treatment - 16 weeks Phase 2: cross-over – 16 weeks Only patients with intolerable seizures or adverse events switched to the cross-over phase Phase 3: combined therapy - 16 weeks
Bill, 1997 (N=287)	Randomized Double Blind Paralell Group	Argentina Brazil Mexico South Africa	Unknown	Good	Phenytoin 8-week Titration Phase: 100 mg and increased bi-weekly based on clinical response to reach 150-800 mg/day at the end of the 8 weeks Mean daily dose at the start of Maintenance treatment: 313.4 mg/day	Oxcarbazepine 8-week Titration Phase: 300 mg and increased bi-weekly based on clinical response to reach 450-2400 mg/day at the end of the 8 weeks Mean daily dose at the start of maintenance treatment: 1028.4 mg/day	56 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Christie, 1997 (N=249)	Randomized Double Blind Parallel Group	Belgium Brazil France Germany The Netherlands South Africa Spain United Kingdom	Unknown	Fair	Valproate Flexible Titration Phase: 300 mg/day increased biweekly based on clinical response during the 8 week period Maintenance Phase: 900-2400 mg three times a day during the 48 week period Mean dose during maintenance phase: 1146.2 mg/day	Oxcarbazepine Flexible Titration Phase: 300 mg/day increased biweekly based on clinical response during the 8 week period Maintenance Phase: 900-2400 mg/day three times a day during the 48 week period Mean dose during maintenance phase: 1052.8 mg/day	56 weeks
Guerreiro, 1997 (N=193)	Randomized Double Blind Parallel Group	Argentina Brazil	Novartis	Fair	Phenytoin Titration: 50 mg/day increased gradually based on clinical response No fixed titration schedule except that patients were to be on a 3 times a daily regimen with daily doses from 150-800 mg/day Maintenance: Daily dose range and 3 times daily regimen were to be continued during the maintenance period	Oxcarbazepine Titration: 150 mg/day increased gradually based on clinical response No fixed titration schedule except that patients were to be on a 3 times daily regimen with daily doses from 450-2400 mg/day Maintenance: Daily dose range and 3 times daily regimen were to be continued during the maintenance period	56 weeks
Chadwick, 1998 (N=292)	Randomized Carbamazepin Arm: Open-Label Gabapentin Arm: Double Blind	Europe Australia South Africa Canada	Parke Davis	Poor	Carbamazepine 600 mg/day	Gabapentin Gabapentin Arm A: 300 mg/day Gabapentin Arm B: 900 mg/day Gabapentin Arm C: 1800 mg/day	24 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Brodie, 1999a (N=150)	Randomized Double Blind Double Dummie Parallel Group	United Kingdom	Unknown	Good	Carbamazepine Weeks 1-2: 100 mg daily Weeks 3-4: 100 mg twice a day Weeks 5-6: 200 mg twice a day Weeks 7-24: 200-2000 mg daily Dosage could be adjusted from week 6 onwards while maintaining the blind After titrating to 400 mg daily, upward adjustments by 200 mg increments were made in response to further seizures. Reductions in dosage by 100 mg decrements were allowed on the emergence of side effects	Lamotrigine Weeks 1-2: 25 mg daily Weeks 3-4: 25 mg twice a day Weeks 5-6: 50 mg twice a day Weeks 7-24: 75-500 mg daily Dosage could be adjusted from week 6 onwards while maintaining the blind After titrating to 100 mg daily, upward adjustments by 50 mg increments were made in response to further seizures. Reductions in dosage 25 mg were allowed on the emergence of side effects	24 weeks
Brodie, 1999b (N=215)	Randomized Controlled Trial Parallel Group	Austria Belgium Czech Republic France Hungary Italy Netherlands Portugal Slovenia South Africa Spain United Kingdom	Unknown	Fair	Valproic Acid Titrated from 0.5 gram/day to a maintenance of 1.5 grams/day by 0.5 gram increments at 2 week intervals	Vigabatrin Titrated from an initial 1 gram/day to a standard 3 grams/day by 1 gram increments at 2 week intervals	12 weeks
Chadwick, 1999 (N=457)	Randomized Double Blind Parallel Group	44 European Centres	Hoechst Marion Roussell	Fair	Carbamazepine Week 1-6: 200 mg/day Maintenance: 600 mg/day Maximum: 1600 mg/day	Vigabatrin Week 1-6: 1000 mg/day Maintenance: 2000 mg/day Maximum: 4000 mg/day	52 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Gobbi, 1999 (N=80)	Prospective Observational open-label, comparative trial	Italy	Unknown	Poor	Carbamazepine Initial dose: 9-20 mg/kg/day Mean initial dose: 17.1 mg/kg/day Maintenance dose: 9-38 mg/kg/day Mean maintenance dose: 18.9 mg/kg/day	Vigabatrin Initial dose: 20-80mg/kg/day Mean initial dose: 46.8mg/kg/day Maintenance dose: 20-90mg/kg/day Mean maintenance dose: 50.5 mg/kg/day	12 months
Steiner, 1999 (N=181)	Randomized Double Blind Parallel Group	United Kingdom Germany Belgium	Wellcome Foundation LTD	Fair	Phenytoin Week 1-2: 200 mg/day at night Week 3-4: 300 mg/day at night From then on, the dose of either drug could be increased by one capsule if seizure control was inadequate and no clinically significant adverse events had occurred Modal and maximal daily doses were 300 and 600 mg respectively	Lamotrigine Week 1-2: 100 mg/day at night Week 3-4: 150 mg/day at night From then on, the dose of either drug could be increased by one capsule if seizure control was inadequate and no clinically significant adverse events had occurred. Modal and maximal daily doses were 150 and 400 mg respectively	48 weeks
Aldenkamp, 2000 (N=53)	Randomized Observer Blinded Parallel Group	Netherlands	Unknown	Good	Valproic Acid A 12-week titration interval with dosage increments of 150 mg/wk until a maximum daily dosage of 1800 mg/day or maximum tolerated dose Mean Dose: 1384 (377.0) mg/day	Topiramate Starting Dose: 25 mg/week Titration: Increased weekly to at least 200mg/day during the first 8 weeks Target Dosage Range: 200 to 400 mg/day Mean Dose: 251.1 (101.8) mg/day	20 weeks
Gillham, 2000 (N=260)	Randomized Double Blind Parallel Group	15 European Countries	Galxo Wellcome	Fair	Carbamazepine Dosing not reported	Lamotrigine Dosing not reported	48 weeks
Biton, 2001 (N=133)	Controlled Randomized Trial Parallel Group	United States	Glaxo Wellcome Incorporated	Fair	Valproic Acid Dose Escalation Phase: starting 10-15 mg/kg/day Maintenance Phase: target dose 20 mg/kg/day Adjustment for clinical efficacy during maintenance phase: 10-60 mg/kg/day	Lamotrigine Dose Escalation Phase: 25 mg/day Maintenance Phase: target dose 200 mg/day Adjustment in dosing for clinical efficacy during maintenance phase: 100-500 mg/day	34 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Cramer, 2001 (N=349)	Randomized Double Blind Parallel Group	United States	Abbott Laboratories	Good	Carbamazepine Dosing not reported Phenytoin Dosing not reported	Tiagabine Dosing not reported	16 weeks
Kwan, 2001 (N=381)	Prospective Observational	Scotland	Unknown	Poor	Carbamazepine Median: 600 mg/day Interquartile Range: 400-600 mg/day Valproic Acid Median: 1000 mg/day Interquartile Range: 825-1500 mg/day	Lamotrigine Median: 200 mg/day Interquartile Range: 150-300 mg/day	5.6 ± 3.4 years
Nieto-Barrera, 2001 (N=618)	Randomized Open label Parallel Group	Italy Slovakia Germany Denmark United Kingdom Spain	Not specified	Good	Carbamazepine Patients aged 2–12 years: 5-40 mg/kg/day Patients aged 13 years or older: 100–1500 mg/day Doses were increased until the best response was obtained according to data sheet recommendations	Lamotrigine During the maintenance phase patients aged 2–12 years: increased by a max of 0.5-1 mg/kg every 1–2 weeks up to 2-15 mg/kg/day Patients aged 13 years or older: Increased by a maximum of 25–50 mg every 1–2 weeks until an optimal response was achieved up to a max of 700 mg/day	24 weeks
Sackellares, 2002 (N= 133)	Randomized Parallel Group	United States	Glaxo Wellcome	Fair	Valproic Acid Dose escalation phase: starting 10-15 mg/kg/day Maintenance phase: target dose 20 mg/kg/day Adjustment for clinical efficacy during maintenance phase: 10-60 mg/kg/day	Lamotrigine Dose escalation phase: 25 mg/day Maintenance phase: target dose 200 mg/day Adjustment in dosing for clinical efficacy during maintenance phase: 100-500 mg/day	34 weeks Health related quality of life evaluated at baseline, week 10 and week 32

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Biton, 2003 (N=38)	Randomized Parallel Group	United States	GlaxoSmithKline	Fair	Valproic Acid Dose Escalation Phase: starting 10-15 mg/kg/day Maintenance Phase: target dose 20 mg/kg/day Adjustment for clinical efficacy during maintenance phase: 10-60 mg/kg/day Mean dose during the maintenance phase: 1520 (379) mg/day	Lamotrigine Dose Escalation Phase: 25 mg/day Maintenance Phase: target dose 200 mg/day Adjustment in dosing for clinical efficacy during maintenance phase: 100-500 mg/day Mean dose during the maintenance phase: 261 (76) mg/day	34 weeks
Meador, 2003 (N= 76)	Randomized Double blind Placebo Controlled Parallel Group	Unknown	Ortho McNeal Pharmaceutical	Fair	Valproic Acid 250 mg/day up to 2,250 mg/day	Topiramate 50 mg/day up to 400 mg/day	24 weeks
Privitera, 2003 (N=613)	Randomized Double Blind Parallel Group	Australia Brazil Belgium Canada Columbia Costa Rica Denmark Finland France Germany Israel Italy Netherlands New Zeland Norway United States United Kingdom South Africa Spain Sweden	Johnson & Johnson	Good	Carbamazepine Starting dose: 200 mg/day increased 200 mg every 2 weeks Final dose: 600 mg/day Valproic Acid Starting dose: 250 mg/day increased weekly in 250 mg increments Final dose: 1250 mg/day	Topiramate 100 mg Starting dose: 25 mg/day increased weekly in 25 mg increments Final dose: 100 mg/day Topiramate 200 mg Starting dose: 25 mg/day increased weekly to 50, 100, 150, and 200 mg/day Final dose: 200 mg/day	6 months after the last patient was randomized

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Clemens, 2004 (N=20)	Prospective Observational Cross-over	Hungary	Unknown	Fair	Carbamazepine Average daily dose during baseline period: 1100 mg/day	Oxcarbazepine At the first evaluation after the baseline period, the patients took carbamazepine as in the baseline period. In the next week, 150 mg oxcarbazepine was substituted for every 100 mg carbamazepine, as proposed for patients with refractory seizures.	Unknown
Coppola, 2004 (N=38)	Randomized Open Label Parallel Group	Italy	Not Sponsored by any commercial organization	Fair	Valproic Acid Started at 10 mg/kg/day and increased by 5 mg/kg/day every 3 days until seizures were controlled or intolerable side effects occurred up to a maximum of 30 mg/kg/day given in three divided doses. Mean daily dose at 3 months: 22.6 mg/kg/day Mean daily dose at 12 months: 25.4 mg/kg/day	Lamotrigine Initial dosing: 0.5 mg/kg twice a day for 2 weeks followed by 1.0 mg/kg/day for an additional 2 days Thereafter doses were increased in 1 mg/kg/day increments every 5 days until seizures were controlled, intolerable adverse effects occurred or a maximum of 12 mg/kg/day had been reached Mean daily dose at 3 months: 6.5 mg/kg/day Mean daily dose at 12 months: 8.3 mg/kg/day	12 months
Fakhoury, 2004 (N=302)	Randomized Open-Label Parallel Group	United States	GlaxoSmithKline	Poor	Carbamazepine Determined by the clinician and intended to be consistent with dosing recommendations in the product label Valproic Acid Determined by the clinician and intended to be consistent with dosing recommendations in the product label	Lamotrigine Added to prestudy AED (carbamazepine or valproic acid) according to the dosing recommendations in the product label	28 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Wheless, 2004 (N=613)	Randomized Double Blind	Unknown	Johnson and Johnson Pharmaceutical Research & Development	Fair	Carbamazepine Starting dose 200 mg/day, increased 200 mg every 2 weeks to a total dose of 600 mg/day Valproic Acid Starting dose: 250 mg/day Dose increased weekly in 250mg increments to a total dose of 1250 mg/day	Topiramate 100 mg Starting dose: 25 mg/day Dose increased weekly in 25 mg increments Topiramate 200 mg Starting dose: 25 mg/day Dose increased weekly to 50, 100, 150 and 200 mg/day	Screening visit Titration phase- 35 days Stabilization – until patient exited or until 6 months after the last patient was enrolled. Study duration was up to 685 days. Mean duration of treatment was 307 days
Rowan, 2005 (N= 593)	Randomized Double Blind Double Dummy Parallel Group	United States	Study funding: Veteran Affairs cooperative study program Study medication provided by: GlaxoSmithKline Pfizer	Fair	Carbamazepine Target dose: 600 mg/day Titration: started at 200 mg/day and increased by 200 mg/day every 2 weeks to 600 mg/day to the target of 600 mg/day	Gabapentin Target dose: 1500 mg/day Titration: started at 300 mg/day and increased by 300 mg/day every 3 days to the target of 1500 mg/day Lamotrigine Target dose: 150 mg/day Titration: started at 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg/day for 1 week, followed by 150 mg/day	52 weeks
Sobaniec, 2005 (N= 54)	Prospective Observational	Poland	None specified	Fair	Carbamazepine 18 mg/kg every 12 hours	Vigabatrin 50 mg/kg every 12 hours	24 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Steinhoff, 2005 (N=269)	Randomized Open Label Parallel Group	Germany	GlaxoSmithKline	Good	<p>Carbamazepine Daily dose in adults: 200-400 mg/day Recommended maintenance dose in adults: 600-1200 mg/day Daily dose in patients between 11 and 15 years of age: 200-300 mg/day Recommended maintenance dose in children between 11 and 15 years of age: 600-1000 mg/day</p> <p>Valproic Acid Initial dose: 5-10 mg/kg/day Titration: increased every 4-7th day by approximately 5 mg/kg Recommended daily maintenance dose for children between 6 and 14 years of age or persons with a body weight between 20-40 kg: 600-1200 mg/day Recommended daily maintenance dose for adolescents from 14 years of age or older or persons with a body weight between 40-60 kg: 600-1500 mg Recommended daily maintenance dose for adults weighing at least 60 kg: 1200-2100 mg/day</p>	<p>Lamotrigine Week 1-2: 25 mg/day Week 3-4: 50 mg/day Week 5 and on: 100 mg/day or 50 mg twice a day Recommended maintenance dose: 100-200 mg/day The investigators were allowed to escalate the dose further for clinical reasons up to a maximum of 500 mg/day</p>	24 weeks
Babayigit, 2006 (N=68)	Retrospective Observational (Case Control)	Turkey	Unknown	Fair	<p>Carbamazepine 15-25 mg/kg/day</p> <p>Valproic Acid 15-40 mg/kg/day</p>	<p>Oxcarbazepine 15-30 mg/kg/day</p>	4 months

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Brodie, 2007 (N=576)	Randomized Double Blind Parallel Group	12 European Countries and South Africa	UCB Pharma	Good	Carbamazepine-Controlled Release Titration Period: 200 mg/day Dosing Level 1: 200 mg twice a day Patients experiencing a seizure during the first evaluation period had their dose increased over 2 weeks with intermediate daily doses of 600 mg Dosing Level 2: 400 mg twice a day Patients experiencing a seizure at dose level 2 progressed to dose level 2 with intermediate dosing of 600 mg twice a day Dosing Level 3: 1000 mg/day	Levetiracetam Titration Period: 500 mg/day Dosing Level 1: 500 mg twice a day Patients experiencing a seizure during the first eval period had their dose increased over 2 weeks with intermediate daily doses of 1500mg Dosing Level 2: 1000 mg twice a day Patients experiencing a seizure at dose level 2 progressed to dose level 3 with intermediate dosing of 1500 mg twice a day Dose Level 3: 2500 mg/day	Up to 1 year Patients achieving the primary endpoint (6-month seizure freedom) continued on treatment for a further 6-month maintenance period
Donati, 2007 (N=112)	Randomized Open-label Active-Control Three-Arm Parallel Group	7 European countries	Novartis	Poor	Carbamazepine Mean daily dose: 14.4 (3.6) mg/kg/day Valproic Acid Mean daily dose 20.7 (7.5) mg/kg/day	Oxcarbazepine Mean daily dose: 19.6 (6.4) mg/kg/day	6 months
Kang, 2007 (N=112)	Randomized Observer Blinded Open-label Parallel Group	Korea	Johnson & Johnson	Fair	Carbamazepine Initial dose: 10 mg/kg.day Titration dose: 20 mg/kg/day over 4 weeks Maximum dose: 30 mg/kg/day Average daily dose during maintenance phase: 3.4 (1.6) mg/kg/day	Topiramate Initial dose: 12.5 mg/day Titration dose: to at least 50 mg/day in patients < 30 kg and 75 mg/day in patients > 30 kg over 4 weeks Maximum dose: 4 mg/kg/day Average daily dose during maintenance phase: 21.6 (3.2) mg/kg/day	28 weeks
Kim, 2007 (N=33)	Prospective Observational	Korea	Unknown	Poor	Carbamazepine Dose not reported Valproic Acid Dose not reported	Lamotrigine Dose not reported	6 months

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Levisohn, 2007 (N= 28)	Randomized, Open Label Parallel Group	United States	Unknown	Poor	Valproic Acid Median daily dose: 750 mg/day	Topiramate Median daily dose: 250 mg/day	26 weeks
Marson, 2007 SANAD Arm A (N= 1721)	Randomized Open Label Parallel Group	United Kingdom	Health Technology Assessment Program GlaxoSmithKline Janssen-Cilag Novartis Pfizer Sanofi-Synthelabo Wellcome Trust	Fair	Carbamazepine Maintenance dose (above 16 years of age): 600 mg/day Maintenance dose (children under 16 years of age): 15-20 mg/kg/day	Lamotrigine Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mg/kg/day Gabapentin Maintenance dose (above 16 years of age): 1200 mg/day Maintenance dose (children under 16 years of age): 30-45 mg/kg/day Topiramate Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mg/kg/day Oxcarbazepine Maintenance dose (above 16 years of age): 900 mg/day Maintenance dose (children under 16 years of age): 15-30mg/kg/day	Primary outcome measures: 1.) time from randomization to treatment failure (stopping randomized drug because of inadequate seizure control, intolerable side-effects, or both; or the addition of other antiepileptic drugs, whichever was earliest) 2.) the time from randomization to a 1-year period of remission of seizures Secondary outcome measures: 1.) time from randomization to a first seizure 2.) time to achieve a 2-year period of remission of seizures

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Marson, 2007 SANAD Arm B (N= 716)	Randomized Open Label Parallel Group	United Kingdom	Health Technology Assessment Program GlaxoSmithKline Janssen-Cilag Novartis Pfizer Sanofi-Synthelabo Wellcome Trust	Fair	Valporic Acid Maintenance dose (above 16 years of age): 1000 mg/day Maintenance dose (children under 16 years of age): 20-30 mg/kg/day	Lamotrigine Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mg/kg/day Topiramate Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mg/kg/day	Primary outcome measures: 1.) time from randomization to treatment failure (stopping randomized drug because of inadequate seizure control, intolerable side-effects, or both; or the addition of other antiepileptic drugs, whichever was earliest) 2.) the time from randomization to a 1-year period of remission of seizures Secondary outcome measures: 1.) time from randomization to a first seizure 2.) time to achieve a 2-year period of remission of seizures

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Saetre, 2007 (N= 186)	Randomized Double Blind Double Dummy Parallel Group	Croatia Finland France Italy Norway	GlaxoSmithKline	Good	Carbamazepine Initial dose: 100 mg/day Maintenance dose: 400 mg/day Maximum dose: 2000 mg/day Titration: 100 mg/day for 2 weeks increased to 100 mg twice a day for 2 weeks, then increased to 200 mg twice a day up to a max of 1000 mg twice a day	Lamotrigine Initial dose: 25 mg/day Maintenance dose: 100 mg/day Maximum dose: 500 mg/day Titration: 25mg/day for 2 weeks increased to 25 mg twice a day for 2 weeks, then increased to 50 mg twice a day up to a max of 250 mg twice a day	40 weeks
Stephen, 2007 (N=225)	Randomized Open-label Parallel Group	United Kingdom	Unknown	Good	Valproic Acid Titration: Weeks 1-2: 500 mg/day Weeks 3-4: 500 mg twice daily Weeks 5-6: - Weeks 7-8: - Weeks 9-10: - Target dose: 1000 mg/day Dosage adjustments: 200-500 mg/day	Lamotrigine Titration: Weeks 1-2: 25 mg/day Weeks 3-4: 25 mg twice daily Weeks 5-6: 50mg twice daily Weeks 7-8: 50 mg/100 mg Weeks 9-10: 100 mg twice daily Target dose: 200 mg/day Dosage adjustments 25-50 mg/day	1 year
Morrell, 2008 (N=447)	Randomized Open label Parallel Group	Asia Europe North America South America	GlaxoSmithKline	Good	Valproic Acid Target maintenance dose: 1000 mg/day.	Lamotrigine The target maintenance dose was 100 to 200 mg/day with the dose not to exceed 500 mg/day. The target doses for lamotrigine added to enzyme-inducing AED and nonenzyme inducing AED were 200 to 400mg/day and 100 to 200mg/day, respectively	1 year
Pack, 2008 (N=93)	Prospective Observational Cross Sectional	United States	National Institute of Health GlaxoSmithKline	Poor	Carbamazepine Dose not specified Phenytoin Dose not specified Valproate Dose not specified	Lamotrigine Dose not specified	1 year

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Perry, 2008 (N=86)	Retrospective Observational Cohort study	United States	UCB, Inc	Fair	Carbamazepine Dose not specified	Levetiracetam Dose not specified	Mean duration of followup for the carbamazepine group in months: 33.5 (17.8) Meanduration of followup for the levetiracetam group in months: 23.1 (12.7)
Kim, 2009 (N=146)	Prospective Observational	Korea	Unknown	Poor	Carbamazepine Mean dose: 12.8 (3.2) mg/kg/day	Topiramate Mean dose: 4.9 (2.5) mg/kg/day	48 months
Kwan, 2009 (N= 81)	Randomized Open Label Parallel Group	China	Unknown	Poor	Valproic Acid Initial dose: 400 mg/day Maintenance dose: 800 mg/day Mean daily dose: 796 mg/day	Lamotrigine Starting dose: 25 mg/day Maintenance dose: 100 mg/day Mean daily dose: 108 mg/day	12 months
Ma, 2009 (N= 497)	Prospective Observational	China	Foundation	Fair	Carbamazepine Daily dose required by the majority of patients: 12.59 (4.76) mg/kg/day Valproic Acid Daily dose required by the majority of patients: 21.12 (6.74) mg/kg/day	Topiramate Daily dose required by the majority of patients: 4.68 (0.85) mg/kg/day	1 year
Glauser, 2010 (N= 451)	Randomized Double Blind Active Comparator	United States	Study Funding: National Institute of Health Medications provided by: Pfizer Abbott Laboratories GlaxoSmithKline	Good	Ethosuximide Mean dose 33.5 (15.3)mg/kg/day Valproic Acid Mean dose 34.9 (15.8)mg/kg/day	Lamotrigine Mean dose 9.7 (6.3) mg/kg/day	16 weeks

Table F-5. Study design and populations of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Followup
Helmstaedter, 2010 (N=222)	Prospective Observational Open-label Non-interventional Controlled Surveillance Study	Germany	Industry: UCB Pharma	Poor	Carbamazepine Choice of drug and dose was left to the doctors Mean dose at baseline: 717 ± 300 mg/day Mean dose at followup: 789 ± 357 mg/day	Levetiracetam Choice of drug and dose was left to the doctors Mean dose at baseline: 1261 ± 460 Mean dose at followup: 1311 ± 500	6 months
Ramsay, 2010 (N=261)	Randomized Double Blind Double Dummie Active Comparator	United States	Ortho-McNeil Janssen	Good	Phenytoin Initial target dose: 1000 mg, given as 3 divided doses on Day 1 (400, 300 and 300 mg, respectively, at 2-hour intervals) Maintenance Period: 300 mg/day	Topiramate Initial target dose: 100 mg/day, given as 3 divided doses on Day 1 (50, 25 and 25 mg, respectively, at 2-hour intervals) Maintenance Period: 50 mg twice a day	4 weeks

AED = antiepileptic drug; N = sample size

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Reinikainen, 1987 (N= 40)	Adult patients with chronic epilepsy on phenytoin monotherapy with unsatisfactory seizure control or unwanted effects entered the study	Pregnancy or a desire to become pregnant Organic heart disease, especially atrioventricular block, liver, kidney or thyroid dis, abnormally low leukocyte or platelet counts, inoperable tumours Known hypersensitivity to tricyclic antidepressants or carbamazepine, and uncooperative patients Also patients treated concomitantly with oral anticoagulants, propoxyphene and dextropropoxyphene, tetracycline, clofibrate, monoamine oxidase inhibitors and tricyclic antidepressants were excluded
Danner, 1988 (N=25)	Previously untreated newly diagnosed patients	Patients with other neurological disorders, neoplasms, diabetes, alcoholism, hepatic or renal diseases, or any other condition or medication which could interfere with neuronal function
Dam, 1989 (N=194)	Men or women aged 15-65 years, suffering from newly diagnosed and previously untreated epilepsy Only patients with primary generalized seizures (tonic-clonic seizures), and with partial seizures with or without secondary generalization, according to the International Classification of Epileptic Seizures	Women who were pregnant or trying to become pregnant Patients with known heart, liver, kidney and thyroid disorders Patients with abnormally low leukocyte and/or platelet counts, inoperable tumors or known hypersensitivity to CBZ or tricyclic antidepressants Patients who were being treated with drugs known to interact with CBZ were also excluded
Sachdeo, 1992 (N=44)	Men and women, aged 18yrs and older >90 lbs Patients with uncontrolled partial onset seizures classified according to the ICS EEG or video/telemetry consistent with partial onset seizures Current AED regimen consisting of one AED at therapeutic plasma levels, with a second permitted if the plasma level was sub-therapeutic 8 or more partial onset seizures during a 56-day baseline No evidence of progressive CNS lesions on CNS MRI or CT Awareness seizures Adequate birth control measures	Status epilepticus Poor compliance history Current benzodiazepine use Recent drug or alcohol abuse Significant medical illness Previous suicide attempts Included only if failed only 1 AED at clinically toxic doses

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Faught, 1993 (N=111)	<p>Patients with partial onset seizure with or without secondary generalization</p> <p>Seizures were classified according to the International Classification of Seizures</p> <p>During the 56-day baseline period, patients were required to have eight or more partial onset seizures, have no more than 20 consecutive seizure-free days, and take only one standard AED at a therapeutic level</p> <p>Second AED could be taken if the serum/plasma level was less than 50% of the accepted low for therapeutic range</p> <p>Abnormal EEG consistent with a seizure disorder, CT or MRI confirming the absence of a progressive lesion, weight more than 41 kg, an ECG without significant findings, and, if a female of childbearing potential, the use of an accepted method of birth control</p>	<p>Patients were excluded who had a history of status epilepticus in the previous 3 months while receiving an adequate dose of an AED, a treatable or progressive seizure etiology, a seizure pattern characterized by clusters, a history of benzodiazepine use on a regular basis, significant psychiatric disorders, serious medical conditions, poor compliance, drug or alcohol abuse within the previous year, or suicide attempts</p> <p>Patients who, by history, had taken more than one AED at clinically toxic dose without adequate seizure control were excluded</p>
Brodie, 1995 (N=260)	<p>Patients 13 years and older</p> <p>Newly diagnosed epilepsy</p> <p>Stratified according to type of seizures – partial seizures without secondary generalization, and primary or secondary generalized tonic-clonic seizures</p> <p>No patient had received previous treatment with antiepileptic drug</p>	-
Kalviainen, 1995 (N=100)	<p>A total of 100 patients aged 15 to 64 years who had had at least two unprovoked epileptic seizures during the previous 2 years or one seizure and distinct electroencephalographic changes indicative of epilepsy were included in the study</p>	<p>Patients with alcohol-related seizures, current alcohol or other drug abuse, progressive neurologic disorders, mental retardation, severe psychiatric problems, or other severe medical disorders were excluded from the study</p>
Sabers, 1995 (N= 52)	<p>Patients with newly diagnosed epilepsy and patients with epilepsy admitted as in- or out-patients to the University Clinic of Neurology, Hvidovre Hospital 1984-1988 who had been without any antiepileptic drug treatment for a period of at least 4 months</p>	<p>Patients were excluded if they had severe brain damage, any medical disease which may cause encephalopathy, progressive brain disorder, or were drug or alcohol abusers</p>
Reunanen, 1996 (N= 343)	<p>Patients (either sex) >12 years of age</p> <p>Confident diagnosis of newly diagnosed or recurrent epilepsy, with partial and/or generalised tonic-clonic seizures classifiable by the International Classification of Seizures</p> <p>Patients with current epilepsy were defined as those who had previous chronic treatment for epilepsy but no more than two doses of antiepileptic drug in the 6 months before inclusion</p> <p>At least two seizures in the previous 6 months, with at least one in the previous 3 months, but no more than 30 in any one of the preceding 6 months or a history of status epilepticus</p> <p>No antiepileptic medication in the 6 months prior to the trial other than 1 or 2 doses of acute treatment</p>	<p>Presence of other significant organic or psychiatric disease or abnormal laboratory values</p> <p>Abuse of any medication or substances, which might have interfered with the study objectives</p> <p>Pregnancy, lactation or exposure to risk of pregnancy</p>

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Tanganelli, 1996 (N= 51)	Age between 18 and 65 years At least two untreated and unprovoked seizures, complex partial (CP) type, with or without secondary generalization, in the previous 8 weeks (run-in)	History of alcohol or drug abuse Presence of a brain tumor or progressive neurological disease An IQ score < 90 Presence or history of psychiatric, cardiac, renal, hepatic or metabolic disease, pregnancy or the risk of pregnancy
Bill, 1997 (N=287)	Age: 16-65 years New onset epilepsy Partial seizures with or without secondary generalization Generalized tonic clonic seizures without partial onset A minimum of 2 seizures separated by 48 hours within the 6 months preceding entry No prior AED except for emergency treatment of seizures for a maximum of 3 weeks prior to entry	Pregnancy risk History of status epilepticus Sever psych illness or mental retardation Progressive neurologic disorder Alcoholism Drug abuse Any significant organic disease
Christie, 1997 (N=249)	Age: 15-65 years Newly diagnosed epilepsy with partial seizures with or without secondary generalization or generalized tonic-clonic seizures without partial onset Patients had to have a minimum of two seizures separated by at least 48 hours within the 6 months preceding trial entry No previous AED treatment was allowed except for emergency treatment of seizures for a maximum of 3 weeks prior to trial entry	Pregnancy or risk of becoming pregnant History of status epileptius Severe psychiatric illness Sever mental retardation Progressive neurologic disorder Alcoholism or drug abuse Significant organic disease
Guerreiro, 1997 (N=193)	Patients had to have a minimum of 2 seizures, separted by at least 48 hours, in the 6 months before entering the study No previous AED treatment was allowed except for emergency treatment of seizures for a mazimum of 3 weeks prior to trial enrolment	Pregnancy or risk of becoming pregnant, history of status epilepticus, severe psychiatric illness or sever mental retardation, progressive neurologic disorder, alcoholism or drug abuse, and any significant organic disease
Chadwick, 1998 (N=292)	Patients with newly diagnosed partial epilepsy who were AED therapy naïve or who had received fewer than 2 weeks of AED therapy, which was discontinued before study entry Patients were also accepted if they had a history of epilepsy in remission for at least 2 years without AED treatment but were experiencing a recurrence of seizures Within the 6 months before the start of study medication, eligible patients had to have had at least two unprovoked, reliably evaluated and classified partial seizures or generalized tonic-clonic seizures At least 12 years of age and weighed between 40 and 110 kg Women of childbearing potential were not lactating, had a reliable method of contraception during the study	Idiopathic generalized epilepsy defined as a family history of epilepsy, morning myoclonus, generalized tonic clonic seizures on awakening, or generalized spike or wave on EEG Patients were also excluded from the study if they had ever experienced status epilepticus, had pregressive encephalopathy or findings suggesting a progressive structural lesion in the CNS, had taken an investigational drug within the past 3 months, had a medical or psychiatric condition or disease that could affect the study outcome

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Brodie, 1999a (N=150)	Patients age 65 years and above with newly diagnosed epilepsy Each patient reported 2 or more seizures of any type during the previous year with at least once event during the past 6 months Standard ILAE definitions of idiopathic, symptomatic and cryptogenic epilepsies	-
Brodie, 1999b (N=215)	Patients between the ages of 12-75 years with simple or complex partial seizures with or without secondary generalization who were inadequately controlled on carbamazepine monotherapy Experienced a minimum of 1 seizure a month for the previous 6 months At least 6 seizures in the last 3 months Pre-study carbamazepine must have been at the highest tolerated dose within an effective concentration range (1-4 mg/l) measured at least twice during the preceding 6 months	Patients who failed to respond to carbamazepine due to poor tolerability
Chadwick, 1999 (N=457)	Newly diagnosed epilepsy Age: 16-25 years Experienced at least 2 seizures in the previous 12 months	Occurrence of generalized seizure types
Gobbi, 1999 (N=80)	All types of partial epilepsy (including idiopathic cases) with onset in infancy, childhood or adolescence; a history of at least three seizures after the onset of epilepsy; and no previous treatment with any other AED	Patients with known brain tumor; progressive disease; hepatic, renal, cardiac or gastrointestinal disease; psychiatric or behavioral disturbances Patients with infantile spasms were also excluded
Steiner, 1999 (N=181)	Patients aged 14-75 years were eligible after 2 or more such seizures in the previous 6 months and at least 1 in the previous 3 months	Patients with absence seizures Previous treatment for epilepsy with any AED Chronic medical disorders Severe mental subnormality Abuse of alcohol or other substances Pregnancy or risk of becoming pregnant Clinically significant abnormal labs Severe mental abnormalities

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Aldenkamp, 2000 (N=53)	<p>Patient with localization-related epilepsy with partial-onset seizures Aged 18-60 years Patients with minimum weight of 45 kg Steady state treatment with carbamazepine monotherapy for at least 28 days Epilepsy uncontrolled on carbamazepine or requiring another AED for other reasons</p>	<p>Evidence of progressive cerebral lesion, degenerative disorder, malignancy, or history of malignancy in the past 5 years Cognitive impairment that could either interfere with the cognitive testing procedure Females who do not practice reliable contraception Non-epileptic seizures Documented history with generalized status epilepticus in the past 3 months Unstable medical disease in the past 2 years including cardiovascular, hepatic, renal, gynecological, musculoskeletal, gastrointestinal, metabolic or endocrine disease History of alcohol or drug abuse, psychiatric disorder requiring electroconvulsive therapy or of major tranquilizers (neuroleptics, antidepressants, or monoamine oxidase inhibitors) in the past 6 months Patients who are schizophrenic or who have exhibited any psychotic symptoms, regular treatment with antihistamines, metoclopramide, central nervous system active compounds, or an experimental drug during the past 30 days Patient who have taken topiramate previously History of poor compliance with antiepileptic treatment or inability to maintain a seizure calendar History of nephrolithiasis and patients who have taken any medication associated with nephrolithiasis; and use of acetazolamide, zonisimide, triamterene, or vitamin C within the past month</p>
Gillham, 2000 (N=260)	<p>Patients 13 years and older Newly diagnosed epilepsy Stratified according to type of seizures – partial seizures without secondary generalization, and primary or secondary generalized tonic-clonic seizures No patient had received previous treatment with antiepileptic drug</p>	-

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Biton, 2001 (N=133)	Patients age >12 years with newly or previously diagnosed epilepsy and who were experiencing any seizure type classifiable by the International Classification of Seizures	Previous use for more than 90 days of lamotrigine, divalproex sodium, valproic acid, or gabapentin Current use of an AED unless the AED could be withdrawn safely before randomization of the patient Chronic use of any medication that could influence seizure control Any medical condition requiring corticosteroid therapy growth hormone or testosterone; any acute or progressive neurologic or severe psychiatric disease Adherence to the ketogenic diet Participation in a weight-change program or any medical condition associated with significant changes in body weight Pregnancy
Cramer, 2001 (N=349)	Patients taking carbamazepine monotherapy Patients were included if their seizures were poorly controlled with baseline AED as defined as four or more complex seizures per month	-
Kwan, 2001 (N=381)	The study included unselected patients in whom epilepsy was diagnosed and treatment was initiated at the Epilepsy Unit in the Western Infirmary in Glasgow, Scotland between 1 January 1984 and 31 December 1997 Only those who had never received AED therapy before were included in the analysis	-
Nieto-Barrera, 2001 (N=618)	Age of 2 yrs and greater Patients with newly diagnosed or with currently untreated partial epilepsy Seizures had to be easily recognised by the patients (or carer) and able to be classified by the International Classification of Seizures (1981) Patients had experienced at least 2 partial seizures in the 6 months preceding the study, with at least 1 partial seizure or at least one secondarily generalised tonic-clonic seizure in the preceding 3 months, and evidence of focal radiological or EEG abnormalities	-

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Sackellares, 2002 (N= 133)	<p>At least 12 years of age Diagnosed with epilepsy Experienced any seizure type classifiable by the International Classification of Seizures If female, had a negative urine or serum pregnancy test at screening and agreed to use acceptable contraceptive methods during the study or were incapable of bearing children</p>	<p>Previous use for more than 90 days of lamotrigine, divalproex sodium, valproic acid, or gabapentin Current use of an antiepileptic drug unless the drug could be withdrawn safely prior to randomization Use of any investigational drug within the previous 12 weeks Chronic use of any medication that could influence seizure control Any acute or progressive neurological or severe psychiatric disease Any medical condition associated with significant changes in body weight; adherence to the ketogenic diet; participation in a weight-change program Current or planned use of vagal stimulation to control seizures</p>
Biton, 2003 (N=38)	<p>Age ≥ 12 years Any type easily classifiable by the International Classification of Seizures Patients with new onset epilepsy or previously diagnosed epilepsy or who could safely be withdrawn from any concurrent antiepilepsy drug prior to randomization</p>	<p>Previous use of lamotrigine or valproate for more than a total of 90 days Any contraindication or history of significant side effects with their use; treatment with vagal nerve stimulation or chronic use of a med that could influence seizure control Current use of an AED unless the AED could be withdrawn safely before randomization Severe psychiatric disorder Acute or progressive neurologic disorder or severe mental abnormality rendering the patient unable to comply with study objectives Substance abuse Diseases requiring corticosteroid growth hormone or testosterone use Adherence to a ketogenic diet Participation in wt change program Medical conditions associated with weight change Use of an investigational drug 12 weeks prior to or during enrolment Any significant chronic renal hepatic or cardiac disease Substance abuse Pregnancy</p>

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Meador, 2003 (N= 76)	<p>Age: 16-55 years with an IQ \geq 70</p> <p>Have at least three partial-onset seizures during a 28-day baseline phase despite stable dosages of carbamazepine monotherapy (trough blood level, 7 to 13 g/mL)</p> <p>AED other than carbamazepine had to be discontinued 28 days before the baseline visit</p> <p>Women had to be incapable of bearing children or be practicing adequate birth control and have a negative pregnancy test within 2 weeks of entering the study</p> <p>Patients needed to have CT or MRI confirmed absence of progressive cerebral lesion</p>	<p>Nonepileptic seizures, treatable cause of seizures</p> <p>Progressive neurologic disorders; status epilepticus within past 3 months.</p> <p>History of major medical disease within past 2 years or malignancy within past 5 years</p> <p>History of alcohol or drug abuse during previous year</p> <p>History of psychiatric or mood disorder requiring electroconvulsive therapy, tranquilizers, antidepressants, or monoamine oxidase inhibitors; schizophrenia, other psychotic symptomatology, or suicide attempt; use of benzodiazepines, barbiturates, metoclopramide hydrochloride, or routine antihistamine</p> <p>History of nephrolithiasis. Patients using acetazolamide, zonisamide, or triamterene; vitamin C (1 g/d); chronic antacids or calcium supplements; or any medication associated with nephrolithiasis within the past month were excluded</p> <p>Schizophrenia, other psychotic symptoms, experimental drug or device within 1 month</p> <p>History of poor compliance with past AED therapy or inability to take medication or maintain seizure calendar independently or with assistance</p> <p>Patients previously treated with topiramate were also excluded</p>
Privitera, 2003 (N=613)	<p>Patients at least 6 years of age and weigh >30 kg</p> <p>Epilepsy diagnosed within the 3 months before study entry</p> <p>Never been treated for epilepsy or treated <6 weeks with no more than one AED if temporary or urgent AED use was necessary</p> <p>Females had to be incapable of bearing children or be practicing adequate birth control and have a negative pregnancy test within 1 week of entering the study</p> <p>The absence of a progressive cerebral lesion was confirmed by computed tomography or magnetic resonance imaging prior to study entry</p>	<p>Non-epileptic seizures or a treatable cause of seizures</p> <p>Progressive or degenerative disorder; significant history of unstable medical disease within previous 2 years or malignancy within previous 5 years; psychiatric or mood disorder requiring electroconvulsive or drug therapy within previous 6 months, suicide attempt, mental retardation or impairment; alcohol or drug abuse</p> <p>History of nephrolithiasis; clinically significant laboratory or electrocardiographic abnormalities; inability to take medication either independently or with assistance</p> <p>Treatment with an experimental drug or device within previous 30 days</p> <p>Treatment with benzodiazepines or barbiturates on more than an occasional basis</p> <p>Patients using acetazolamide, zonisamide, or triamterene within 1 month of study entry were excluded because of an increased possibility of renal stone formation</p>

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Clemens, 2004 (N=20)	Adult (>18 years) patients with partial epilepsy and presumably insufficient efficacy of carbamazepine monotherapy	Alcohol and drug abuse, pregnancy or breast feeding, non-compliance, any significant medical condition except epilepsy, which could interfere with the measurements or interpretation of the results.
Coppola, 2004 (N=38)	Age: 3-13 years Newly diagnosed typical absence seizures associated with generalized synchronous 3-Hz spike-and-wave activity lasting >3 seconds occurring spontaneously during one of two trials of 3-min hyperventilation with a 1- to 2- min rest between trials clearly observable signs of typical absence seizures (e.g. staring or impairment of consciousness) on the video record normal clinical neurologic and CT/MRI examination and informed consent by parents or caregivers.	Absences with marked eyelid or perioral myoclonus (eyelid or perioral myoclonia with absences) absences with marked limb and trunk rhythmic myoclonic jerks (myoclonic absence epilepsy) absences with single ictal myoclonic jerks of the limbs trunk or head absences with mild or not clinically detectable impairment of consciousness (e.g. juvenile myoclonic epilepsy) other types of epileptic seizures stimulus-sensitive absences: photosensitive pattern-sensitive self-induced pattern-sensitive irregular arrhythmic spike/multiple spike and slow-wave EEG discharges with marked variations of discharge frequency; central-temporal or occipital focal EEG discharges or abnormal background EEG activity; known or suspected brain lesion; progressive neurologic illness; psychiatric disorder requiring medication Chronic cardiovascular renal or hepatic disease and any disease that could interfere with drug absorption distribution metabolism or excretion; Long-term comedication with other drugs Suspected poor compliance.
Fakhoury, 2004 (N=302)	Patients ≥ 16 years of age diagnosed with epilepsy and experiencing any seizure type classifiable by the International League of Seizures were eligible for the study if they had been treated with one AED for a minimum of 4 weeks prior to screening and had experienced at least two seizures during the 8 weeks before screening Patients were determined by a clinician to be appropriate candidates for add-on therapy with lamotrigine, carbamazepine, or valproate and possible candidates for conversion to monotherapy with lamotrigine, carbamazepine, or valproate Females were eligible only if they had a negative urine or serum pregnancy test at screening and agreed to use acceptable contraceptive methods during the study or were incapable of bearing children	Patients were excluded if they were treated with more than one AED at screening or if they were being treated with phenobarbital or primidone that could not be withdrawn over an 8 week period.

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Wheless, 2004 (N=119)	<p>Children and adolescent (age 6 and up, ≥ 30 kg) Diagnosed epilepsy within 3 months before study enrollment Never treated for epilepsy, although temporary or emergency AED use for <6 wks was allowed, as was history of AED treatment for a self limiting condition such as febrile seizures Absence of progressive cerebral lesion confirmed by CT or MRI prior to study entry</p>	<p>Nonepileptic seizures or a treatable cause for seizures Progressive or degenerative disorder Significant history of unstable medical disease within the previous 2 years or malignancy within the previous 5 years Psychiatric or mood disorder requiring ECT or drug therapy within the previous 6 months Suicide attempt, mental retardation or impairment, alcohol or drug abuse Chronic treatment with benzodiazepines, treatment with experimental drug or device within the previous 30 days History of nephrolithiasis, clinically significant lab or ECG abnormalities, treatment with experimental medication/device within 30 days, patients using acetazolamide, zonisamide, triamterene within 1 month of study</p>
Sobaniec, 2005 (N= 54)	<p>Patients aged 2-17 years, with history of partial seizures with or without secondary generalization with at least two seizures in 6 months prior to entry into the study Patients on vigabrin or carbamazepine therapy Patients had to be physically healthy for their age, with no history of major chronic illness</p>	<p>Patients with chronic epilepsy Patients with a history of sensitivity or adverse reactions to vigabatin or carbamazepine Children with a significant history of heart disease, history of other neurological or psychiatric disorders Patients requiring concomitant medications which could interfere with patients' compliance or study conduct, i.e. sedatives, hypnotics, antidepressants, and neuroleptics Participation in a study with another experimental drug within 4 weeks prior to entering the study Patients with any disease of the gastrointestinal system, liver or kidneys, or abnormal condition which compromises a function of the systems and could result in a possibility of altered absorption, excessive Accumulation or impaired metabolism or excretion of the study drug. Clinically changed values of lab tests</p>
Steinhoff, 2005 (N=239)	<p>Patients 12 years of age and greater with newly diagnosed epilepsy Unequivocal diagnosis of ≥ 1 seizure and electroclinical or imaging features indicating the onset of an epilepsy syndrome requiring AED treatment</p>	<p>None specified</p>

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Rowan, 2005 (N= 593)	Untreated newly diagnosed patients with epileptic seizures and were untreated, treated only acutely (<4 weeks), or treated but with subtherapeutic levels A minimum of 1 seizure during the 3 months preceding enrollment was required	No restriction regarding concomitant diseases was imposed excepting those conditions likely to lead to a life expectancy of less than 12 months, progressive neurologic disease, or conditions that would significantly affect the response to treatment Patients on chronic AEDs Severe psychiatric conditions, current alcoholism, illicit drug use, or a history of noncompliance
Babayigit, 2006 (N=68)	Patients were chosen from normally active outpatients who had no other diseases	Excluded from the study were children who had used a different antiepileptic drug in the past, those with abnormal neurologic examination findings, with detected pathology in brain imaging techniques, as well as children who had motor-mental retardation and progressive brain disease, malnutrition, family history of osteoporosis, any disorder affecting growth and development, and additive medication usage that may affect bone metabolism
Brodie, 2007 (N=576)	Age: ≥ 16 years Newly Diagnosed Partial or Generalized seizures with clear focal origin Generalized Tonic-Clonic seizures without clear focal origin Experienced ≥ 2 unprovoked seizures separated by at least 48 hours during the past year with at least 1 seizure during the previous 3 months	Pseudoseizures Seizures occurring only in clusters Clinical ECG findings suggestive of idiopathic generalized-epilepsy
Donati, 2007 (N=112)	Previously untreated male or female patients aged 6 to <17 years with a history of at least two unprovoked partial seizures (including all seizure subtypes of simple and complex partial seizures and partial seizures evolving to secondarily generalized seizures) were included in the study	Patients with more than two secondarily generalized tonic-clonic seizures within the 3 months prior to randomisation were excluded In addition, patients were excluded if they had a history of clinically relevant psychiatric disorders, attention deficit disorder (minimal brain dysfunction in children), comorbid neurologic disease (other than epilepsy), or other diseases adversely affecting cognitive abilities
Kang, 2007 (N=112)	Patients 5-15 years old with normal intelligence that had at least two partial seizures during 6 months at baseline. Clinical and electroencephalography findings compatible with benign rolandic epilepsy in addition to at least one of the following: parent and/or patient wanted to take antiepileptic drugs; daytime seizures; at least 1 episode of a convulsive seizure during 6 months. Study entry required magnetic resonance imaging to confirm the absence of a progressive cerebral lesion.	Evidence of a progressive cerebral lesion or neurodegenerative metabolic disorder. Cognitive impairment that could interfere with the cognitive testing procedure History of psychiatric disorder requiring major tranquilizers in the past 6 months Regular treatment with antihistamines, central nervous system active compounds during the past 30 days History of poor compliance with antiepileptic treatment or inability to maintain a seizure calendar independently or with assistance History of nephrolithiasis and patients who had taken any medication associated with nephrolithiasis Patients previously treated with topiramate or carbamazepine

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Kim, 2007 (N=33)	Patients aged 18-50 years with newly diagnosed, drug-naïve, epilepsy	Patients with epilepsy were excluded if they had: (1) a history of taking antiepileptic or other medications that affect bone metabolism (e.g., steroids, diuretics, vitamin D, calcium supplements, bisphosphonates, calcitonin) (2) had any endocrine or medical disorders (e.g., hypothyroidism, renal diseases) (3) had a history of nutritional deficiency or excessive alcohol intake (more than five drinks per day for > 1 year) (4) had limitations in ambulation or daily physical activity (5) were pregnant or breastfeeding within the previous 6 months (6) were menopausal or on hormonal treatments (7) had any progressive neurological disorders other than epilepsy
Levisohn, 2007 (N= 28)	Adolescents/adults (12–65 years old, P25 kg) with a confirmed diagnosis of JME. Diagnostic criteria included myoclonic jerks, seizure onset at 8–26 years of age, and coexistent generalized tonic-clonic seizures with generalized epileptiform abnormalities on EEG consistent with JME Patients had to have active epilepsy in the form of myoclonus or P1 PGTCS in the 3 months before study entry Topiramate or valproate could be initiated as monotherapy or as an adjunct to another AED (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy Females of childbearing potential had to be premenarchal, physically incapable of bearing children, or practicing an acceptable method of contraception	Exclusion criteria included: Previous discontinuation of topiramate or valproate due to an adverse event, abnormal cranial CT or MRI scan Dementia or mental retardation Progressive myoclonic epilepsy Clinically unstable medical conditions History of nephrolithiasis SGOT and/or SGPT levels greater than two times the upper limit of the normal range Co-therapy with a carbonic anhydrase inhibitor or barbiturate AED Use of an experimental medication or device within 30 days of study entry.
Marson, 2007 SANAD Arm A (N= 1721)	Patients were included in arm A of SANAD if they had a history of two or more clinically definite unprovoked epileptic seizures in the previous year and if carbamazepine was deemed the better standard treatment option, compared with valproate, by the recruiting clinician This allocation allowed inclusion of patients with newly diagnosed epilepsy, patients who had failed treatment with previous monotherapy (as long as the drug failure did not include one of the drugs present in the randomisation), and patients who had entered a period of remission from seizures but had relapsed after withdrawal of treatment	Patients were excluded if: The clinician or patient felt that treatment was contraindicated All their seizures had been acute symptomatic seizures (including febrile seizures) They were aged 4 years or younger There was a history of progressive neurological disease

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Marson, 2007 SANAD Arm B (N= 716)	<p>Patients were included in arm B of SANAD if they had a history of two or more clinically definite unprovoked epileptic seizures in the previous year and if the recruiting seizures, and a history of epilepsy in a first-degree family member</p> <p>Clinicians were asked to identify seizures and epilepsy syndromes by International League Against Epilepsy classifications as far as was possible, at least to differentiate between partial onset (focal) or generalized onset seizures</p> <p>However, where there was uncertainty, patients were recorded as having unclassified convulsive or other unclassified seizures. Results of any electroencephalogram or brain imaging around the time of randomisation were recorded</p>	<p>Patients were excluded if:</p> <p>The clinician or patient felt that treatment was contraindicated</p> <p>All their seizures had been acute symptomatic seizures (including febrile seizures)</p> <p>They were aged 4 years or younger</p> <p>There was a history of progressive neurological disease</p>
Saetre, 2007 (N= 186)	<p>Age ≥ 65 years</p> <p>Newly diagnosed epilepsy, with a history of two or more recurrent unprovoked seizures either partial (with or without secondary generalization) or primarily generalized tonic– clonic, and at least one of the seizures during the previous 6 months</p> <p>Clinical indication to initiate AED treatment</p> <p>Life expectancy >1 year</p>	<p>A history of absence, tonic, atonic or myoclonic seizures</p> <p>Greater than >2-week intake of any AED in the previous 6 months, or any previous intake of carbamazepine or lamotrigine</p> <p>Treatment with any AED for five elimination half-lives in the period immediately preceding study entry</p> <p>Severe psychiatric disease or severe intellectual impairment</p> <p>Acute or chronic hepatic failure; Significant unpaired AV defect;</p> <p>Alcohol or substance abuse</p> <p>Abnormal blood or chemistry tests</p>
Stephen, 2007 (N=225)	<p>Age 13 yrs and over</p> <p>Newly diagnosed epilepsy</p> <p>A minimum of two unprovoked seizures (irrespective of seizure type), with at least one witnessed event, were required for inclusion, although individuals presenting with a single seizure and relevant underlying neuropathology could also be recruited</p>	<p>Pregnancy or planning to be pregnant</p> <p>Previous exposure to valproic acid or lamotrigine or who were taking warfarin, were specifically excluded</p>

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Morrell, 2008 (N=447)	<p>Females 13-40 years of age</p> <p>Seizure Classification:</p> <p>Confident diagnosis of epilepsy and seizures that could be recognized by the subject or a caregiver</p> <p>All subjects had either newly diagnosed/untreated epilepsy (ie, fewer than 2 weeks of prior antiepileptic drug treatment) or inadequately controlled epilepsy despite treatment with a single antiepileptic drug for at least 3 months</p> <p>Subjects treated for uncomplicated febrile seizures before age 7 were eligible to participate</p>	<p>Pregnant, less than 6 months postpartum, breast-feeding, or planning a pregnancy during the course of the study or within 3 weeks after the last dose of study drug</p> <p>BMI more than 35 kg/m²</p> <p>Previous treatment with lamotrigine, valproate, or felbamate</p> <p>Women chronically treated with any other medication (other than one chronic antiepileptic drug) known to influence seizure control</p> <p>For newly diagnosed/untreated subjects, treatment for up to 2 weeks with an antiepileptic drug other than lamotrigine, valproate, or felbamate was allowed before enrolment in the study; however, the antiepileptic drug was to be discontinued within 2 weeks after the initiation of study medication</p> <p>Medical conditions or past surgeries that could affect hormone levels or menstrual function (eg, oophorectomy, adrenal dysfunction, Cushing's syndrome, diabetes, thyroid dysfunction)</p> <p>Serious or unstable medical or psychological condition, a current history of alcohol or drug abuse, clinically significant impairment of renal or hepatic function, or use of any investigational drug within the 30 days before study enrolment</p> <p>Women taking hormone medications, abnormal labs (increased androgen levels or signs of decreased ovarian reserve)</p>
Pack, 2008 (N=93)	<p>Premenopausal women aged between 18 and 40 years with epilepsy and with normal menstrual cycles participated in the study</p> <p>All were receiving a single AED (carbamazepine, lamotrigine, phenytoin, or valproate) for at least 6 months before enrollment</p>	<p>Pregnant and postmenopausal women</p> <p>Impaired motor function, diseases that affect the skeleton (primary hyperparathyroidism, Paget disease, multiple myeloma)</p> <p>Patients on glucocorticoids and excessive doses of vitamin D or A</p>
Perry, 2008 (N=86)	<p>Patients were required to be less than 16 years of age at the time carbamazepine or levetiracetam was initiated as initial monotherapy for newly diagnosed partial epilepsy and to be followed clinically for at least 6 months</p>	<p>Patients were excluded if the diagnosis of nonepileptic events was confirmed by video-electroencephalography (EEG), or if the chart had been lost or destroyed</p>
Kim, 2009 (N=146)	<p>Children with epilepsy under the age of 2 treated at the pediatric neurology clinic in Kyungpook National University Hospital, Daegu, Korea</p>	-

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Kwan, 2009 (N= 81)	<p>Chinese patients with epilepsy aged between 18 and 55 years and not receiving AED therapy were recruited</p> <p>Patients had either newly diagnosed, untreated epilepsy or a recurrence of seizures after a period of remission with AED therapy completely withdrawn for at least a year</p> <p>Seizures and epilepsy syndromes were classified according to international guidelines</p> <p>Both male and premenopausal female patients were eligible for inclusion</p>	<p>Women were excluded if pregnant, breastfeeding, planning a pregnancy during the course of the study, diagnosed as having PCOS, oophorectomized, taking oral contraceptive pills or hormone replacement therapy, or postmenopausal</p> <p>Patients were also excluded if they had medical conditions or existing treatment that could affect hormone or insulin concentrations (e.g., diabetes mellitus, adrenal dysfunction, thyroid dysfunction, glucocorticoid therapy)</p>
Ma, 2009 (N= 497)	<p>Patients whose epilepsy was diagnosed and treated at the Neurology Department of the Beijing Children's Hospital between 1 January 2000 and 31 December 2004, with follow-up lasting through December 2007</p> <p>In all, 520 children who followed a treatment regimen for more than 1 year and who had not previously received antiepileptic drugs therapy were retrospectively studied</p>	-
Glauser, 2010 (N= 451)	<p>Children between 2.5 and 13 years of age were eligible to participate if they met the following criteria:</p> <p>Had childhood absence epilepsy of new onset that was clinically diagnosed according to the International League Against Epilepsy classification of epilepsy syndromes (including frequent clinical absence seizures and reported normal development)</p> <p>Had bilateral synchronous, symmetric spike waves (2.7 to 5 Hz) on a normal background with at least 1 electrographically recorded seizure lasting 3 seconds or more on a 1-hour, awake video EEG</p> <p>Weighed 10 kg or more</p> <p>Had a body-mass index below the 99th percentile</p> <p>Had a normal complete blood count and normal levels of serum alanine aminotransferase, serum aspartate aminotransferase, and bilirubin</p> <p>The girls had to be premenarchal</p>	<p>Children were ineligible if they met any of the following criteria:</p> <p>Had received antiseizure medication for more than 7 days before randomization</p> <p>Had a history of nonfebrile seizures other than absence seizures (e.g. afebrile generalized tonic-clonic or myoclonic seizures)</p> <p>Had a history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy (e.g., generalized tonic-clonic or myoclonic seizures)</p> <p>Had a history of a severe dermatologic reaction to any medication, or had a history of major psychiatric disease, autistic- spectrum disorder, or any clinically significant medical condition</p>
Helmstaedter, 2010 (N=222)	<p>In a multicenter setting, physicians were asked to prescribe either carbamazepine or levetiracetam to patients with newly diagnosed epilepsy or patients being considered for a drug change.</p> <p>Diagnosis of epilepsy, age >16, and cognitive assessment at baseline and at the 6-month followup.</p>	-

Table F-6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year (N)	Inclusion Criteria	Exclusion Criteria
Ramsay, 2010 (N=261)	12 to 65 years of age Weight ≥110 lbs 1 to 20 unprovoked complex partial or Primary/secondarily generalized tonic clonic seizures within the past 3 months seizures indicative of new-onset epilepsy or epilepsy relapse candidates for rapid initiation of AED therapy	AED use ≤30 days prior to randomization

AED = antiepileptic drugs; AV defect = atrioventricular defect; BMI = body mass index; CNS = central nervous system; CP = complex partial seizures; CT = x-ray computed tomography; ECG = electrocardiogram; ECT= electroconvulsive therapy; EEG = electroencephalography; ICS = International Classification of Epileptic Seizures; ILAE = International League Against Epilepsy; IQ = intelligence quotient; JME = juvenile myoclonic epilepsy; MRI = magnetic resonance imaging; N = sample size; - = not reported; PCOS = polycystic ovary disease; PE = partial epilepsy; SGTCS = partial generalized tonic clonic seizures; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B = Standard and New Antiepileptic Drugs Trial Arm B; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Table F-7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Mean Age (SD)	Male (%)	Mean Body Weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Danner 1988*	Carbamazepine	13	-	-	-	-	-	-	-	-
	Oxcarbazepine	12	-	-	-	-	-	-	-	-
Dam, 1989	Carbamazepine	100	-	51	68 (13)	-	-	-	-	-
	Oxcarbazepine	94	-	48	67 (13)	-	-	-	-	-
Faught, 1993	Valproate	55	34.5	36	72.2	85	9.09	-	-	5.45
	Felbamate	56	33.4	57	73.8	80	12.5	-	-	7.14
Brodie, 1995	Carbamazepine	129	-	45	-	-	-	-	-	-
	Lamotrigine	131	-	41	-	-	-	-	-	-
Kalviainen, 1995	Carbamazepine	50	37 (16)	48	-	-	-	-	-	-
	Vigabatrin	50	33 (16)	42	-	-	-	-	-	-
Sabers, 1995	Carbamazepine	11	32.5	72.7	-	-	-	-	-	-
	Valproic Acid	11	22.8	54.5	-	-	-	-	-	-
	Phenobarbital	9	31.1	66.7	-	-	-	-	-	-
	Phenytoin	11	36.8	72.7	-	-	-	-	-	-
	Oxcarbazepine	10	38.8	50	-	-	-	-	-	-
Tanganelli, 1996	Carbamazepine	25	34.8	60	-	-	-	-	-	-
	Vigabatrin	26	37.9	62	-	-	-	-	-	-
Reunanen, 1996	Carbamazepine	117		50	69	-	-	-	-	-
	Lamotrigine 100 mg	115	30	54	71	-	-	-	-	-
	Lamotrigine 200 mg	111	33	58	69	-	-	-	-	-
Bill, 1997	Phenytoin	144	26.6	64	64.9	47	16	-	-	37
	Oxcarbazepine	143	27.1	57	63.6	50	15	-	-	34
Christie, 1997	Valproic Acid	121	32.47 (-)	55.4	70.2 (-)	-	-	-	-	-
	Oxcarbazepine	128	32.45 (-)	46.9	69.9 (-)	-	-	-	-	-
Guerreiro, 1997	Pheynition	96	10.85	52	40.7	83	6.25	-	-	10.4
	Oxcarbazepine	97	10.22	47	36.4	82	11	-	-	6.19
Chadwick, 1998	Carbamazepine	74	34 (16.4)	44	-	-	-	-	-	-
	Gabapentin 300 mg	72	37 (17.3)	56	-	-	-	-	-	-
	Gabapentin 900 mg	72	34 (16.0)	49	-	-	-	-	-	-
	Gabapentin 1800 mg	74	37 (16.9)	55	-	-	-	-	-	-

Table F-7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Mean Body Weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Brodie, 1999a	Carbamazepine	48	76 (-)	58	68	-	-	-	-	-
	Lamotrigine	102	77 (-)	54	68	-	-	-	-	-
Brodie, 1999b	Valproic Acid	107	-	50.5		-	-	-	-	-
	Vigabatrin	108	-	48.1		-	-	-	-	-
Chadwick, 1999	Carbamazepine	226	36 (16)	54	-	-	-	-	-	-
	Vigabatrin	220	35 (15)	53	-	-	-	-	-	-
Gobbi, 1999	Carbamazepine	40	7.8	55	-	-	-	-	-	-
	Vigabatrin	40	7.5	45	-	-	-	-	-	-
Steiner, 1999	Phenytoin	95	-	57	-	-	-	-	-	-
	Lamotrigine	86	-	55	-	-	-	-	-	-
Aldenkamp, 2000	Valproic Acid	29	39.4 (11.4)	52	76.2 (18.0)	-	-	-	-	-
	Topiramate	24	34.7 (10.2)	63	75.9 (17.5)	-	-	-	-	-
Gillham, 2000	Carbamazepine	129	-	-	-	-	-	-	-	-
	Lamotrigine	131	-	-	-	-	-	-	-	-
Biton, 2001	Valproate	68	30.1 (14)	46	-	88	9	0	3	-
	Lamotrigine	65	34.5 (16)	42	-	86	8	3	3	-
Cramer, 2001	Carbamazepine	76	41 (-)	55	-	-	-	-	-	--
	Tiagabine	67	41 (-)	46	-	-	-	-	-	-
	Phenytoin	101	33 (-)	35	-	-	-	-	-	-
	Tiagabine	105	37 (-)	45	-	-	-	-	-	-
Kwan, 2001 [†]	Carbamazepine	212	35.2 (19.4)	51	-	-	-	-	-	-
	Sodium Valproate	101			-	-	-	-	-	-
	Lamotrigine	78			-	-	-	-	-	-
Nieto-Barrera, 2001	Carbamazepine	201	-	47	20	-	-	-	-	-
	Lamotrigine	417	-	47	19	-	-	-	-	-
Sackellares, 2002	Valproate	55	33.8 (12.4)	45	-	-	-	-	-	-
	Lamotrigine	53	39 (13.8)	42	-	-	-	-	-	-
Biton, 2003	Valproate	20	16.0 (3)	45	64 (16.8)	90	5	0	5	-
	Lamotrigine	18	16.2 (3)	33	64 (15.5)	89	0	11	0	-
Meador, 2003	Valproate	29	37	52	-	-	-	-	-	-
	Topiramate	34	41	35	-	-	-	-	-	-

Table F-7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Mean Body Weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Privitera, 2003	Carbamazepine	126	-	52	-	-	-	-	-	-
	Valproic Acid	78	-	44	-	-	-	-	-	-
	Topiramate 100 mg	210	-	55	-	-	-	-	-	-
	Topiramate 200 mg	199	-	55	-	-	-	-	-	-
Clemens, 2004	Carbamazepine	20	24	38	-	-	-	-	-	-
	Oxcarbazepine	20	24	38	-	-	-	-	-	-
Coppola, 2004	Valproic Acid	19	-	52.6	-	-	-	-	-	-
	Lamotrigine	19	-	36.8	-	-	-	-	-	-
Fakhoury, 2004	Carbamazepine	46	40.3 (12.9)	46	-	-	-	-	-	-
	Lamotrigine	98	41.0 (14.8)	41	-	-	-	-	-	-
	Valproic Acid	53	39.0 (12.7)	38	-	-	-	-	-	-
	Lamotrigine	105	38.3 (13.3)	44	-	-	-	-	-	-
Wheless, 2004	Carbamazepine	23	12	35	-	-	-	-	-	-
	Valproic Acid	19	13	42	-	-	-	-	-	-
	Topiramate 100 mg	38	13	59	-	-	-	-	-	-
	Topirate 200 mg	39	13	68	-	-	-	-	-	-
Rowan, 2005	Carbamazepine	198	71.9 (7.7)	93.8	-	67.2	26.3		2.5	Other: 4
	Gabapentin	195	72.9 (7.5)	96.7	-	70.3	22.6		5.1	Other: 2.1
	Lamotrigine	200	71.9 (7.4)	97.5	-	69.5	23.5		5.5	Other: 1.5
Steinhoff, 2005	Carbamazepine	88	43.1 (17.3)	61.4	-	-	-	-	-	-
	Lamotrigine	88	46.6 (18.8)	59.1	-	-	-	-	-	-
	Valproate	30	23.3 (10.7)	46.7	-	-	-	-	-	-
	Lamotrigine	33	22.3 (13.0)	39.4	-	-	-	-	-	-

Table F-7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Mean Body Weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Sobaniec, 2005	Carbamazepine	28	9.01 (3.20)	61	-	-	-	-	-	-
	Vigabratin	26	9.90 (2.30)	50	-	-	-	-	-	-
Babayigit, 2006	Carbamazepine	23	12.4 (3.93)	61	43.9 (15.51)	-	-	-	-	-
	Valproic Acid	31	11.18 (4.07)	4	38.15 (16.89)	-	-	-	-	-
	Oxcarbazepine	14	13.13 (3.17)	36	46.56 (13.65)	-	-	-	-	-
Brodie, 2007	Carbamazepine-Controlled Release	291	15.8	58.8	73.6 (15.2)	92.1	3.4	1.4	-	6.0
	Levetiracetam	285	16.6	51.2	73.7 (16.8)	91.9	1.8	0.4	-	3.1
Donati 2007	Carbamazepine	28	-	57.1	-	-	-	-	-	-
	Valproic Acid	29	-	48.3	-	-	-	-	-	-
	Oxcarbazepine	55	-	38.2	-	-	-	-	-	-
Kang, 2007	Carbamazepine	54	8.7 (2.0)	59	31.0 (33.7)	-	-	-	-	-
	Topiramate	58	8.7 (1.9)	55	30.6 (31.2)	-	-	-	-	-
Kim, 2007	Carbamazepine	10	25.9 (11.3)	80	-	-	-	-	-	-
	Valproic Acid	15	26.0 (11.0)	66	-	-	-	-	-	-
	Lamotrigine	8	24.1 (9.9)	25	-	-	-	-	-	-
Levisohn, 2007	Valproic Acid	9	-	46	-	-	-	-	-	-
	Topiramate	19	-	32	-	-	-	-	-	-
Marson 2007	Carbamazepine	378	39.2 (18.3)	55.0	-	-	-	-	-	-

Table F-7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Mean Body Weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
SANAD Arm	Gabapentin	377	37.8 (17.9)	54.9	-	-	-	-	-	-
	Lamotrigine	378	36.8 (18.3)	55.0	-	-	-	-	-	-
	Oxcarbazepine	210	40.1 (18.0)	52.9	-	-	-	-	-	-
	Topiramate	378	38.4 (18.6)	55.0	-	-	-	-	-	-
Marson 2007 SANAD Arm B	Valproic Acid	238	22.5 (14.5)	60.1	-	-	-	-	-	-
	Lamotrigine	239	22.8 (14.3)	59.4	-	-	-	-	-	-
	Topiramate	239	22.3 (13.3)	59.4	-	-	-	-	-	-
Saetre, 2007	Carbamazepine – Sustained Release	91	73.1 (5.5)	49	73.9 (12.7)	-	-	-	-	-
	Lamotrigine	93	74.3 (6.2)	62	71.3 (11.8)	-	-	-	-	-
Stephen, 2007	Valproic Acid	111	-	56	Male: 76.4 (14.6) Female: 63.6 (13.6)	-	-	-	-	-
	Lamotrigine	114	-	47	Male: 76.3 (18.7) Female: 66.7(12.6)	-	-	-	-	-
Morrell, 2008	Valproate	222	22.9 (7.3)	0	56.0 (11.6)	51	4	-	8	
	Lamotrigine	219	21.8 (6.3)	0	55.4 (11.0)	55	3	-	5	

Table F-7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Mean Body Weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Pack, 2008	Carbamazepine	41	34 (5)	0	66 (18)	76	-	-	-	-
	Valproate	14	30 (7)	0	66 (17)	67	-	-	-	-
	Phenytoin	15	33 (5)	0	70 (23)	47	-	-	-	-
	Lamotrigine	23	30 (6)	0	73 (17)	61	-	-	-	-
Perry, 2008	Carbamazepine	20	-	13	-	-	-	-	-	-
	Levetiracetam	66	-	48	-	-	-	-	-	-
Kim, 2009	Carbamazepine	105	8.4 (5.6) months	42.9	-	-	-	-	-	-
	Topiramate	41	(6.4) months	53.7	-	-	-	-	-	-
Kwan, 2009	Valproic Acid	44	Male: 30.9 Female: 36.9	50	-	-	-	-	-	-
	Lamotrigine	37	Male: 35.4 Female: 32.5	49	-	-	-	-	-	-
Ma, 2009 [‡]	Carbamazepine	120	6.8 (3.6)	-	-	-	-	-	-	-
	Valproic Acid	234		-	-	-	-	-	-	-
	Topiramate	143		-	-	-	-	-	-	-
Glauser, 2010	Valproic Acid	147	-	48	-	73	20	-	-	7
	Ethosuximide	155	-	42	-	71	21	-	-	8
	Lamotrigine	149	-	38	-	79	17	-	-	4
Helmstaedter, 2010	Carbamazepine	84	48.8 (18.3)	60	-	-	-	-	-	-
	Levetiracetam	138	47.3 (20.3)	51	-	-	-	-	-	-

Table F-7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Mean Age (SD)	Male (%)	Mean Body Weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Ramsay, 2010	Phenytoin	127	35.3 (15.5)	56.7	82.2 (19.0)	58.3	27.6	0.8	-	13.4
	Topiramate	132	33.2 (14.1)	40.2	83.5 (25.9)	68.2	22.7	0	-	9.1

- = not reported; N = sample size; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B = Standard and New Antiepileptic Drugs Trial Arm B; SD = standard deviation

*Age and % male are reported but can not be determined for each treatment group

† Mean age and % male is not reported for the individual drugs, but is reported for the total population

‡ For the whole population and not for individual treatment groups

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Reinikainen, 1987	Carbamazepine	18	-	-	-	-	-	39	-	-	-	22	-	Mixed: 22 Unclassifiable: 5 Simple/complex partial: 17
	Oxcarbazepine	16	-	-	-	-	-	25	-	-	-	38	-	Mixed: 31 Unclassifiable: 6 Simple/complex partial: 6
Danner, 1988	Carbamazepine	13	-	-	-	-	-	-	-	-	-	-	-	
	Oxcarbazepine	12	-	-	-	-	-	-	-	-	-	-	-	
Dam, 1989	Carbamazepine	100	-	-	-	-	-	-	-	-	-	-	-	
	Oxcarbazepine	94	-	-	-	-	-	-	-	-	-	-	-	
Sachdeo, 1992	Valproate	22	-	100	-	-	-	100	-	-	-	-	-	-
	Felbamate	22	-	100	-	-	-	100	-	-	-	-	-	-
Faught, 1993	Valproic Acid	55	-	-	-	-	Mean Baseline Seizure Frequency per 28 days: 21.3	86	-	-	-	25	-	
	Felbamate	56	-	-	-	-	Mean Baseline Seizure Frequency per 28 days: 12.4	68	-	-	-	32	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Brodie, 1995	Carbamazepine	129	100	-	-	-		57	-	-	-	48	-	
	Lamotrigine	131	100	-	-	-		56	-	-	-	46	-	
Kalviainen, 1995	Carbamazepine	50	-	-	-	-	-	22	-	8	2	-	-	
	Vigabatrin	50	-	-	-	-	-	20	-	8	8	-	-	
Reunanen, 1996	Carbamazepine	117	-	-	Mean age at first seizure: 28	-	-	-	-	-	-	-	-	-
	Lamotrigine 100 mg	115	-	-	Mean age at first seizure: 29	-	-	-	-	-	-	-	-	-
	Lamotrigine 200 mg	111	-	-	Mean age at first seizure: 26	-	-	-	-	-	-	-	-	-
Tanganelli, 1996	Carbamazepine	25	-	-	-	-	-	-	-	100	-	-	-	-
	Vigabatrin	26	-	-	-	-	-	-	-	100	-	-	-	-

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Bill, 1997	Phenytoin	144	-	-	-	Mean duration since onset of seizures in weeks: 89.4	Mean number of seizures at baseline: 20.0 Mean seizure frequency per week at baseline: 0.84	68.1	-	-	31.9	-	-	
	Oxcarbazepine	143	-	-	-	Mean duration since onset of seizures in weeks: 94.6	Mean number of seizures at baseline: 17.5 Mean seizure frequency per week at baseline: 0.98	58.7	-	-	40.6	-	-	No seizure type defined: 0.7
Christie, 1997	Valproic Acid	121	100	-	-	Mean duration in weeks since onset: 181	Mean seizure frequency per week at baseline: 1.09	64.5	-	-	35.5	-	-	
	Oxcarbazepine	128	122	-	-	Mean duration in weeks since onset: 178	Mean seizure frequency per week at baseline: 0.58	59.4	-	-	40.6	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Guerreiro, 1997	Pheynition	96	100	0	-	Mean number of weeks since onset of seizures: 37.7	-	81.3	-	-	17.7	-	-	No type indicated: 1
	Oxcarbazepine	97	100	0	-	Mean number of weeks since onset of seizures: 30.2	-	75.2	-	-	22.7	-	-	No type indicated: 2.1

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Chadwick, 1998	Carbamazepine	74	100	-	-	Mean duration of epilepsy in months: 1.3 (2.3)	-	-	43	43	50	23	-	
	Gabapentin 300 mg	72	100	-	-	Mean duration of epilepsy in months: 1.0 (2.2)	-	-	24	39	44	31	-	
	Gabapentin 900 mg	72	100	-	-	Mean duration of epilepsy in months: 0.6 (1.0)	-	-	29	44	53	19	-	
	Gabapentin 1800 mg	74	100	-	-	Mean duration of epilepsy in months: 1.5 (4.5)	-	-	36	46	55	15	-	
Brodie, 1999a	Carbamazepine	48	100	-	-	-	-	-	-	-	-	-	-	
	Lamotrigine	102	100	-	-	-	-	-	-	-	-	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Brodie, 1999b	Valproic Acid	107	-	100	-	-	Mean number of seizures at baseline per month: 6.9	-	-	-	-	-	-	-
	Vigabatrin	108	-	100	-	-	Mean number of seizures at baseline per month: 6.8	-	-	-	-	-	-	-
Chadwick, 1999	Carbamazepine	226	100	-	-	-	-	-	28	40	66	-	-	-
	Vigabatrin	220	100	-	-	-	-	-	34	42	63	-	-	-
Gobbi, 1999	Carbamazepine	40	-	-	-	-	-	33	50	43	-	18	-	-
	Vigabatrin	37	-	-	-	-	-	46	62	62	-	0	-	-
Steiner, 1999	Phenytoin	95	-	-	25	-	-	27	21	-	-	52	-	-
	Lamotrigine	86	-	-	25	-	-	28	23	-	-	49	-	-
Aldenkamp, 2000	Vaproic Acid	29	-	-	-	-	Median baseline seizure rate per month: 5.8	-	-	-	-	-	-	-
	Topiramate	24	-	-	-	-	Median baseline seizure rate per month: 5.9	-	-	-	-	-	-	-
Gillham, 2000	Carbamazepine	129	-	-	-	-	-	-	-	-	-	-	-	-
	Lamotrigine	131	-	-	-	-	-	-	-	-	-	-	-	-

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Biton, 2001	Valproate	68	35	-	26 (13) N=31	-	-	26		24		81		
	Lamotrigine	65	34	-	28 (16) N=34	-	-	28		26		77		
Cramer, 2001	Carbamazepine	76	0	100	-	Mean duration of epilepsy in years: 21	Mean number of complex partial seizures per month: 15 (30) n=76	-	-	100	-	-	-	
	Tiagabine	67	0	100	-	Mean duration of epilepsy in years: 23	Mean number of complex partial seizures per month: 29 (82) n=66	-	-	99	-	-	-	
	Phenytoin	101	0	100	-	Mean duration of epilepsy in years: 20	Mean number of complex partial seizures per month: 22 (66) N=100	-	-	100	-	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
	Tiagabine	105	0	100	-	Mean duration of epilepsy in years: 25	Mean number of complex partial seizures per month: 13 (28) N=104	-	-	100	-	-	-	
Kwan, 2001	Carbamazepine	212	100	-	-	-	-	-	-	-	-	-	-	
	Valproic Acid	101	100	0	-	-	-	-	-	-	-	-	-	
	Lamotrigine	78	100	0	-	-	-	-	-	-	-	-	-	
Nieto-Barrera, 2001	Carbamazepine	201	100	-	-	-	Mean number of seizures at baseline per month: 6.84	63	16	39	1	-	-	-
	Lamotrigine	417	100	-	-	-	Mean number of seizures at baseline per month: 10.07	55	21	44	1	-	-	-
Sackellares, 2002	Valproate	55	-	-	-	-	-	-	-	-	-	-	-	-
	Lamotrigine	53	-	-	-	-	-	-	-	-	-	-	-	-
Biton, 2003	Valproate	20	-	-	15.5 N=12	-	-	0	-	-	100	-	-	
	Lamotrigine	18	-	-	14.9 N=14	-	-	11	-	-	89	-	-	
Meador, 2003	Valproate	29	-	-	-	-	-	-	-	-	-	-	-	
	Topiramate	34	-	-	-	-	-	-	-	-	-	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Privitera, 2003	Carbamazepine	126	-	-	-	-	-	73	-	-	28	-	-	Unclassified: 1
	Valproic Acid	78	-	-	-	-	-	42	-	-	63	-	-	Unclassified: 1
	Topiramate 100 mg	210	-	-	-	-	-	64 ^{\$}	-	-	38 ^{\$}	-	-	Unclassified: 3
	Topiramate 200 mg	199	-	-	-	-	-	64 ^{\$}	-	-	38 ^{\$}	-	-	Unclassified: 3
Clemens, 2004	Carbamazepine	20	-	-	-	-	-	-	-	-	-	-	-	
	Oxcarbazepine	20	-	-	-	-	-	-	-	-	-	-	-	
Coppola, 2004	Valproic Acid	19	100	0	7.5	Mean duration of epilepsy in years: 6.9 months	-	-	-	-	-	-	100	
	Lamotrigine	19	100	0	7.5	Mean duration of epilepsy in years: 4.5 months	-	-	-	-	-	-	100	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Fakhoury, 2004	Carbamazepine	46	0	100	-	-	Mean number of seizures during the 2 months prior to screening: 17.7 (50.1)	30	33	70	-	-		
	Lamotrigine	98	0	100	-	-	Mean number of seizures during the 2 months prior to screening: 14.2 (37.6)	40	26	57	-	-		
	Valproic Acid	53	-	-	-	-	Mean number of seizures during the 2 months prior to screening: 8.3 (14.3)	-	28	72	36	-	-	
	Lamotrigine	105	-	-	-	-	Mean number of seizures during the 2 months prior to screening: 6.6 (11.0)	-	33	62	29	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Wheless, 2004	Carbamazepine	23	-	-	-	-	-	74	-	-	22			Unclassified: 0
	Valproate	19	-	-	-	-	-	32	-	-	74			Unclassified: 1
	Topiramate 100mg/day	38	-	-	-	-	-	57*	-	-	38*	-	-	Unclassified: 10*
	Topirarte 200mg/day	39	-	-	-	-	-	57 *	-	-	38*	-	-	Unclassified: 10*
Rowan, 2005	Carbamazepine	198	-	-	-	-		4.7	13.5	42.0	-	29.0	-	Generalized tonic clonic and partial: 10.9 Mixed partial: 4.7
	Gabapentin	195	-	-	-	-		6.8	11.5	42.2	-	22.4	-	Generalized tonic clonic and partial: 2 Mixed partial: 6.8
	Lamotrigine	200	-	-	-	-		4.1	14.3	45.4	-	24.5	-	Generalized tonic clonic and partial: 11.7 Mixed partial: 4.1
Sobaniec, 2005	Carbamazepine	28	-	-	-	-	-	71	4	25	-	-	-	
	Vigabratin	26	-	-	-	-	-	88	4	8	-	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Steinhoff, 2005	Carbamazepine	88	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 12.4 (27.3)	-	-	-	-	-	-	-
	Lamotrigine	88	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 12.9 (37.1)	-	-	-	-	-	-	-
	Valproate	30	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 23 (52.5)	-	-	-	-	-	-	-
	Lamotrigine	33	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 16.4 (43.6)	-	-	-	-	-	-	-

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Babayigit, 2006 ^f	Carbamazepine	23	-	-	-	-	-	42	-	-	58	-	-	
	Valproic Acid	31	-	-	-	-	-	42	-	-	39	-	-	
	Oxcarbazepine	14	-	-	-	-	-	42	-	-	58	-	-	
Brodie, 2007	Carbamazepine -Controlled Release	291	100	-	-	-	-	79.7	-	-	-	20.3	-	
	Levetiracetam	285	100	-	-	-	-	80	-	-	-	20	-	
Donati, 2007	Carbamazepine	28	0	100	-	-	-	57.1	32.1	60.7	-	-	-	
	Valproic Acid	29	0	100	-	-	-	37.9	41.4	57.1	-	-	-	
	Oxcarbazepine	55	0	100	-	-	-	56.4	41.8	41.8	-	-	-	
Kang, 2007	Carbamazepine	54	-	-	-	Mean time since first seizure in months: 7.9 (9.2)	-	-	-	-	-	-	-	-
	Topiramate	58	-	-	-	Mean time since first seizure in months: 8.4 (11.2)	-	-	-	-	-	-	-	-
Kim, 2007	Carbamazepine	10	100	0	-	-	-	70	-	-	30	-	-	
	Valproic Acid	15	100	0	-	-	-	33	-	-	66	-	-	
	Lamotrigine	8	100	0	-	-	-	25	-	-	75	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Levisohn, 2007	Valproic Acid	9	-	-	-	-	-	-	-	-	-	44	22	
	Topiramate	19	-	-	-	-	-	-	-	-	-	63	11	
Marson, 2007 SANAD Arm A	Carbamazepine	378	-	-	-	-	-	1.1	-	-	0.8	-	-	
	Gabapentin	377	-	-	-	-	-	1.3	-	-	0.8	-	-	
	Lamotrigine	378	-	-	-	-	-	1.6	-	-	1.1	-	-	
	Oxcarbazepine	210	-	-	-	-	-	1.4	-	-	2.4	-	-	
	Topiramate	378	-	-	-	-	-	1.6	-	-	1.9	-	-	
Marson, 2007 SANAD Arm B	Valproic Acid	238	-	-	18.3 (13.7)	-	-	0	-	-	64.7	-	-	
	Lamotrigine	239	-	-	17.5 (12.1)	-	-	0.4	-	-	60.7	-	-	
	Topiramate	239	-	-	17.6 (11.5)	-	-	0.8	-	-	63.5	-	-	
Saetre, 2007	Carbamazepine - Sustained Release	91	-	-	-	Mean time elapsed from diagnosis of epilepsy in months: 1.3 (4.2)	-	-	-	-	-	-	-	-
	Lamotrigine	93	-	-	-	Mean time elapsed from diagnosis of epilepsy in months: 1.3 (3.7)	-	-	-	-	-	-	-	-

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Stephen, 2007	Valproate	111	100	-	-	-	-	52 [‡]	-	-	-	21 [‡]	-	Juvenile myoclonic epilepsy: 0.08
	Lamotrigine	114	100	-	-	-	-	52 [‡]	-	-	-	21 [‡]	-	Juvenile myoclonic epilepsy: 0.08
Morrell, 2008	Valproate	222	85	15	Mean age at first seizure: 19.1 (8.2)	3.8 (5.7)	-	36	-	-	59	-	-	Both partial and generalized: 2
	Lamotrigine	219	80	20	Mean age at first seizure: 18.3 (7.4)	3.4 (5.3)	-	38	-	-	59	-	-	Both partial and generalized: 3
Pack, 2008	Carbamazepine	41	-	100	-	-	-	-	-	-	-	-	-	-
	Valproate	14	-	100	-	-	-	-	-	-	-	-	-	-
	Phenytoin	15	-	100	-	-	-	-	-	-	-	-	-	-
	Lamotrigine	23	-	100	-	-	-	-	-	-	-	-	-	-
Perry, 2008	Carbamazepine	20	-	-	-	-	-	-	-	-	-	-	-	-
	Levetiracetam	66	-	-	-	-	-	-	-	-	-	-	-	-
Kim, 2009	Carbamazepine	105	-	-	-	-	-	43.8	-	-	46.7	-	-	
	Topiramate	41	-	-	-	-	-	19.5	-	-	70.7	-	-	
Kwan, 2009	Valproic Acid	44	-	-	-	-	-	36	-	-	64	-	-	
	Lamotrigine	37	-	-	-	-	-	43	-	-	58	-	-	

Table F-8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	New Onset Epilepsy (%)	Chronic Epilepsy (%)	Mean age at Onset (SD)	Mean Epilepsy Duration (SD)	Mean Number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Glauser, 2010	Ethosuximide	155	100	-	-	-	-	-	-	-	-	-	100	
	Valproic Acid	147	100	-	-	-	-	-	-	-	-	-	100	
	Lamotrigine	149	100	-	-	-	-	-	-	-	-	-	100	
Helmstaedter, 2010	Carbamazepine	84	100	0	45.8 (19.2)	2.6 (7.4)	-	-	-	-	-	-	-	-
	Levetiracetam	138	100	0	46.1 (20.4)	1.1 (3.6)	-	-	-	-	-	-	-	-
Ramsay, 2010	Phenytoin	127	-	-	34.0 (16.4)	1.3 (4.9)	-	-	11.8	22.0	48.8	-	2.4	Myoclonic: 0.8
	Topiramate	132	-	-	31.3 (15.9)	1.8 (5.8)	-	-	6.8	28.8	38.6	-	3.8	Myoclonic: 2.3

*Values represent percentages of combined Topiramate 100 mg and Topiramate 200 mg groups

† Values represent percentages for all patients combined and not by treatment group

‡ Values represent percentages for all patients combined and not by treatment group

§ Values represent percentages of combined Topiramate 100 mg and Topiramate 200 mg group

- = not reported; N = sample size; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; Arm B = Standard and New Antiepileptic Drugs Trial Arm B

Table F-9. Prior or concurrent antiepileptic drug use in studies comparing newer versus older antiepileptic drugs

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Reinikainen, 1987 N= 40	Carbamazepine	18			100						
	Oxcarbazepine	16			100						
Danner, 1988	Carbamazepine	13	-	-	-	-	-	-	-	-	-
	Oxcarbazepine	12	-	-	-	-	-	-	-	-	-
Dam, 1989	Carbamazepine	100	-	-	-	-	-	-	-	-	-
	Oxcarbazepine	94	-	-	-	-	-	-	-	-	-
Sachedo, 1992	Valproic Acid	22	0	45	14	0.09	0			32	Primidone: 0
	Felbamate	22	0	36	0.05	0.05	0.05			45	
Faight, 1993	Valproate	55	-	-	-	-	-	-	-	-	-
	Felbamate	56	-	-	-	-	-	-	-	-	-
Brodie, 1995	Carbamazepine	129	100								
	Lamotrigine	131	100								
Kalviannen, 1995	Carbamazepine	50	100								
	Vigabatrin	50	100								
Sabers, 1995	Carbamazepine	11	100								
	Phenobarbital	9	100								
	Phenytoin	11	100								
	Valproic Acid	11	100								
	Oxcarbazepine	10	100								
Tanganelli, 1995	Carbamazepine		100								
	Vigabatrin		100								
Bill, 1997	Phenytoin	144	100	-	-	-	-	-	-	-	-
	Oxcarbazepine	143	100	-	-	-	-	-	-	-	-
Christie, 1997	Valproic Acid	121	-	-	-	-	-	-	-	-	-
	Oxcarbazepine	128	-	-	-	-	-	-	-	-	-
Chadwick, 1998	Carbamazepine	74	-	-	-	-	-	-	-	-	-
	Gabapentin 300 mg	72	-	-	-	-	-	-	-	-	-
	Gabapentin 900 mg	72	-	-	-	-	-	-	-	-	-
	Gabapentin 1800 mg	74	-	-	-	-	-	-	-	-	-
Brodie, 1999a	Carbamazepine	48	-	-	-	-	-	-	-	-	-
	Lamotrigine	102	-	-	-	-	-	-	-	-	-
Brodie, 1999b	Valproate	107		100							
	Vigabatrin	108		100							
Chadwick, 1999	Carbamazepine	226	100								
	Vigabatrin	220	100								

Table F-9. Prior or concurrent antiepileptic drug use in studies comparing newer versus older antiepileptic drugs (continued)

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Gobbi, 1999	Carbamazepine	40	100								
	Vigabatrin	40	100								
Steiner, 1999	Phenytoin		100								
	Lamotrigine		100								
Gillham, 2000	Carbamazepine	129	-	-	-	-	-	-	-	-	-
	Lamotrigine	131	-	-	-	-	-	-	-	-	-
Biton, 2001	Valproate	68	35	26	49	-	-	-	-	-	41
	Lamotrigine	65	34	15	48	-	-	-	-	-	29
Cramer, 2001	Carbamazepine	76			100						
	Tiagabine	67			100						
	Phenytoin	101		100							
	Tiagabine	105		100							
Kwan, 2001	Carbamazepine	212	100								
	Lamotrigine	78	100								
	Valproic Acid	101	100								
	Lamotrigine	78	100								
Nieto-Barrera, 2001	Carbamazepine	201	100	-	-	-	-	-	-	-	-
	Lamotrigine	417	100	-	-	-	-	-	-	-	-
Sackellares, 2002	Valproic Acid	55	-	-	-	-	-	-	-	-	-
	Lamotrigine	53	-	-	-	-	-	-	-	-	-
Biton, 2003	Valproate	20	50	5	25	10			6	-	-
	Lamotrigine	18	39	28	39	6	6	6		-	-
Meador, 2003	Valproic Acid	29	-	-	-	-	-	-	-	-	-
	Topiramate	34	-	-	-	-	-	-	-	-	-
Privitera, 2003	Carbamazepine	126	62	-	-	-	-	-	-	-	-
	Valproic Acid	78	59	-	-	-	-	-	-	-	-
	Topiramate 100 mg	210	58*	-	-	-	-	-	-	-	-
	Topiramate 200 mg	199	58*	-	-	-	-	-	-	-	-
Clemens, 2004	Carbamazepine	21		100							
	Oxcarbazepine	20		100							
Coppola, 2004	Valproic Acid	19	-	-	-	-	-	-	-	-	-
	Lamotrigine	19	-	-	-	-	-	-	-	-	-

Table F-9. Prior or concurrent antiepileptic drug use in studies comparing newer versus older antiepileptic drugs (continued)

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Fakhoury, 2004	Carbamazepine	46		2	48	37	4	7			Topiramate:2 Clonazepam: 0 Primidone: 0 Felbamate: 0 Mephytoin: 0
	Lamotrigine	98		0	39	46	3	7			Topiramate:3 Clonazepam:1 Primidone: 1 Felbamate: 0 Mephytoin: 0
	Valproic Acid	53		53	32	0	2	6			Topiramate: 2 Clonazepam: 2 Primidone: 2 Felbamate: 0 Mephytoin: 0
	Lamotrigine	105		56	29	0	4	7			Topiramate: 2 Clonazepam: 0 Primidone: 0 Felbamate: <1 Mephytoin: <1
Wheless, 2004	Carbamazepine	23	-	-	-	-	-	-	-	-	-
	Valproic Acid	19	-	-	-	-	-	-	-	-	-
	Topiramate 100 mg	38	-	-	-	-	-	-	-	-	-
	Topiramate 200 mg	39	-	-	-	-	-	-	-	-	-
Rowan, 2005	Carbamazepine	198	100								
	Gabapentin	195	100								
	Lamotrigine	200	100								
Sobianiec, 2005	Carbamazepine			100							
	Vigabatrin										Vigabatrin: 100
Steinhoff, 2005	Carbamazepine	88	-	-	-	-	-	-	-	-	-
	Lamotrigine	88	-	-	-	-	-	-	-	-	-
	Valproic Acid	33	-	-	-	-	-	-	-	-	-
	Lamotrigine	30	-	-	-	-	-	-	-	-	-

Table F-9. Prior or concurrent antiepileptic drug use in studies comparing newer versus older antiepileptic drugs (continued)

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Babayigit, 2006	Carbamazepine	23		100							
	Valproic Acid	31				100					
	Oxcarbazepine	14									Oxcarbazepine: 100
Brodie, 2007	Carbamazepine-Controlled Release	291	-	-	-	-	-	-	-	-	-
	Levetiracetam	288	-	-	-	-	-	-	-	-	-
Donati, 2007	Carbamazepine	28	100								
	Oxcarbazepine	55	100								
	Valproic Acid	29	100								
	Oxcarbazepine	55	100								
Kim, 2007	Carbamazepine	10	100								
	Valproic Acid	15	100								
	Lamotrigine	8	100								
Levisohn, 2007	Valproic Acid	9	44	0	22	11					Oxcarbazepine: 0 Lamotrigine: 11 Ethosuximide: 11
	Topiramate	19	63	16	5	5					Oxcarbazepine: 5 Lamotrigine: 5
Marson, 2007 SANAD Arm A	Carbamazepine	378	81.8								Monotherapy not optimally treated: 15.9
	Gabapentin	377	81.2								Monotherapy not optimally treated: 15.9
	Lamotrigine	378	81.5								Monotherapy not optimally treated: 16.1
	Oxcarbazepine	210	86.2								Monotherapy not optimally treated: 15.9
	Topiramate	378	81.5								Monotherapy not optimally treated: 11.9

Table F-9. Prior or concurrent antiepileptic drug use in studies comparing newer versus older antiepileptic drugs (continued)

Study, Year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Marson, 2007 SANAD Arm B	Valproic Acid	238	87.7								Monotherapy not optimally treated: 8.8
	Lamotrigine	239	87.9								Monotherapy not optimally treated: 8.0
	Topiramate	239	87.5								Monotherapy not optimally treated: 8.4
Saetre, 2007	Carbamazepine	92	-	-	-	-	-	-	-	-	-
	Lamotrigine	94	-	-	-	-	-	-	-	-	-
Stephen, 2007	Valproic Acid	111	-	-	-	-	-	-	-	-	-
	Lamotrigine	114	-	-	-	-	-	-	-	-	-
Morrell, 2008	Valproate	222	85	5	3	-	4	-	-	-	Other: 2
	Lamotrigine	219	80	8	4	-	4	-	-	-	Other: 5
Pack, 2008	Carbamazepine	41		100							
	Valproate	14				100					
	Pheytoin	15			100						
	Lamotrigine	23		100							
Perry, 2008	Carbamazepine	20	-	-	-	-	-	-	-	-	-
	Levetiracetam	66	-	-	-	-	-	-	-	-	-
Kim, 2009	Carbamazepine	105	-	-	-	-	-	-	-	-	-
	Topiramate	41	-	-	-	-	-	-	-	-	-
Ma, 2009	Carbamazepine	120	-	-	-	-	-	-	-	-	-
	Valproic Acid	234	-	-	-	-	-	-	-	-	-
	Topiramate	143	-	-	-	-	-	-	-	-	-
Glauser, 2010	Ethosuximide	155	-	-	-	-	-	-	-	-	-
	Valproic Acid	174	-	-	-	-	-	-	-	-	-
	Lamotrigine	149	-	-	-	-	-	-	-	-	-
Helmstaedter, 2010	Carbamazepine	84	100								
	Levetiracetam	138	100								
Ramsay 2010	Phenytoin	127	-	-	-	-	-	-	-	-	-
	Topiramate	132	-	-	-	-	-	-	-	-	-

*Values represent percentages of combined Topiramate 100 mg and Topiramate 200 mg groups

- = not reported; N = sample size; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; Arm B = Standard and New Antiepileptic Drugs Trial Arm B

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Appendix G. Additional Evidence Tables

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Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>							
Rascati, 200	Cases	991	-	-	-	-	-
	Controls	2973	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-
	Controls	1248	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-
	Controls	8847	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	537 of 2095 switched to generic and then back to brand (26.5%)
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	635 of 1963 switched to generic and then back to brand (31.1%)
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-

Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
<i>Carbamazepine</i>							
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	Seizure frequency: 6.1 (12.9)	6 patients	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		Seizure frequency: 4.9 (9.2)	6 patients	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	8 Patients	-	-	-
	Carbamazepine (Ethical Generics)		-	8 Patients	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	4 patients	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	2 patients	-	-	-

Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	18	Seizure frequency: 0.22 (0.20) per day	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		Seizure frequency: 0.25 (0.14) per day	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	198 events	-	-	-
	Carbamazepine Slow Release (Laakefarmos) Tablets		-	109 events	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	5 patients 10 events	-	-	-
	Carbamazepine (Central Poly) Tablets		-	2 patients 5 events	-	-	-
	Carbamazepine (Condrugs) Tablets		-	7 patients 14 events	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	3 patients 5 events	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	One patient*†			-
	Generic (Pharmachemie) Tablets	12	-				-
	Generic (Pharbita) Tablets	12	-				-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-

Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	20.8% of patients who switched to generic carbamazepine CR switched back to Tegretol CR.
	Carbamazepine CR (manufacturer not reported)						
Clobazam							
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	328
	Clobazam (manufacturers not reported)		-	-	-	-	
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	44.1% of patients who switched to generic clobazam switched back to Frisium
	Clobazam (manufacturer not reported)						
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	30.9% of patients who switch to generic gabapentin switched back to Neurontin
	Gabapentin (manufacturer not reported)						
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	149
	Lamotrigine (manufacturers not reported)						

Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	Of the 187 patients on Lamictal who switched to generic, 51 (27.5%) switched back to brand.
	Lamotrigine (manufacturer(s) not reported)						
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>							
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-

Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	There was no statistically significant difference in seizure frequencies	43 events	-	-	-
	Phenytoin (Boots) tablets			30 events	-	-	-
	Phenytoin (Evans) tablets			60 events	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	5 patients 13 events	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	-	2 patients 22 events	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	2 patients 45 events	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	2 patients 3 events	-	-	-
Mikati 1992 ^a	Dilantin (Parke-Davis) capsules	10	"The number of patients and their low seizure frequency do not allow for any meaningful comparison of efficacy"	-	-	-	-
	Phenytoin (Phenytext, manufacturer not reported) capsules			-	-	-	-

Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
Soryal, 1992 ^a	Epanutin (Parke-Davis) capsules	14	No statistically significant differences were found in seizure frequency between the formulations	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (Regent) tablets		-	-	-	-	-
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	12.5%
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	12.5%
Paradis 2009 ^a	Topamax (Ortho-McNeil)	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-

Table G-1. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency, Mean (SD)	Breakthrough Seizures, Patients (n) and Events (n)	Status Epilepticus, Events (n)	Dose Required for Efficacy, Mean (SD)	Switchback, Events (n)
Valproic Acid							
Vadney, 1997	Depakene (Abbott)	64	There was no significant difference in the mean number of seizures on either Depakene (50.89, n=64) or valproic acid (49.83, n=64), p=0.89. 31 patients had no seizures throughout the study. 10 patients had an equal number of seizures on both Depakene and valproic acid. Of the 23 patients with uncontrolled epilepsy, there was no change in seizure patterns based on monthly seizure counts between one year prior and one year after the study	11 patients had more seizures on Depakene than valproic acid	-	-	-
	Valproic acid (Solvay)			12 patients had more seizures on valproic acid than Depakene	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	422
	Valproic Acid (manufacturers not reported)		-	-	-	-	

^aReports on same database as Duh 2009

^{*}Whether patient was receiving innovator or generic at time was not reported

[†]Two events during brand CBZ phase

- = not reported; event (n) = number of events; N = sample size; patients (n) = number of patients with event

Table G-2. Withdrawals and discontinuations in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Overall Withdrawals or Discontinuations (n)	Withdrawals Due To Ineffective Treatment (n)	Withdrawals Due To ADRs (n)	ADRs Contributing to Withdrawals (List, % of Patients)
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>						
Rascati, 2009	Cases	991	-	-	-	-
	Controls	2973	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-
	Controls	1248	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-
	Controls	8847	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-
<i>Carbamazepine</i>						
Kauko; 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	0	0	0	0
	Carbamazepine (AWD Dresden) Tablets		0	0	0	0

Table G-2. Withdrawals and discontinuations in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Overall Withdrawals or Discontinuations (n)	Withdrawals Due To Ineffective Treatment (n)	Withdrawals Due To ADRs (n)	ADRs Contributing to Withdrawals (List, % of Patients)
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	0	0	0	0
	Generic Carbamazepine (Parke Davis) Tablets		0	0	0	0
Hartley, 1990	Tegretol (Ciba-Geigy)	23	1	0	1	100 – macular rash
	Carbamazepine (Ethical Generics)		0	0	0	0
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	0	0	0	-
	Carbamazepine (Ethical Generics) Tablets		0	0	0	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	2	1	1	5
	Carbamazepine (Lemmon Co) Tablets		0	0	0	0
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	2	2	0	0
	Carbamazepine (Lemmon Co) Tablets		3	2	1	0
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	0	0	0	0
	Carbamazepine (Laakefarmos) Tablets		0	0	0	0
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	0	0	0	0
	Generic (Pharmachemie) Tablets	12	0	0	0	0
	Generic (Pharbita) Tablets	12	0	0	0	0

Table G-2. Withdrawals and discontinuations in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Overall Withdrawals or Discontinuations (n)	Withdrawals Due To Ineffective Treatment (n)	Withdrawals Due To ADRs (n)	ADRs Contributing to Withdrawals (List, % of Patients)
Garnett, 2005	Tegretol (Novartis) Tablets	275	157	-	-	-
	Generic (Various/Unspecified) Tablets	705	469	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-
<i>Clobazam</i>						
Andermann 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-
<i>Gabapentin</i>						
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-
<i>Lamotrigine</i>						
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-
LeLorier, 2008	Lamictal (GlaxoSmithKline)	671	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-

Table G-2. Withdrawals and discontinuations in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Overall Withdrawals or Discontinuations (n)	Withdrawals Due To Ineffective Treatment (n)	Withdrawals Due To ADRs (n)	ADRs Contributing to Withdrawals (List, % of Patients)
Nielsen, 2008a	Lamictal	9	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-
<i>Levetiracetam Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>						
Lund, 1974	Epanutin (Parke-Davis) capsules	9	0	0	0	0
	Phenytoin sodium (Leo) capsules		0	0	0	0
Chen, 1982	Epanutin (Parke-Davis) capsules	20	2*	0	0	0
	Phenytoin sodium (Boots) tablets					
	Phenytoin sodium (Cox) tablets					
	Phenytoin sodium (Kerfoot) tablets					
	Phenytoin sodium (McCarthy UK) tablets					
Hodges, 1986	Phenytoin (Parke-Davis) capsules	30	11*	-	-	-
	Phenytoin (Boots) tablets					
	Phenytoin (Evans) tablets					
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	0	0	0	0
	Phenytoin (Epsolin, Cadila) tablets	15	0	0	0	0
	Phenytoin (Eptoin, Boots India) tablets	15	0	0	0	0
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	0	0	0	0
Mikati 1992 ^a	Dilantin (Parke-Davis) capsules	10	2 Brand 2 Generic †	1 Brand 2 Generic	1 Brand 0 Generic	Allergic rash (100%) in Brand 0% in generic
	Phenytoin (Phenytext, manufacturer not reported) capsules					

Table G-2. Withdrawals and discontinuations in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Overall Withdrawals or Discontinuations (n)	Withdrawals Due To Ineffective Treatment (n)	Withdrawals Due To ADRs (n)	ADRs Contributing to Withdrawals (List, % of Patients)
Soryal, 1992 ^a	Epanutin (Parke-Davis) capsules	17	3*	0	0	0
	Phenytoin sodium (Evans) tablets					
	Phenytoin sodium (APS) tablets					
	Phenytoin sodium (Cox) tablets					
	Phenytoin sodium (Kerfoot) tablets					
	Phenytoin sodium (Regent) tablets					
Topiramate						
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-
Paradis, 2009 ^a	Topamax (Ortho-McNeil)	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-
Valproic Acid						
Vadney, 1997	Depakene (Abbott)	72	8†	-	-	-
	Valproic acid (Solvay)					
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-

^aReports on same database as Duh 2009

*Overall result of all the groups combined, results not given separately

† Overall only 3 patients did not complete 6 months of study, but 1 patient did not finish either of the two groups

‡ Overall results of 2 groups combined. Results not given separately

- = not reported; N = sample size; n = number of patients who withdrew

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>									
Rascati, 2009	Cases	991	-	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-	-	-
	Controls	8847	-	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	11.86 events/person-years	0.15 events/person-years	1.02 days/event	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	14.26 events/person-years (unadjusted rate ratio with 95% CI = 1.20 (1.19-1.21); adjusted rate ratio (1.20 (1.19-1.21))	0.20 events/person-years (unadjusted rate ratio with 95% CI = 1.35 (1.27-1.43); adjusted rate ratio (1.31 (1.24-1.40))	1.38 days/events (unadjusted rate ratio with 95% CI = 1.36 (1.33-1.39); adjusted rate ratio (1.33 (1.30-1.36))	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	23.33 events/person-years	0.34 events/person-years	2.33 days/event	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	28.36 events/person-years (unadjusted rate ratio with 95% CI = 1.22 (1.21-1.22); adjusted rate ratio (1.16 (1.16-1.17))	0.47 events/person-years (unadjusted rate ratio with 95% CI = 1.38 (1.32-1.43); adjusted rate ratio (1.30 (1.25-1.36))	3.29 days/event (unadjusted rate ratio with 95% CI = 1.41 (1.39-1.43); adjusted rate ratio (1.34 (1.32-1.36))	-	-	-
Carbamazepine									
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	0	-	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		0	-	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	0	-	-	-	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		0	-	-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	0	-	-	-	-	-	-
	Carbamazepine (Ethical Generics)		0	-	-	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	0	-	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		0	-	-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	0	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		0	-	-	-	-	-	-
Oles 1992b	Tegretol (Ciba-Geigy) Tablets	20	0	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		0	-	-	-	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	21	0	-	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		0	-	-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	0	-	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	0	-	-	-	-	-	-
	Generic (Pharbita) Tablets	12	0	-	-	-	-	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-	-
<i>Clobazam</i>									
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-	-	-
<i>Gabapentin</i>									
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
<i>Lamotrigine</i>									
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	449	-	8.24 visits per patient per year	0.49 visits per patient per year	3.29 days per patient per year	-	-	-
	Lamotrigine (manufacturer(s) not reported)	222	-	9.25 visits per patient per year	0.56 visits per patient per year	4.86 days per patient per year	-	-	-
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-	-	-
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>									
Lund, 1974	Epanutin (Parke-Davis) capsules	9	0	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		0	-	-	-	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
Chen, 1982	Epanutin (Parke-Davis) capsules	18	0	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablet		0	-	-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		0	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	0	-	-	-	-	-	-
	Phenytoin (Boots) tablets		0	-	-	-	-	-	-
	Phenytoin (Evans) tablets		0	-	-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	0	-	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	0	-	-	-	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	0	-	-	-	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	0	-	-	-	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
Mikati 1992 ^a	Dilantin (Parke-Davis) capsules	10	0	-	-	-	-	-	-
	Phenytoin (Phenytek, manufacturer not reported) capsules		0	-	-	-	-	-	-
Soryal 1992 ^a	Epanutin (Parke-Davis) capsules	14	0	-	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (APS) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Regent) tablets		0	-	-	-	-	-	-
Topiramate									
Duh, 2009	Topamax (Ortho-McNeil)	875	-	9.07 outpatient visits/person-year	0.48 events/person-year	2.55 days	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	9.48 outpatient visits/person-year	0.52 events/person-year	3.22 days	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	8.74 outpatient visits/person-year	0.83 events/person-year	3.88 days	-	-	-

Table G-3. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Deaths	Office/ER Visits (n)	Hospitalizations, Events (n)	Hospital Duration, Mean (SD)	Composite of Ambulance/ER/ Hospitalizations, Events (n)	Loss of Drivers License, Events (n)	Loss of Employment, Events (n)
Paradis, 2009 ^b	Topamax (Ortho-McNeil)	-	-	9.0 outpatient visits/person-year	0.5 events/person-year	2.4 days	-	-	-
	Topiramate (Various manufacturers)	-	-	9.1 outpatient visits/person-year	0.6 events/person-year	3.1 days	-	-	-
Valproic Acid									
Vadney, 1997	Depakene (Abbott)	64	0	-	-	-	-	-	-
	Valproic acid (Solvay)		0	-	-	-	-	-	-
Andermann, 2007 ^c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-	-

^aCrossover study

^bReports on same database as Duh 2009

- = not reported; N = sample size; n = number of events; SD = standard deviation

Table G-4. Secondary seizure injury in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Type of Injury	Events (n)
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>				
Rascati, 2009	Cases	991	-	-
	Controls	2973	-	-
Zachry, 2009	Cases	416	-	-
	Controls	1248	-	-
Devine, 2010	Cases	2949	-	-
	Controls	8847	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-
<i>Carbamazepine</i>				
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-

Table G-4. Secondary seizure injury in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Type of Injury	Events (n)
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	-
	Carbamazepine (Ethical Generics)		-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-
Oles 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	21	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-
	Carbamazepine (Central Poly) Tablets		-	-
	Carbamazepine (Condrugs) Tablets		-	-
	Carbamazepine (Pharmaland) Tablets		-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-
	Generic (Pharmachemie) Tablets	12	-	-
	Generic (Pharbita) Tablets	12	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-
	Generic (Various/Unspecified) Tablets	705	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-
	Carbamazepine CR (manufacturer not reported)		-	-
Clobazam				
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-
	Clobazam (manufacturers not reported)		-	-

Table G-4. Secondary seizure injury in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Type of Injury	Events (n)
LeLorier 2008b	Frisium (manufacturer not reported)	1060	-	-
	Clobazam (manufacturer not reported)		-	-
<i>Gabapentin</i>				
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-
	Gabapentin (manufacturer not reported)		-	-
<i>Lamotrigine</i>				
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-
	Lamotrigine (manufacturers not reported)		-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone Phenytoin</i>				
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-
	Phenytoin sodium (Leo) capsules		-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-
	Phenytoin sodium (Boots) tablets		-	-
	Phenytoin sodium (Cox) tablets		-	-
	Phenytoin sodium (Kerfoot) tablets		-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-

Table G-4. Secondary seizure injury in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Type of Injury	Events (n)
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-
	Phenytoin (Boots) tablets		-	-
	Phenytoin (Evans) tablets		-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	-
Mikati, 1992a	Dilantin (Parke-Davis) capsules	10	-	-
	Phenytoin (Phenytext, manufacturer not reported) capsules		-	-
Soryal, 1992 ^a	Epanutin (Parke-Davis) capsules	14	-	-
	Phenytoin sodium (Evans) tablets		-	-
	Phenytoin sodium (APS) tablets		-	-
	Phenytoin sodium (Cox) tablets		-	-
	Phenytoin sodium (Kerfoot) tablets		-	-
	Phenytoin sodium (Regent) tablets		-	-
Topiramate				
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-

Table G-4. Secondary seizure injury in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Type of Injury	Events (n)
Paradis, 2009 ^b	Topamax (Ortho-McNeil)	-	-	-
	Topiramate (Various manufacturers)	-	-	-
<i>Valproic Acid</i>				
Vadney, 1997	Depakene (Abbott)	64	-	-
	Valproic acid (Solvay)		-	-
Andermann, 2007 ^c	Depakene (manufacturer not reported)	2017	-	-
	Valproic Acid (manufacturers not reported)		-	-

- = not reported; N = sample size; n = number of events

^aCrossover Study

^bReports on same database as Duh 2009

Table G-5. Change from baseline in health-related quality of life in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3
Unspecified Innovator and Brand Antiepileptic Drug Products							
Rascati, 2009	Cases	991	-	-	-	-	-
	Controls	2973	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-
	Controls	1248	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-
	Controls	8847	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Carbamazepine							
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	-	-	-	-
	Carbamazepine (Ethical Generics)		-	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	21	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-

Table G-5. Change from baseline in health-related quality of life in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	-	-	-	-	-
	Generic (Pharbita) Tablets	12	-	-	-	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-
Clobazam							
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-
Nielsen, 2008a	Lamictal	9	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin							
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-

Table G-5. Change from baseline in health-related quality of life in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3
Kishore, 1986	Phenytoin (Boots) tablets		-	-	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-
	Dilantin (Parke-Davis, India) capsules	15					
	Phenytoin (Epsolin, Cadila) tablets	15					
	Phenytoin (Eptoin, Boots India) tablets	15					
Mikati, 1992	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15					
	Dilantin (Parke-Davis) capsules	10	-	-	-	-	-
Soryal, 1992	Phenytoin (Phenytext, manufacturer not reported) capsules		-	-	-	-	-
	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-
Paradis 2009 ^b	Topamax (Ortho-McNeil)	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-
Valproic Acid							
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-

- = not reported; N = sample size

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>								
Rascati, 2009	Cases	991	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-	-
	Controls	8847	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
Carbamazepine								
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	6.18 (2.21)	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	5.57 (1.61)	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	5.43 (2.06)	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	4.89 (1.87)	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	7.1 (1.9)	154.8 (41.9)	-	47.6 (16.5)
	Carbamazepine (AWD Dresden) Tablets		-	-	7.0 (1.1)	153.5 (24.9)	-	63.0 (12.0)
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	10.1 (4.0) mcg/mL	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-	9.6 (3.6) mcg/mL	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	22	9.46 (1.78)	5.75 (1.37)	-	-	-	-
	Carbamazepine (Ethical Generics)		9.50 (2.17)	5.83 (1.64)	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	10.2 (1.8) mcg/mL	-	8.20 (1.46) mcg/mL	98.9 (17.0) mcg/mL	3.6 (0.5) h	-
	Carbamazepine (Ethical Generics) Tablets		9.91 (2.31) mcg/mL	-	8.12 (2.12) mcg/mL	97.4 (25.4) mcg/mL	3.1 (0.7) h	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	19	9.8 (2.1)	-	-	54.9 (11.7)	3.5 (1.6)	-
	Carbamazepine (Lemmon Co) Tablets		10.0 (2.1)	-	-	55.2 (11.2)	3.2 (1.0)	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	17	12.2 (2.1)	-	-	67.2 (10.9) mcg/mL	3.5 (1.5)	-
	Carbamazepine (Lemmon Co) Tablets		12.4 (1.7)	-	-	69.7 (9.9) mcg/mL	3.3 (1.0)	-

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	5.7 (1.4)	4.5 (1.2)	5.2 (1.3)	62.0 (15.7)	4.5 (2.8)	-
	Carbamazepine (Laakefarmos) Tablets		6.5 (1.5)	4.9 (1.1)	5.8 (1.3)	69.0 (15.3)	4.0 (1.9)	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	10.5 (2.92)	8.13 (2.78)	-	85.59 (48)	3.17 (1.33)	-
	Carbamazepine (Central Poly) Tablets		10.95 (2.55)	8.20 (2.95)	-	84.98 (39.49)	2.67 (1.18)	-
	Carbamazepine (Condrugs) Tablets		10.54 (3.36)	8.29 (2.06)	-	92.98 (43.68)	2.94 (1.25)	-
	Carbamazepine (Pharmaland) Tablets		10.95 (2.25)	7.40 (2.55)	-	98.21 (129.17)	3.28 (1.32)	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	8.28 (1.1) mg/L	5.84 (0.97) mg/L	-	87.98 (12.51) mg/L	13.83 (0.58) h	2.44 (0.18) mg/L
	Generic (Pharmachemie) Tablets	12	8.17 (1.55) mg/L	6.06 (1.47) mg/L	-	87.52 (17.54) mg/L	14.83 (0.58) h	2.11 (0.22)
	Generic (Pharbita) Tablets	12	8.67 (1.96) mg/L	6.25 (1.37) mg/L	-	92.90 (20.84) mg/L	14.25 (0.42) h	2.42 (0.65) mg/L
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-
Clobazam								
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-	-
<i>Gabapentin</i>								
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-
<i>Lamotrigine</i>								
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-
Nielsen, 2008a	Lamictal	9	44.89 (8.46)	30.89 (6.11)	-	359.38 (72.87)	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		44.78 (10.31)	31.78 (8.73)	-	348.88 (89.86)	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-	-
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>								
Lund, 1974	Epanutin (Parke-Davis) capsules	9	*	*	*	*	*	*
	Phenytoin sodium (Leo) capsules		*	*	*	*	*	*

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	43.6 (22.5) mcg/ml	-	-	8.0 to 104.0
	Phenytoin sodium (Boots) tablets		-	-	45.9 (20.8) mcg/ml	-	-	9.0 to 79.0 mcg/ml
	Phenytoin sodium (Cox) tablets		-	-	39.2 (18.0) mcg/ml	-	-	11.0 to 69.0 mcg/ml
	Phenytoin sodium (Kerfoot) tablets		-	-	41.1 (16.5) mcg/ml	-	-	10.0 to 71.0 mcg/ml
	Phenytoin sodium (McCarthy UK) tablets		-	-	44.1 (21.3) mcg/ml	-	-	11.0 to 77.0 mcg/ml
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-	-
	Phenytoin (Boots) tablets		-	-	-	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15			5.45 (3.12) mcg/ml			2.06 to 10.2 mcg/ml
	Phenytoin (Epsolin, Cadila) tablets	15			9.27 (7.7) mcg/ml			3.1 to 27.9 mcg/ml
	Phenytoin (Eptoin, Boots India) tablets	15			8.3 (6.6) mcg/ml			1.9 to 24.8 mcg/ml
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15			8.77 (6.7) mcg/ml			1.2 to 29.4 mcg/ml

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	-	-	Total 11.9 (4.9) mcg/ml Free 0.93 (0.48) mcg/ml	-	-	also reported concentration per dose
	Phenytoin (Phenytext, manufacturer not reported) capsules		-	-	Total 14.2 (8.2) mcg/ml Free 1.14 (0.64) mcg/ml	-	-	-
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	16.4 (5.7) mcg/ml	-	-	174.6 (58.8) mcg/ml*hr	There was no significant difference in T _{max} between the formulations (p<0.066)	-
	Phenytoin sodium (Evans) tablets		15.1 (5.5) mcg/ml	-	-	155.9 (55.6) mcg/ml*hr	There was no significant difference in T _{max} between the formulations (p<0.066)	-
	Phenytoin sodium (APS) tablets		15.6 (5.5) mcg/ml	-	-	160.7 (53.7) mcg/ml*hr	There was no significant difference in T _{max} between the formulations (p<0.066)	-

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
Soryal, 1992 (continued)	Phenytoin sodium (Cox) tablets		18.2 (7.6) mcg/ml	-	-	187.5 (82.8) mcg/ml*hr	There was no significant difference in T _{max} between the formulations (p<0.066)	-
	Phenytoin sodium (Kerfoot) tablets		15.1 (5.4) mcg/ml	-	-	148.2 (60.9) mcg/ml*hr	There was no significant difference in T _{max} between the formulations (p<0.066)	-
	Phenytoin sodium (Regent) tablets		13.1 (4.2) mcg/ml	-	-	132.8 (44.4) mcg/ml*hr	There was no significant difference in T _{max} between the formulations (p<0.066)	-
Topiramate								
Duh, 2009	Topamax (Ortho- McNeil)	875	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-
Paradis 2009 ^b	Topamax (Ortho- McNeil)	-	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-	-

Table G-6. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	C _{max}	C _{min}	C _{ss}	AUC	T _{max}	Range
<i>Valproic Acid</i>								
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-

- = not reported; AUC = area under the curve; C_{max} = maximum concentration; C_{min} = minimum concentration at steady state; C_{ss} = average steady-state concentration; N = sample size; T_{max} = time to maximum concentration

*A statistically significant increase in the plasma level of phenytoin occurred in 5 out of 9 patients after change from one brand of sodium-DPH (Epanutin, Parke-Davis) to another (Na-DPH, Leo)

Table G-7. Adverse events in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Overall Adverse Events	Adverse Events Without Study Withdrawal	Skin Rash	Hypotension	Suicidal Ideation
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>							
Rascati, 2009	Cases	991	-	-	-	-	-
	Controls	2973	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-
	Controls	1248	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-
	Controls	8847	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
<i>Carbamazepine</i>							
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-

**Table G-7. Adverse events in controlled studies comparing innovator versus generic antiepileptic drugs
(continued)**

Study, Year	Group	N	Overall Adverse Events	Adverse Events Without Study Withdrawal	Skin Rash	Hypotension	Suicidal Ideation
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	43	43	2	-	-
	Generic Carbamazepine (Parke Davis) Tablets		45	45	2	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	-	1	-	-
	Carbamazepine (Ethical Generics)		-	-	0	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba- Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-

**Table G-7. Adverse events in controlled studies comparing innovator versus generic antiepileptic drugs
(continued)**

Study, Year	Group	N	Overall Adverse Events	Adverse Events Without Study Withdrawal	Skin Rash	Hypotension	Suicidal Ideation
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	-	-	-	-	-
	Generic (Pharbita) Tablets	12	-	-	-	-	-
Garnett 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-
Clobazam							
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-

Table G-7. Adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Overall Adverse Events	Adverse Events Without Study Withdrawal	Skin Rash	Hypotension	Suicidal Ideation
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>							
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	4	*	-	-	-
	Phenytoin (Boots) tablets	19	3	*	-	-	-
	Phenytoin (Evans) tablets	19	3	*	-	-	-

**Table G-7. Adverse events in controlled studies comparing innovator versus generic antiepileptic drugs
(continued)**

Study, Year	Group	N	Overall Adverse Events	Adverse Events Without Study Withdrawal	Skin Rash	Hypotension	Suicidal Ideation
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	-	-	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	-	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	-	-	-	-
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	†	†	†	†	†
	Phenytoin (Phenytext, manufacturer not reported) capsules		‡	‡	‡	‡	‡
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	§	§	§	§	§
	Phenytoin sodium (Evans) tablets		§	§	§	§	§
	Phenytoin sodium (APS) tablets		§	§	§	§	§
	Phenytoin sodium (Cox) tablets		§	§	§	§	§
	Phenytoin sodium (Kerfoot) tablets		§	§	§	§	§
	Phenytoin sodium (Regent) tablets		§	§	§	§	§
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-

Table G-7. Adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Overall Adverse Events	Adverse Events Without Study Withdrawal	Skin Rash	Hypotension	Suicidal Ideation
Paradis, 2009 ^b	Topamax (Ortho-McNeil)	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-
Valproic Acid							
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-
Andermann, 2007 ^c	Depakene (manufacturer not reported)	2017	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-

- = not reported; N = sample size

*Overall, side effects appeared more frequently with increasing serum levels, but this was not statistically significant.

†Incidence of adverse events was not statistically significant between two groups. ($p>0.25$) The most common side effects included headaches, GI upset, fatigue, dizziness, and lethargy.

*One patient developed intolerable side effects after changing from brand to generic therapy, with gradual onset of difficulty in concentration, headaches, ataxia, diplopia, and progressive somnolence.

§No statistically significant differences were found when comparing incidence of side effects. Commonly experienced side effects included headache, drowsiness, visual disturbances, mental slowness, fatigue, and malaise.

Table G-8. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Combined Neurological Events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
<i>Unspecified Innovator and Brand Antiepileptic Drug Products</i>											
Rascati, 2009	Cases	991	-	-	-	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-	-	-	-	-
	Controls	8847	-	-	-	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-

Table G-8. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Combined Neurological Events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
<i>Carbamazepine</i>											
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	4	2	7	-	7	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-	-	4	1	7	-	6	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	0	-	-	0	-	0	-	0	-
	Carbamazepine (Ethical Generics)		5	-	-	2	-	1	-	1	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-	-	-

Table G-8. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Combined Neurological Events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-	-	-	-	-
	Carbamazepine (Pharmaland)		-	-	-	-	-	-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	-	-	-	-	-	-	-	-	-
	Generic (Pharbita) Tablets	12	-	-	-	-	-	-	-	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	75.7 events per 1000 person-years	-	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	145.7 events per 1000 person-years	-	-	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-	-	-	-

Table G-8. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Combined Neurological Events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
<i>Clobazam</i>											
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-	-	-	-	-
<i>Gabapentin</i>											
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-	-	-	-
<i>Lamotrigine</i>											
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-	-	-	-	-
Nielsen, 2008a	Lamictal	9	-	-	-	-	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-	-	-	-	-

Table G-8. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Combined Neurological Events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>											
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-	2	-	-	-
	Phenytoin (Boots) tablets		-	-	-	-	-	0	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-	1	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	-	-	-	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	-	-	-	-	-	-	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	-	-	-	-	-	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	-	-	-	-	-	-	-	-
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	-	-	-	-	-	-	-	-	-
	Phenytoin (Phenytext, manufacturer not reported) capsules		-	-	-	-	-	-	-	-	-

Table G-8. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Combined Neurological Events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Regent) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin BP, Thomas Kerfoot		-	-	-	-	-	-	-	-	-
	Phenytoin BP, Regent Laboratories		-	-	-	-	-	-	-	-	-
Topiramate											
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-	-	-	-
Paradis 2009 ^b	Topamax (Ortho-McNeil)	-	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-	-	-	-	-
Valproic Acid											
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-	-	-	-	-

Table G-8. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Combined Neurological Events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-	-	-	-

- = not reported; N = sample size; n = number of events

Table G-9. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs

Study, Year	Group	N	Mood Disorders not Reported (n)	Aggression	Anxiety	Depression	Impaired Cognition	Emotional Lability	Nervousness
Unspecified Innovator and Brand Antiepileptic Drug Products									
Rascati, 2009	Cases	991	-	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-	-	-
	Controls	8847	-	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-
Carbamazepine									
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-

Table G-9. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mood Disorders not Reported (n)	Aggression	Anxiety	Depression	Impaired Cognition	Emotional Lability	Nervousness
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-	-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy) Tablets	23	1	-	-	-	-	-	-
	Carbamazepine (Ethical Generics)		1	-	-	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-	-	-

Table G-9. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mood Disorders not Reported (n)	Aggression	Anxiety	Depression	Impaired Cognition	Emotional Lability	Nervousness
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	Finger Tapping (number of taps): 67.7 (8.7) Visual Reaction Time (ms): 274.0 (36.4) Binary Choice Reaction Time (ms): 364.1 (41.5) Visual Searching Task (s): 9.3 (1.9) Recognition Task (number out of 24): 20.2 (1.5) Neurotoxicity Scale: 6.75 (5.6)	-	-
	Generic (Pharmachemie) Tablets	12	-	-	-	-	Finger Tapping (number of taps): 64.8 (8.2) Visual Reaction Time (ms): 312.0 (76.0) Binary Choice Reaction Time (ms): 415.5 (58.3) Visual Searching Task (s): 7.5 (2.0) Recognition Task (number out of 24): 20.4 (3.2) Neurotoxicity Scale: 13.8 (12.8)	-	-

Table G-9. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mood Disorders not Reported (n)	Aggression	Anxiety	Depression	Impaired Cognition	Emotional Lability	Nervousness
Aldenkamp, 1998 (continued)	Generic (Pharbita) Tablets	12	-	-	-	-	Finger Tapping (number of taps): 62.5 (3.6) Visual Reaction Time (ms): 287.1 (47.6) Binary Choice Reaction Time (ms): 384.9 (44.3) Visual Searching Task (s): 7.8 (3.6) Recognition Task (number out of 24): 19.7 (2.1) Neurotoxicity Scale: 2.92 (2.7)	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-	-
Clobazam									
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-	-	-

Table G-9. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mood Disorders not Reported (n)	Aggression	Anxiety	Depression	Impaired Cognition	Emotional Lability	Nervousness
<i>Gabapentin</i>									
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-	-
<i>Lamotrigine</i>									
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-	-	-
Nielsen, 2008a	Lamictal	9	-	-	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-	-	-
<i>Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin</i>									
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-	-	-

Table G-9. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mood Disorders not Reported (n)	Aggression	Anxiety	Depression	Impaired Cognition	Emotional Lability	Nervousness
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-	-	-
	Phenytoin (Boots) tablets		-	-	-	-	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-						
	Phenytoin (Epsolin, Cadila) tablets	15	-						
	Phenytoin (Eptoin, Boots India) tablets	15	-						
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-						
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	-	-	-	-	-	-	-
	Phenytoin (Phenytext, manufacturer not reported) capsules		-	-	-	-	-	-	-

Table G-9. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs (continued)

Study, Year	Group	N	Mood Disorders not Reported (n)	Aggression	Anxiety	Depression	Impaired Cognition	Emotional Lability	Nervousness
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Regent) tablets		-						
Topiramate									
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-	-
Paradis, 2009 ^b	Topamax (Ortho-McNeil)	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-	-	-
Valproic Acid									
Vadney, 1997	Depakene (Abbott)	64		-	-	-	-	-	-
	Valproic acid (Solvay)			-	-	-	-	-	-
Andermann, 2007 ^c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-	-

- = not reported; N = sample size; n = number of events

Table G-10. Seizure outcomes in studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Change From Baseline in Seizure Frequency Mean (SD)	Time to First Seizure Specify Units
Dam, 1989	Carbamazepine	82	No. seizures per month before treatment: 5.8 (14.7) No of seizures during 48 week maintenance phase treatment: 0.3 (1.4)	-
	Oxcarbazepine	83	No. seizures per month before treatment : 2.9 (7.0) No of seizures during 48 week maintenance phase treatment : 0.4 (3.0)	-
Brodie, 1995	Carbamazepine	129	-	
	Lamotrigine	131	-	There was no significant difference between the drugs in time to first seizure after 6 weeks' treatment for the whole study population Hazard ratio: 0.8 95% CI: 0.6-2.1
Reunanen, 1996*	Carbamazepine	117	-	
	Lamotrigine 100 mg	115	-	Time to first seizure Hazard ratio: 0.8 95% CI: 0.5-1.4
	Lamotrigine 200 mg	111	-	Time to first seizure Hazard ratio: 0.9 95% CI: 0.5-1.6

Table G-10. Seizure outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency Mean (SD)	Time to First Seizure Specify Units
Bill, 1997	Phenytoin		Mean Seizure Frequency per week at Baseline: 0.84 (-) N=144 Mean Seizure Frequency per week during 48 week Maintenance: 0.06 (0.15) N=119	-
	Oxcarbazepine		Mean Seizure Frequency per week at Baseline: 0.98 (-) N=143 Mean Seizure Frequency per week during 48 week Maintenance: 0.08 (0.26) N=118	-
Christie, 1997	Sodium Valproate		Mean seizure frequency/week at baseline: 1.09 (3.13) N=121 Mean seizure frequency during 48 week maintenance treatment: 0.40 (1.95) N=106	-
	Oxcarbazepine		Mean seizure frequency/week at baseline: 0.58 (1.39) N=128 Mean seizure frequency per week during 48 week maintenance treatment: 0.17 (0.81) N=106	-

Table G-10. Seizure outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency Mean (SD)	Time to First Seizure Specify Units
Guerreiro, 1997	Pheynction		Mean Seizure Frequency at Baseline: 0.66/week (-) N=96 Mean Seizure Frequency During 48 week Maintenance: 0.04/ week (-) N=77	-
	Oxcarbazepine		Mean Seizure Frequency at Baseline: 0.68/week (-) N=97 Mean Seizure Frequency During 48 week Maintenance: 0.07/week (-) N=81	-
Chadwick, 1999	Carbamazepine	226	-	Time to first seizure after dose stabilization Adjusted hazard ratio:1.79 95% CI: 1.33-2.40
	Vigabatrin	220	-	Time to first seizure after dose stabilization Adjusted hazard ratio:1.79 95% CI: 1.33-2.40
Steiner, 1999 [†]	Phenytoin	95	-	
	Lamotrigine	86	-	Time to first seizure after 6 weeks of treatment 1.4, 95% CI: 0.8 to 2.3
Privitera, 2003	Carbamazepine	126	-	NS
	Valproic Acid	78	-	NS
	Topiramate 100 mg	210	-	NS
	Topiramate 200 mg	199	-	NS
Wheless, 2004	Carbamazepine	23	-	NS
	Valproate	19	-	NS
	Topiramate 100 mg	38	-	NS
	Topiramate 200 mg	39	-	NS

Table G-10. Seizure outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency Mean (SD)	Time to First Seizure Specify Units
Kang, 2007	Carbamazepine	43	Mean percentage change from baseline to maintenance in seizure frequency -100%	-
	Topiramate	45	Mean percentage change from baseline to maintenance in seizure frequency -100%	-
Marson, 2007* SANAD Arm A	Carbamazepine	378	-	
	Gabapentin	377	-	Pairwise comparison for time to first seizure Hazard ratio: 1.35 95% CI: 1.14-1.60
	Lamotrigine	378	-	Pairwise comparison for time to first seizure Hazard ratio: 1.23 95% CI: 1.04-1.45
	Oxcarbazepine	210	-	Pairwise comparison for time to first seizure Hazard ratio: 1.06 95% CI: 0.84-1.33
	Topiramate	378	-	Pairwise comparison for time to first seizure: Hazard ratio: 1.05 95% CI: 0.89-1.25
Marson, 2007† SANAD Arm B	Valproic Acid	238		
	Lamotrigine	239		Pairwise comparison for time to first seizure Hazard ratio: 0.71 95% CI: 0.57-0.88
	Topiramate	239		Pairwise comparison for time to first seizure Hazard ratio: 0.91 95% CI: 0.73-1.14

Table G-10. Seizure outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Change From Baseline in Seizure Frequency Mean (SD)	Time to First Seizure Specify Units
Ramsay , 2010 [†]	Pheyntoin	127	-	
	Topiramate	132	-	HR: 2.0 95% CI: 0.98-4.12

- = not reported; 95% CI =95% confidence interval; N = sample size; NS = not significant; SANAD Arm A= Standard and New Antiepileptic Drugs Trial Arm A; Arm B = Standard and New Antiepileptic Drugs Trial Arm B; SD = standard deviation

*Carbamazepine group is referent

[†]Phenytoin group is referent

[‡]Valproic acid group is referent

Table G-11. Seizure outcomes in studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Seizure Free for Duration of Study	Seizure Remission for 12-Month Period (%)	Seizure Remission for 24-Month Period (%)	Seizure Frequency Reduction by 50%	Seizure Frequency Reduction by 75%
Danner, 1988	Carbamazepine	13	9	-	-	-	-
	Oxcarbazepine	12	8	-	-	-	-
Dam, 1989	Carbamazepine	82	49	-	-	67	-
	Oxcarbazepine	83	43	-	-	67	-
Brodie, 1995	Carbamazepine	129	49	-	-	-	-
	Lamotrigine	131	51	-	-	-	-
Kalviaine, 1995	Carbamazepine	50	26	-	-	-	-
	Vigabatrin	50	16	-	-	-	-
Sabers 1995	Carbamazepine	11	8	-	-	-	-
	Phenobarbital	9	9	-	-	-	-
	Phenytoin	11	9	-	-	-	-
	Valproic Acid	11	7	-	-	-	-
	Oxcarbazepine	10	5	-	-	-	-
Reunanen, 1996	Carbamazepine	117	64	-	-	-	-
	Lamotrigine 100 mg	115	59	-	-	-	-
	Lamotrigine 200 mg	111	67	-	-	-	-
Tanganelli, 1996	Carbamazepine	25	End of phase 1 before the crossover 14 (56%)	-	-	-	-
	Vigabratin	26	End of phase 1 before the crossover 12 (46.1%)	-	-	-	-
Bill, 1997	Phenytoin	119	69				
	Oxcarbazepine	118	70				
Christie, 1997	Valproic Acid	121	57	-	-	-	-
	Oxcarbazepine	128	60	-	-	-	-
Guerreiro, 1997	Pheynition	77	46	-	-	-	-
	Oxcarbazepine	81	49	-	-	-	-
Brodie, 1999	Carbamazepine	48	10	-	-	-	-
	Lamotrigine	102	40	-	-	-	-
Gobbi, 1999	Carbamazepine	40	29	-	-	-	-
	Vigabatrin	37	22	-	-	-	-
Steiner, 1999	Phenytoin	95	22	-	-	-	-
	Lamotrigine	86	19	-	-	-	-

Table G-11. Seizure outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Seizure Free for Duration of Study	Seizure Remission for 12-Month Period (%)	Seizure Remission for 24-Month Period (%)	Seizure Frequency Reduction by 50%	Seizure Frequency Reduction by 75%
Biton, 2001	Valproate	68	18	-	-	-	-
	Lamotrigine	65	19	-	-	-	-
Kwan, 2001	Carbamazepine	212	88	-	-	-	-
	Valproic Acid	101	59	-	-	-	-
	Lamotrigine	78	48	-	-	-	-
Nieto-Barrera, 2001	Carbamazepine	152	111	-	-	-	-
	Lamotrigine	329	215	-	-	-	-
Biton, 2003	Valproate	20	9	-	-	-	13 of 19 (68%) patients had a 75% reduction from baseline in generalized tonic-clonic seizure frequency from baseline
	Lamotrigine	18	6	-	-	-	10 of 15 (67%) patients had a 75% reduction from baseline in generalized tonic-clonic seizure frequency from baseline
Privitera, 2003	Carbamazepine	126	55	-	-	-	-
	Valproic Acid	78	34	-	-	-	-
	Topiramate 100 mg	210	103	-	-	-	-
	Topiramate 200 mg	199	88	-	-	-	-
Coppola, 2004	Valproic Acid	19	13	-	-	-	-
	Lamotrigine	19	10	-	-	-	-
Fakhoury, 2004	Carbamazepine	25	8	-	-	18	-
	Lamotrigine	55	23	-	-	37	-
	Valproic Acid	21	2	-	-	8	-
	Lamotrigine	51	16	-	-	27	-

Table G-11. Seizure outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Seizure Free for Duration of Study	Seizure Remission for 12-Month Period (%)	Seizure Remission for 24-Month Period (%)	Seizure Frequency Reduction by 50%	Seizure Frequency Reduction by 75%
Wheless, 2004	Carbamazepine	23	9	-	-	-	-
	Valproic Acid	19	10	-	-	-	-
	Topiramate 100 mg	38	24	-	-	-	-
	Topiramate 200 mg	39	23	-	-	-	-
Rowan, 2005	Carbamazepine	70	45	-	-	-	-
	Gabapentin	95	45	-	-	-	-
	Lamotrigine	111	57	-	-	-	-
Steinhoff, 2005	Carbamazepine	88	72	-	-	-	-
	Lamotrigine	88	62	-	-	-	-
	Valproate	30	25	-	-	-	-
	Lamotrigine	33	20	-	-	-	-
Brodie, 2007	Carbamazepine- Controlled Release	291	155	-	-	-	-
	Levetiracetam	285	142	-	-	-	-
Donati, 2007	Carbamazepine	28	13	-	-	-	-
	Valproic Acid	29	16	-	-	-	-
	Oxcarbazepine	55	32	-	-	-	-
Kang, 2007	Carbamazepine	43	30	-	-	-	-
	Topiramate	45	31	-	-	-	-
Levisohn, 2007	Valproic Acid	9	4	-	-	-	-
	Topiramate	19	8	-	-	-	-
Marson, 2007 SANAD Arm A	Carbamazepine	362	-	254	168	-	-
	Gabapentin	359	-	215	132	-	-
	Lamotrigine	365	-	245	155	-	-
	Oxcarbazepine	200	-	128	68	-	-
	Topiramate	358	-	225	140	-	-
Marson, 2007 SANAD Arm B	Valproic Acid	232	-	180	124	-	-
	Lamotrigine	231	-	168	102	-	-
	Topiramate	230	-	178	108	-	-
Saetre, 2007	Carbamazepine – Sustained Release	91	60	-	-	-	-
	Lamotrigine	93	50	-	-	-	-

Table G-11. Seizure outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Seizure Free for Duration of Study	Seizure Remission for 12-Month Period (%)	Seizure Remission for 24-Month Period (%)	Seizure Frequency Reduction by 50%	Seizure Frequency Reduction by 75%
Stephen, 2007	Valproate	111	52	-	-	-	-
	Lamotrigine	114	54	-	-	-	-
Morrell, 2008	Valproate	211	97	-	-	-	-
	Lamotrigine	201	74	-	-	-	-
Perry, 2008	Carbamazepine	11	3	-	-	-	-
	Levetiracetam	25	8	-	-	-	-
Kim, 2009	Carbamazepine	105	-	-	-	-	-
	Topiramate	41	-	-	-	-	-
Kwan, 2009	Valproic Acid	44	13	-	-	-	-
	Lamotrigine	37	17	-	-	-	-
Ma, 2009	Carbamazepine	120	70	-	-	-	-
	Valproic Acid	234	180	-	-	-	-
	Topiramate	143	88	-	-	-	-
Helmstaedter, 2010	Carbamazepine	84	63	-	-	-	-
	Levetiracetam	138	111	-	-	-	-
Ramsay, 2010	Phenytoin	127	117	-	-	-	-
	Topiramate	132	108	-	-	-	-

- = not reported; N = sample size; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; Arm B = Standard and New Antiepileptic Drugs Trial Arm B

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Reinikainen, 1987	Carbamazepine	18	6*	-	-	-	Increased seizures: 2 (6%) Poor compliance: 2 (6%)
	Oxcarbazepine	16		-	-	-	
Danner, 1988	Carbamazepine	13	-	-	-	3	Allergic Rash: 3 (23%)
	Oxcarbazepine	12	-	-	-	1	Allergic Rash: 1(8.33%)
Dam, 1989	Carbamazepine	98	-	2	-	25	Allergy: 16 (16%) Visual Disturbances: 1 (1%) Headache: 1 (1%) Tiredness/fatigue: 3 (3%) Nausea: 1 (1%) Diarrhoea: 2 (2%) Loss of hair: 2 (2%) Leukopenia: 1 (1%) Liver parameters increased: 1 (1%)
	Oxcarbazepine	92	-	2	-	13	Allergy: 9 (10%) Dizziness/vertigo: 2 (2%) Tiredness/fatigue: 1 (1%) Physical lability: 1 (1%)
Sachdeo, 1992	Valproic Acid	22	1	-	-	-	-
	Felbamate	22	1	-	-	-	-

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Brodie, 1995	Carbamazepine	129	63	3	-	27	Rash: 22 (17%) Headache: 3 (2%) Asthenia: 6 (5%) Dizziness: 3 (2%) Vomiting: 1 (1%) Malaise: 5 (4%) Nausea: 3 (2%) Ataxia: 5 (4%) Sleepiness: 5 (4%)
	Lamotrigine	131	46	3	-	15	Rash: 15 (12%) Headache: 5 (4%) Asthenia: 5 (4%) Dizziness: 3 (2%) Vomiting: 3 (2%) Malaise: 1 (1%) Nausea: 1 (1%) Ataxia: 0 Sleepiness: 0
Kalviainen, 1995	Carbamazepine	50	20	3	-	12	Rash: 7 (14%) Hepatotoxicity: 3 (6%) Elevation of blood glucose: 1 (2%) Confusion and personality change: 1 (2%)
	Vigabatrin	50	20	13	-	0	Rash: 0 Hepatotoxicity: 0 Elevation of blood glucose: 0 Confusion and personality change: 0

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Reunanen, 1996	Carbamazepine	117	29	0	-	12	-
	Lamotrigine 100 mg	115	23	1	-	5	-
	Lamotrigine 200 mg	111	10	0	-	5	-
Tanganelli, 1996	Carbamazepine	25	-	-	-	1	-
	Vigabratin	26	-	-	-	0	-
Bill, 1997	Phenytoin	144	61	1	-	16	Rash: 10 (7%) Hirsutism/Gum Hyperplasia: 5 (3.5%) Other: 1 (0.7%)
	Oxcarbazepine	143	56	1	-	5	Rash: 1 (0.7%) Hirsutism/Gum Hyperplasia: 0 Other: 4 (2.8%) (1 patient in the other group withdrew due to suicidal ideation)
Christie, 1997	Sodium Valproate	121	41	6	-	10	Allergic Reaction: 0 Hair loss: 4 (3.31%) Pregnancy: 2 (1.65%) Nausea: 2 (1.65%) Drowsiness: 0 Other: 2 (1.65%)
	Oxcarbazepine	128	52	6	-	15	Allergic Reaction with skin symptoms: 6 (4.69%) Hair Loss: 0 Pregnancy: 1 (0.8%) Drowsiness: 2 (1.56%) Other: 2 (1.56%)

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Guerreiro, 1997	Pheyntion	96	34	3	-	14	Hypertrichosis and/or gingival hyperplasia: 10 (10%) (1 patient also had ataxia) Rash: 4 (4%) (1 patient also had fever, ataxia, dizziness and vomiting)
	Oxcarbazepine	97	24	4	-	2	Rash: 2 (2%)
Chadwick, 1998	Carbamazepine	74	47	-	-	18	-
	Gabapentin 300 mg	72	54	-	-	0	-
	Gabapentin 900 mg	72	44	-	-	3	-
	Gabapentin 1800 mg	74	46	-	-	10	-
Brodie, 1999a	Carbamazepine	48	28	0	-	20	Rash: 9 (19%) Somnolence: 3 (6%) Asthenia: 3 (6%) Nausea: 1 (2%) Incoordination: 1 (2%)
	Lamotrigine	102	30	0	-	18	Rash: 3 (3%) Somnolence: 2 (2%) Asthenia: 1 (1%) Nausea: 3 (3%) Incoordination: 3 (3%)
Brodie, 1999b	Valproate	107	32	19	-	12	-
	Vigabatrin	108	22	11	-	12	-

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Chadwick, 1999 [†]	Carbamazepine	229	97	9		61	-
	Vigabatrin	228	98	23	No significant treatment differences between vigabatrin and carbamazepine groups Hazard ratio: 0.83 95% CI: 0.57-1.20	43	-
Gobbi, 1999	Carbamazepine	40	0	0	-	0	0
	Vigabatrin	37	9	8	-	0	0
Steiner, 1999	Phenytoin	95	50	2	-	18	-
	Lamotrigine	86	45	1	-	13	-
Aldenkamp, 2000	Valproic Acid	30	4	1	-	-	-
	Topiramate	29	8	0	-	-	-
	Lamotrigine	146	18	-	-	35	-
Biton, 2001	Valproate	68	30	-	-	9	-
	Lamotrigine	65	19	-	-	6	-
Kwan, 2001	Carbamazepine	212	124	53	-	57	-
	Sodium Valproate	101	43	26	-	13	-
	Lamotrigine	78	30	20	-	8	-
Nieto-Barrera, 2001	Carbamazepine	201	46	-	-	27	-
	Lamotrigine	417	79	-	-	38	-

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Biton, 2003	Valproate	20	6	-	-	1	Aspiration of fluids: 1(5%)
	Lamotrigine	18	3	-	-	1	Multiple side effects leading to withdrawal for 1 patient including mental confusion insomnia somnolence increased appetite dizziness ataxia nystagmus resting tremor and intention tremor 1 (5.55%)
Meador, 2003	Valproate	29	4	-	-	2	-
	Topiramate	34	7	-	-	6	-
Privitera, 2003	Carbamazepine	126	56	10	-	32	-
	Valproic Acid	78	43	9	-	18	-
	Topiramate 100 mg	210	91	23	-	40	-
	Topiramate 200 mg	199	95	18	-	55	-
Clemens, 2004	Carbamazepine	20	-	-	-	-	-
	Oxcarbazepine	20	-	-	-	1	Rash: 1 (5%)
Coppola, 2004	Valproic Acid	19	3	3	-	0	0
	Lamotrigine	19	6	6	-	0	0
Fakhoury, 2004	Carbamazepine	46	7	-	-	12	-
	Lamotrigine	98	19	-	-	14	-
	Valproic Acid	53	16	-	-	11	-
	Lamotrigine	105	28	-	-	14	-

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Wheless, 2004	Carbamazepine	23	55 [‡]	16 [§]	-	1	-
	Valproic Acid	19			-	6	-
	Topiramate 100 mg	38			-	4	-
	Topiramate 200 mg	39			-	7	-
Rowan, 2005	Carbamazepine	197	127	5	-	61	-
	Gabapentin	194	99	8	-	42	-
	Lamotrigine	199	88	11	-	24	-
Sobaniec, 2005	Carbamazepine	28	0	-	-	-	-
	Vigabratin	26	4	-	-	-	-
Steinhoff, 2005	Carbamazepine	88	29	0	-	17	-
	Lamotrigine	88	24	1	-	7	-
	Valproate	30	4	0	-	1	-
	Lamotrigine	33	5	2	-	2	-

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Brodie, 2007	Carbamazepine-Controlled Release	291	97	13	-	56	Vertigo: 2 (0.7%) Nausea: 3 (1.0%) Asthenia: 3 (1.0%) Fatigue: 4 (1.4%) Ataxia: 3 (1.0) Dizziness: 3 (1.0%) Somnolence: 2 (0.7%) Aggression: 3 (1.0%) Anxiety: 1 (0.3%) Depression: 2 (0.7%) Rash: 9 (3.1%)
	Levetiracetam	285	95	31	-	41	Vertigo: 6 (2.1%) Nausea: 0 Asthenia: 0 Fatigue: 5 (1.8%) Ataxia: 0 Dizziness: 2 (0.7%) Somnolence: 6 (2.1%) Aggression: 0 Anxiety: 3 (1.1%) Depression: 5 (1.8%) Rash: 4 (1.4%)
Kang, 2007	Carbamazepine	54	11	-	-	5	-
	Topiramate	58	13	-	-	6	-
Kim, 2007	Carbamazepine	10	0	0	-	0	-
	Valproic Acid	15	0	0	-	0	-
	Lamotrigine	8	0	0	-	0	-
Levisohn, 2007	Valproic Acid	9	5	0	-	1	-
	Topiramate	19	7	2	-	2	-
Marson 2007	Carbamazepine	378	227	43	-	102	-
	Gabapentin	376	249	99	-	57	-

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
SANAD Arm A	Lamotrigine	378	197	60	-	60	-
	Oxcarbazepine	210	117	24	-	49	-
	Topirimate	374	241	55	-	101	-
Marson 2007 SANAD Arm B	Valproic Acid	238	141	21	-	35	-
	Lamotrigine	237	128	53	-	25	-
	Topirimate	238	154	28	-	57	-
Saetre, 2007	Carbamazepine-Sustained Release	91	30	-	-	23	-
	Lamotrigine	93	25	-	-	13	-
Stephen, 2007	Valproate	111	55	16	-	26	-
	Lamotrigine	114	43	11	-	15	-
Morrell, 2008	Valproate	225	55	1	-	9	-
	Lamotrigine	222	52	2	-	9	-
Perry, 2008	Carbamazepine	20	4	-	-	1	Increased irritability: 1 (5%)
	Levetiracetam	66	22	2	-	8	Behaviour changes : 5 (63%) Irritability or mood change: 1 (12%) Increased seizure frequency Rash: 1(12%) Undetermined: 1(12%)
Kim, 2009	Carbamazepine	105	89	24	-	7	-
	Topiramate	41	31	5	-	1	-
Kwan, 2009	Valproic Acid	44	16	1	-	5	-
	Lamotrigine	37	9	0	-	5	-

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Ma, 2009	Carbamazepine	120	-	21	-	20	-
	Valproic Acid	234	-	40	-	10	-
	Topirimate	143	-	25	-	17	-
Glauser, 2010	Ethosuximide	154	20	-	-	37	Nervous system, behavioural or psychological effects: 12 (32%) Digestive disorders: 9 (24%) Rash: 6 (16%) Fatigue: 3 (8%) Headache: 3 (8%) BMI increase that met exit criterion: 0 Laboratory abnormalities: 1 (3%) Other: 4 (11%)
	Valproic Acid	146	15	-	-	25	Nervous system, behavioural or psychological effects: 20 (57%) Digestive disorders: 6 (17%) Rash: 2 (6%) Fatigue: 5 (14%) Headache: 2 (6%) BMI increase that met exit criterion: 4 (11%) Laboratory abnormalities: 2 (6%) Other: 5 (14%)

Table G-12. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Withdrawal for any Reason (n)	Withdrawal Due to Ineffective Treatment (n)	Time to Withdrawal Due to Ineffective Treatment	Withdrawal Due to Adverse Drug Events (n)	Adverse Drug Events Contributing to Withdrawals n (%)
Glauser, 2010 (continued)	Lamotrigine	146	18	-	-	35	Nervous system, behavioural or psychological effects: 9 (36%) Digestive disorders: 3 (12%) Rash: 5 (20%) Fatigue: 2 (8%) Headache: 2 (8%) BMI increase that met exit criterion: 1 (4%) Laboratory abnormalities: 2 (8%) Other: 4 (16%)
Ramsay, 2010	Phenytoin		17 N=128	-	-	17 N=127	Cognitive adverse events: 2 (1.5%)
	Topiramate		27 N=133	-	-	9 N=132	Skin Rash: 8 (6.3%)

- = not reported; n = number of patients with event; N = sample size; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B = Standard and New Antiepileptic Drugs Trial Arm B

*6 patients withdrew for any reason from the total population

†Carbamazepine group is referent

*55 patients withdrew for any reason from the total population

§16 patients withdrew from the total population due to lack of efficacy

Table G-13. Final health outcomes in studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Deaths (n)	Office/ ER Visits (n)	Hospitalizations Events (n)	Composite of Ambulance/ER/ Hospitalizations Events (n)
Reunanen, 1996	Carbamazepine	117	0	-	-	-
	Lamotrigine 100 mg	115	1	-	-	-
	Lamotrigine 200 mg	111	1	-	-	-
Bill, 1997	Phenytoin	144	2	-	-	-
	Oxcarbazepine	143	0	-	-	-
Brodie, 1999a	Carbamazepine	48	2	-	3	-
	Lamotrigine	102	0	-	0	-
Brodie, 1999b	Valproate	107	0	-	-	-
	Vigabatrin	108	0	-	-	-
Chadwick, 1999	Carbamazepine	229	1	-	-	-
	Vigabatrin	228	2	-	-	-
Steiner, 1999	Phenytoin	95	2	-	-	-
	Lamotrigine	86	0	-	-	-
Fakhoury, 2004	Carbamazepine	46	0	-	-	-
	Lamotrigine	98	2	-	-	-
	Valproic Acid	53	0	-	-	-
	Lamotrigine	105	1	-	-	-
Rowan, 2005	Carbamazepine	198	15	-	-	-
	Gabapentin	195	11	-	-	-
	Lamotrigine	200	8	-	-	-
Marson, 2007 SANAD Arm B	Valproic Acid	238	4	-	-	-
	Lamotrigine	239	4	-	-	-
	Topirimate	239	3	-	-	-
Marson, 2007 SANAD Arm A	Carbamazepine	378	18	-	-	-
	Gabapentin	377	19	-	-	-
	Lamotrigine	378	12	-	-	-
	Oxcarbazepine	210	5	-	-	-
	Topirimate	378	17	-	-	-

Table G-13. Final health outcomes in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Deaths (n)	Office/ ER Visits (n)	Hospitalizations Events (n)	Composite of Ambulance/ER/ Hospitalizations Events (n)
Glauser, 2010	Ethosuximide	154	-	-	4	-
	Valproic Acid	146	-	-	2	-
	Lamotirgine	146	-	-	2	-
Ramsay, 2010	Phenytoin	127	0	-	-	-
	Topiramate	132	0	-	-	-

- = not reported; ER = emergency room; N = sample size; (n) = number of deaths or events; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B = Standard and New Antiepileptic Drugs Trial Arm B

Table G-14. Health-related quality of life for studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Cramer, 2001					Work-driving-social relations	Attention-concentration	Memory	Language	Seizure worry
	Carbamazepine		QOLIE-89	60.2 (18)* N=55	Change from baseline in subscore: 8.0 P=0.004 N=33	Change from baseline in subscore: 3.5 P=NS N=33	Change from baseline in subscore: 1.3 P=NS N=33	Change from baseline in subscore: 3.0 P=NS N=33	Change from baseline in subscore: 11.8 P=0.016 N=33
	Tiagabine		QOLIE-89	61.0 (19)* N=47	Change from baseline in subscore: 7.1 P=NS N=14	Change from baseline in subscore: 6.5 P=0.002 N=14	Change from baseline in subscore: 7.4 P=0.042 N=14	Change from baseline in subscore: 12.9 P=0.004 N=14	Change from baseline in subscore: 11.6 P=0.03 N=14
					Role limit-physical	Seizure Worry			
	Phenytoin		QOLIE-89	63.0 (17)* N=58	Change from baseline in subscore: 11.2 P=NS N=28	Change from baseline in subscore: 12.2 P=0.007 N=28	-	-	-
	Tiagabine		QOLIE-89	62.0 (16)* N=66	Change from baseline in subscore: -11.3 P=NS N=23	Change from baseline in subscore: 9.2 P=0.032 N=23	-	-	-

Table G-14. Health-related quality of life for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Gillham, 2000	Carbamazepine	60	SEALS Inventory	Change from baseline in total score: 0.32 P=0.394	-	-	-	-	-
	Lamotrigine	73	SEALS Inventory	Change from baseline in total score: -3.08 P<0.001	-	-	-	-	-
Helmstaedter, 2010	Carbamazepine	84	WHO-5	Patients with a decline from baseline: N=2 Patients with an improvement from baseline: N=19	-	-	-	-	-
	Levetiracetam	138	WHO-5	Patients with a decline from baseline: N=7 Patients with an improvement from baseline: N=44	-	-	-	-	-
Marson, 2007 SANAD Arm A					Anxiety †	Depression †	Adverse Events Profile †	Neurotoxicity †	
	Carbamazepine	195	NEWQOL	-					
	Gabapentin	197	NEWQOL	-	-0.01 (-0.78 to 0.76)	0.28 (-0.37 to 0.94)	0.60 (-1.15 to 2.34)	-0.12 (-2.86 to 2.63)	
	Lamotrigine	177	NEWQOL	-	-0.09 (-0.88 to 0.70)	-0.35 (-1.02 to 0.33)	0.47 (-1.38 to 2.32)	-1.30 (-4.09 to 1.50)	
	Oxcarbazepine	92	NEWQOL	-	-0.13 (-1.10 to 0.83)	-0.29 (-1.11 to 0.53)	0.45 (-1.83 to 2.72)	-0.72 (-4.12 to 2.68)	
	Topiramate	172	NEWQOL	-	-0.84 (-1.63 to -0.04)	0.09 (-0.59 to 0.77)	-0.60 (-2.42 to 1.23)	-1.60 (-4.43 to 1.24)	

Table G-14. Health-related quality of life for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Marson, 2007 SANAD Arm A					Anxiety ‡	Depression ‡	Global Quality of Life ‡		
	Carbamazepine	195	NEWQOL	-					
	Gabapentin	197	NEWQOL	-	1.02 (0.65 to 1.59)	1.34 (0.81 to 2.21)	0.88 (0.61 to 1.28)		
	Lamotrigine	177	NEWQOL	-	0.96 (0.61 to 1.52)	0.74 (0.44 to 1.27)	0.76 (0.52 to 1.12)		
	Oxcarbazepine	92	NEWQOL	-	1.02 (0.58 to 1.79)	1.13 (0.57 to 2.24)	1.34 (0.84 to 2.15)		
	Topiramate	172	NEWQOL	-	0.62 (0.38 to 0.99)	1.13 (0.68 to 1.89)	0.91 (0.62 to 1.34)		
Marson, 2007 SANAD Arm A									
	Carbamazepine	195	EQ-5D §						
	Gabapentin	197	EQ-5D	0.01 (-0.04 to 0.06)					
	Lamotrigine	177	EQ-5D	0.02 (-0.03 to 0.06)					
	Oxcarbazepine	92	EQ-5D	0.01 (-0.05 to 0.07)					
	Topiramate	172	EQ-5D	0.03 (-0.02 to 0.08)					
Marson, 2007 SANAD Arm B					Anxiety	Depression	Adverse Events Profile	Neurotoxicity	
	Valproic Acid	73	NEWQOL	-					
	Lamotrigine	68	NEWQOL	-	0.89 (-0.34 to 2.12)	-0.48 (-1.41 to 0.45)	0.73 (-2.52 to 3.89)	-1.29 (-5.34 to 2.75)	
	Topiramate	68	NEWQOL	-	-0.08 (-1.31 to 1.15)	-0.40 (-1.34 to 0.54)	-0.08 (-3.29 to 3.26)	-0.37 (-4.48 to 3.75)	
Marson, 2007 SANAD Arm B					Anxiety ¶	Depression ¶	Global Quality of Life ¶		
	Valproic Acid	73	NEWQOL	-					
	Lamotrigine	68	NEWQOL	-	1.40 (0.46 to 3.10)	0.82 (0.33 to 2.07)	1.17 (0.64 to 2.16)		
	Topiramate	68	NEWQOL	-	0.87 (0.37 to 2.00)	0.81 (0.31 to 2.09)	0.95 (0.51 to 1.77)		

Table G-14. Health-related quality of life for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Marson, 2007 SANAD Arm B	Valproic Acid	73	EQ-5D#						
	Lamotrigine	68	EQ-5D	0.02 (-0.04 to 0.08)					
	Topiramate	68	EQ-5D	0.04 (-0.002 to 0.10)					
Meador, 2003	Valproic Acid	25	QOLIE-89	Baseline: 61 (16)* Maintenance: 61 (17)*	-	-	-	-	-
	Topiramate	27	QOLIE-89	Baseline: 57 (15)* Maintenance: 59 (14)*	-	-	-	-	-
Saetre, 2010	Carbamazepine-Sustained Release	50	SEALS Inventory	Difference in median score from week 0 to week 40: -1.5 (-26.0 to 44.0) † †	-	-	-	-	-
	Lamotrigine	55	SEALS Inventory	Difference in median score from week 0 to week 40: -2.0 (-32.0 to 44.0) † † P=0.54 for comparison of difference in median SEALS score between Carbamazepine-Sustained-Release group and Lamotrigine group	-	-	-	-	-

Table G-14. Health-related quality of life for studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Scale Used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Sackellares, 2002					Health Perception	Energy/Fatigue	Social Isolation	Medication effects	Attention/concentration
	Valproate	55	QOLIE-89	-	Odds ratio: 4.0 95% CI: 1.6-10.6	Odds ratio: 2.3 95% CI: 1.1-5.3	Odds ratio: 2.8 95% CI: 1.1-7.6	Odds ratio: 2.3 95% CI: 0.9-5.7	Odds ratio: 2.1 95% CI: 0.9-4.8
	Lamotrigine	53	QOLIE-89	-					
Steiner, 1999	Phenytoin	95	SEALS Inventory	Estimated difference between treatments in the overall change from baseline: 4.0 95% CI: 0.7-7.3 P=0.02	-	-	-	-	-
	Lamotrigine	86	SEALS Inventory		-	-	-	-	-

- = not reported; EQ-5D = Descriptive Health Related Quality of Life States; HR = Hazard Ratio; N = sample size; NEWQOL = Newly Diagnosed Epilepsy Quality of Life; QOLIE-89 = Quality of Life in Epilepsy-89; SEALS Inventory = Side Effect and Life Satisfaction Inventory; WHO-5 = World Health Organization-Five Well-Being Index
*mean (standard deviation)

†continuous measures of NEWQOL, carbamazepine is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI

‡ordinal measures of NEWQOL, carbamazepine is referent and values for ordinal measures are the exponential coefficients from a proportional odds model, with 95% CIs, such that values represent the odds of increasing severity of outcome

§continuous measures of EQ-5D, carbamazepine is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI

||continuous measures of NEWQOL, valproic acid is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI

¶ordinal measures of NEWQOL, valproic acid is referent and values for ordinal measures are the exponential coefficients from a proportional odds model, with 95% CIs, such that values represent the odds of increasing severity of outcome

#continuous measures of EQ-5D, valproic acid is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI

**lamotrigine is referent

##Reports health-related quality of life data from Sactre 2007

††delta in SEALS score from 0 to 40 weeks (median)

Table G-15. Adverse events in studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Overall Adverse Events (n)	Adverse Events Without Study Withdrawal (n)	Skin Rash (n)	Hypotension (n)	Suicidal Ideation (n)	Nausea (n)	Vomiting (n)
Reinikainen, 1987	Carbamazepine	18	-	11	-	-	-	1	-
	Oxcarbazepine	16	-	7	-	-	-	0	-
Dam, 1989	Carbamazepine	98	73	-	-	0	-	-	-
	Oxcarbazepine	92	63	-	-	0	-	-	-
Sachdeo, 1992	Valproic Acid	22	-	-	-	-	-	-	-
	Felbamate	22	-	-	-	-	-	1	3
Faught, 1993	Valproate	39	28	-	1	-	-	1	2
	Felbamate	38	19	-	1	-	-	0	2
Brodie, 1995	Carbamazepine	129	-	-	25	-	-	2	9
	Lamotrigine	131	-	-	25	-	-	1	12
Kalviainen, 1995	Carbamazepine	45	55	55	-	-	-	-	-
	Vigabatrin	43	49	49	-	-	-	-	-
Reunanen, 1996	Carbamazepine	117	-	-	10	-	-	9	-
	Lamotrigine 100 mg	115	-	-	6	-	-	7	-
	Lamotrigine 200 mg	111	-	-	9	-	-	7	-
Tanganelli, 1996	Carbamazepine	25	24	-	1	-	-	4 events	-
	Vigabatrin	26	14	-	0	-	-	1 event	-
Bill, 1997	Phenytoin	142	122	-	16	-	-	16	-
	Oxcarbazepine	136	114	-	12	-	-	13	-
Christie, 1997	Sodium Valproate	121	106	-	-	-	-	14	-
	Oxcarbazepine	128	115	-	-	-	-	11	-
Guerreiro, 1997	Pheynition	94	79	-	5	-	-	7	5
	Oxcarbazepine	96	84	-	4	-	-	5	0
Brodie, 1999a	Carbamazepine	48	-	-	12	-	-	-	3
	Lamotrigine	102	-	-	9	-	-	-	9
Chadwick, 1999	Carbamazepine	229	195	134	22	-	-	-	-
	Vigabatrin	228	191	148	7	-	-	-	-
Gobbi, 1999	Carbamazepine	40	-	-	-	-	-	-	-
	Vigabatrin	37	-	-	-	-	-	-	-
Steiner, 1999	Phenytoin	95	59	52	9	-	-	4	-
	Lamotrigine	86	36	37	12	-	-	7	-
Biton, 2001	Valproate	68	-	-	-	-	-	16	9
	Lamotrigine	65	-	-	-	-	-	8	4
Kwan, 2001	Carbamazepine	212	78	-	22	-	-	-	-
	Valproate	101	15	-	0	-	-	-	-
	Lamotrigine	78	9	-	3	-	-	0	-

Table G-15. Adverse events in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Overall Adverse Events (n)	Adverse Events Without Study Withdrawal (n)	Skin Rash (n)	Hypotension (n)	Suicidal Ideation (n)	Nausea (n)	Vomiting (n)
Nieto-Barrera, 2001	Carbamazepine	215	300	-	20	-	-	-	-
	Lamotrigine	452	586	-	42	-	-	-	-
Biton, 2003	Valproate	20	12	-	1	-	-	3	1
	Lamotrigine	18	14	-	1	-	-	4	4
Privitera, 2003	Carbamazepine	126	-	-	10	-	-	25	-
	Valproic Acid	78	-	-	5	-	-	11	-
	Topiramate 100 mg	210	-	-	6	-	-	15	-
	Topiramate 200 mg	199	-	-	4	-	-	28	-
Clemens, 2004	Carbamazepine	20	0	-	-	-	-	-	-
	Oxcarbazepine	20	1	-	1	-	-	-	-
Coppola, 2004	Valproic Acid	19	2	2	0	-	-	-	-
	Lamotrigine	19	6	6	1	-	-	-	-
Fakhoury, 2004	Carbamazepine	46	33	-	-	-	-	4	-
	Lamotrigine	98	61	-	-	-	-	1	-
	Valproic Acid	53	37	-	-	-	-	7	-
	Lamotrigine	105	56	-	-	-	-	6	-
Wheless, 2004	Carbamazepine	23	-	-	-	-	-	4	2
	Valproate	19	-	-	-	-	-	2	0
	Topiramate 100 mg	38	-	-	-	-	-	2	4
	Topiramate 200 mg	39	-	-	-	-	-	2	2
Rowan, 2005	Carbamazepine	171	-	-	6	-	-	-	-
	Gabapentin	177	-	-	0	-	-	-	-
	Lamotrigine	183	-	-	1	-	-	-	-
Sobaniec, 2005	Carbamazepine	28	-	-	-	-	-	-	-
	Vigabratin	26	-	-	-	-	-	-	-
Steinhoff, 2005	Carbamazepine	88	65	-	8	-	-	-	-
	Lamotrigine	88	38	-	5	-	-	5	-
	Valproic Acid	30	16	-	-	-	-	-	-
	Lamotrigine	33	15	-	4	-	-	-	-
Brodie, 2007	Carbamazepine-Controlled Release	291	235	-	16	-	-	31	-
	Levetiracetam	285	227	-	8	-	-	20	-

Table G-15. Adverse events in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Overall Adverse Events (n)	Adverse Events Without Study Withdrawal (n)	Skin Rash (n)	Hypotension (n)	Suicidal Ideation (n)	Nausea (n)	Vomiting (n)
Donati, 2007	Carbamazepine	28	17	-	3	-	-	-	-
	Valproic Acid	29	17	-	0	-	-	-	-
	Oxcarbazepine	55	31	-	4	-	-	-	-
Kang, 2007	Carbamazepine	54	-	19	8	-	-	-	-
	Topiramate	58	-	16	1	-	-	-	-
Levisohn, 2007	Valproic Acid	9	-	-	2	-	-	3	-
	Topiramate	19	-	-	0	-	-	1	-
Marson, 2007 SANAD Arm A	Carbamazepine	378	-	-	38	-	-	9	-
	Gabapentin	377	-	-	13	-	-	7	-
	Lamotrigine	378	-	-	17	-	-	9	-
	Oxcarbazepine	210	-	-	20	-	-	15	-
	Topiramate	378	-	-	17	-	-	4	-
Marson, 2007 SANAD Arm B	Valproic Acid	238	-	-	2	-	-	4	-
	Lamotrigine	239	-	-	13	-	-	4	-
	Topiramate	239	-	-	1	-	-	2	-
Saetre, 2007	Carbamazepine – Sustained Release	92	51	-	12	-	-	-	-
	Lamotrigine	93	51	-	5	-	-	-	-
Morrell, 2008	Valproate	222	122	123	9	-	-	16	16
	Lamotrigine	219	123	210	10	-	-	3	6
Perry, 2008	Carbamazepine	20	14	-	0	-	-	-	-
	Levetiracetam	66	30	-	1	-	-	-	-
Kim, 2009	Carbamazepine	105	21	-	4	-	-	-	-
	Topiramate	41	12	-	0	-	-	-	-
Kwan, 2009	Valproic Acid	43	-	-	0	-	-	-	-
	Lamotrigine	37	-	-	4	-	-	-	-
Ma, 2009	Carbamazepine	120	31	11	15	-	-	-	-
	Valproic Acid	234	44	34	2	-	-	-	-
	Topiramate	143	46	29	1	-	-	-	-
Ramsay, 2010	Phenytoin	127	-	-	10	-	1	12	-
	Topiramate	132	-	-	1	-	0	9	-

- = not reported; adverse events without study withdrawal (n) = number of events; hypotension (n) = number of patients with hypotension; N = sample size; overall adverse events (n) = number of events; nausea (n) = number of patients with nausea; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B = Standard and New Antiepileptic Drugs Trial Arm B; skin rash (n) = number of patients with skin rash; suicidal ideation (n) = number of patients with suicidal ideation; vomiting (n) = number of patients with vomiting

Table G-16. Neurological adverse events in studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Dizziness (n)	Fatigue (n)	Headache (n)	Somnolence (n)
Reinikainen, 1987	Carbamazepine	18	-	-	1	-
	Oxcarbazepine	16	-	-	0	-
Faught, 1993	Valproate	39	2	2	9	2
	Felbamate	38	1	0	3	1
Brodie, 1995	Carbamazepine	129	22	-	32	29
	Lamotrigine	131	16	-	39	16
Kalviainen, 1995	Carbamazepine	45	9	-	1	-
	Vigabatrin	43	3	-	1	-
Reunanen, 1996	Carbamazepine	117	11.7	-	11	20
	Lamotrigine 100 mg	115	7	-	21	7
	Lamotrigine 200 mg	111	5	-	20	7
Tanganelli, 1996	Carbamazepine	25	9 events	-	0 events	-
	Vigabatin	26	1 event	-	4 events	-
Bill, 1997	Phenytoin	142	22	-	27	41
	Oxcarbazepine	136	18	-	20	41
Christie, 1997	Valproic Acid	121	14	-	21	24
	Oxcarbazepine	128	13	-	13	19
Guerreiro, 1997	Pheynction	94	21	-	14	28
	Oxcarbazepine	96	9	-	13	24
Chadwick, 1998	Carbamazepine	74	10	22	10	10
	Gabapentin 300 mg	72	5	9	10	2
	Gabapentin 900 mg	72	11	9	10	5
	Gabapentin 1800 mg	74	11	6	10	5
Chadwick, 1999	Carbamazepine	229	29	50	48	-
	Vigabatrin	228	29	45	47	-
Brodie, 1999	Carbamazepine	48	8	-	8	14
	Lamotrigine	102	10	-	9	12
Steiner, 1999	Phenytoin	95	11	-	18	27
	Lamotrigine	86	8	-	9	6
Biton, 2001	Valproate	68	6	-	4	16
	Lamotrigine	65	7	-	9	5
Kwan, 2001	Carbamazepine	212	10	4	12	6
	Sodium Valproate	101	1	0	4	1
	Lamotrigine	78	0	0	2	1
Nieto-Barrera, 2001	Carbamazepine	215	18	-	25	21
	Lamotrigine	452	31	-	44	17
Biton, 2003	Valproate	20	3	-	3	3
	Lamotrigine	18	4	-	5	1

Table G-16. Neurological adverse events in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Dizziness (n)	Fatigue (n)	Headache (n)	Somnolence (n)
Privitera, 2003	Carbamazepine	126	16	29	29	-
	Valproic Acid	78	10	18	18	-
	Topiramate 100 mg	210	13	20	25	-
	Topiramate 200 mg	199	12	23	18	-
Coppola, 2004	Valproic Acid	19	-	-	0	-
	Lamotrigine	19	-	-	2	-
Fakhoury, 2004	Carbamazepine	46	11	-	4	12
	Lamotrigine	98	17	-	5	13
	Valproic Acid	53	6	-	4	7
	Lamotrigine	105	16	-	11	11
Wheless, 2004	Carbamazepine	23	4	4	5	3
	Valproic Acid	19	0	4	3	6
	Topiramate 100 mg	38	2	6	14	5
	Topiramate 200 mg	39	2	10	6	2
Rowan, 2005	Carbamazepine	171	55	-	30	-
	Gabapentin	177	50	-	27	-
	Lamotrigine	183	50	-	35	-
Steinhoff, 2005	Carbamazepine	88	-	38	-	-
	Lamotrigine	88	4	13	5	-
	Valproic Acid	30	-	5	-	-
	Lamotrigine	33	3	3	-	-
Sobaniec, 2005	Carbamazepine	28	-	-	-	4
	Vigabratin	26	-	-	-	2
Brodie, 2007	Carbamazepine- Controlled Release	291	40	41	74	27
	Levetiracetam	285	31	47	59	32
Donati, 2007	Carbamazepine	28	0	4	2	-
	Valproic Acid	29	0	2	7	-
	Oxcarbazepine	55	4	7	6	-
Kang, 2007	Carbamazepine	54	1	-	-	5
	Topiramate	58	1	-	-	7
Levisohn, 2007	Valproic Acid	9	1	3	1	0
	Topiramate	19	2	2	5	2
Marson, 2007 SANAD Arm A	Carbamazepine	378	14	-	21	-
	Gabapentin	377	23	-	20	-
	Lamotrigine	378	15	-	21	-
	Oxcarbazepine	210	13	-	9	-
	Topiramate	378	15	-	17	-

Table G-16. Neurological adverse events in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Dizziness (n)	Fatigue (n)	Headache (n)	Somnolence (n)
Marson, 2007 SANAD Arm B	Valproic Acid	238	1	-	5	-
	Lamotrigine	239	3	-	6	-
	Topiramate	239	6	-	7	-
Saetre, 2007	Carbamazepine– Sustained Release	92	9	-	10	-
	Lamotrigine	93	13	-	10	-
Stephen, 2007	Valproic Acid	111	-	-	-	-
	Lamotrigine	114	-	-	-	-
Morrell, 2008	Valproate	222	10	-	39	-
	Lamotrigine	219	11	-	29	-
Pack, 2008	Carbamazepine	41	-	-	-	-
	Valproate	14	-	-	-	-
	Phenytoin	15	-	-	-	-
	Lamotrigine	23	-	-	-	-
Perry, 2008	Carbamazepine	20	2	-	-	8
	Levetiracetam	66	1	-	-	6
Kwan, 2009	Valproic Acid	43	-	-	4	-
	Lamotrigine	37	-	-	1	-
Ma, 2009	Carbamazepine	120	2	-	6	1
	Valproic Acid	234	3	-	9	3
	Topiramate	143	1	-	3	0
Glauser, 2010	Ethosuximide	155	9	15	19	14
	Valproic Acid	147	2	18	12	4
	Lamotrigine	149	4	13	12	3
Ramsay, 2010	Phenytoin	127	35	11	15	18
	Topiramate	132	26	12	11	16

- = not reported; dizziness (n) = number of patients with dizziness; fatigue (n) = number of patients with fatigue; headache (n) = number of patients with headache; N = sample size; SANAD Arm A = Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B = Standard and New Antiepileptic Drugs Trial Arm B; somnolence (n) = number of patients with somnolence

Table G-17. Cosmetic adverse effects in studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	Acne (n)	Alopecia (n)	Gum Hyperplasia (n)
Dam, 1989	Carbamazepine	98	-	2	-
	Oxcarbazepine	92	-	0	-
Kalviainen, 1995	Carbamazepine	45	-	0	-
	Vigabatrin	43	-	1	-
Bill 1997	Phenytoin	142	3	-	18
	Oxcarbazepine	136	8	-	2
Christie, 1997	Sodium Valproate	121	-	21	-
	Oxcarbazepine	128	-	11	-
Guerreiro, 1997	Pheynition	94	-	-	24
	Oxcarbazepine	96	-	-	2
Biton, 2001	Valproate	68	-	7	-
	Lamotrigine	65	-	2	-
Biton, 2003	Valproate	20	-	3	-
	Lamotrigine	18	-	0	-
Privitera, 2003	Carbamazepine	126	-	2	-
	Valproic Acid	78	-	14	-
	Topiramate 100 mg	210	-	4	-
	Topiramate 200 mg	199	-	2	-
Fakhoury, 2004	Carbamazepine	46	-	1	-
	Lamotrigine	98	-	3	-
	Valproic Acid	53	-	6	-
	Lamotrigine	105	-	1	-
Wheless, 2004	Carbamazepine	23	-	1	-
	Valproate	19	-	2	-
	Topiramate 100 mg	38	-	0	-
	Topiramate 200 mg	39	-	0	-
Steinhoff, 2005	Carbamazepine	88	-	-	-
	Lamotrigine	88	-	4	-
	Valproate	30	-	3	-
	Lamotrigine	33	-	2	-
Donati, 2007	Carbamazepine	28	-	1	-
	Valproic Acid	29	-	3	-
	Oxcarbazepine	55	-	0	-
Levisohn, 2007	Valproic Acid	9	-	3	-
	Topirimate	19	-	2	-
Stephen, 2007	Valproate	111	-	-	-
	Lamotrigine	114	-	-	-
Morrell, 2008	Valproate	222	-	25	-
	Lamotrigine	219	-	3	-

Table G-17. Cosmetic adverse effects in studies comparing older versus newer antiepileptic drugs (continued)

Study, Year	Group	N	Acne (n)	Alopecia (n)	Gum Hyperplasia (n)
Kim, 2009	Carbamazepine	105	-	1	-
	Topiramate	41	-	0	-

- = not reported; acne (n) = number of patients with acne; alopecia (n) = number of patients with alopecia; gum hyperplasia (n) = number of patients with gum hyperplasia;
N = sample size

Table G-18. Change in bone mineral density from baseline in studies comparing older versus newer antiepileptic drugs

Study year	Group	N	Bone Mineral Density (gm/cm ²) Mean (SD)	Bone Mineral Density (gm/cm ²) Mean (SD)	Bone Mineral Density (gm/cm ²) Mean (SD)	Bone Mineral Density (gm/cm ²) Mean (SD)	Bone Mineral Density (gm/cm ²) Mean (SD)
Babayigit, 2006	Carbamazepine	23	Lumbar Vertebrae 1 0.648 (0.162)	Lumbar Vertebrae 2 0.72 (0.173)	Lumbar Vertebrae 3 0.732 (0.164)	Lumbar Vertebrae 4 0.744 (0.188)	Lumbar Vertebrae Total 0.665 (0.199)
	Valproic Acid	31	Lumbar Vertebrae 1 0.596 (0.191)	Lumbar Vertebrae 2 0.666 (0.213)	Lumbar Vertebrae 3 0.692 (0.206)	Lumbar Vertebrae 4 0.694 (0.194)	Lumbar Vertebrae Total 0.665 (0.199)
	Oxcarbazepine	14	Lumbar Vertebrae 1 0.679 (0.188)	Lumbar Vertebrae 2 0.747 (0.188)	Lumbar Vertebrae 3 0.771 (0.196)	Lumbar Vertebrae 4 0.767 (0.195)	Lumbar Vertebrae Total 0.744 (0.188)
Pack, 2008	Carbamazepine	41	Lumbar Spine Baseline: 1.016 (0.12) 1 year: 1.021 (0.12)	Femoral Neck Baseline: 0.792 (0.10) 1 year: 0.794 (0.10)	Total Hip Baseline: 0.889 (0.12) 1 year: 0.892 (0.11)	-	-
	Valproate	14	Lumbar Spine Baseline: 0.998 (0.15) 1 year: 0.999 (0.16)	Femoral Neck Baseline: 0.838 (0.18) 1 year: 0.843 (0.18)	Total Hip Baseline: 0.926 (0.18) 1 year: 0.931 (0.19)	-	-
	Phenytoin	15	Lumbar Spine Baseline: 1.073 (0.16) 1 year: 1.077 (0.17)	Femoral Neck Baseline: 0.871 (0.18) 1 year: 0.849 (0.16)	Total Hip Baseline: 0.962 (0.15) 1 year: 0.961 (0.15)	-	-
	Lamotrigine	23	Lumbar Spine Baseline: 1.068 (0.11) 1 year: 1.066 (0.09)	Femoral Neck Baseline: 0.835 (0.11) 1 year: 0.828 (0.11)	Total Hip Baseline: 0.922 (0.11) 1 year: 0.920 (0.11)	-	-

- = not reported; N = sample size; SD = standard deviation

Table G-19. Change in bone mineral density Z score in studies comparing older versus newer antiepileptic drugs

Study Year	Group	N	Bone Mineral Density Z Score Mean (SD)
Kim, 2007	Carbamazepine	10	Before: 0.42 (0.26) After: -0.34 (0.35)
	Valproic Acid	15	Before: 0.61 (0.41) After: 0.06 (0.30)
	Lamotrigine	8	Before:0.60 (0.17) After:0.48 (0.18)

N = sample size; SD = standard deviation

Table G-20. Serious adverse events for individual antiepileptic drugs

Antiepileptic Drug	Black Boxed Warning	Warnings
Carbamazepine	Serious Dermatologic Reactions Including Toxic Epidermal Necrosis and Stevens-Johnson Syndrome Aplastic Anemia Agranulocytosis	Increased Risk of Suicidal Ideation and Behavior
Clonazepam	None	None
Ethosuximide	None	Blood Discrasias Systemic Lupus Erythematosus Increased Risk of Suicidal Ideation and Behavior
Felbamate	Aplastic Anemia Hepatic Failure	Increased Risk of Suicidal Ideation and Behavior
Gabapentin	None	Increased Risk of Suicidal Ideation and Behavior
Lacosamide	None	Increased Risk of Suicidal Ideation and Behavior
Lamotrigine	Life Threatening Skin Rashes Including Stevens-Johnson Syndrome, Toxic Epidermal Necrosis and or Skin Rash Related Death	1. Life Threatening Hypersensitivity Reactions Acute Multi Organ Failure Blood Dyscrasias Increased Risk of Suicidal Ideation and Behavior
Levetiracetam	None	Decreased Red and White Blood Cells Increased Risk of Suicidal Ideation and Behavior
Oxcarbazepine	None	Clinically Significant Hyponatremia Anaphylaxis Angioedema Multi-Organ Hypersensitivity Reaction Stevens-Johnson Syndrome Agranulocytosis Aplastic Anemia Pancytopenia Increased Risk of Suicidal Ideation and Behavior
Phenobarbital	None	None
Phenytoin	None	Skin Reactions Including Exfoliative Dermatitis, Stevens-Johnson Syndrome and Toxic Epidermal Necrosis Anticonvulsant Hypersensitivity Syndrome with Multi-Organ Involvement Increased Risk of Suicidal Ideation and Behavior
Primidone	None	Increased Risk of Suicidal Ideation and Behavior
Pregabalin	None	Angioedema Hypersensitivity Reactions Increased Risk of Suicidal Ideation and Behavior

Table G-20. Serious adverse events for individual antiepileptic drugs (continued)

Antiepileptic Drug	Black Boxed Warning	Warnings
Rufinamide	None	QT Shortening Multi-Organ Hypersensitivity Increased Risk of Suicidal Ideation and Behavior
Tiagabine	None	Sudden Unexpected Death in Epilepsy Increased Risk of Suicidal Ideation and Behavior
Topiramate	None	Acute Myopia and Closed Angle Glaucoma Increased Risk of Suicidal Ideation and Behavior
Valproic Acid	Hepatotoxicity Pancreatitis Teratogenicity Including Neural Tube Defects	Thrombocytopenia
Vigabatrin	Reduced Visual Acuity Permanent Vision Loss Progressive and Permanent Bilateral Concentric Visual Field Constriction	Increased Risk of Suicidal Ideation and Behavior
Zonisamide	None	Serious Skin Reactions Including Toxic Epidermal Necrosis and Stevens-Johnson Syndrome Aplastic Anemia Agranulocytosis Increased Risk of Suicidal Ideation and Behavior

Appendix H. Strength of Evidence for Outcomes

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Table H-1. Strength of evidence for final outcome evaluations for innovator versus generic antiepileptic drugs under Key Question 1

Outcome	Brand AED	Generic AEDs	Number of Studies	Design	Risk of Bias	Quality Assessment			Summary
						Inconsistency	Indirectness	Imprecision	Quality
Mortality			0						Insufficient

AEDs = antiepileptic drugs

Table H-2. Strength of evidence for medical service utilization for innovator versus generic antiepileptic drugs under Key Question 1

Outcome	Brand AED	Generic AEDs	Number of Studies	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Outpatient medical care utilization (Office or ER visit)	Various	Various	4	Observational	Very serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Hospitalizations	Various	Various	4	Observational	Very serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Ambulance Services			0						Insufficient	Important
Composite of medical services	Various	Various	3	Observational	Serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Insufficient	Important
Hospital stay duration	Various	Various	4	Observational	Very serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Low	Important

AED = antiepileptic drug; ER = emergency room

Table H-3. Strength of evidence for health related quality of life for innovator versus generic antiepileptic drugs under Key Question 1

Outcome	Brand AED	Generic AEDs	Number of Studies	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Health-related quality of life			0						Insufficient	Important

AED = antiepileptic drug

Table H-4. Strength of evidence for final health outcomes for innovator versus generic antiepileptic drugs Key Question 1

Outcome	Brand AED	Generic AEDs	Number of Studies	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Seizure Occurrence/ breakthrough seizure	Carbamazepine	8 Generics	5	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	3 Generics	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Valproic Acid	1 Generic	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Phenytoin Valproic Acid	12 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Seizure Frequency	Carbamazepine	2 Generics	2	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
	Valproic Acid	1 Generic	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Valproic Acid	3 Generics	3	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Time to first seizure			0						Insufficient	Important
Incidence of status epilepticus			0						Insufficient	Important
Seizure remission			0						Insufficient	Important
Secondary seizure injury			0						Insufficient	Important

AED = antiepileptic drug; RCT = randomized controlled trial

Table H-5. Strength of evidence for withdrawals due to adverse events for innovator versus generic antiepileptic drugs in Key Question 1

Outcome	Brand AED	Generic AEDs	Number of Studies	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Total withdrawals	Carbamazepine	(9, 1) Generics	8 (7, 1)	RCTs, Observational	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	5 Generics	3 (2, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin	(14, 1) Generics	11 (9, 1, 1)	RCTs, non-randomized and OBS trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Carbamazepine	9 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	5 Generics	3 (2, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin	14 Generics	10 (9, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Withdrawals due to adverse events	Carbamazepine	9 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	5 Generics	3 (2, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin	14 Generics	10 (9, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

AED = antiepileptic drug; RCT = randomized controlled trial

Table H-6. Strength of evidence for pharmacokinetic effects for innovator versus generic antiepileptic drugs Key Question 2

Outcome	Brand AED	Generic AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Cmax	Carbamazepine	10 Generics	6	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Lamotrigine	1 Generic	1	Non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Phenytoin	5 Generics	1	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin Lamotrigine	16 Generics	8 (7, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Cmin	Carbamazepine	9 Generics	5 (4, 1)	RCTs, non-blinded trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Lamotrigine	1 Generic	1	Non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Lamotrigine	10 Generics	6 (4, 1, 1)	RCTs, non-randomized trial, non-blinded trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Css	Carbamazepine	4 Generics	4	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	8 Generics	3	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
	Carbamazepine Phenytoin	12 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

Table H-6. Strength of evidence for pharmacokinetic effects for innovator versus generic antiepileptic drugs Key Question 2 (continued)

Outcome	Brand AED	Generic AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
AUC	Carbamazepine	10 Generics	6	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Lamotrigine	1 Generic	1	Non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Phenytoin	5 Generics	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Lamotrigine Phenytoin	16 Generics	8 (7, 1)	RCTs and non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Tmax	Carbamazepine	9 Generics	5	RCTs	Serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important

AED = antiepileptic drug; RCT = randomized controlled trial

Table H-7. Strength of evidence for incidence of adverse events for innovator versus generic antiepileptic drugs in Key Question 3

Outcome	Brand AED	Generic AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Incidence of ADRs	Carbamazepine	1 Generic	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Phenytoin	2 Generics	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Phenytoin	3 Generics	2	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Incidence of Skin Rash	Carbamazepine	2 Generics	2	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Loss of drivers license			0						Insufficient	Important
Loss of employment			0						Insufficient	Important
Switchback rates			0						Insufficient	Important

AED = antiepileptic drug; RCT = randomized controlled trial

Table H-8. Strength of evidence for final outcome evaluations for older versus newer antiepileptic drugs under key question 1

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Mortality	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	6	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Mortality	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Mortality	Valproic Acid	Lamotrigine Topiramate Vigabatrin	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

AED =antiepileptic drug; Obs =bservational study; RCT = randomized controlled trial

Table H-9. Strength of evidence for medical service utilization for older versus newer antiepileptic drugs under key question 1

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Use of medical services			0						Insufficient	Important
Use of ambulance services			0						Insufficient	Important
Outpatient medical care utilization			0						Insufficient	Important
Hospitalizations	Carbamazepine	Lamotrigine	1	RCT	No risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Hospitalizations	Ethsuximide	Lamotrigine	1	RCT	No risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Hospitalizations	Valproic Acid	Lamotrigine	1	RCT	No risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Ambulance Services			0						Insufficient	Important
Outpatient medical care utilization			0						Insufficient	Important
Composite of medical services			0						Insufficient	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-10. Strength of evidence for health related quality of life for older versus newer antiepileptic drugs under key question 1

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Health related quality of life	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Tiagabine Topiramate	4	RCTs	No serious risk of bias	No graded	No serious indirectness	Serious imprecision	Insufficient	Important
Health related quality of life	Carbamazepine Sustained-Release	Levetiracetam	1	Obs	Serious risk of bias	No graded	No serious indirectness	Serious imprecision	Insufficient	Important
Health related quality of life	Phenytoin	Lamotrigine Tiagabine	2	RCTs	No serious risk of bias	No graded	No serious indirectness	Serious imprecision	Insufficient	Important
Health related quality of life	Valproic Acid	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	No graded	No serious indirectness	Serious imprecision	Insufficient	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-11. Strength of evidence for final health outcomes for olderer versus newer antiepileptic drugs key question 1

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Time to first seizure	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	6	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Time to first seizure	Phenytoin	Lamotrigine Topiramate	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Time to first seizure	Valproic Acid	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Change from baseline in seizure frequency	Carbamazepine	Oxcarbazepine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Serious imprecision	Insufficient	Important
Change from baseline in seizure frequency	Phenytoin	Oxcarbazepine	2	RCTs	Very serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Insufficient	Important
Change from baseline in seizure frequency	Valproic Acid	Oxcarbazepine	1	RCT	Very serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
12 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	2	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Low	Important

Table H-11. Strength of evidence for final health outcomes for older versus newer antiepileptic drugs key question 1 (continued)

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
12 Month Seizure Remission	Valproic Acid	Lamotrigine Topiramate	1	RCT	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
24 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate	1	RCT	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
24 Month Seizure Remission	Valproic Acid	Lamotrigine Topiramate	1	RCT	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Seizure freedom	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin Levetiracetam	20 (15, 5)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Seizure freedom	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	3 (2, 1)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Seizure freedom	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	5 (4, 1)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Seizure freedom	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	15 (12, 3)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-12. Strength of evidence for withdrawals due to adverse events for older versus newer antiepileptic drugs in key question 1

Outcome	Older AED	Newer AED	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Total withdrawals	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	21 (16, 5)	RCTs and Observational	No serious risk of bias	Very serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Total withdrawals	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Total withdrawals	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	No graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Total withdrawals	Phenytoin	Lamotrigine Oxcarbazepine	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Total withdrawals	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate Vigabatrin	19 (17, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	16 (11, 5)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Carbamazepine Controlled Release	Lamotrigine	1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Insufficient	Important
Withdrawals due to lack of efficacy	Phenytoin	Lamotrigine Oxcarbazepine	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	15 (12, 3)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

Table H-12. Strength of evidence for withdrawals due to adverse events for older versus newer antiepileptic drugs in key question 1 (continued)

Outcome	Older AED	Newer AED	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Withdrawals due to adverse events	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	24 (18, 6)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Withdrawals due to adverse events	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk or bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Withdrawals due to adverse events	Ethosuximide	Lamotrigine	1	RCT	No serious risk or bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Withdrawals due to adverse events	Phenytoin	Lamotrigine Oxcarbazepine	3	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Withdrawals due to adverse events	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	18 (16, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-13. Strength of evidence for neurologic adverse events for older versus newer antiepileptic drugs in Key Question 3

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Headache	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	17 (15, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	17 (15, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Fatigue	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	7	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Low	Important
Fatigue	Carbamazepine Controlled Release	Levetiracetam	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Fatigue	Phenytoin	Topiramate	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important

Table H-13. Strength of evidence for neurologic adverse events for older versus newer antiepileptic drugs in Key Question 3 (continued)

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Fatigue	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	8	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Fatigue	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Somnolence	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Topiramate Vigabatrin	12 (8, 4)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Somnolence	Carbamazepine Controlled Release	Levetiracetam	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Somnolence	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Somnolence	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	11 (9, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Somnolence	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	No serious imprecision	Insufficient	Important

Table H-13. Strength of evidence for neurologic adverse events for older versus newer antiepileptic drugs in Key Question 3 (continued)

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Dizziness	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	19 (16, 3)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Dizziness	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Dizziness	Phenytoin	Lamotrigine Oxcarbazepine	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Dizziness	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	14 (12, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Dizziness	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Impotent

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-14. Strength of evidence for incidence of adverse events for older versus newer antiepileptic drugs in key question 3

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Nausea	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	8	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Nausea	Carbamazepine Controlled Release	Levetiracetam	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Nausea	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Nausea	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	11	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Vomiting	Carbamazepine	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Vomiting	Phenytoin	Oxcarbazepine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	No serious imprecision	Insufficient	Important
Vomiting	Valproic Acid	Felbamate Lamotrigine Topiramate	5	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Skin Rash	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	18 (13, 5)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important

Table H-14. Strength of evidence for incidence of adverse events for older versus newer antiepileptic drugs in key question 3 (continued)

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Skin Rash	Carbamzepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Skin Rash	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Skin Rash	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	12 (10, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-15. Strength of evidence for cognition and mood for older versus newer antiepileptic drugs in Key Question 3

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Cognition	Carbamazepine	Oxcarbazepine Tiagabine Topiramate Vigabatrin	4	RCTs	No serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Insufficient	Important
Cognition	Phenytoin	Tiagabine	1	RCT	No serious risk of bias	Not graded	Serious indirectness	Serious imprecision	Insufficient	Important
Cognition	Valproic Acid	Oxcarbazepine Topiramate	5 (3, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	Serious indirectness	Very serious imprecision	Insufficient	Important
Mood	Carbamazepine	Tiagabine	1	RCT	No serious risk of bias	Not graded	Serious indirectness	No serious imprecision	Insufficient	Important
Mood	Phenytoin	Tagabine	1	RCT	No serious risk of bias	Not graded	Serious indirectness	Serious imprecision	Insufficient	Important
Mood	Valproic Acid	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Insufficient	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-16. Strength of evidence for bone mineral density for older versus newer antiepileptic drugs in key question 3

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Bone Mineral Density	Carbamazepine	Lamotrigine Oxcarbazepine	3	Observational	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Insufficient	Important
Bone Mineral Density	Phenytoin	Lamotrigine	1	Observational	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Insufficient	Important
Bone Mineral Density	Valproic Acid	Lamotrigine Oxcarbazepine	3	Observational	Serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Insufficient	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Table H-17. Strength of evidence for cosmetic adverse effects for older versus newer antiepileptic drugs Key Question 3

Outcome	Older AED	Newer AEDs	Number of Studies (RCTs, Obs)	Design	Risk of Bias	Quality Assessment			Summary of Findings	
						Inconsistency	Indirectness	Imprecision	Quality	Importance
Alopecia	Carbamazepine	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	6	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Alopecia	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	8	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Acne	Phenytoin	Oxcarbazepine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Gum Hyperplasia	Phenytoin	Oxcarbazepine	2	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	High	Important

AED = antiepileptic drug; Obs = observational study; RCT = randomized controlled trial

Appendix I. Applicability of Individual Studies and the Body of Evidence

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Table I-1. Evaluation of applicability for individual studies for innovator versus generic antiepileptic drug evaluation

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Zachry, 2009 N=1664	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Population, Outcomes	In this study, patients were switched from one version of the medication to another "A" rated version. This could be from innovator to generic, generic to generic, or generic to innovator. As such it is not a true comparison of innovator to generic switching. ADRs not reported
Rascati, 2009 N=3964	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Population, Outcomes	In this study, patients were switched from one version of the medication to another "A" rated version. This could be from innovator to generic, generic to generic, or generic to innovator. As such it is not a true comparison of innovator to generic switching. ADRs not reported
Devine, 2010 N=11796	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Population, Outcomes	In this study, patients were switched from one version of the medication to another "A" rated version. This could be from innovator to generic, generic to generic, or generic to innovator. As such it is not a true comparison of innovator to generic switching. ADRs not reported
Labiner, 2010a N=18125	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Outcomes	ADRs not reported
Labiner 2010b N=15500	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Outcomes	ADRs not reported
Kauko, 1974 N=20	Study Designation: Efficacy study Composite Score: 1 of 7	Intention to treat analysis	Population, Intervention, Comparator, Outcomes, Setting	Only in mentally retarded patients No final health outcomes reported Short duration of followup (30 days) Small sample size (only 20 patients enrolled) ADRs not reported Institutionalized facility for mentally retarded Conducted in Europe Study conducted before 1990

Table I-1. Evaluation of applicability for individual studies for innovator versus generic antiepileptic drug evaluation (continued)

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Glende, 1983 N=5	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Outcomes, Setting	Short duration of followup (4 weeks total, 2 weeks per group) Small sample size (only 5 patients enrolled) Conducted in Europe Study conducted before 1990
Jumao-as, 1989 N=10	Study Designation: Effectiveness study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Setting	Short duration of followup (10 weeks total, 5 weeks per group) Small sample size (only 10 patients enrolled) Study conducted before 1990
Hartley, 1990 N=23	Study Designation: Efficacy study Composite Score: 3 of 7	Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Population, Intervention, Comparator, Outcomes, Setting	Patients all young (6–15 years) No final health outcomes reported Short study duration (12 weeks total, 6 weeks per group) Small sample size (only 23 patients enrolled) Patients withdrawn were taken out of the final analysis Conducted in Europe
Hartley, 1991 N=12	Study Designation: Efficacy study Composite Score: 2 of 7	Intention to treat analysis Enrolled primary care population	Population, Intervention, Comparator, Outcomes, Setting	Patients all young (6.5–15 years) No final health outcomes reported No ADRs reported Small sample size (only 12 patients enrolled) Short duration of followup (12 weeks total, 6 weeks per group) Conducted in Europe
Oles, 1992a N=20	Study Designation: Efficacy study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Population, Intervention, Comparator	Patients had to be 13 years or older Patients had to be seizure free for extended time (5 months to 2 years) Had to have been receiving carbamazepine for at least 6 months Small sample size (only 20 patients enrolled) Short duration of followup (3 months in each group)

Table I-1. Evaluation of applicability for individual studies for innovator versus generic antiepileptic drug evaluation (continued)

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Oles 1992b N=20	Study Designation: Efficacy study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Population, Intervention, Comparator	Patients had to be 13 years or older Patients had to have refractory seizures (at least 2 per month in previous 3 months) Had to have been receiving CBZ for at least 6 months Small sample size (only 20 patients enrolled) Short duration of followup (3 months in each group)
Reunanen, 1992 N=21	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Setting	Small sample size (only 21 patients enrolled) Short duration of followup (3 months in each group) Conducted in Europe
Silpakit, 1997 N=18	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Setting	Small sample size (only 18 patients enrolled) Short duration of followup (12 weeks total, 3 weeks on each phase) Conducted in Asia
Aldenkamp, 1998 N=12	Study Designation: Efficacy study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Setting	Small sample size (only 12 patients enrolled) Short duration of followup (9 days total, 3 days per therapy) Conducted in Europe
LeLorier, 2008a N=671	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes, Setting	No ADRs reported Conducted in Canada
LeLorier, 2008b N=1060	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Outcomes, Setting	No final health outcomes reported No ADRs reported Conducted in Canada
LeLorier, 2008c N=202	Study Designation: Efficacy study Composite Score: 2 of 7	Less stringent eligibility criteria Adequate study duration	Outcomes, Setting	No final health outcomes reported No ADRs reported Conducted in Canada

Table I-1. Evaluation of applicability for individual studies for innovator versus generic antiepileptic drug evaluation (continued)

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
LeLorier 2008d N=851	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate study sample	Outcomes, Setting	No final health outcomes reported No ADRs reported Conducted in Canada
Andermann, 2007a N=1142	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Population, Outcomes, Setting	Population not well specified No final health outcomes reported No ADRs reported Conducted in Canada
Andermann, 2007b N=1600	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Population, Outcomes, Setting	Population not well specified No final health outcomes reported No ADRs reported Conducted in Canada
Andermann, 2007c N=2017	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Population, Outcomes, Setting	Population not well specified No final health outcomes reported No ADRs reported Conducted in Canada
Nielsen, 2008a N=9	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Outcomes, Setting	No final health outcomes reported No ADRs reported Short duration of followup (2 weeks on innovator and 7-15 days on generic) Small sample size (only 9 patients enrolled) Conducted in Europe
Lund, 1974 N=9	Study Designation: Efficacy study Composite Score: 3 of 7	Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Population, Setting	Patients treated with drug for at least one year admitted to hospital to exclude irregular drug intake No final health outcomes reported Short duration of followup (8 days on innovator and 11 days on generic) Small sample size (only 9 patients enrolled) Conducted in Europe Conducted before 1990

Table I-1. Evaluation of applicability for individual studies for innovator versus generic antiepileptic drug evaluation (continued)

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Chen, 1982 N=18	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Outcomes, Setting	No final health outcomes reported Short duration of followup (9 weeks total, 3 weeks per therapy) Small sample size (only 20 patients enrolled) Conducted in Europe Conducted before 1990
Hodges, 1986 N=30	Study Designation: Efficacy study Composite Score: 3 of 7	Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Population, Intervention, Comparator, Setting	Only pediatric patients (3–15 years) Short duration of followup (12 weeks total, 4 weeks on each therapy) Small sample size (only 30 patients enrolled) Conducted in Europe Conducted before 1990
Kishore, 1986 N=60	Study Designation: Effectiveness study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Setting	Short duration of followup (3 months) Small sample size (only 60 patients enrolled) Conducted in Asia Conducted before 1990
Mikati, 1992 N=10	Study Designation: Effectiveness study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Adequate study duration Intention to treat analysis Enrolled primary care population	Intervention, Comparator	Small sample size (only 10 pts enrolled)
Soryal, 1992 N=14	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Setting	Short duration of followup (4 weeks per therapy) Small sample size (only 14 patients enrolled) Conducted in Europe
Duh, 2009 N=948	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes, Setting	No ADRs reported Conducted in Canada
Paradis, 2009 ^a N=1164	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes, Setting	No ADRs reported Conducted in Canada

Table I-1. Evaluation of applicability for individual studies for innovator versus generic antiepileptic drug evaluation (continued)

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Vadney, 1997 N=64	Study Designation: Efficacy study Composite Score: 2 of 7	Assessed final health outcomes Assessed adverse outcomes	Population, Intervention, Comparator	Limited to patients with mental retardation Short duration of followup (8 weeks total, 4 weeks on each therapy) Small sample size (only 64 patients enrolled)

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Reinikainen, 1987 N=40	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed adverse outcomes Assessed final health outcomes Less stringent eligibility criteria Adequate study duration with clinically relevant treatments	Population	Small sample size (40 patients)
Danner, 1988 N= 25	Study Designation: Efficacy study Composite Score: 3 of 7	Adequate followup period Adequate study duration with clinically relevant treatments Less stringent eligibility criteria	Population Outcomes	Small sample size (25 patients) Assessed only neurological outcomes
Dam, 1989 N= 194	Study Designation: Efficacy Study Composite Score: 6 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Assessed final health outcomes Assessed adverse outcomes Adequate sample size	Population	Conducted in Denmark, Finland, Norway and Sweden
Sachdeo, 1992 N= 44	Study Designation: Efficacy and Safety study Composite Score: 3 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes	Population	Short follow up period Only partial-onset seizures Small sample size (44 patients)
Brodie, 1995 N=260	Study Designation: Efficacy Study Composite Score: 5 of 7	Adequate sample size Adequate study duration with clinically relevant treatments Enrolled primary care population Less stringent eligibility criteria Assessed final health outcomes	Outcomes	Adverse events not reported
Kalviainen, 1995 N= 100	Study Designation: Efficacy and Safety study Composite Score: 5 of 7	Enrolled a primary care population Adequate sample size Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome	Population	Only patients aged 15–64 years
Reunanen, 1995 N=343	Study Designation: Efficacy Study Composite Score: 5 of 7	Adequate sample size Assessed final health outcomes Assessed adverse outcomes Less stringent eligibility criteria Enrolled primary care population	Outcomes	Short Study Duration (26 weeks)

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Sabers 1995 N= 52	Study Designation: Effectiveness study Composite Score: 2 of 7	Less stringent eligibility criteria Adequate study duration with clinically relevant treatments	Population Outcomes	No final health outcomes reported Did not report adverse events Small sample size (52 patients)
Reunanen, 1996 N= 343	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Adequate sample size Enrolled primary care population	None	None
Tanganelli, 1996 N= 51	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis Enrolled primary care population	Population	Only patients with complex partial seizures Small sample size (51 patients)
Bill, 1997 N=287	Study Designation: Efficacy Study Composite Score: 5 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate sample size Assessed final health outcomes Adequate study duration with clinically relevant treatments	None	Adverse events not reported
Christie, 1997 N=249	Study Designation: Efficacy Study Composite Score: 5 of 7	Less stringent eligibility criteria Enrolled primary care population Adequate study duration with clinically relevant treatments Assessed final health outcomes Assessed adverse outcomes	Population	Conducted in Belgium, Brazil, France, Germany, the Netherlands and South Africa
Guerreiro, 1997 N= 193	Study Designation: Efficacy study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Enrolled primary care population	Population Setting	Only enrolled children and adolescents Only patients with partial seizures and generalized tonic-clonic seizures without partial onset (GTCS) Conducted in South America (Brazil & Argentina)

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Chadwick, 1998 N=292	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	None	None
Brodie, 1999a N= 150	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Adequate sample size	Population	Enrolled only patients >65 yrs old
Brodie, 1999b N=215	Study Designation: Efficacy Study Composite Score: 5 of 7	Adequate sample size Enrolled primary care population Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes	None	12-week maintenance phase
Chadwick, 1999 N=457	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used intention to treat analysis Assessed adverse outcomes	Population	Conducted in 44 centers in the United Kingdom, Denmark, Finland, Israel, France, South Africa, Spain, Switzerland, and Australia
Gobbi, 1999 N= 80	Study Designation: Efficacy and Safety study Composite Score: 4 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis	Population	Enrolled only children with partial epilepsy Small sample size (80 patients)
Steiner, 1999 N= 181	Study Designation: Efficacy and safety study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Less stringent eligibility criteria	Population	Patients aged 14–75years Patients with absence seizures not eligible High dropout rate in the study (50%)

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Dodrill, 2000 N= 277	Study Designation: Effectiveness study Composite Score: 2 of 7	Adequate study duration with clinically relevant treatments Adequate sample size	Population Outcome	Only adults with uncontrolled partial seizures were enrolled Did not assess adverse outcomes Reports only neuropsychological outcomes
Gillham, 2000 N= 260	Study Designation: Effectiveness study Composite Score: 3 of 7	Adequate study duration with clinically relevant treatments Adequate sample size Less stringent eligibility criteria	Outcomes	Assessed only health-related quality of life Did not assess adverse outcomes
Biton, 2001 N=133	Study Designation: Efficacy Study Composite Score: 3 of 7	Less stringent eligibility criteria Enrolled primary care population Adequate study duration with clinically relevant treatments Assessed adverse outcomes	Outcomes	Reported weight, safety/tolerability data only
Cramer, 2001 N=349	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed final health outcomes Enrolled primary care population Less stringent eligibility criteria Adequate sample size	Outcomes	Short study duration (16 weeks) Adverse events not reported
Kwan, 2001 N= 391	Study Designation: Efficacy, effectiveness and safety study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcome Adequate sample size Adequate study duration with clinically relevant treatments	Population	Only patients from a single tertiary hospital in Glasgow
Nieto-Barrera, 2001 N=618	Study Designation: Efficacy Study Composite Score: 5 of 7	Enrolled primary care population Adequate sample size Assessed final health outcomes Less stringent eligibility criteria Assessed adverse events	None	Short study duration (24 weeks long)
Sackellares, 2002 N= 133	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes	Did not asses adverse events

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Biton, 2003 N=38	Study Designation: Efficacy Study Composite Score: 2 of 7	Adequate study duration with clinically relevant treatments Assessed adverse outcomes	Population Outcomes	Small sample size (38 patients) Reported weight, safety/tolerability data only Enrolled only pts 12–20 yrs old
Faught, 2003 N= 111	Study Designation: Efficacy study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcomes Adequate sample size Used intention to treat analysis	Population	Only patients with uncontrolled partial onset seizures Short study duration (112 days)
Kim, 2009 N= 146	Study Designation: Effectiveness and safety study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Enrolled a primary care population	Population	Only enrolled patients < 2yrs Conducted in Korea
Meador, 2003 N= 76	Study Designation: Efficacy Study Composite Score: 3 of 7	Use intention to treat analysis Enrolled primary care population Less stringent eligibility criteria	Population Outcomes	Only reported cognitive/Behavioral outcomes Short study duration (20 weeks) Did not report adverse outcomes Small Sample Size (63 patient)
Privitera, 2003 N=613	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Assessed adverse outcomes Adequate sample size Assessed final health outcomes Adequate study duration with clinically relevant treatments Use intention to treat analysis	None	None
Clemens, 2004 N= 21	Study Designation: Efficacy Study Composite Score: 2 of 7	Less stringent eligibility criteria Enrolled primary care population	Population Outcomes	Small sample size (21 patients) Only reported EEG outcomes Short study duration (4 weeks) Did not report adverse events
Coppola, 2004 N= 38	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed adverse outcomes Assessed final health outcomes Used Intention to treat analysis Adequate study duration with clinically relevant treatments	Population	Only patients 3–17 yrs old Small sample size (38 patients)

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Fakhoury, 2004 N= 302	Study Designation: Efficacy and Safety Composite Score: 4 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size	Population	Enrolled only patients ≥ 16 yrs
Wheless, 2004 N= 119	Study Designation: Efficacy and safety study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis	Population	Only enrolled patients aged ≤ 16 yrs
Babayigit, 2005 N=68	Study Designation: Efficacy Study Composite Score: 0 of 7	None	Population Outcomes	Children only, one site Small sample size (68 patients) Only Bone Mineral Density and other markers Did not report adverse events
Rowan, 2005 N= 593	Study Designation: Efficacy and Safety study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Adequate sample size	Population	Only older patients were included Study in Veterans Administration patients in the United States
Sobaniec, 2005 N= 54	Study Designation: Efficacy and safety study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcome Used intention to treat analysis	Population	Only patients age 2–17 yrs with history of partial seizures Only one site in Poland Short follow-up period Small sample size (54 patients)
Steinhoff, 2005 N= 269	Study Designation: Efficacy and safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis	Population	Only enrolled patients with newly diagnosed epilepsy >12 yrs of age

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Brodie, 2007 N=576	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Used Intention to treat analysis Adequate sample size Assesses final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes	None	None
Donati, 2007 N= 112	Study Designation: Efficacy study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis	Population	Only enrolled patients aged 6 to <17 yrs Assessed only cognitive function
Kang, 2007 N=112	Study Designation: Efficacy, effectiveness and safety study Composite Score: 6 of 7	Enrolled a primary care population Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse events Use intention to treat analysis	Population	Conducted in Korea Enrolled only patients 5-15 yrs
Kim, 2007 N= 33	Study Designation: Safety study Composite Score: 4 of 7	Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis	Population Setting Outcome	Only patients aged 18 to 50 years Small sample size (33 patients) Conducted in Korea Did not assess final health outcome, only BMD was assessed
Levisohn, 2007 N=28	Study Designation: Efficacy Study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Only JME patients Small sample size (28 patients)
Marson, 2007 N=716	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Conducted in the United Kingdom

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Marson, 2007 N=1721	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility Criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Conducted in the United Kingdom
Saetre, 2007 N=186	Study Designation: Effectiveness, efficacy, and safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis Adequate sample size	Population	Older adults > 65 yrs only Only partial and primary generalized seizures
Stephen, 2007 N= 225	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis Less stringent eligibility criteria	None	None
Morrell, 2008 N=447	Study Designation: Efficacy Study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Assessed adverse events Adequate sample size Used intention to treat analysis	Population Outcomes	Only hormone effects studied Enrolled only women, 13-40 yrs old, with regular menstrual cycles
Pack, 2005/2008 N=93	Study Designation: Efficacy Study Composite Score: 1 of 7	Adequate study duration with clinically relevant treatments	Population Outcomes	Enrolled only women 18-40 yrs old Did not report adverse events Study reported bone outcomes only Small sample size
Perry, 2008 N=86	Study Designation: Efficacy Study Composite Score: 3 of 7	Assessed adverse events Assessed final health outcomes Adequate study duration with clinically relevant treatments	Population	Enrolled patients <16 yrs old with newly diagnosed partial epilepsy Small sample size (86 patients)

Table I-2. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs (continued)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Kwan, 2009 N=81	Study Designation: Efficacy study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Used intention to treat analysis Enrolled a primary care population	Population	Conducted in China Small sample size (81patients)
Ma, 2009 N=497	Study Designation: Efficacy Study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Assessed adverse outcomes	Population	Only one center in children
Glauser, 2010 N=497	Study Designation: Efficacy and Safety study Composite Score: 5 of 7	Used Intention to treat analysis Adequate sample size Assesses final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes	Population	Enrolled only children between the ages of 2.5 and 13 yrs with absence epilepsy
Helmstaedter, 2010 N=222	Study Designation: Efficacy Study Composite Score: 5 of 7	Enrolled primary care population Less stringent eligibility Criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes	Population Outcomes	Enrolled adults age 16 and older Multicenter
Ramsay, 2010 N=497	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Short study duration only 28 weeks

Table I-3. Applicability rating for final outcome evaluations for innovator versus generic antiepileptic drugs under Key Question 1

Outcome	Brand AED	Generic AEDs	Strength of Ability	Strength of Applicability	Overall AED Analysis	Comments
Mortality						No studies to assess strength of evidence

AEDs = antiepileptic drugs; RCT = randomized controlled trial

Table I-4. Applicability rating for medical service utilization for innovator versus generic antiepileptic drugs under Key Question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion With Description of Applicability	Overall AED Analysis	Comments
Outpatient medical care utilization (Office or ER visit)	Various	Various	Moderate	None of the four reports specified that they were limited to “A” rated versions of the generic AED. One report was conducted in the United States and the other three in Canada. The average age ranged between 33.7 and 52.5 years and the percentage of male participants ranged from 32.3 and 50.8%. No harms were being evaluated.	2 out of the 4 trials that evaluated this endpoint showed that outpatient visits were more frequent during the generic period compared to the brand periods and the other 2 trials showed no significant difference in outpatient visits between brand and generic periods.	
Hospitalizations	Various	Various	Moderate	None of the four reports specified that they were limited to “A” rated versions of the generic AED. One study was conducted in the United States and the other three in Canada. The average age ranged between 33.7 and 52.5 years and the percentage of male participants ranged from 32.3 and 50.8%. No harms were being evaluated.	2 out of the 4 trials that evaluated this endpoint showed hospitalizations were more frequent during the generic period compared to the brand periods. The third study showed no significant difference between generic and brand periods. The fourth study showed that multiple generic AED use was associated with higher hospitalization versus brand AED use and difference between single generic and brand AED use was not significant.	
Ambulance Services						No studies to assess strength of evidence

Table I-4. Applicability rating for medical service utilization for innovator versus generic antiepileptic drugs under Key Question 1 (continued)

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion With Description of Applicability	Overall AED Analysis	Comments
Composite of medical services	Various	Various	Moderate	All three studies were conducted in USA and all used “A” rated versions of the generic AED. Not a true comparison of innovator vs. generic since patients could be switched from one “A” rated generic to another “A” rated generic. The average age ranged between 35.6 and 42.0 years and the percentage of male participants ranged from 43.9 and 49%. No harms were being evaluated.	In the first and second study, cases were patients that had ambulance visit, ER visit or inpatient hospitalization and in the third study, cases were patients that had ER visit or inpatient hospitalization and controls in all three studies were patients that had office visits during the specified time period. In all three studies, 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 third study, after adjusting for potential confounders, the odds ratio between the switch and acute epilepsy exacerbation (defined as ER visit or hospitalization) was 1.08 (95% CI: 0.91–1.29). When the time evaluated was extended to 180 days, the adjusted odds ratio of acute epilepsy exacerbations increased to 1.14 (95% CI: 0.99–1.31).	
Hospital stay duration	Various	Various	Moderate	None of the four reports specified that they were limited to “A” rated versions of the generic AED. One study was conducted in the United States and the other three in Canada. The average age ranged between 33.7 and 52.5 years and the percentage of male participants ranged from 32.3 and 50.8%. No harms were being evaluated.	All 4 studies showed that average length of hospital stay was longer during the generic period compared to the brand periods.	

AED = antiepileptic drug; ER = emergency room; RCT = randomized controlled trial

Table I-5. Applicability rating for health related quality of life for innovator versus generic antiepileptic drugs under Key Question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion With Description of Applicability	Overall AED Analysis	Comments
Health-related quality of life						No studies to assess strength of evidence

AED = antiepileptic drug

Table I-6. Applicability rating for final health outcomes for innovator versus generic antiepileptic drugs Key Question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis	Comments
Seizure Occurrence/ breakthrough seizure	Carbamazepine Phenytoin Valproic Acid	12 Generics	Low	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.7 to 72 years and percent of male participants ranged from 50 to 100%. Body weight ranged from 35 to 94 kg in the four studies that reported it. Patients with both partial and generalized seizure types were enrolled in the two studies that reported it. All studies had fairly short duration of follow-up with maximum of 3 months per treatment group and small sample size (total n=195). All studies were conducted before 2000.	The risk of experiencing a seizure is non-significantly decreased by 11% when generic antiepileptic medications are used versus their associated innovator products [RR 0.89 (0.65 to 1.21)]	
Seizure Frequency	Carbamazepine Valproic Acid	3 Generics	Low	All 3 studies were conducted in USA. Average age ranged from 17 to 72 years and percent of male participants was 100% in the one study that reported it. Body weight ranged from 35 to 94 kg in the one study that reported it. Seizure type of patients was not reported in these 3 studies. All 3 studies had fairly short duration of follow-up with maximum of 3 months per treatment group and small sample size (total n=94). All studies were conducted before 2000	The seizure frequency is non-significantly higher in the generic antiepileptic medication group versus the innovator group [SMD 0.03 (-0.08 to 0.14) seizures over the evaluative period]	
Time to first seizure						No studies to assess strength of evidence
Incidence of status epilepticus						No studies to assess strength of evidence
Seizure remission						No studies to assess strength of evidence
Secondary seizure injury						No studies to assess strength of evidence

AED = antiepileptic drug; RCT = randomized controlled trial

Table I-7. Applicability rating for withdrawals due to adverse events for innovator versus generic antiepileptic drugs in key question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion With Description of Applicability	Overall AED Analysis
Total withdrawals	Carbamazepine Phenytoin	(14, 1) Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Body weight ranged from 35.5 to 83 kg in the three studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly short duration of follow-up with maximum of 3 months per group and small sample size (total n=202). All studies were conducted before 2000.	The risk of withdrawals for any reason is non-significantly decreased by 10% when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications (RR 0.90 [0.39, 2.08])
Withdrawals due to lack of efficacy	Carbamazepine Phenytoin	14 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Body weight ranged from 35.5 to 83 kg in the three studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly short duration of followup with maximum of 3 months per group and small sample size (total n=202). All studies were conducted before 2000.	The risk of withdrawals due to ineffective treatment is non-significantly increased by 2% when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications (RR 1.02 [0.41 to 2.54]).
Withdrawals due to adverse events	Carbamazepine Phenytoin	14 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Body weight ranged from 35.5 to 83 kg in the three studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly short duration of follow-up with maximum of 3 months per group and small sample size (total n=202). All studies were conducted before 2000.	The risk of withdrawals due to adverse effects is non-significantly decreased by 21% when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications (RR 0.79 [0.28 to 2.20])

AED = antiepileptic drug; RCT = randomized controlled trial

Table I-8. Applicability rating for pharmacokinetic effects for innovator versus generic antiepileptic drugs Key Question 2

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion With Description of Applicability	Overall AED Analysis
Cmax	Carbamazepine Phenytoin Lamotrigine	16 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 67 years and percent of male participants ranged from 35 to 75%. Average body weight ranged from 35.8 to 53.9 kg in the two studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=149).	The standardized mean difference in the generic antiepileptic medication group was non-significantly higher than the innovator antiepileptic medication group (SMD 0.10 [-0.13 to 0.32]).
Cmin	Carbamazepine Lamotrigine	10 Generics	Low	Studies were conducted in Europe & Asia, but none were conducted in USA. Average age ranged from 7 to 45.1 years and percent of male participants ranged from 40 to 70%. Average body weight ranged from 35.8 to 53.9 kg in the two studies that reported it. Patients with various different seizure types were enrolled in the 4 studies that reported it. All studies had fairly small sample size (total n=103).	The standardized mean difference in the generic group was non-significantly higher than the generic antiepileptic medication group (SMD 0.05 [-0.21 to 0.31]).
Css	Carbamazepine Phenytoin	12 Generics	Low	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Average body weight ranged from 49 to 83 kg in the two studies that reported it. Patients with both partial and generalized seizure types were enrolled in the two studies that reported it. All studies had fairly small sample size (total n=136).	The standardized mean difference in the generic group was non-significantly higher than the innovator antiepileptic medication group (SMD 0.18 [-0.09 to 0.45]).
AUC	Carbamazepine Lamotrigine Phenytoin	16 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 67 years and percent of male participants ranged from 35 to 80%. Average body weight ranged from 50 to 83 kg in the two studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=131).	The standardized mean difference in the generic group was non-significantly higher than the innovator antiepileptic medication group (SMD 0.05 [-0.18 to 0.28]).
Tmax	Carbamazepine	9 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 45.1 years and percent of male participants ranged from 40 to 75%. Average body weight was 53.9 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=103).	The weighted mean difference for Tmax in generic carbamazepine group was same as the innovator carbamazepine group([WMD 0.00 [-0.43 to 0.43] hours).

AED = antiepileptic drug; RCT = randomized controlled trial

Table I-9. Applicability rating for neurologic adverse events for innovator versus generic antiepileptic drugs in key question 3

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion With Description of Applicability	Overall AED Analysis
Headache	Carbamazepine Phenytoin	4 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 9.5 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=63).	The relative risk in the generic group was non-significantly lower than the innovator antiepileptic medication group (RR 0.95 [0.55 to 1.64]).
Diplopia	Carbamazepine	2 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 10.7 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=33).	The relative risk in the generic group was non-significantly higher than the innovator antiepileptic medication group (RR 1.28 [0.38 to 4.31]).
Somnolence	Carbamazepine	2 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 10.7 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=33).	The relative risk in the generic group was non-significantly lower than the innovator antiepileptic medication group (RR 0.90 [0.48 to 1.70]).

AED = antiepileptic drug; RCT = randomized controlled trial

Table I-10. Applicability rating for incidence of adverse events and other outcomes for innovator versus generic antiepileptic drugs in Key Question 3

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis	Comments
Incidence of ADRs	Carbamazepine Phenytoin	3 Generics	Low	Studies were conducted in U.S. & Europe. Average age ranged from 9.5 to 70 years and percent of male participants ranged from 60 to 100. Patients with various different seizure types were enrolled in the one study that specified seizure type. Both studies had fairly small sample size (total n=40).	The relative risk in the generic group was non-significantly higher than the innovator antiepileptic medication group (IRR 1.01 [0.68 to 1.51]).	Risk of Bias: Not "A" rated generics Inconsistency: I ² : 0% Imprecision: IRR 1.01 (0.68 to 1.51) non-significant findings
Incidence of Skin Rash	Carbamazepine	2 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 10.7 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=33).	The relative risk in the generic group was non-significantly lower than the innovator antiepileptic medication group (IRR 0.74 [0.14 to 3.94]).	Risk of Bias: Not "A" rated generics Inconsistency: I ² : N/A Imprecision: IRR 0.74 (0.14 to 3.94) non-significant findings
Loss of drivers license						No studies to assess strength of evidence
Loss of employment						No studies to assess strength of evidence
Switchback rates						No studies to assess strength of evidence

AED = antiepileptic drug; RCT = randomized controlled trial

Table I-11. Strength of applicability for the body of evidence evaluating mortality for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Mortality	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not reduce the risk of mortality. Overall applicability is limited because the duration of followup for the trials included in the evaluation is not adequate to evaluate mortality, the majority of the trials evaluated were conducted in the United Kingdom and multiple newer antiepileptic drugs are compared to a carbamazepine.
Mortality	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with phenytoin, newer antiepileptic drugs did not reduce the risk of mortality. Overall applicability is limited because the duration of follow up for the trials included in the evaluation is not adequate to evaluate mortality, two of the trials were conducted outside of the United States in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin.
Mortality	Valproic Acid	Lamotrigine Topiramate Vigabatrin	Moderate	Compared with valproic acid, newer antiepileptic drugs did not reduce the risk of mortality. Overall applicability is limited because the duration of follow up for the trials included in the evaluation is not adequate to evaluate mortality, two of the trials included in the evaluation took place in the United Kingdom and multiple newer antiepileptic drugs were compared to valproic acid.

AED = antiepileptic drug

Table I-12. Strength of applicability for medical service utilization for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability	Comments
Use of medical services					No studies to assess strength of evidence
Use of ambulance services					No studies to assess strength of evidence
Outpatient medical care utilization					No studies to assess strength of evidence
Hospitalizations					No studies to assess strength of evidence
Hospitalizations					No studies to assess strength of evidence
Hospitalizations					No studies to assess strength of evidence
Ambulance Services					No studies to assess strength of evidence
Outpatient medical care utilization					No studies to assess strength of evidence
Composite of medical services					No studies to assess strength of evidence

AED = antiepileptic drug

Table I-13. Strength of applicability for health related quality of life for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Health-related quality of life	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Tiagabine Topiramate	Low	Compared to carbamazepine, newer antiepileptic drugs showed an improvement in health related quality of life. Overall applicability is limited because the majority of the trials included in the evaluation were conducted in the United Kingdom and multiple newer antiepileptics are compared to a carbamazepine.
Health-related quality of life	Phenytoin	Lamotrigine Tiagabine	Moderate	Compared to phenytoin, newer antiepileptic drugs did not show an improvement in health related quality of life. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin.
Health-related quality of life	Valproic Acid	Lamotrigine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs did not show an improvement in health related quality of life. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.

AED = antiepileptic drug

Table I-14. Strength of applicability for final health outcomes for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Time to first seizure	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not increase the time to first seizure. Overall applicability is limited because all of the trials included in the evaluation were conducted in the Europe and multiple antiepileptic drugs are compared to carbamazepine.
Time to first seizure	Phenytoin	Lamotrigine Topiramate	Moderate	Compared with phenytoin, newer antiepileptic drugs did not increase the time to first seizure. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin and because only one of the trials included in the evaluation was designed to evaluate time to first seizure as a primary efficacy endpoint.
Time to first seizure	Valproic Acid	Lamotrigine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs did not increase the time to first seizure. Overall applicability is limited because one of the trials included in the analysis was conducted in children between the ages of 6 and 16 years and multiple antiepileptic drugs were compared to valproic acid.
Change from baseline in seizure frequency	Carbamazepine	Oxcarbazepine	Moderate	Compared with carbamazepine, oxcarbazepine did not decrease the number of seizures from baseline. Overall applicability is limited because the trial was conducted in sites in Denmark, Finland, Norway and Sweden.
Change from baseline in seizure frequency	Phenytoin	Oxcarbazepine	Low	There was not enough data from the trials included to evaluate the change from baseline in seizure frequency oxcarbazepine when was compared to phenytoin. Overall applicability is limited by the lack of reported data.
Change from baseline in seizure frequency	Valproic Acid	Oxcarbazepine	Low	There was not enough data from the trials included to evaluate the change from baseline in seizure frequency when oxcarbazepine was compared to valproic acid. Overall applicability is limited by lack of reported data and because the only trial included in the evaluation was conducted at centers in Belgium, Brazil, France, Germany, the Netherlands and South Africa.
12 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not increase 12 month seizure remission. Overall applicability was limited because the trials included in the analysis were conducted in the United Kingdom, Denmark, Finland, Israel, France, South Africa, Spain, Switzerland and Australia and multiple newer antiepileptic drugs were compared to carbamazepine.

Table I-14. Strength of applicability for final health outcomes for older versus newer antiepileptic drugs (continued)

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
12 Month Seizure Remission	Valproic Acid	Lamotrigine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs did not increase 12 month seizure remission. Overall applicability is limited because the trial evaluating 12 month seizure remission was conducted in the United Kingdom and multiple newer antiepileptic drugs were compared to valproic acid.
24 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not increase 12 month seizure remission. Overall applicability is limited because the trial evaluating 12 month seizure remission was conducted in the United Kingdom and multiple newer antiepileptic drugs were compared to carbamazepine.
24 Month Seizure Remission	Valproic Acid	Lamotrigine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs did not increase 12-month seizure remission. Overall applicability is limited because the trial evaluating 12 month seizure remission was conducted in the United Kingdom and multiple newer antiepileptic drugs were compared to valproic acid.
Seizure freedom	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin Levetiracetam	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not increase seizure freedom. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine and the majority of the trials included were conducted in Europe and Scandinavia.
Seizure freedom	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared with controlled or sustained release carbamazepine, newer antiepileptic drugs did not increase seizure freedom. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Seizure freedom	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with phenytoin, newer antiepileptic drugs do not increase seizure freedom. Overall applicability is limited because the majority of the studies included in the study were conducted in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin.

Table I-14. Strength of applicability for final health outcomes for older versus newer antiepileptic drugs (continued)

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Seizure freedom	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs do not increase seizure freedom. Overall applicability is limited because half of the studies included in the evaluation were conducted outside of the United States in China and Europe and multiple newer antiepileptic drugs were compared to valproic acid

AED = antiepileptic drug

Table I-15. Strength of applicability for withdrawals due to adverse events for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AED	Strength of Applicability	Conclusion With Description of Applicability
Total withdrawals	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine and the majority of the trials included were conducted in Europe and Scandinavia.
Total withdrawals	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared with controlled or sustained release carbamazepine, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Total withdrawals	Ethosuximide	Lamotrigine	Low	Compared with ethosuximide, lamotrigine did not reduce withdrawal for any reason. Overall applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.
Total withdrawals	Phenytoin	Lamotrigine Oxcarbazepine	Moderate	Compared with phenytoin, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to the United States population is limited because the majority of the trials included in the analysis were conducted outside of the United States in Argentina, Brazil and the United Kingdom.
Total withdrawals	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with valproic acid, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because half of the studies included in the evaluation were conducted outside of the United States in China and Europe and multiple newer antiepileptic drugs were compared to valproic acid.
Withdrawals due to lack of efficacy	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs increased withdrawal due to lack of efficacy. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine and the majority of the trials included were conducted in Europe and Scandinavia.
Withdrawals due to lack of efficacy	Carbamazepine Controlled Release	Lamotrigine	Low	Compared with controlled release carbamazepine, lamotrigine increased withdrawal due to lack of efficacy. Overall applicability is limited to the United States because patients enrolled in Europe and South Africa.

Table I-15. Strength of applicability for withdrawals due to adverse events for older versus newer antiepileptic drugs (continued)

Outcome	Older AED	Newer AED	Strength of Applicability	Conclusion With Description of Applicability
Withdrawals due to lack of efficacy	Phenytoin	Lamotrigine Oxcarbazepine	Moderate	Compared with phenytoin, newer antiepileptics did not increase withdrawal due to lack of efficacy. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to the United States population is limited because the majority of the trials included in the analysis were conducted outside of the United States in Argentina, Brazil and the United Kingdom.
Withdrawals due to lack of efficacy	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with valproic acid, newer antiepileptic drugs did not increase withdrawal due to lack of efficacy. Overall applicability is limited because half of the studies included in the evaluation were conducted outside of the United States in China and Europe and multiple newer antiepileptic drugs were compared to valproic acid.
Withdrawals due to adverse events	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs decreased withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepileptics were compared to carbamazepine and the majority of the studies included in the evaluation were conducted in Europe.
Withdrawals due to adverse events	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared with controlled or sustained release carbamazepine, newer antiepileptic drugs decreased withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Withdrawals due to adverse events	Ethosuximide	Lamotrigine	Low	Compared with ethosuximide, lamotrigine did not decrease withdrawal due to adverse events. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.
Withdrawals due to adverse events	Phenytoin	Lamotrigine Oxcarbazepine	Moderate	Compared with phenytoin, newer antiepileptics did not decrease withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to the United States population is limited because the majority of the trials included in the analysis were conducted outside of the United States in Argentina, Brazil and the United Kingdom.

Table I-15. Strength of applicability for withdrawals due to adverse events for older versus newer antiepileptic drugs (continued)

Outcome	Older AED	Newer AED	Strength of Applicability	Conclusion With Description of Applicability
Withdrawals due to adverse events	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with valproic acid, newer antiepileptic drugs did not decrease withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.

AED = antiepileptic drug

Table I-16. Strength of applicability for neurologic adverse events for newer versus older antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Headache	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptics were compared to carbamazepine. Applicability is limited to the United States population because the majority of the trials included in the evaluation were conducted in Europe.
Headache	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared with controlled or sustained release carbamazepine, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe, and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Headache	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with phenytoin, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to a United States population is limited because only one of the trials included in the analysis was conducted in the United States while the rest were conducted in Europe, South America, and South Africa.
Headache	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Headache	Ethosuximide	Lamotrigine	Low	Compared with ethosuximide, lamotrigine did not decrease the incidence of headache. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.
Fatigue	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability to a patient population in the United States is limited because the majority of the trials included in the evaluation were conducted in Europe.
Fatigue	Carbamazepine Controlled Release	Levetiracetam	Low	Compared with controlled release carbamazepine, levetiracetam did not decrease the incidence of fatigue. Overall applicability to a patient population in the United States is limited because the trial was conducted in Europe and South Africa. Applicability to a pediatric patient population is limited because the trial enrolled patients 16 years of age and older.

Table I-16. Strength of applicability for neurologic adverse events for newer versus older antiepileptic drugs (continued)

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Fatigue	Phenytoin	Topiramate	Low	Compared with phenytoin, topiramate did not decrease the incidence of headache. Applicability to a pediatric patient population is limited because the trial enrolled patients 12 years of age and older.
Fatigue	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs decreased the incidence of fatigue. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Fatigue	Ethosuximide	Lamotrigine	Low	Compared with ethosuximide, lamotrigine decreased the incidence of headache. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.
Somnolence	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs decreased the incidence of somnolence. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability to a United States population is limited because only three of the trials included in the analysis was conducted in the United States while the rest were conducted in Europe, China, and South Africa.
Somnolence	Carbamazepine Controlled Release	Levetiracetam	Low	Compared with controlled release carbamazepine, levetiracetam did not reduce the incidence of somnolence. Applicability to a patient population in the United States is limited because the trial was conducted in Europe and South Africa. Applicability to a pediatric population is limited because the trial was conducted in adolescents and adults 16 years of age and above.
Somnolence	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with phenytoin, newer antiepileptic drugs did not reduce the incidence of somnolence. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to a United States population is limited because only one of the trials included in the analysis was conducted in the United States while the rest were conducted in Europe, South America and South Africa.
Somnolence	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs reduced the incidence of somnolence. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Somnolence	Ethosuximide	Lamotrigine	Low	Compared with ethosuximide, lamotrigine decreased the incidence of somnolence. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.

Table I-16. Strength of applicability for neurologic adverse events for newer versus older antiepileptic drugs (continued)

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Dizziness	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs decreased the incidence of dizziness. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine.
Dizziness	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared with controlled or sustained release carbamazepine, newer antiepileptic drugs did not decrease the incidence of dizziness. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Dizziness	Phenytoin	Lamotrigine Oxcarbazepine	Moderate	Compared with phenytoin, newer antiepileptic drugs did not decrease the incidence of dizziness. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to a patient population in the United States is limited because the trials included in the analysis were conducted in Europe and South America.
Dizziness	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs did not decrease the incidence of dizziness. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Dizziness	Ethosuximide	Lamotrigine	Low	Compared with ethosuximide, lamotrigine did not decrease the incidence of dizziness. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.

AED = antiepileptic drug

Table I-17. Strength of applicability for incidence of adverse events for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Nausea	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not decrease the incidence of nausea. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability to a United States patient population is limited because the majority of the studies included in the evaluation were conducted in Europe.
Nausea	Carbamazepine Controlled Release	Levetiracetam	Low	Compared with controlled release carbamazepine, levetiracetam did not decrease the incidence of nausea. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe, and South Africa.
Nausea	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with phenytoin, newer antiepileptic drugs did not decrease the incidence of nausea. Overall applicability is limited because the majority of the studies included in the study were conducted in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin.
Nausea	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with patients who received valproic acid, patients who received newer antiepileptic drugs had a decreased incidence of nausea. Overall applicability was limited because multiple newer antiepileptic drugs were compared to valproic acid.
Vomiting	Carbamazepine	Lamotrigine Topiramate	Moderate	Compared with patients treated with carbamazepine, patients treated with newer antiepileptic drugs did not have a decreased incidence of vomiting. Overall applicability was limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability is limited to the United States patient population because 2 of the 3 trials included in the evaluation were conducted in the United Kingdom.
Vomiting	Phenytoin	Oxcarbazepine	Low	Compared with patients treated with phenytoin, patients treated with oxcarbazepine had a decreased incidence of vomiting. Applicability to a patient populations in the United States because the trial was conducted in Argentina and Brazil. Applicability to an adult patient population is also limited because the trial was conducted in children and adolescents.
Vomiting	Valproic Acid	Felbamate Lamotrigine Topiramate	Moderate	Compared with patients treated with valproic acid, patients treated with newer antiepileptic drugs did not have a decreased incidence of vomiting. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid. Applicability to an adult patient population is limited because the majority of the trials included in the evaluation were conducted in children.

Table I-17. Strength of applicability for incidence of adverse events for older versus newer antiepileptic drugs (continued)

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Skin Rash	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with patients treated with carbamazepine, patients treated with newer antiepileptic drugs had a decreased incidence of skin rash. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine.
Skin Rash	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Moderate	Compared with patients treated with controlled or sustained release carbamazepine, patients treated with newer antiepileptic drugs had a decreased incidence of skin rash. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe, and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Skin Rash	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with patients treated with phenytoin, patients treated with newer antiepileptic drugs did not have a decrease in the incidence of skin rash. Overall applicability is limited because the majority of the studies included in the study were conducted in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin.
Skin Rash	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with patients treated with valproic acid, patients treated with newer antiepileptic drugs did not have a decreased incidence of skin rash. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.

AED = antiepileptic drug

Table I-18. Strength of applicability for bone mineral density for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Bone Mineral Density	Carbamazepine	Lamotrigine Oxcarbazepine	Low	Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability is limited to a patient population in the United States because only one of the three trials included in the analysis was conducted in the United States and the other trials were conducted in Turkey and Korea. Applicability is also limited to an adult male population as the largest trial included in the analysis was conducted in adult women.
Bone Mineral Density	Phenytoin	Lamotrigine	Low	Applicability is limited to an adult male population because the trial was conducted in adult women.
Bone Mineral Density	Valproic Acid	Lamotrigine Oxcarbazepine	Low	Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability is limited to a patient population in the United States because only one of the three trials included in the analysis was conducted in the United States and the other trials were conducted in Turkey and Korea. Applicability is also limited to an adult male population as the largest trial included in the analysis was conducted in adult women.

AED = antiepileptic drug

Table I-19. Strength of applicability for cosmetic adverse effects for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion With Description of Applicability
Alopecia	Carbamazepine	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not decrease the incidence of alopecia. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine.
Alopecia	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with valproic acid, newer antiepileptic drugs decreased the incidence of alopecia. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Acne	Phenytoin	Oxcarbazepine	Low	Compared with phenytoin, oxcarbazepine did not decrease the incidence of acne. Applicability to a patient population in the United States is limited because the trial was conducted in Europe, South America, and South Africa.
Gum Hyperplasia	Phenytoin	Oxcarbazepine	Low	Compared with phenytoin, oxcarbazepine decreased the incidence of gum hyperplasia. Applicability to a patient population in the United States is limited because the trials included in the evaluation were conducted in Europe, South America, and South Africa.

AED = antiepileptic drug

Appendix J. Forest Plots of Meta-analysis of Efficacy and Safety Endpoints

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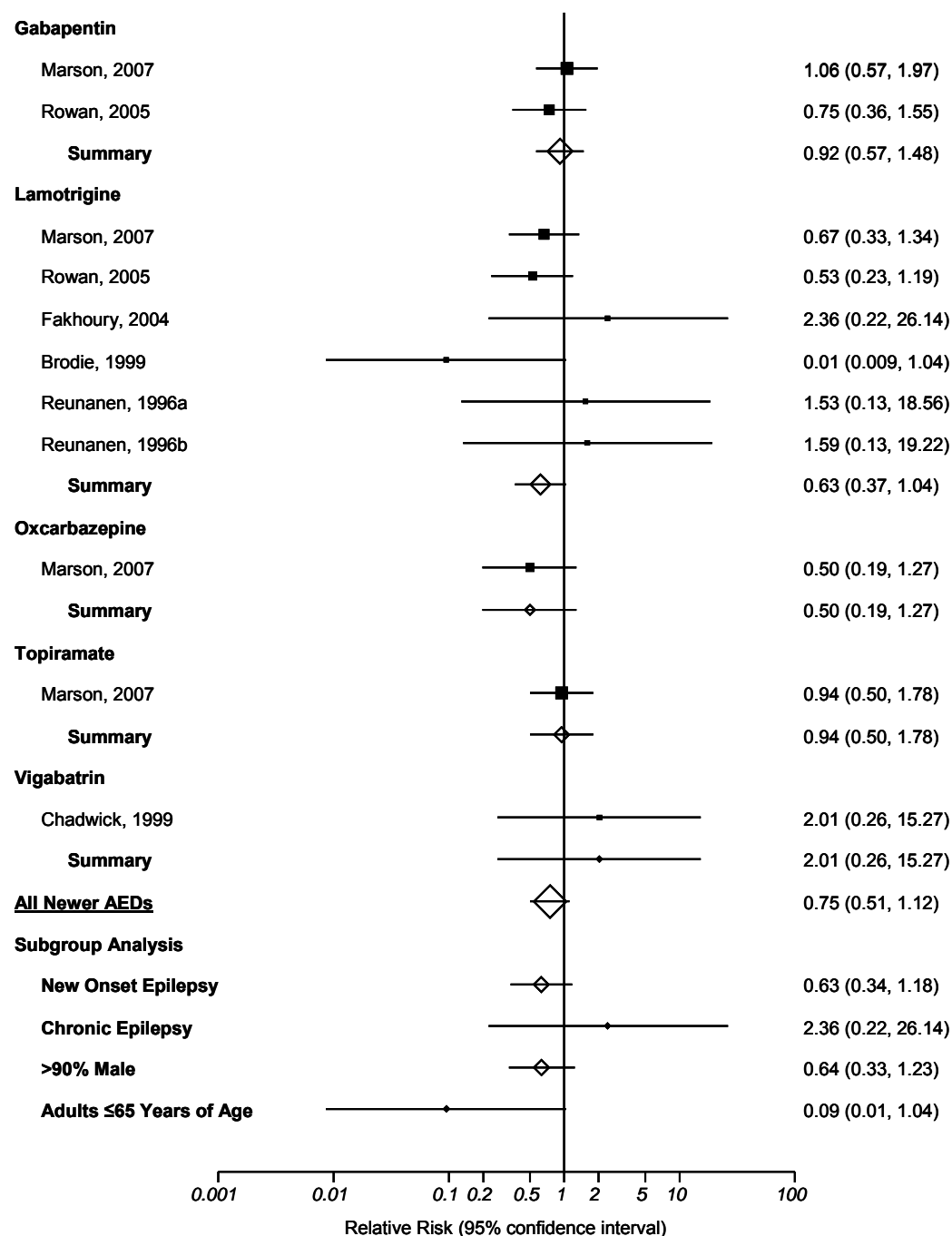
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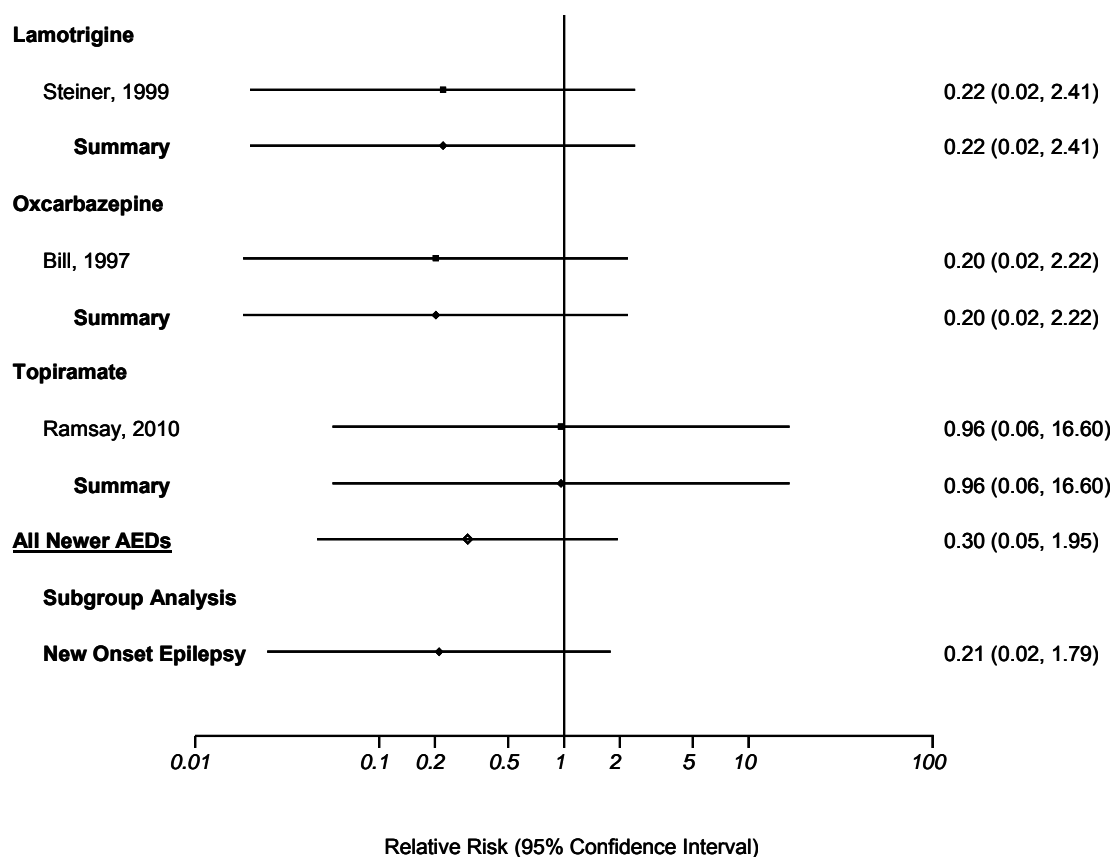
Figure J-1. Composite forest plot of meta-analysis of mortality in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial

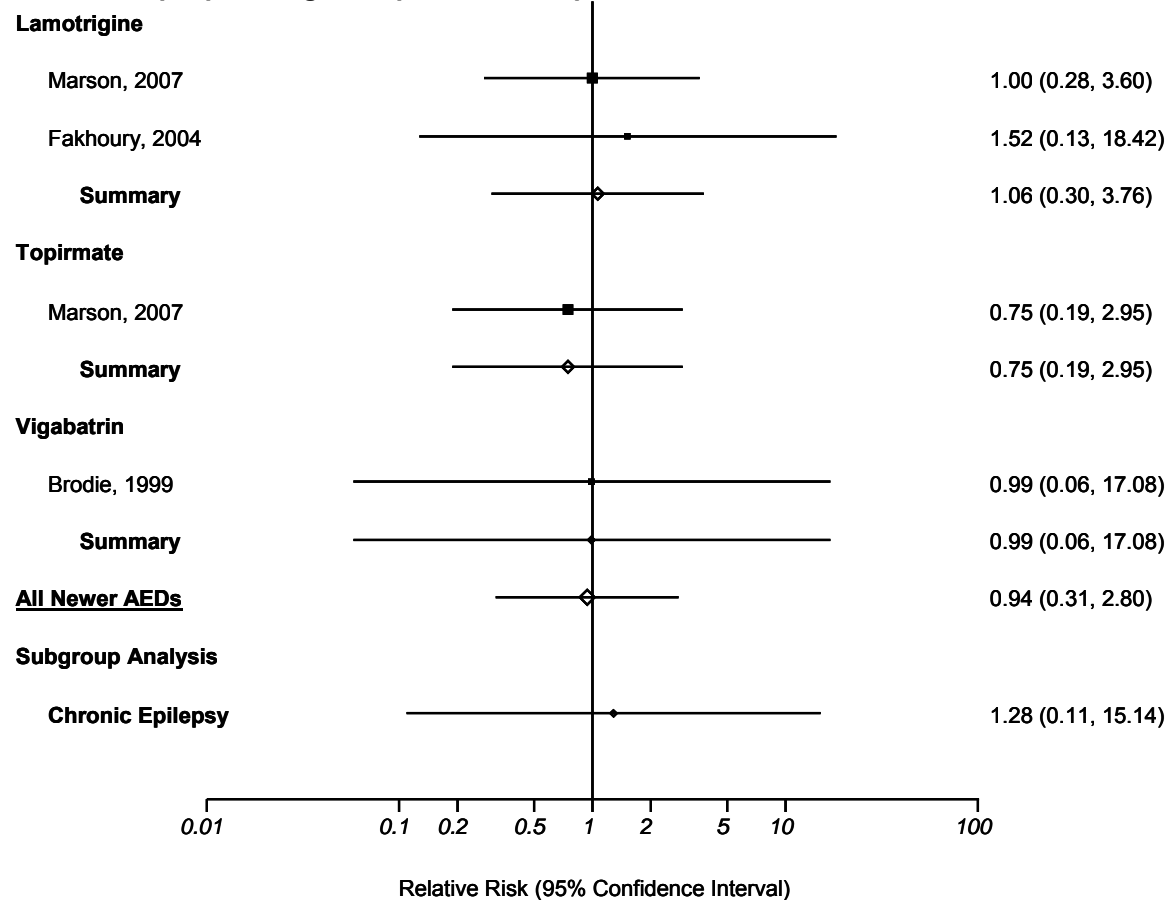
Figure J-2. Composite forest plot of meta-analysis of mortality in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

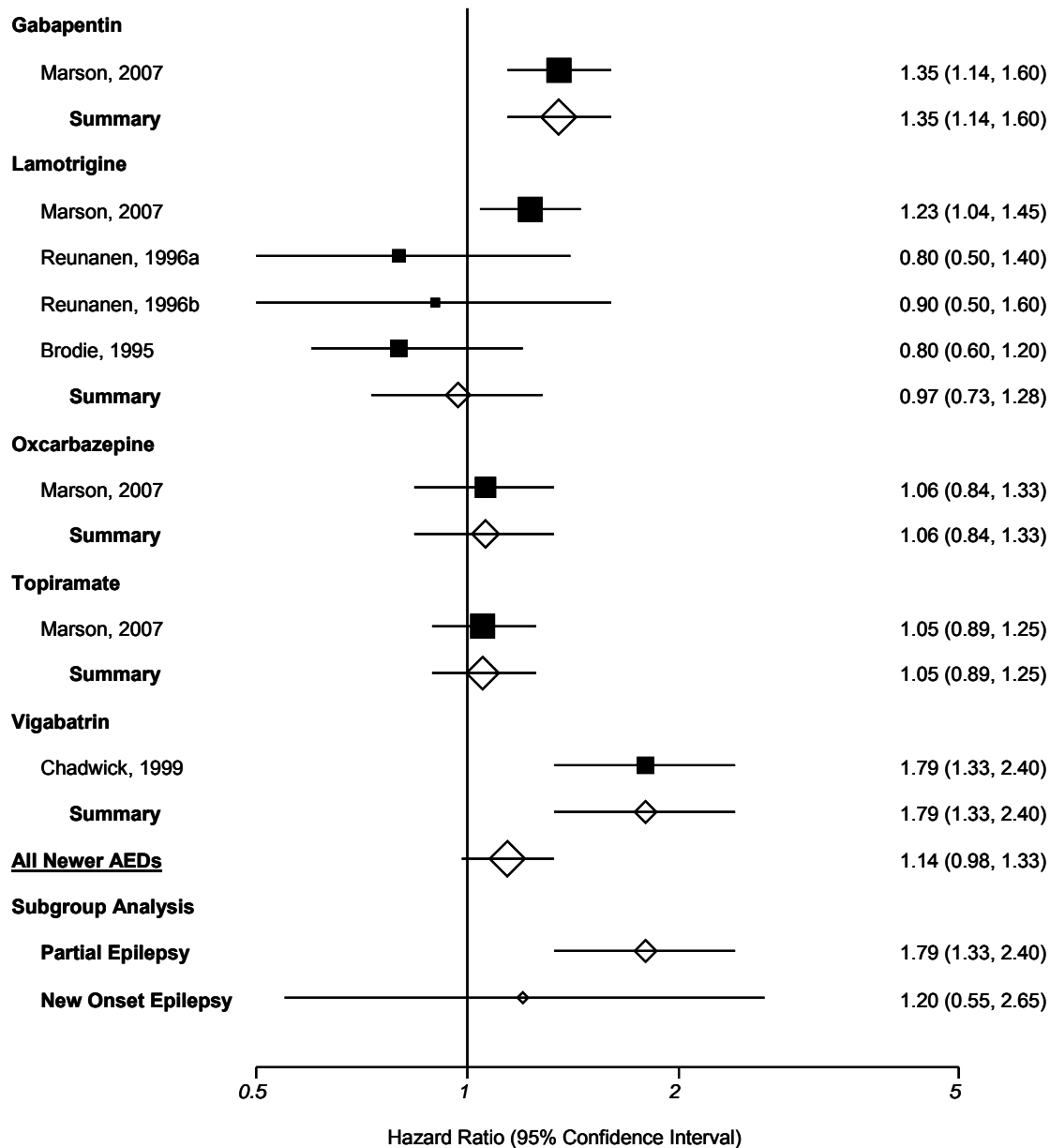
Figure J-3. Composite forest plot of meta-analysis of mortality in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

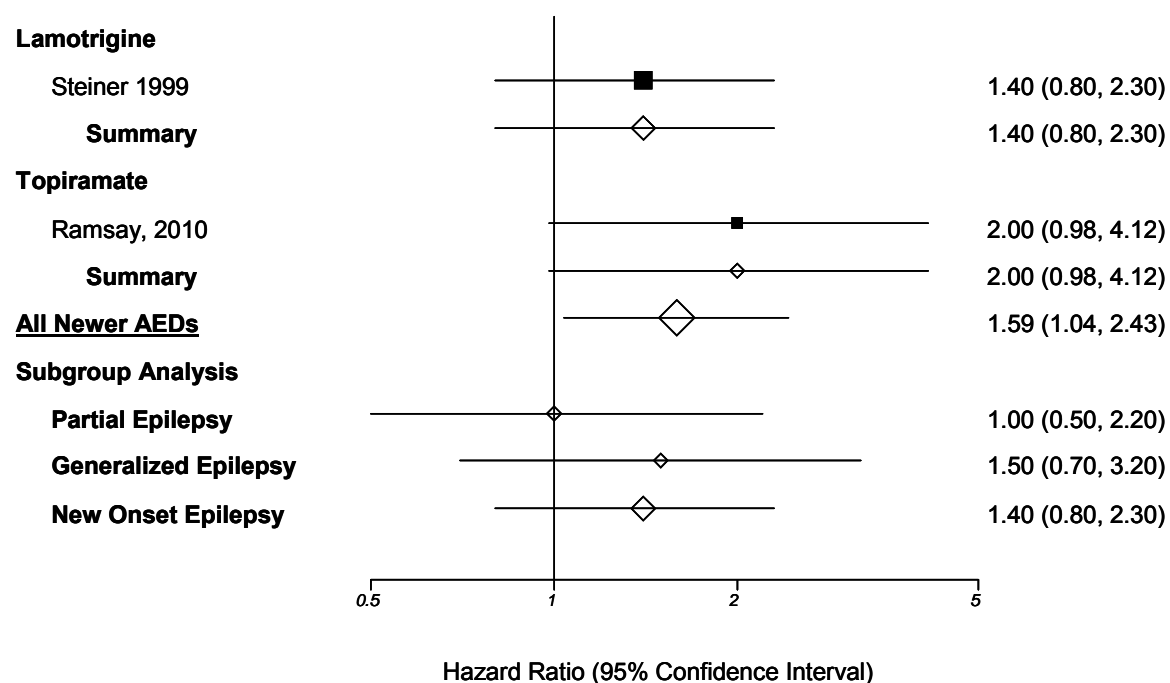
Figure J-4. Composite forest plot of meta-analysis of time to first seizure in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

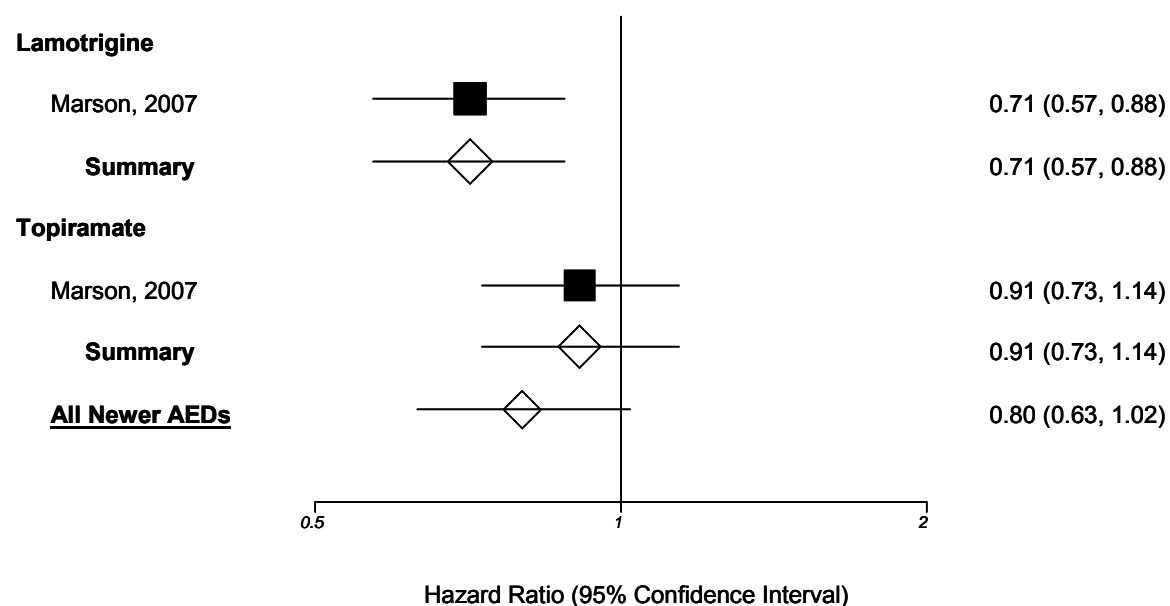
Figure J-5. Composite forest plot of meta-analysis of time to first seizure in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

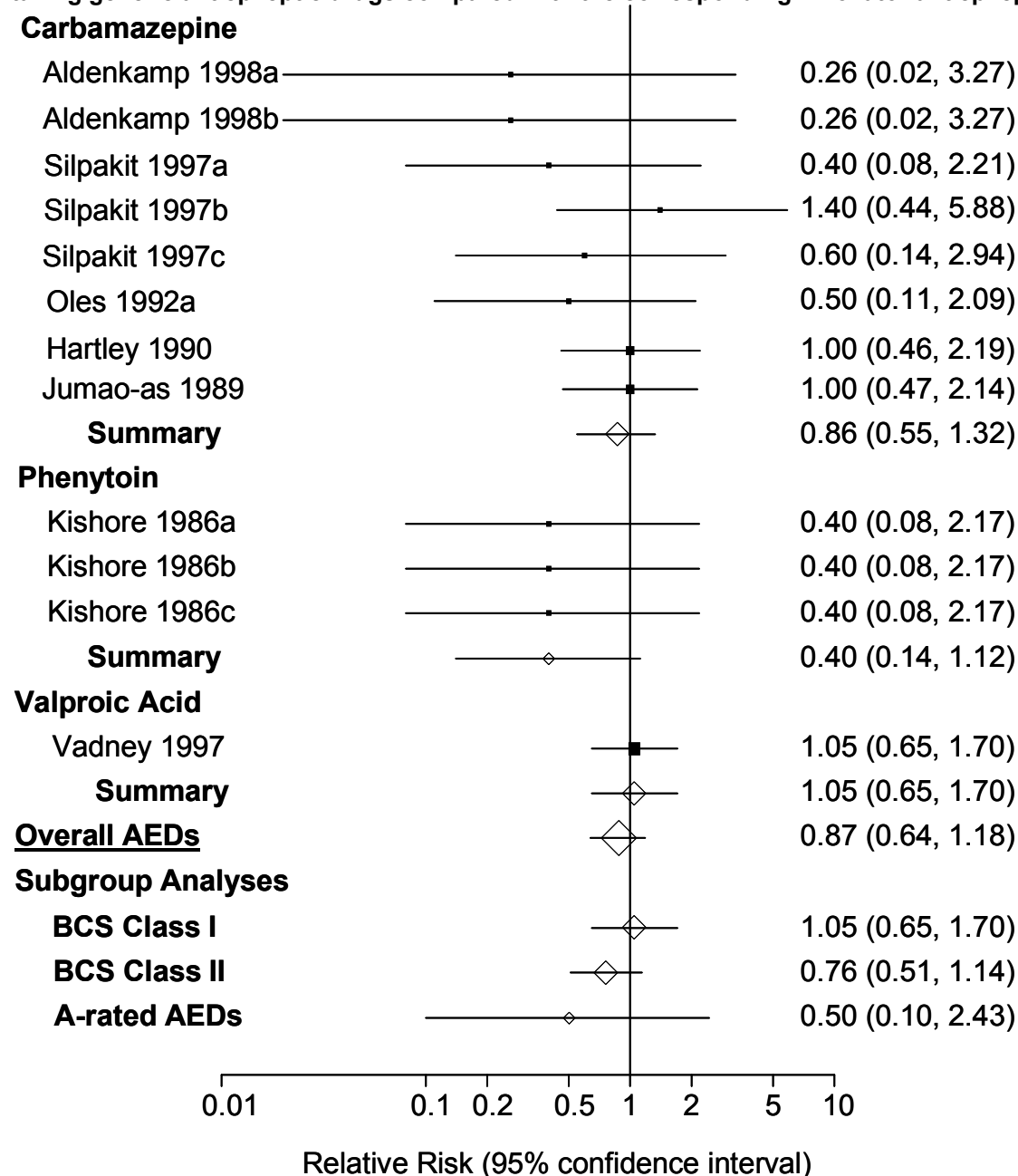
Figure J-6. Composite forest plot of meta-analysis of time to first seizure in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

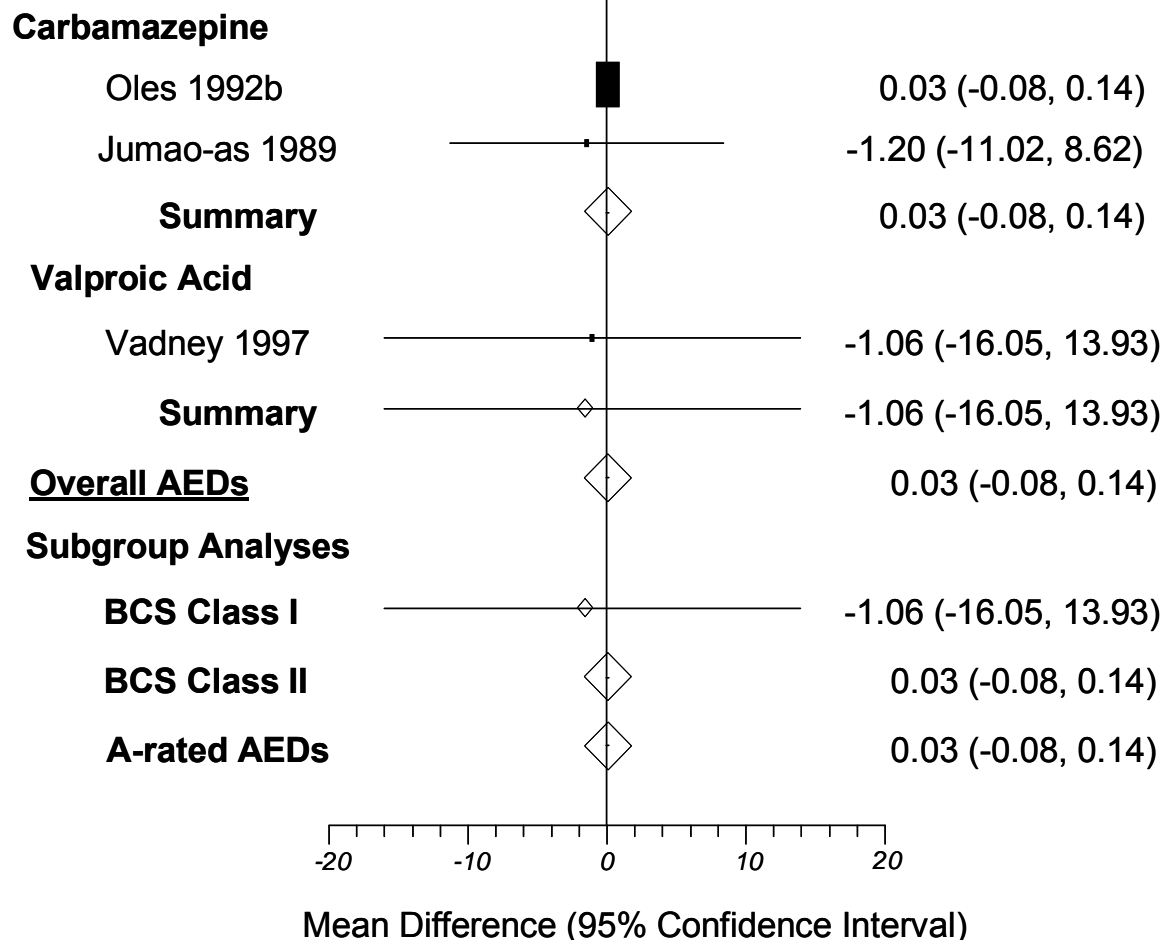
Figure J-7. Composite forest plot of meta-analysis of seizure occurrence in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug



AEDs = antiepileptic drugs; BCS = biopharmaceutics classification system

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

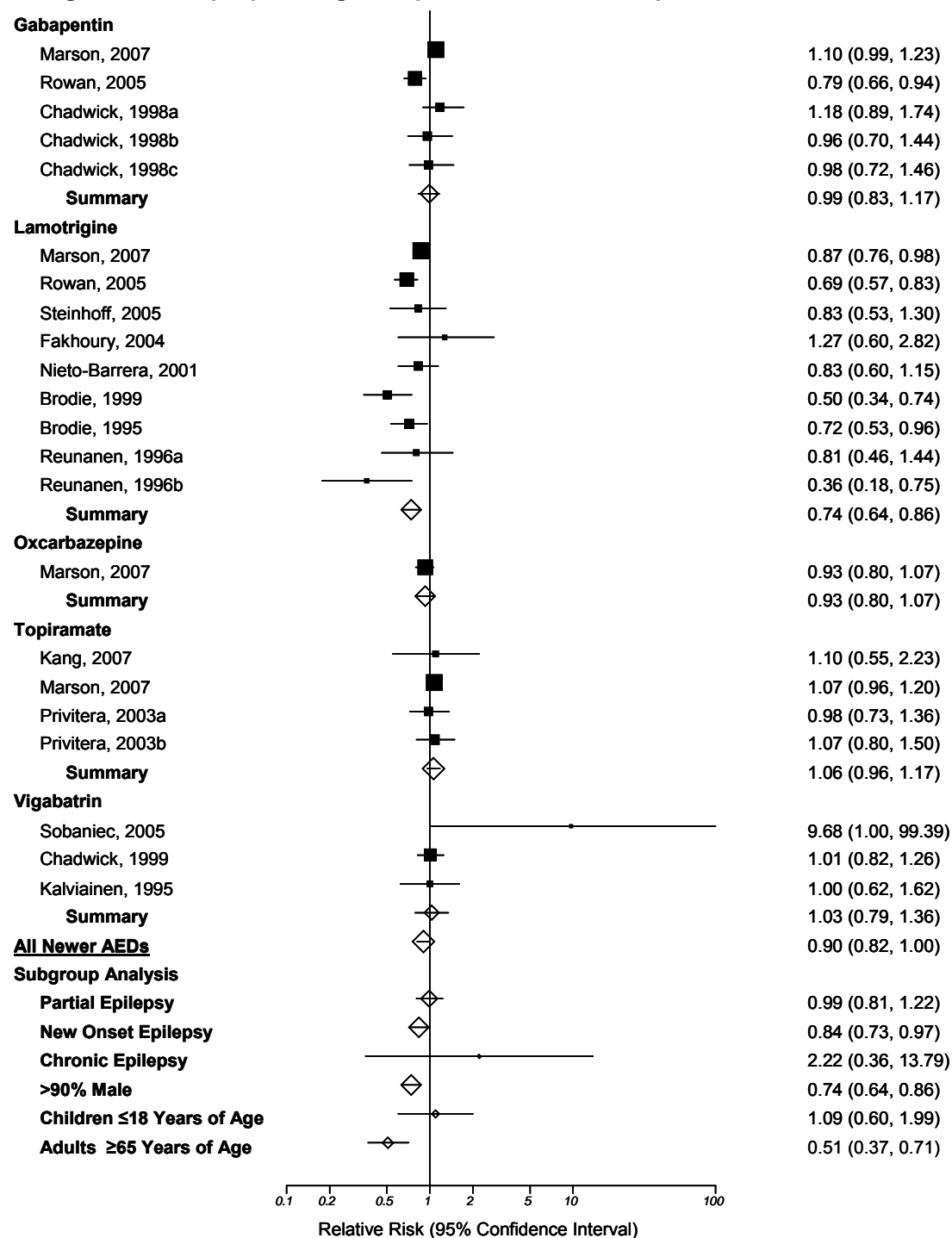
Figure J-8. Composite forest plot of meta-analysis of seizure frequency in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug



AEDs = antiepileptic drugs; BCS = biopharmaceutics classification system

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 0 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

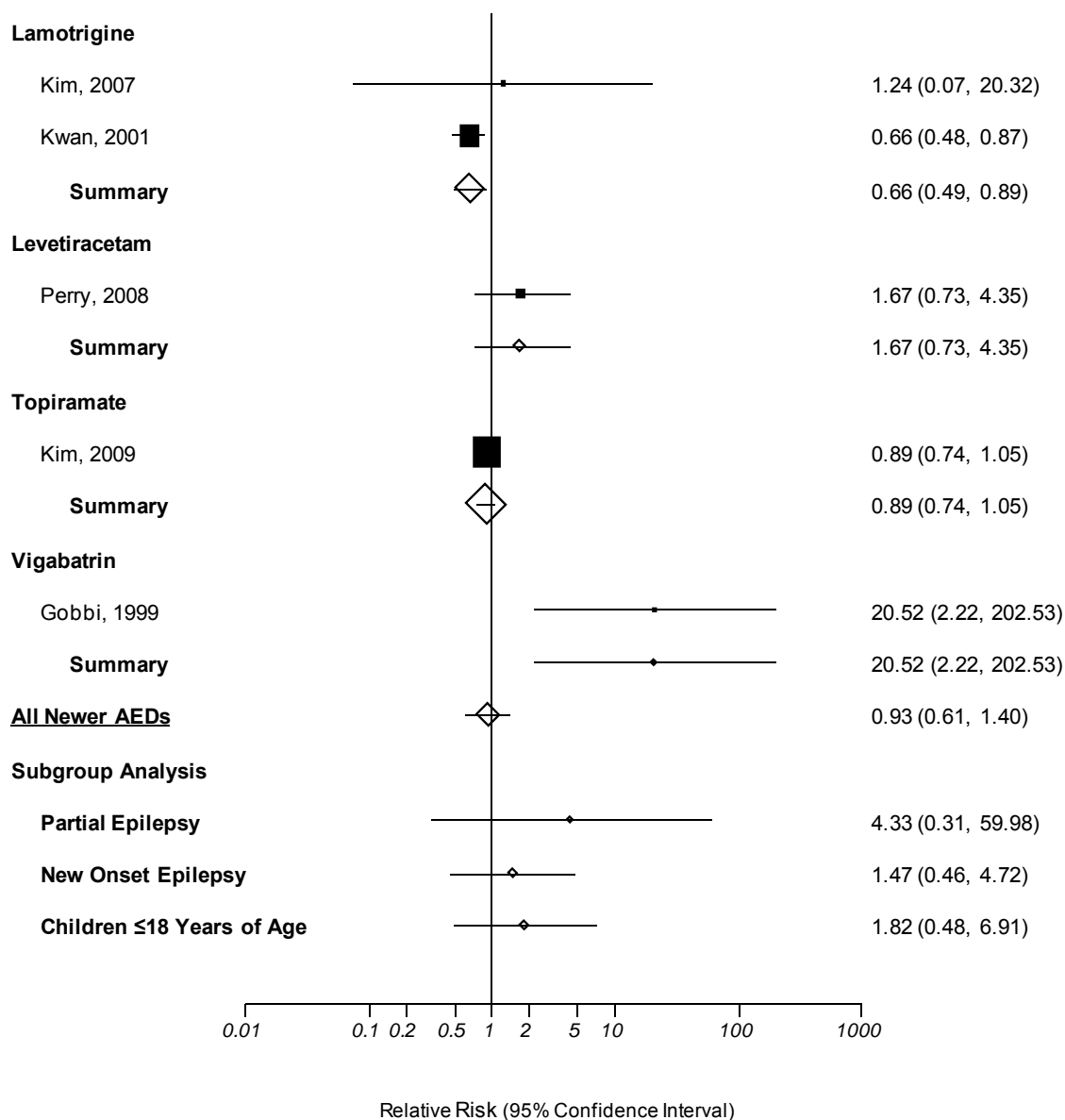
Figure J-9. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

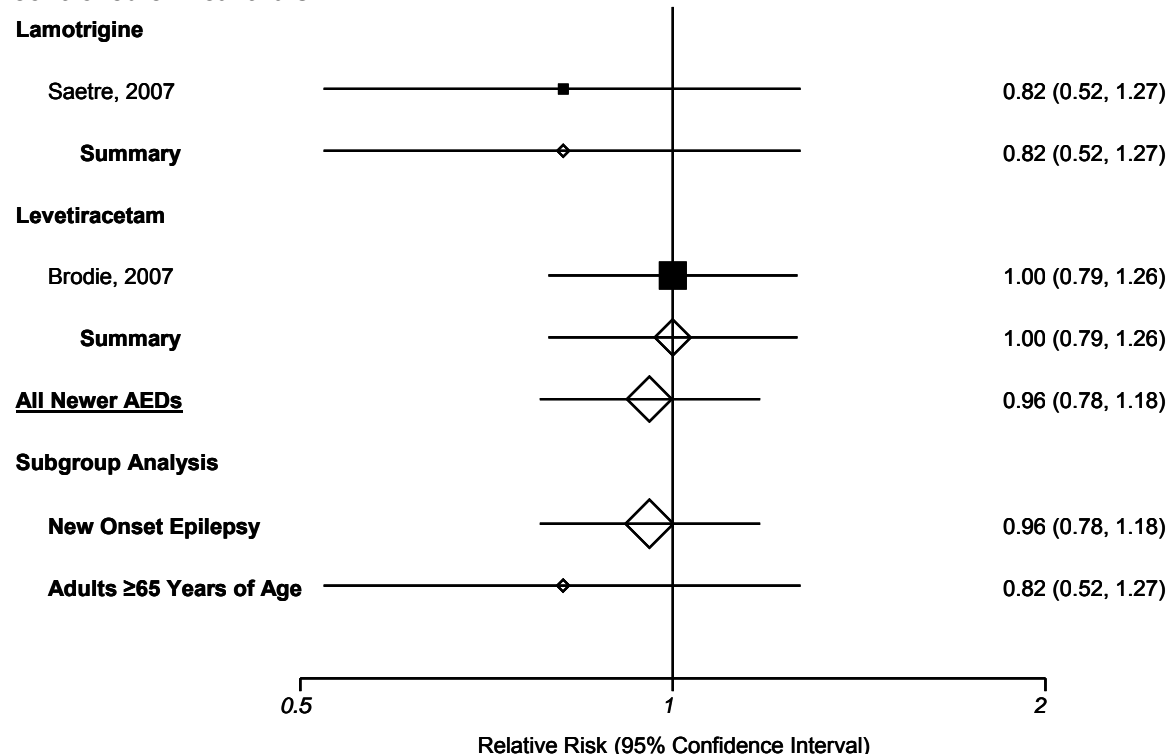
Figure J-10. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

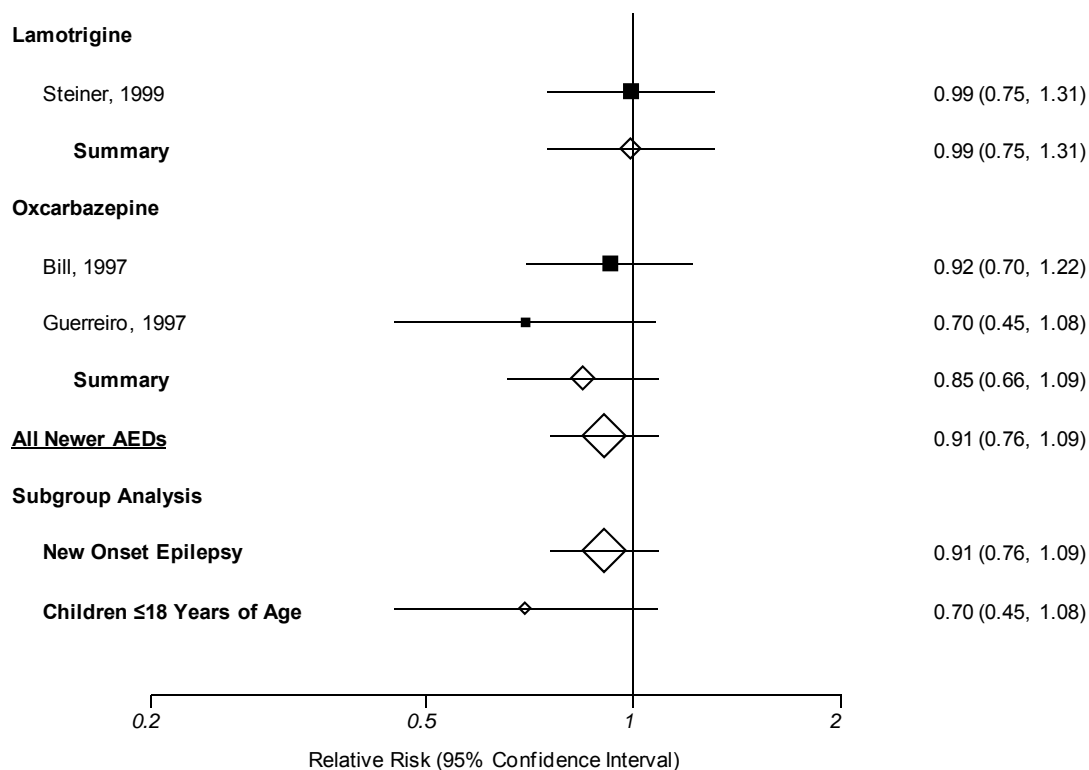
Figure J-11. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared with controlled or sustained release carbamazepine in controlled clinical trials



AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

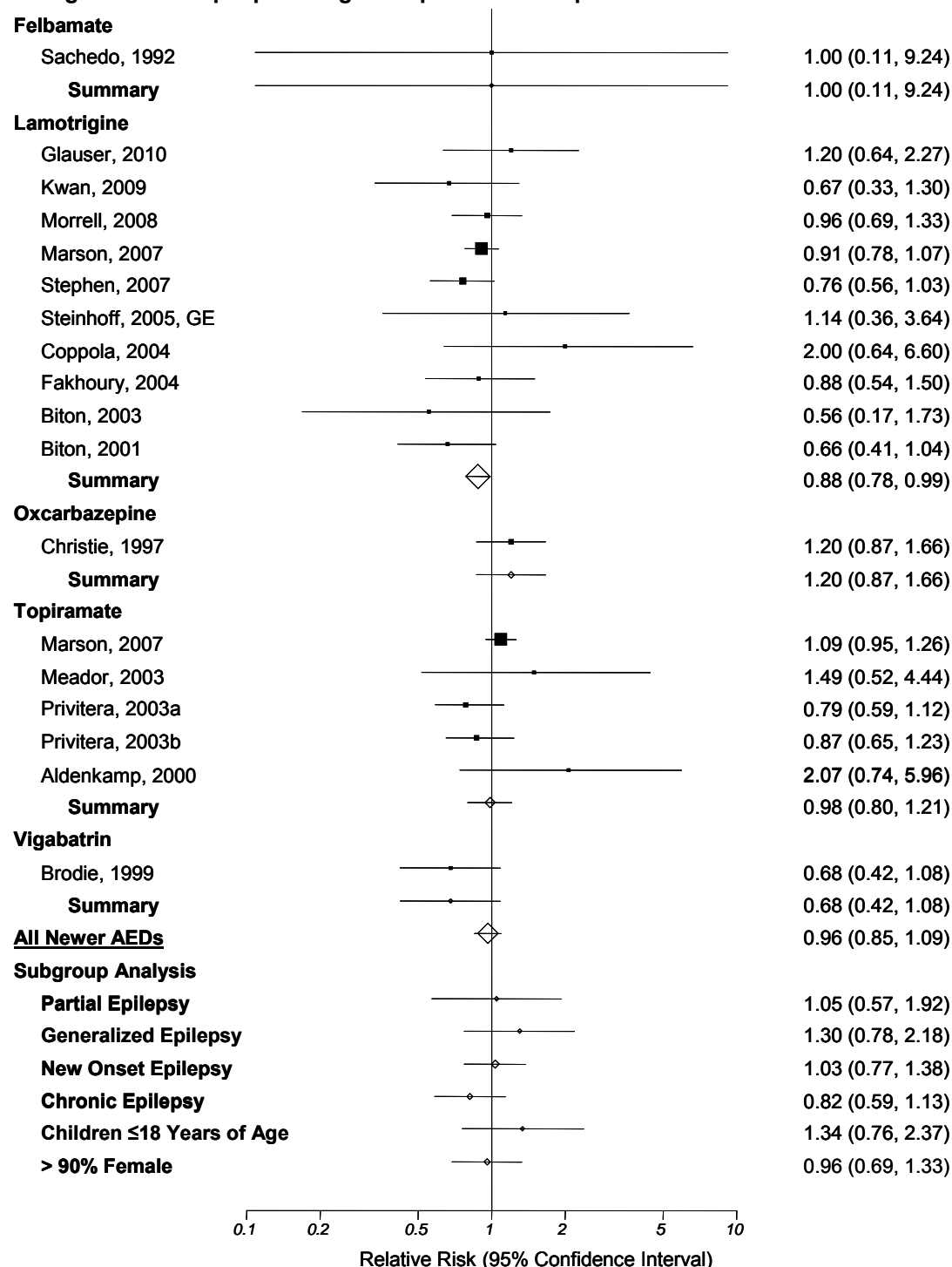
Figure J-12. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

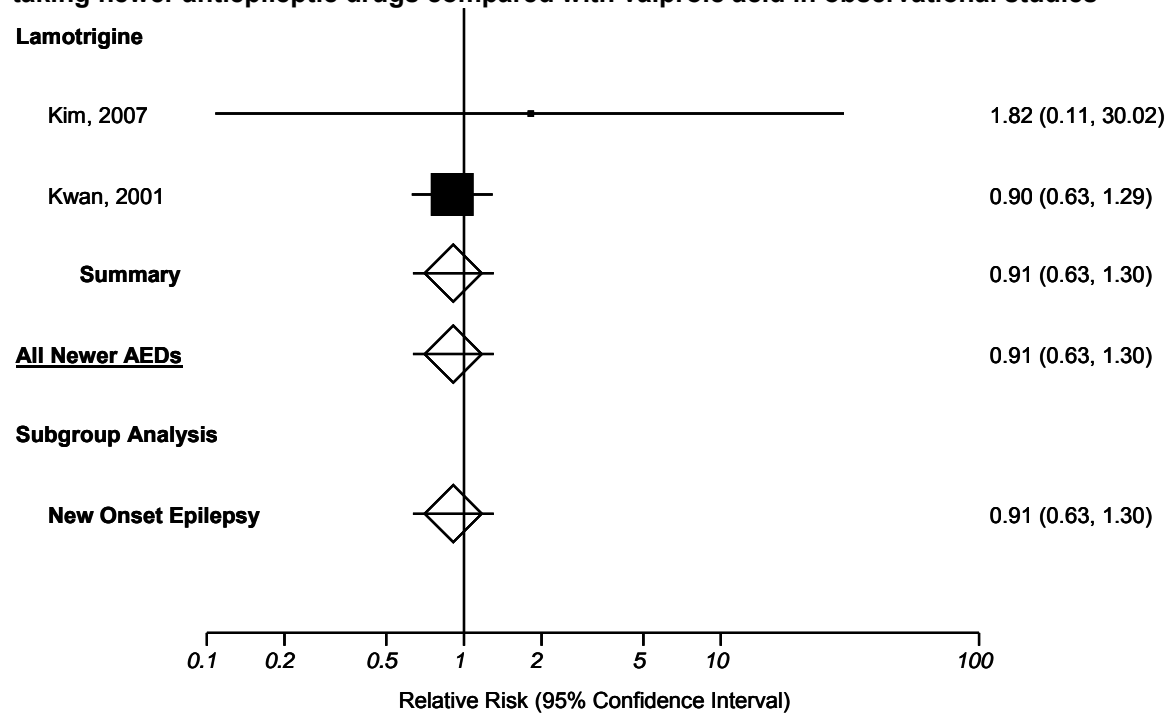
Figure J-13. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

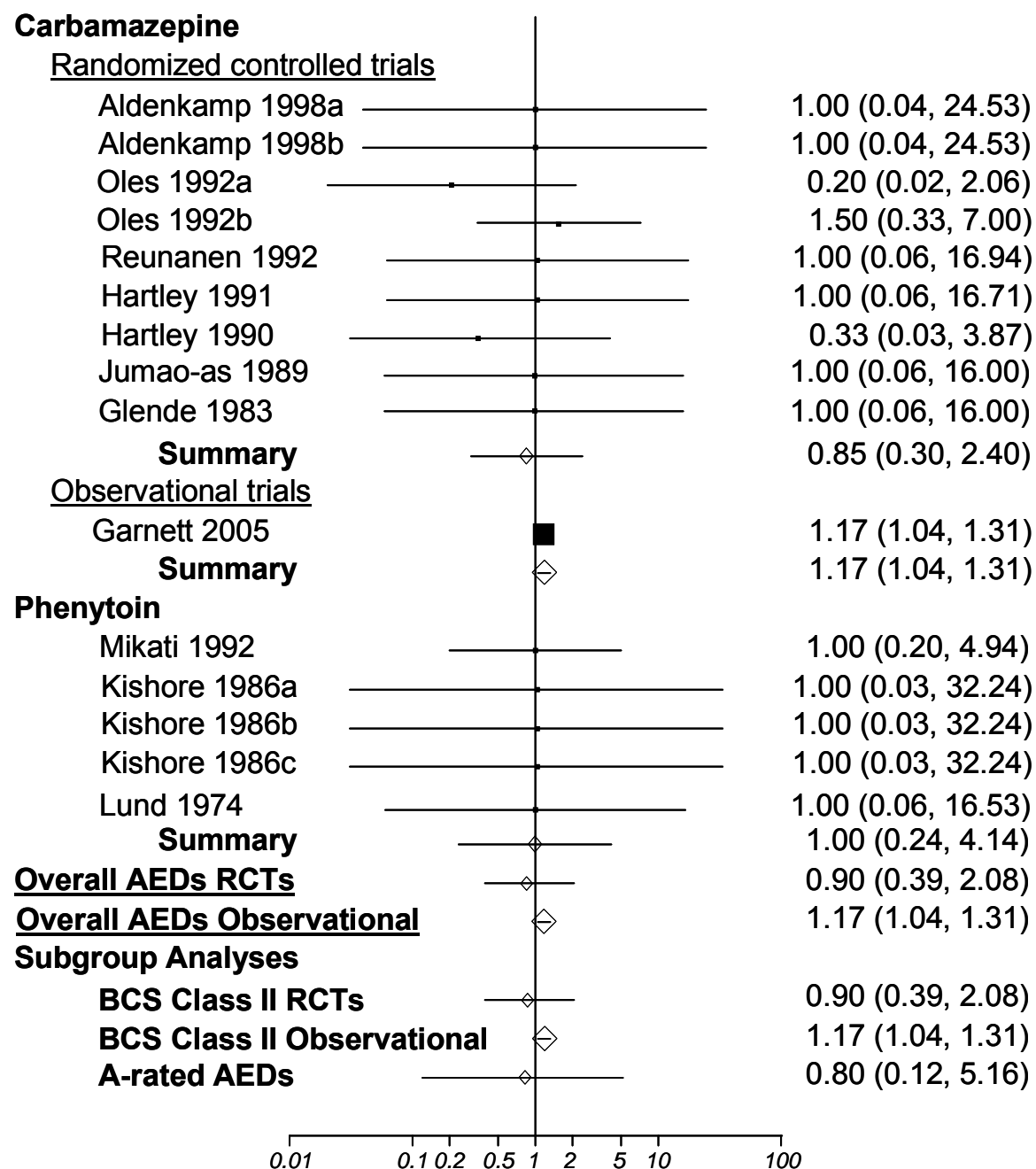
Figure J-14. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure J-15. Composite forest plot of meta-analysis of withdrawals for any reason in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug

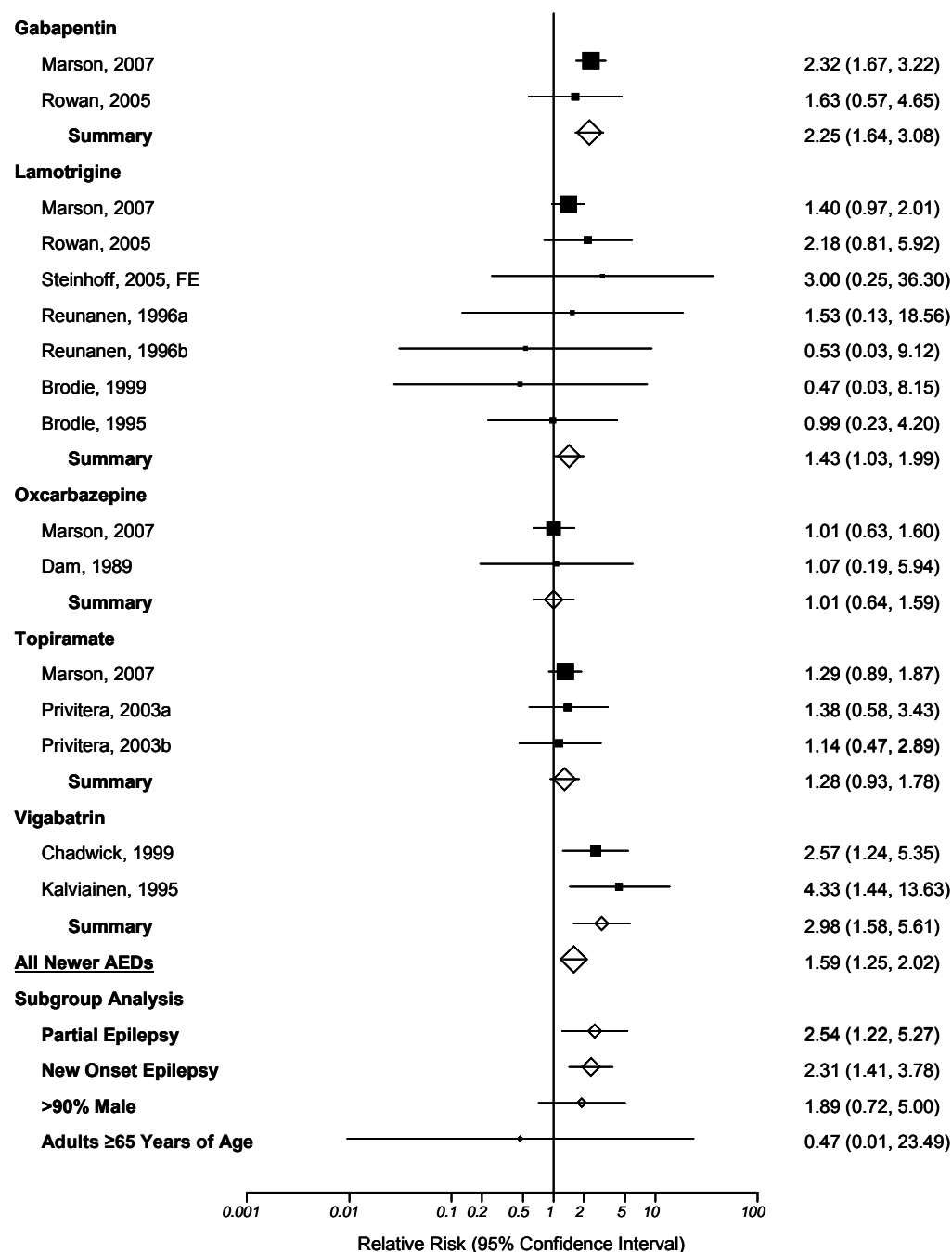


Relative Risk (95% Confidence Interval)

AEDs = antiepileptic drugs; BCS = biopharmaceutics classification system; RCTs = randomized controlled trials

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

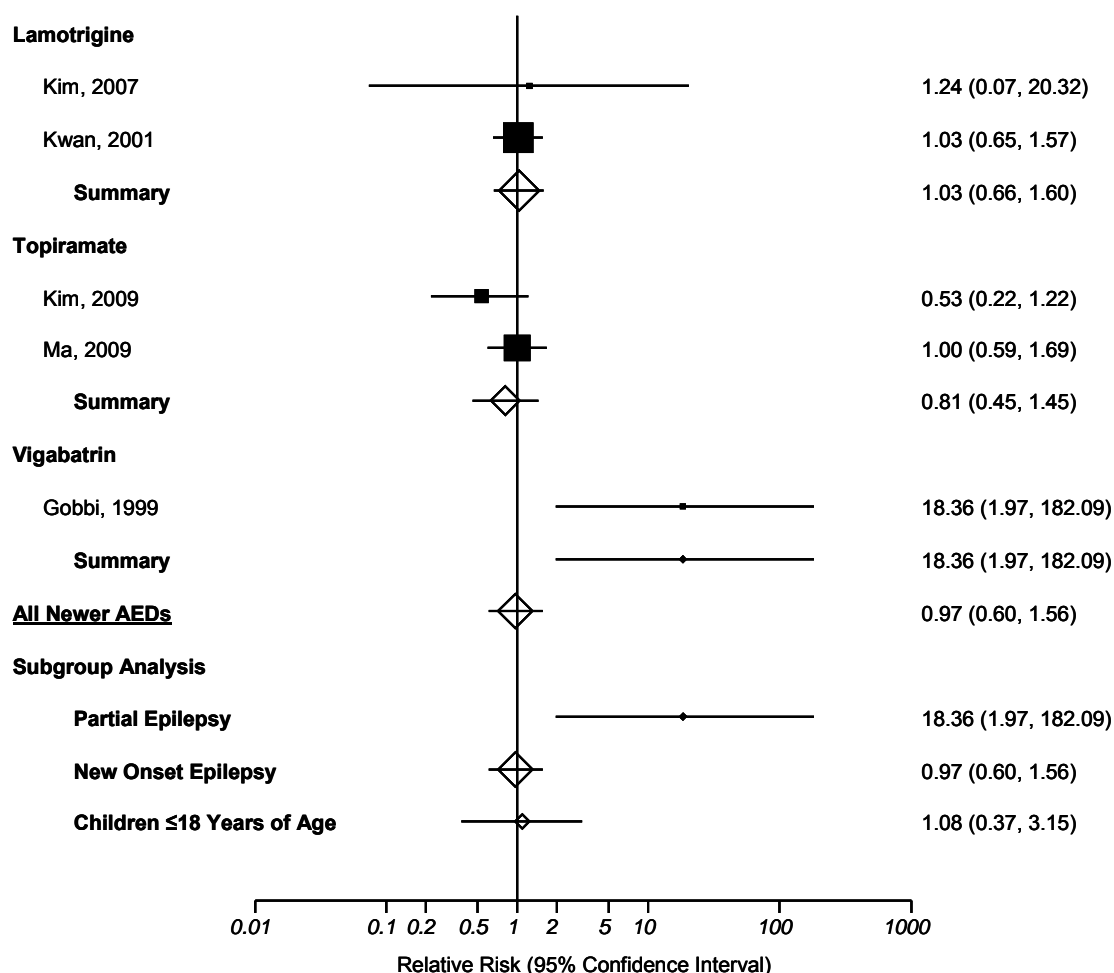
Figure J-16. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs=antiepileptic drugs, FE=focalized epilepsy

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

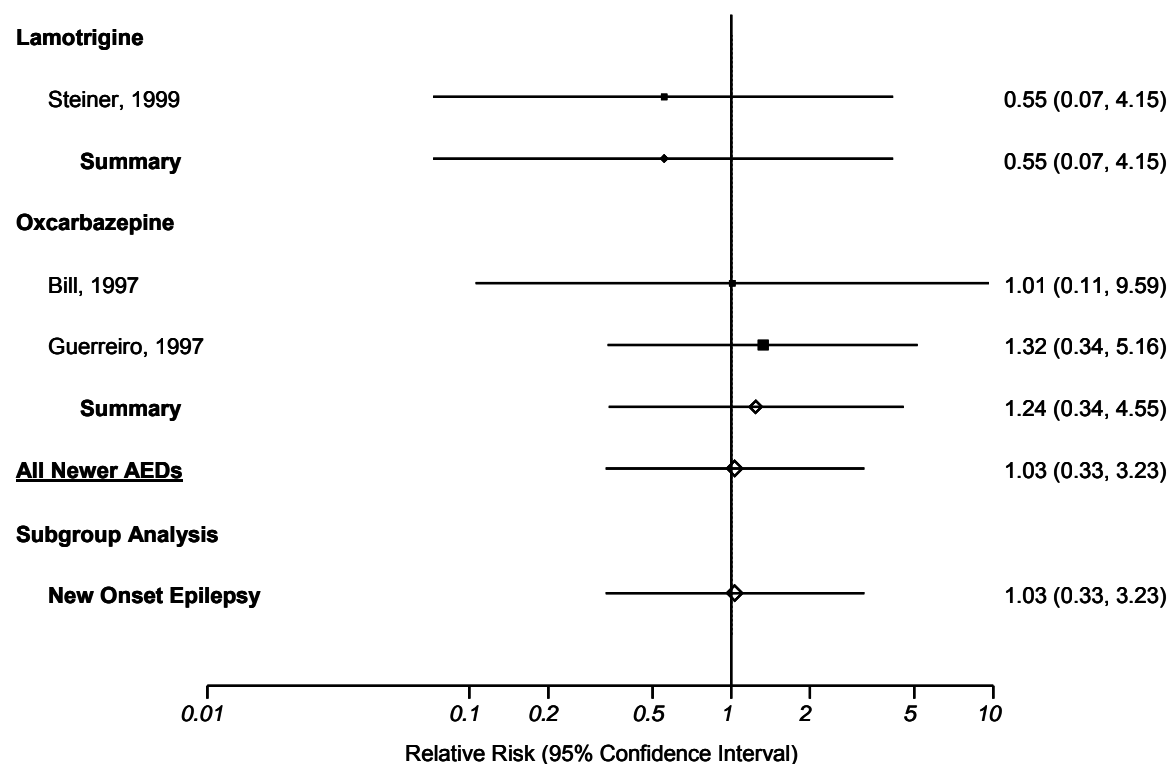
Figure J-17. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

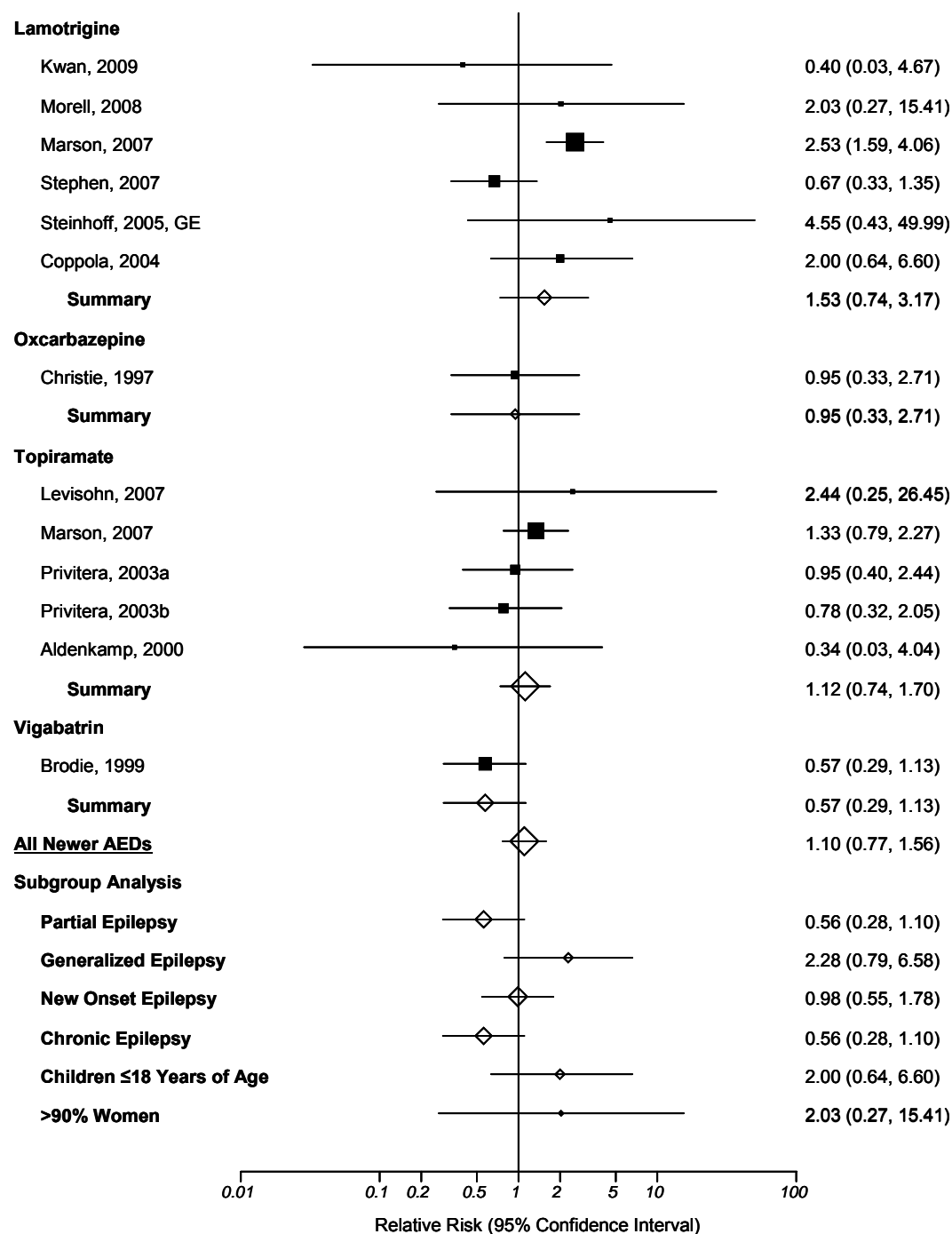
Figure J-18. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

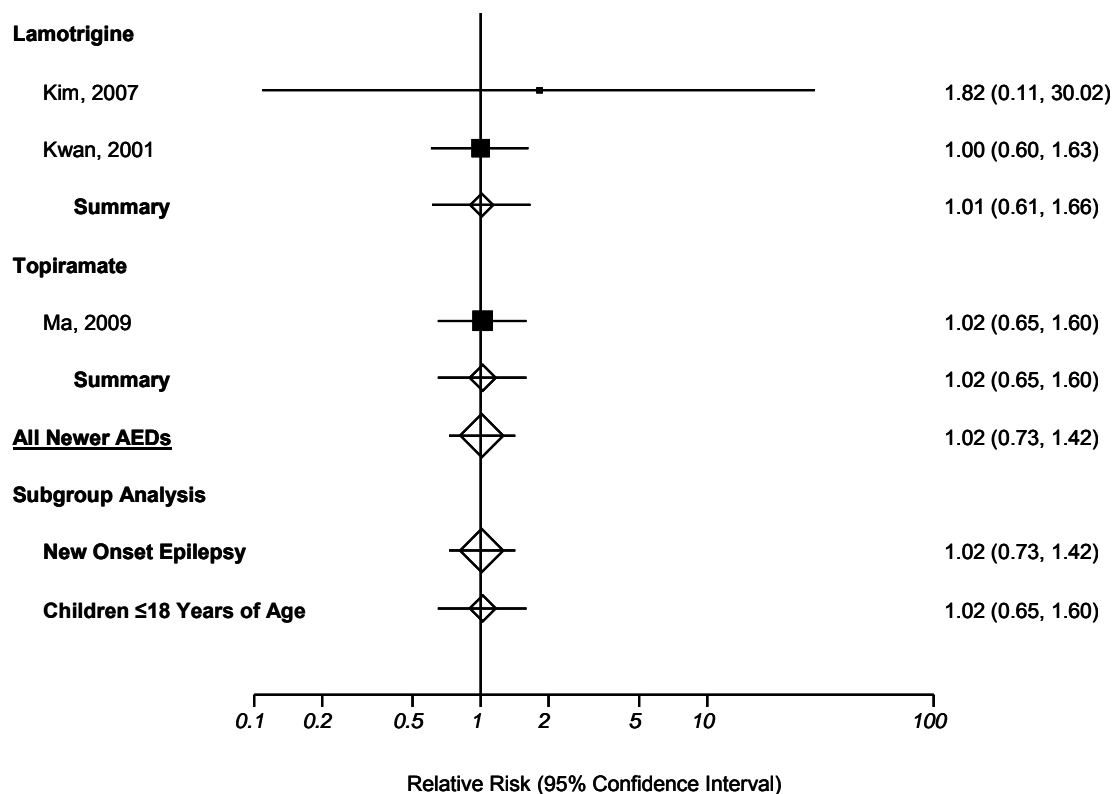
Figure J-19. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs; GE = generalized epilepsy

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

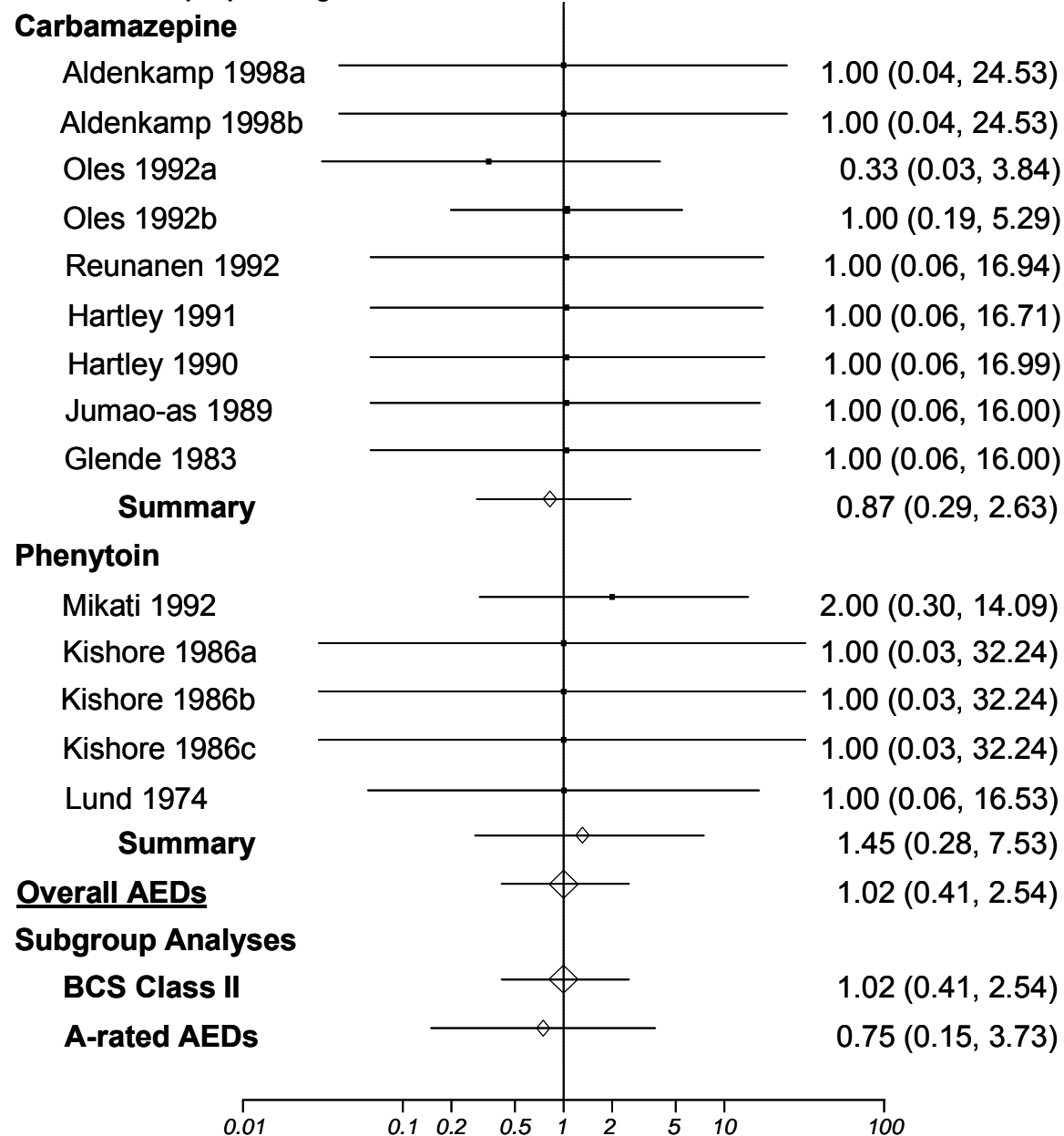
Figure J-20. Composite forest plot of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure J-21. Composite forest plot of meta-analysis of withdrawals due to lack of efficacy in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug

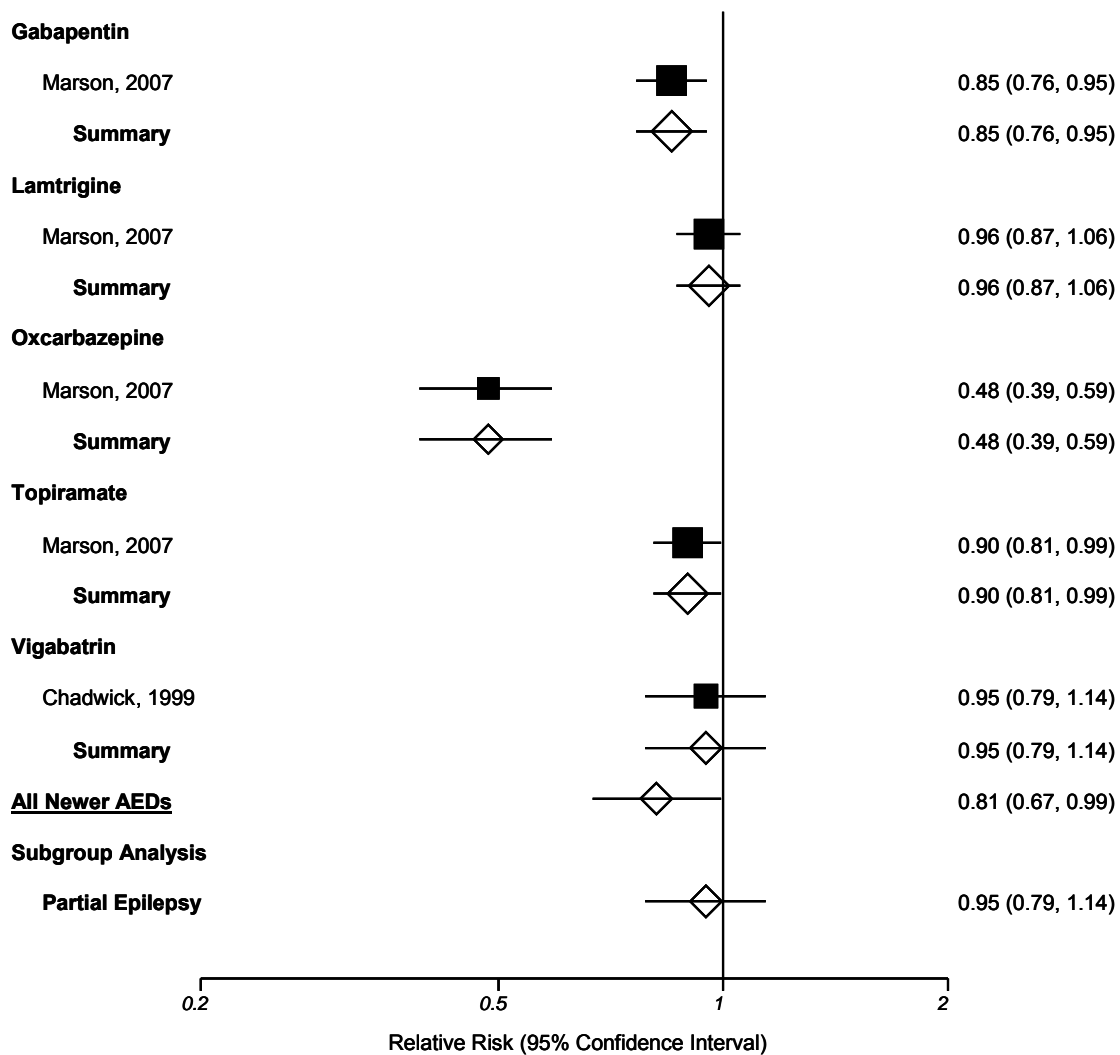


Relative Risk (95% Confidence Interval)

AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

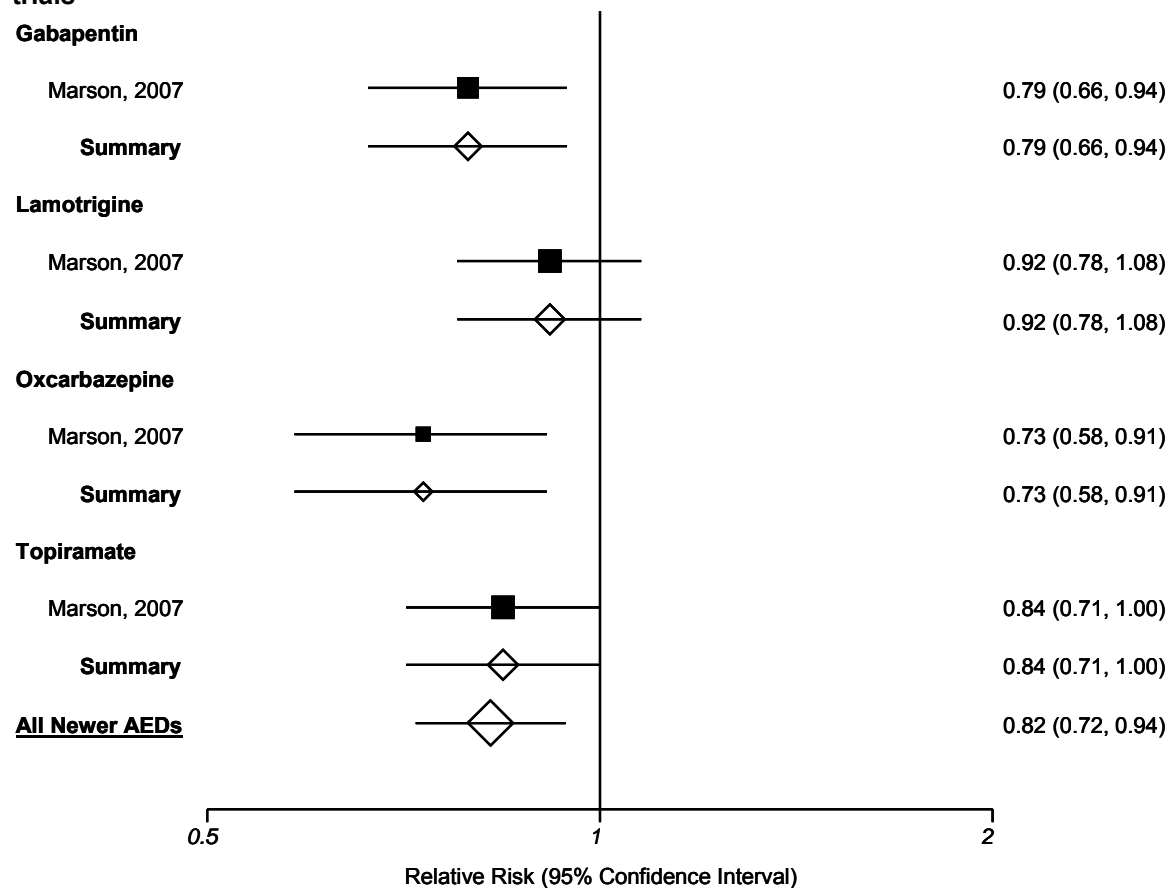
Figure J-22. Composite forest plot of meta-analysis of twelve-month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

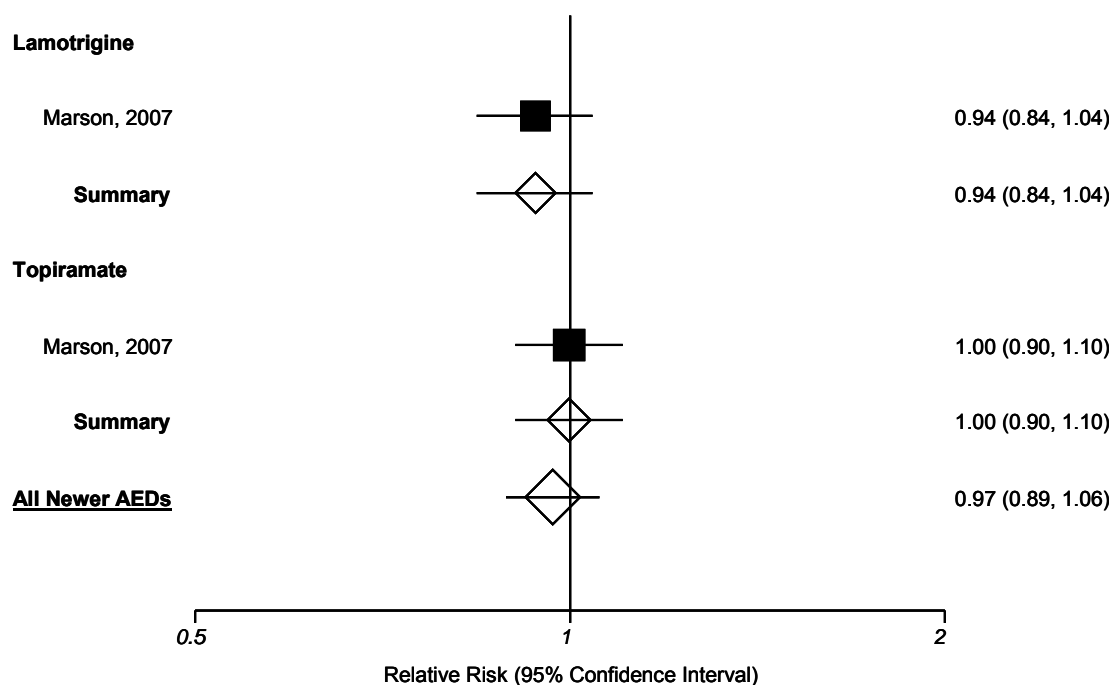
Figure J-23. Composite forest plot of meta-analysis of 24-month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

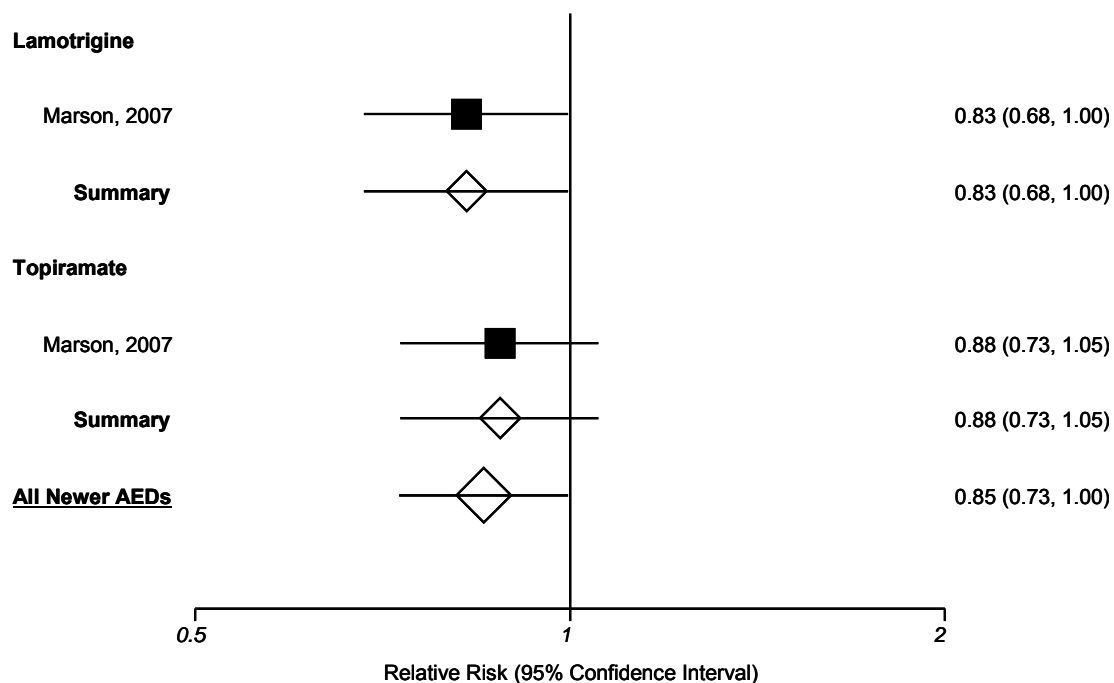
Figure J-24. Composite forest plot of meta-analysis of 12-month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

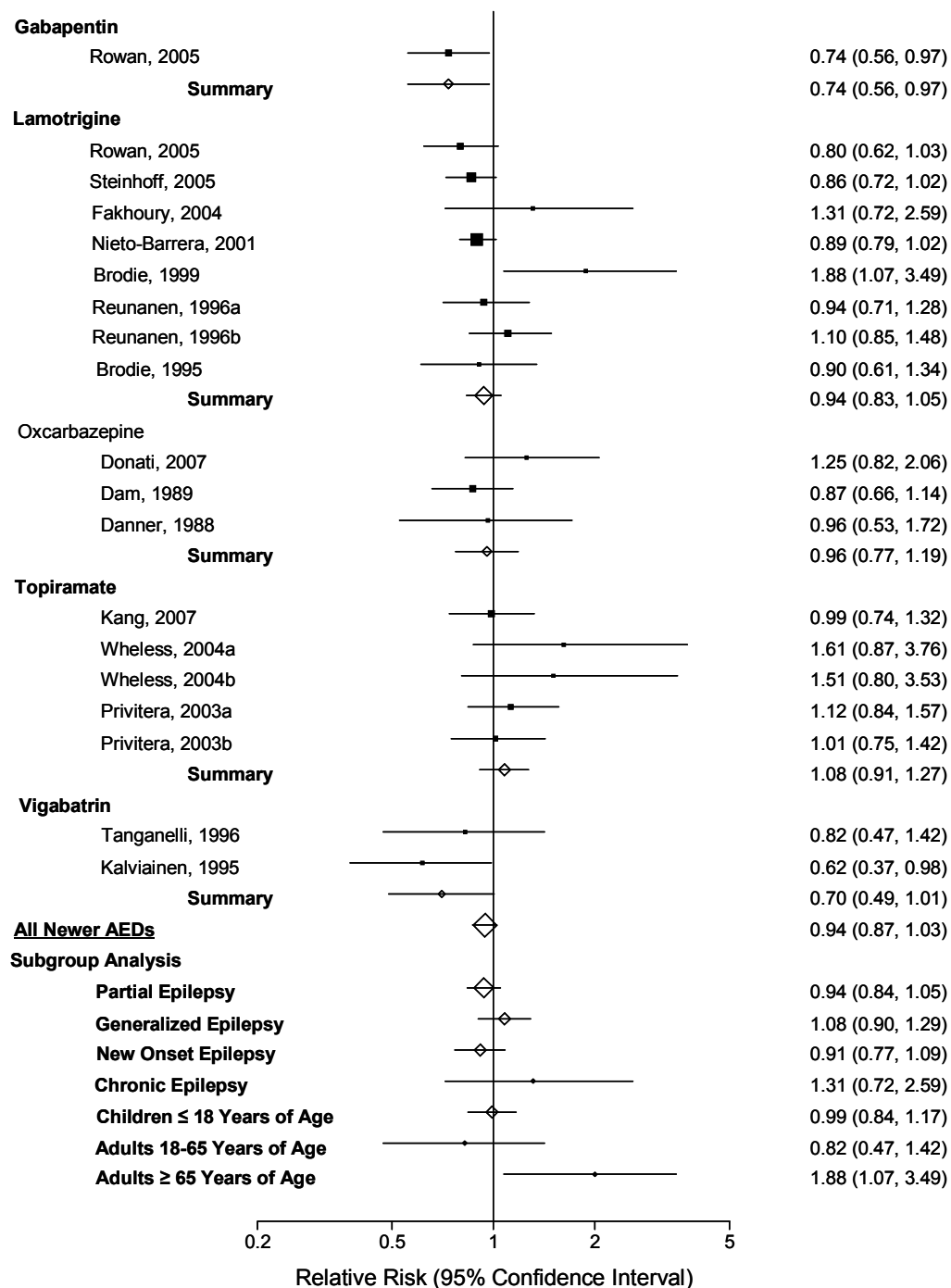
Figure J-25. Composite forest plot of meta-analysis of 24-month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

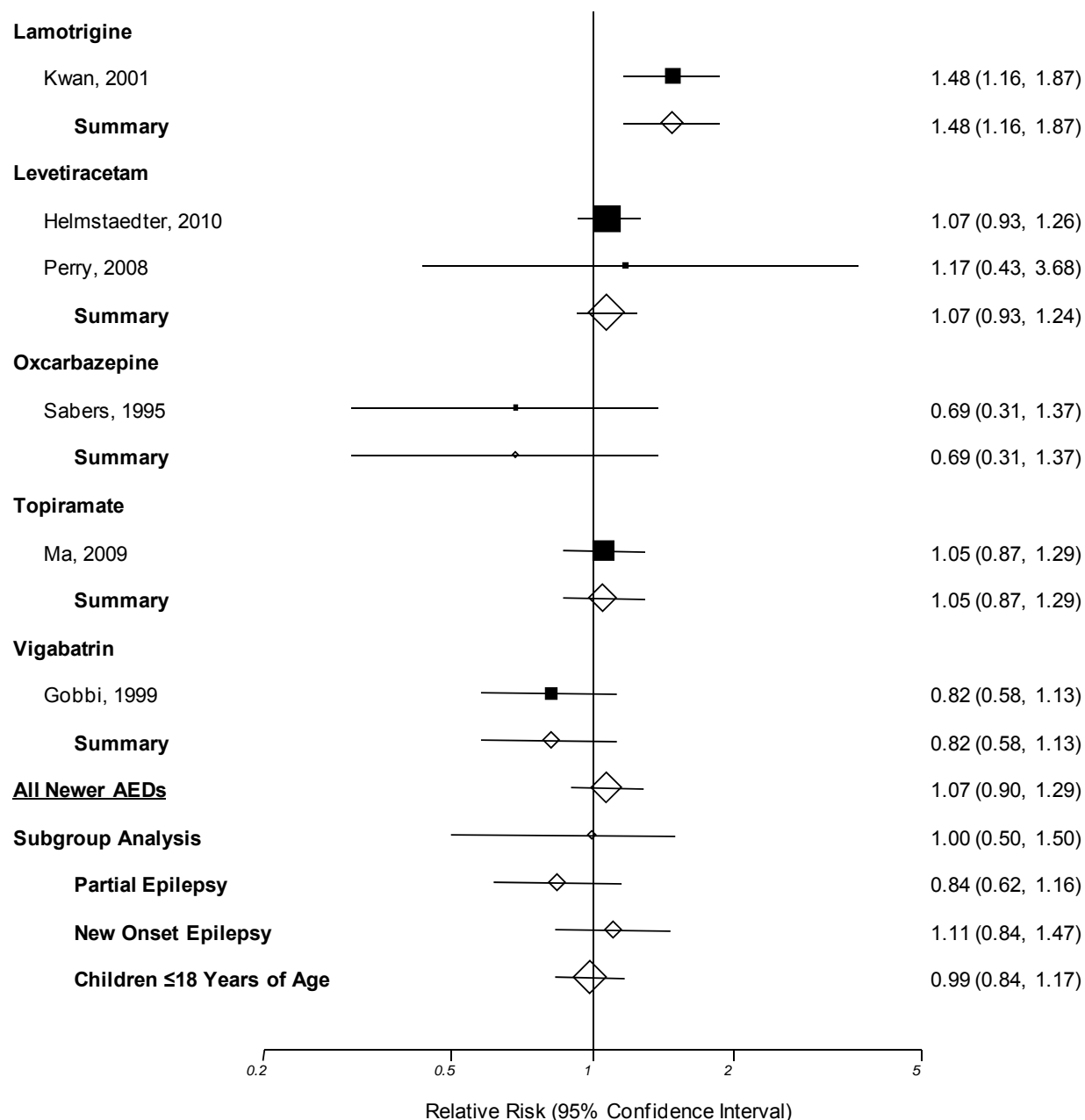
Figure J-26. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

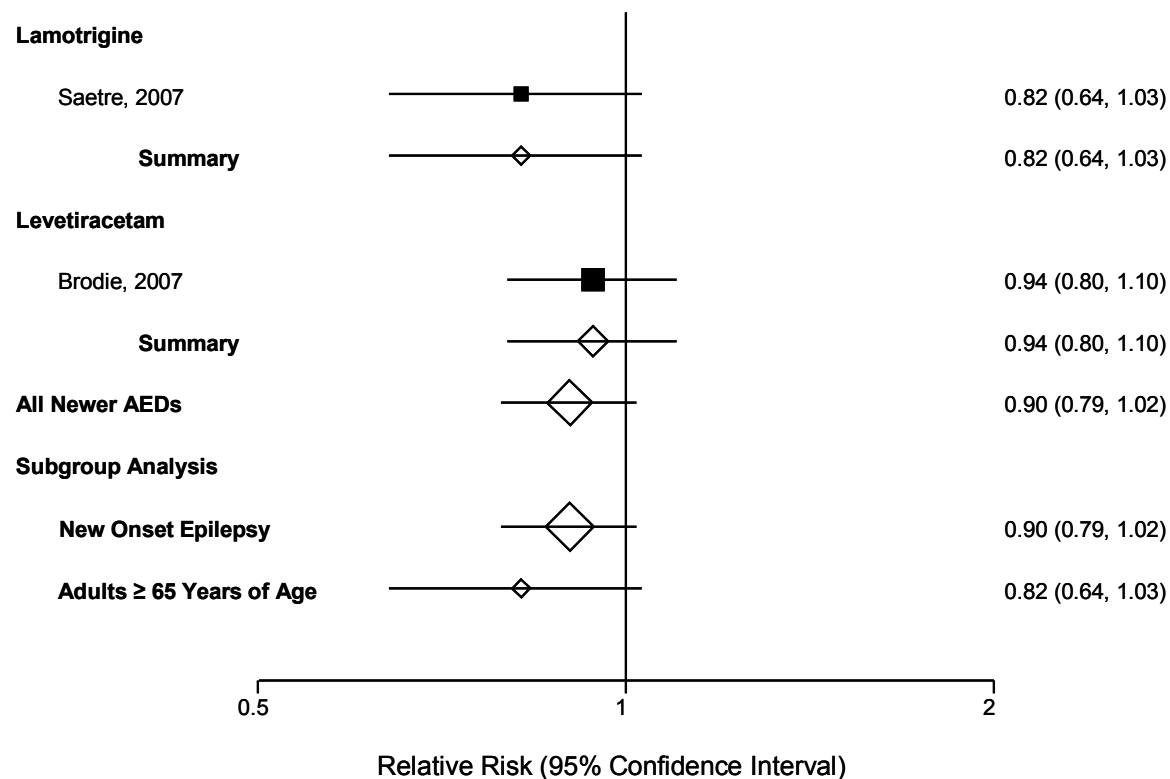
Figure J-27. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

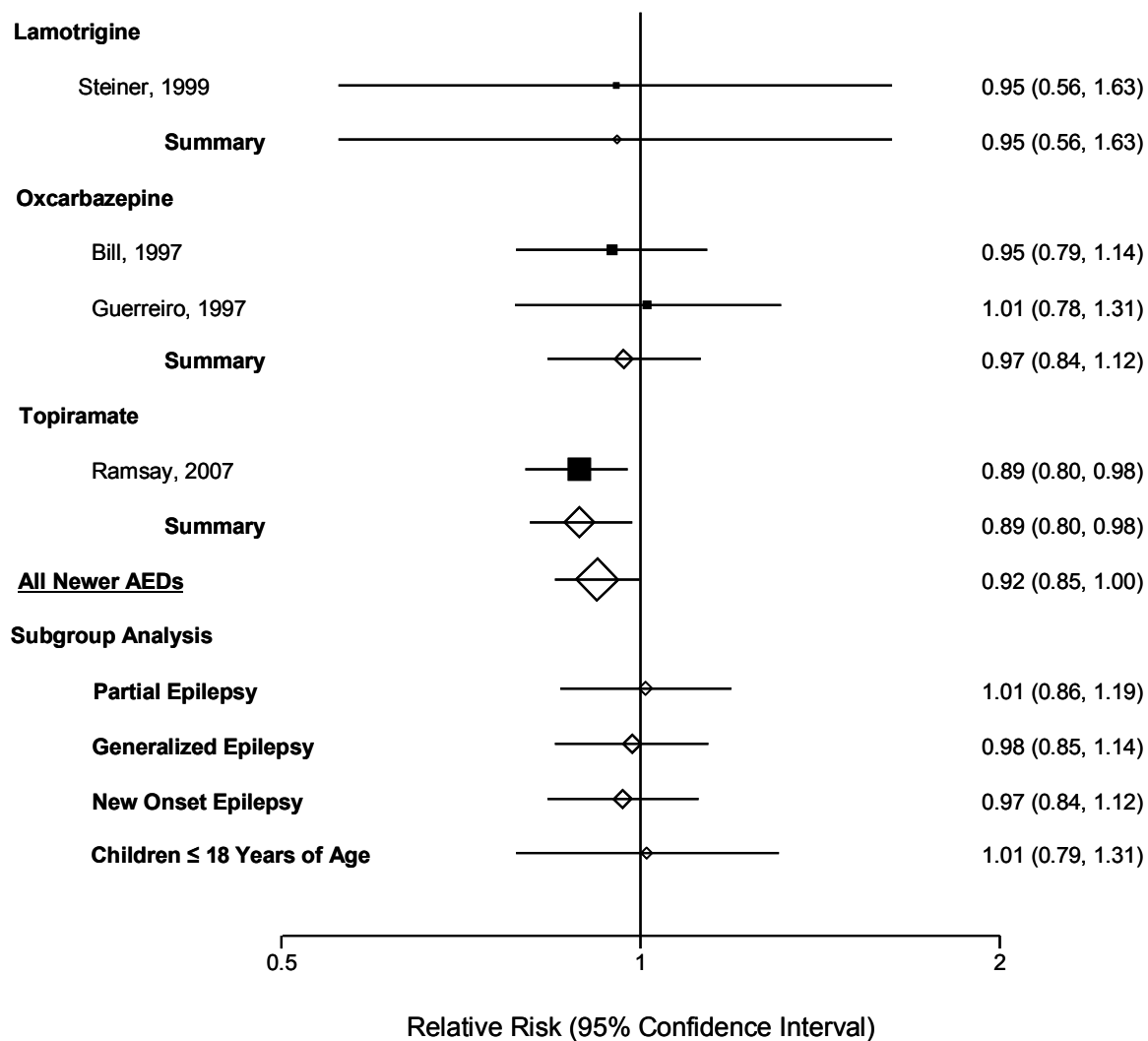
Figure J-28. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared with controlled or sustained release carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

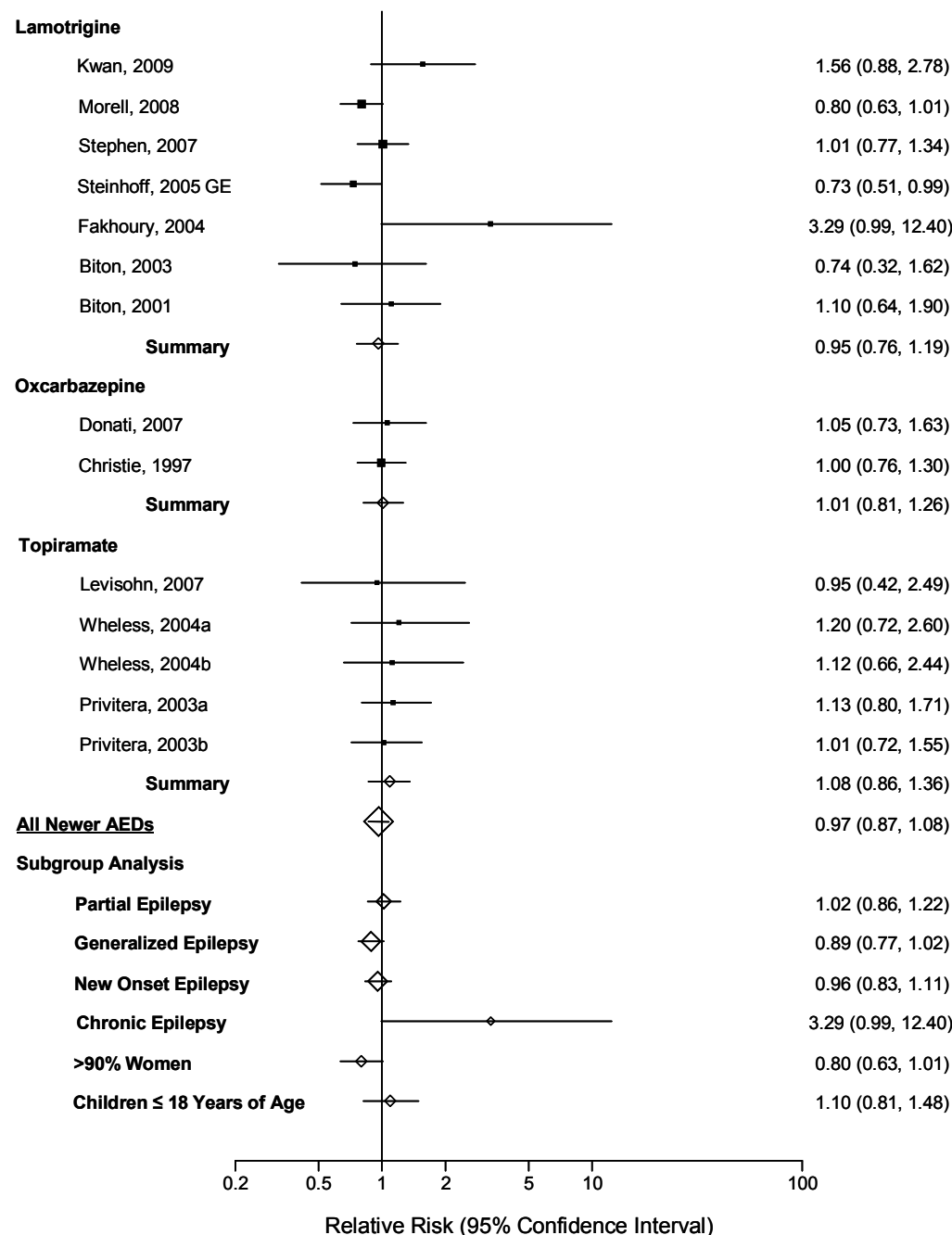
Figure J-29. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

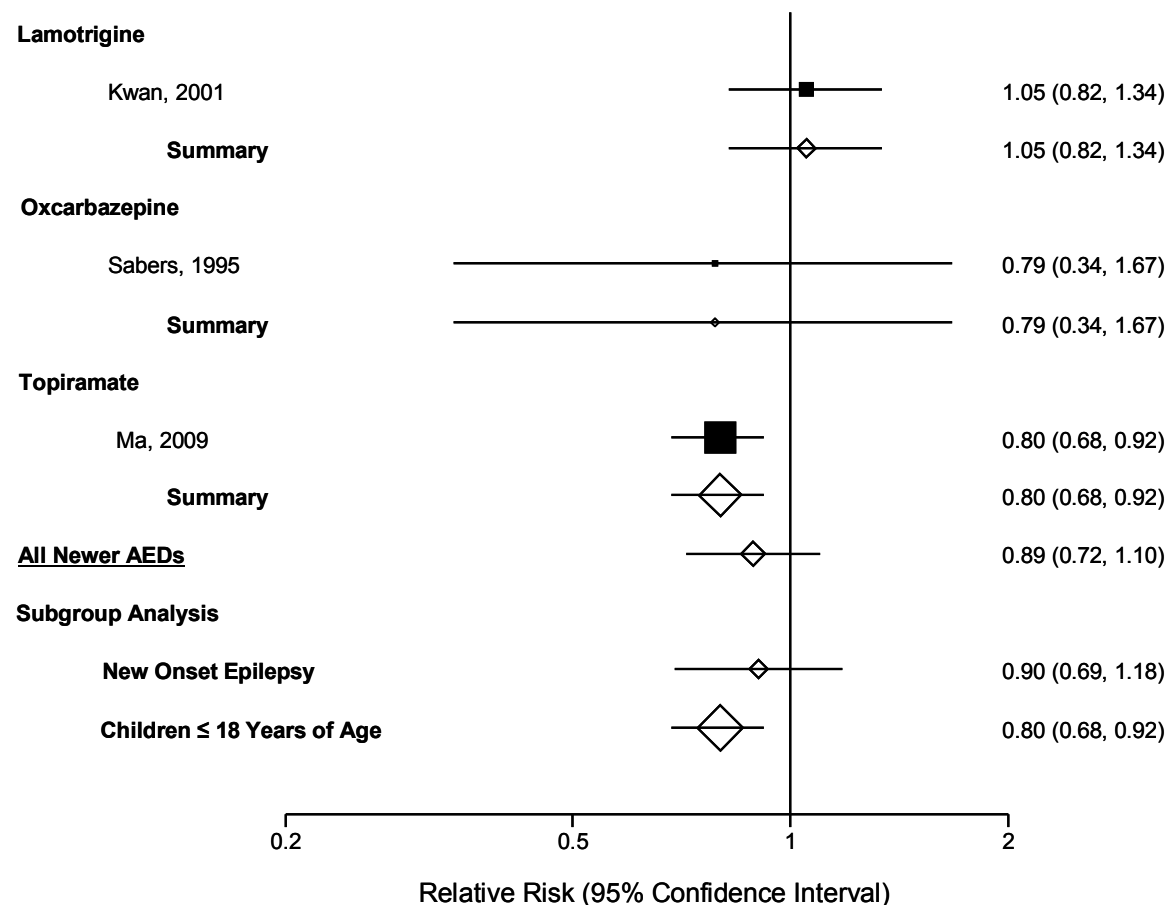
Figure J-30. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure J-31. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies

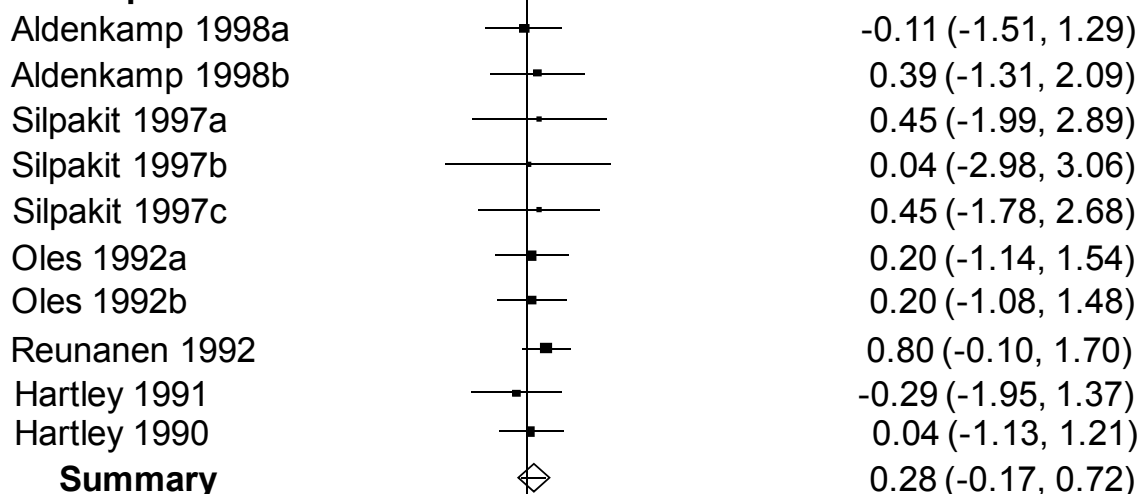


AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure J-32. Composite forest plot of meta-analysis of maximum concentration (Cmax) in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug

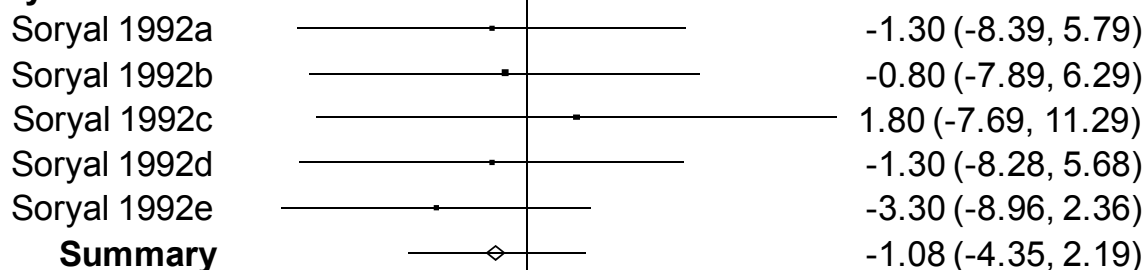
Carbamazepine



Lamotrigine



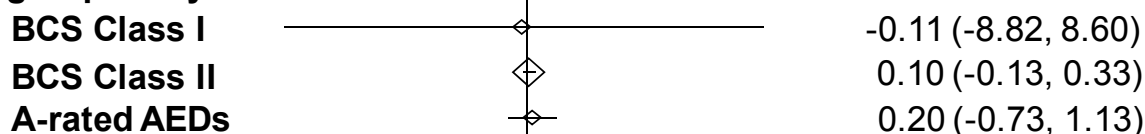
Phenytoin



Overall AEDs



Subgroup Analyses



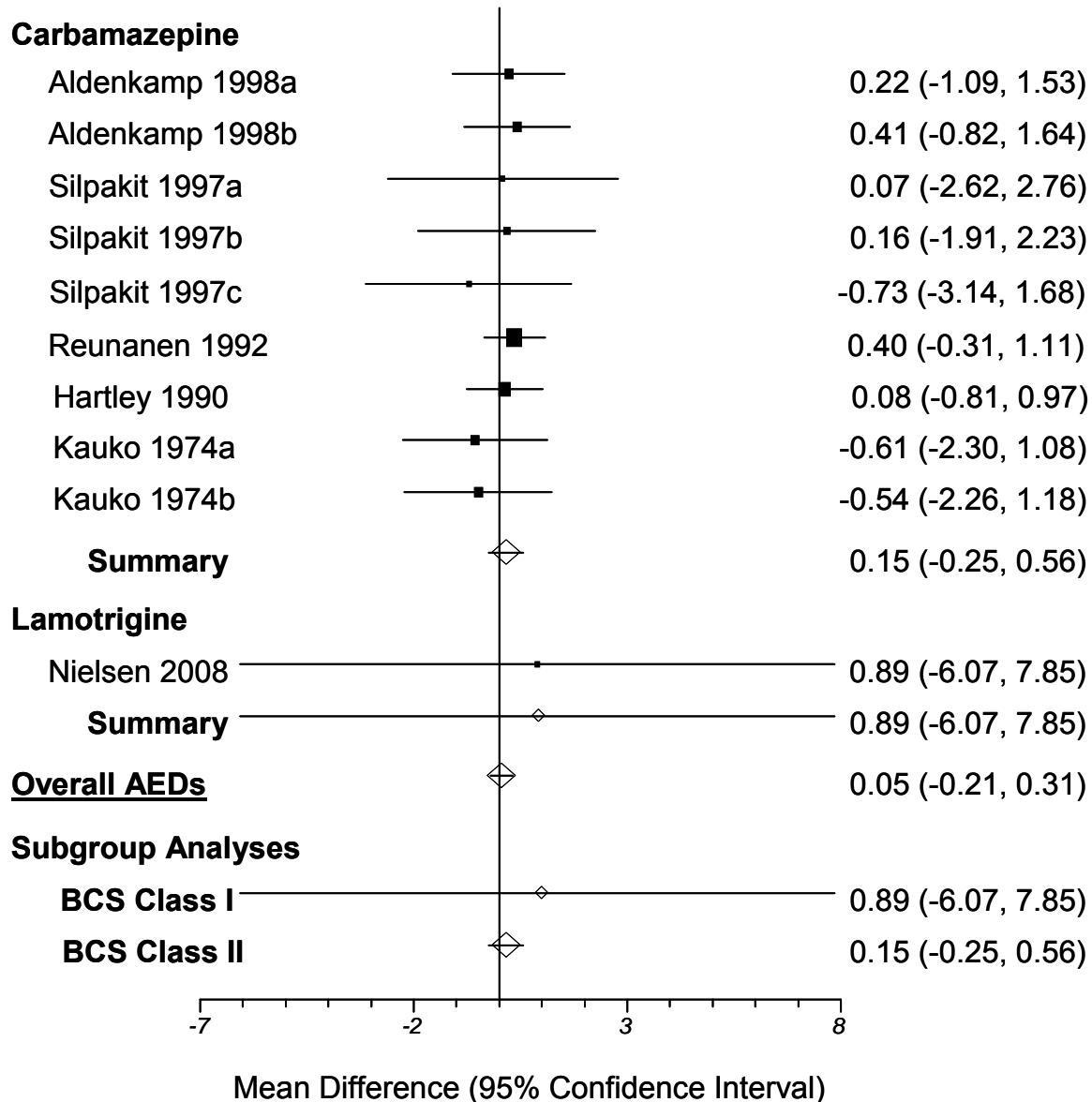
-10 -5 0 5 10 15

Mean Difference (95% Confidence Interval)

AEDs = antiepileptic drugs; BCS = biopharmaceutics classification system; Cmax = maximum concentration

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

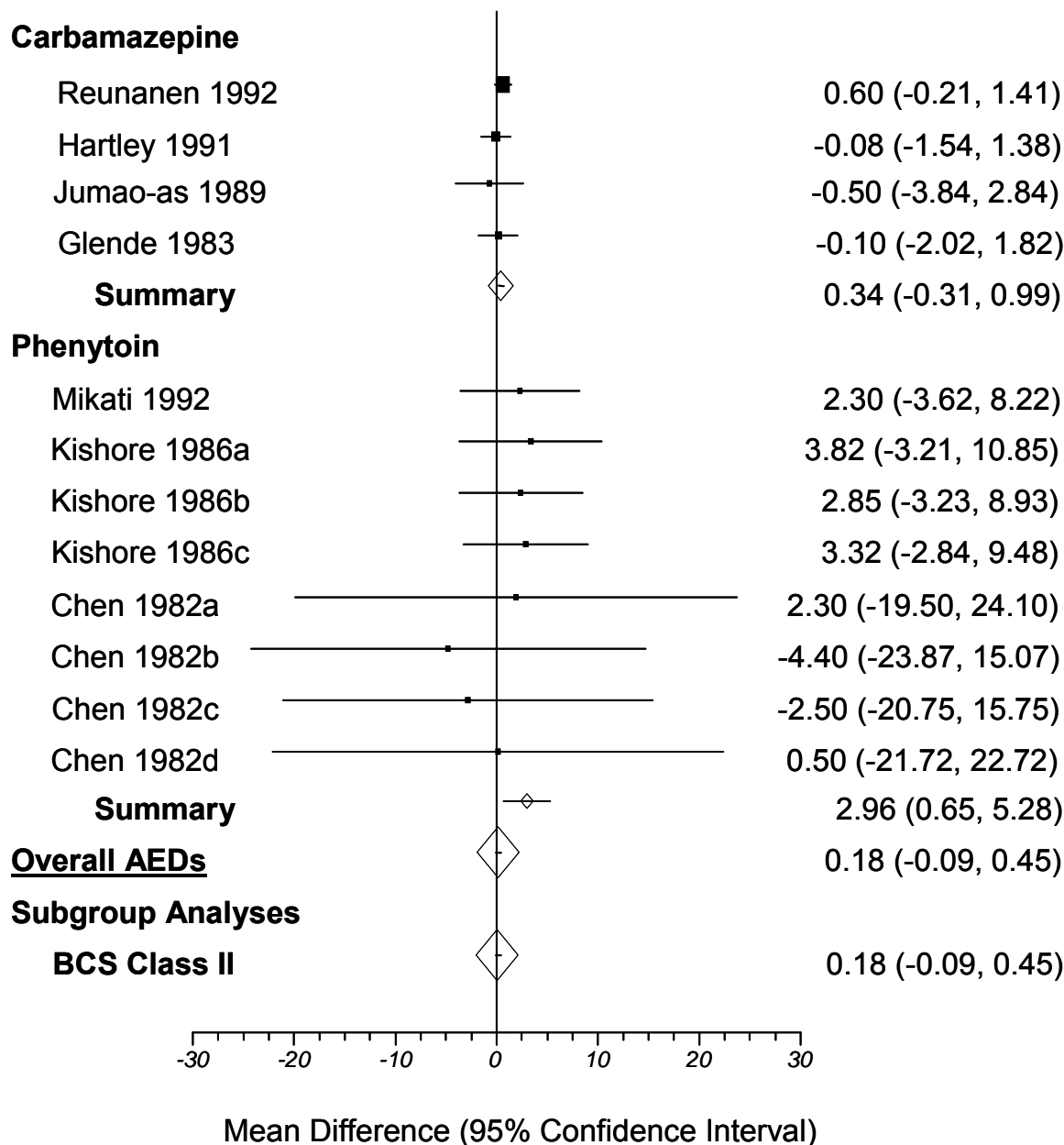
Figure J-33. Composite forest plot of meta-analysis of minimum concentration (Cmin) in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug



AEDs = antiepileptic drugs; BCS = biopharmaceutics classification system; Cmin = minimum concentration

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure J-34. Composite forest plot of meta-analysis of steady-state concentration (Css) in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug

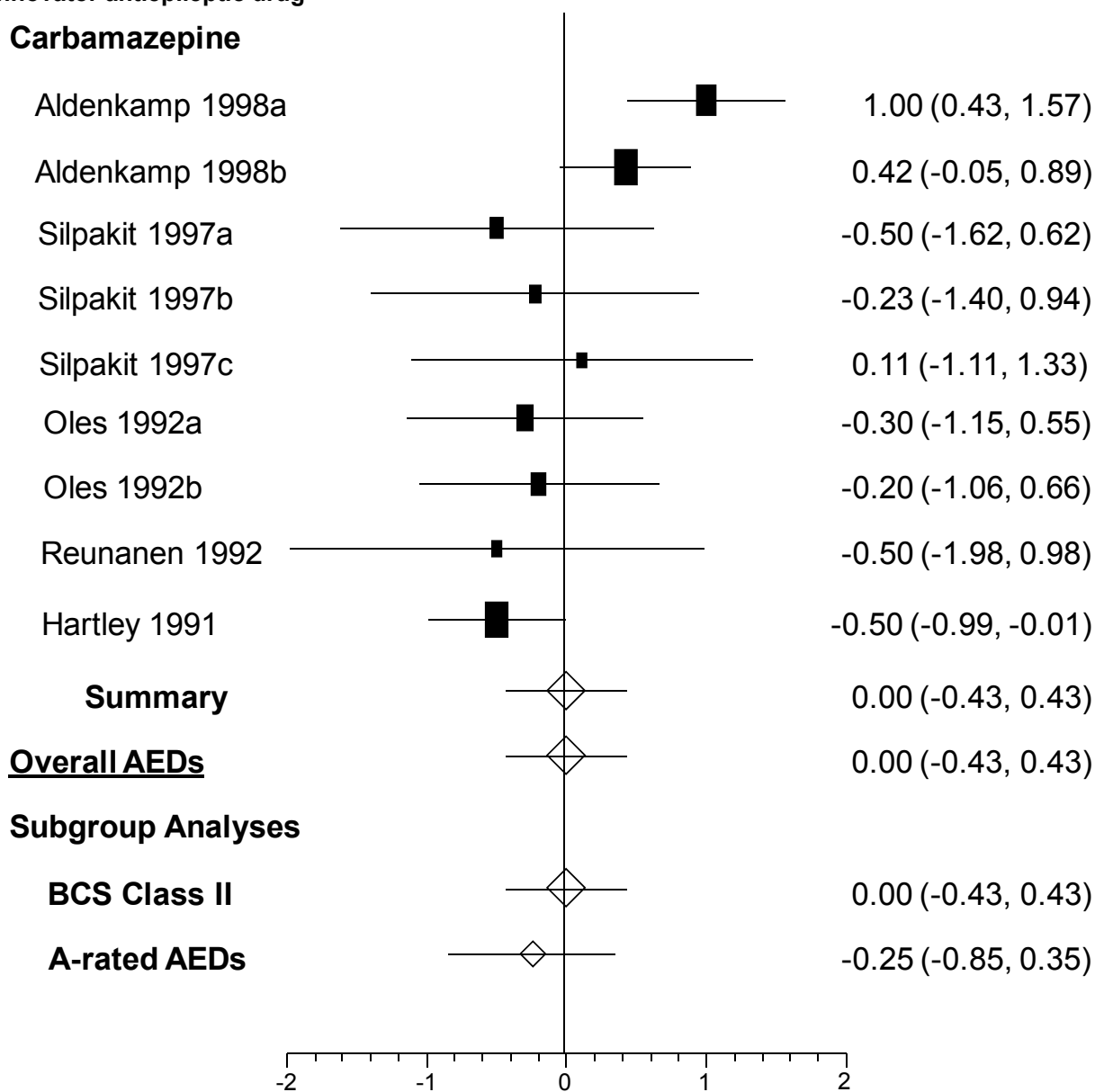


AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; Css=concentration at steady-state

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure J-35. Composite forest plot of meta-analysis of time to maximum concentration (Tmax) in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug

Carbamazepine

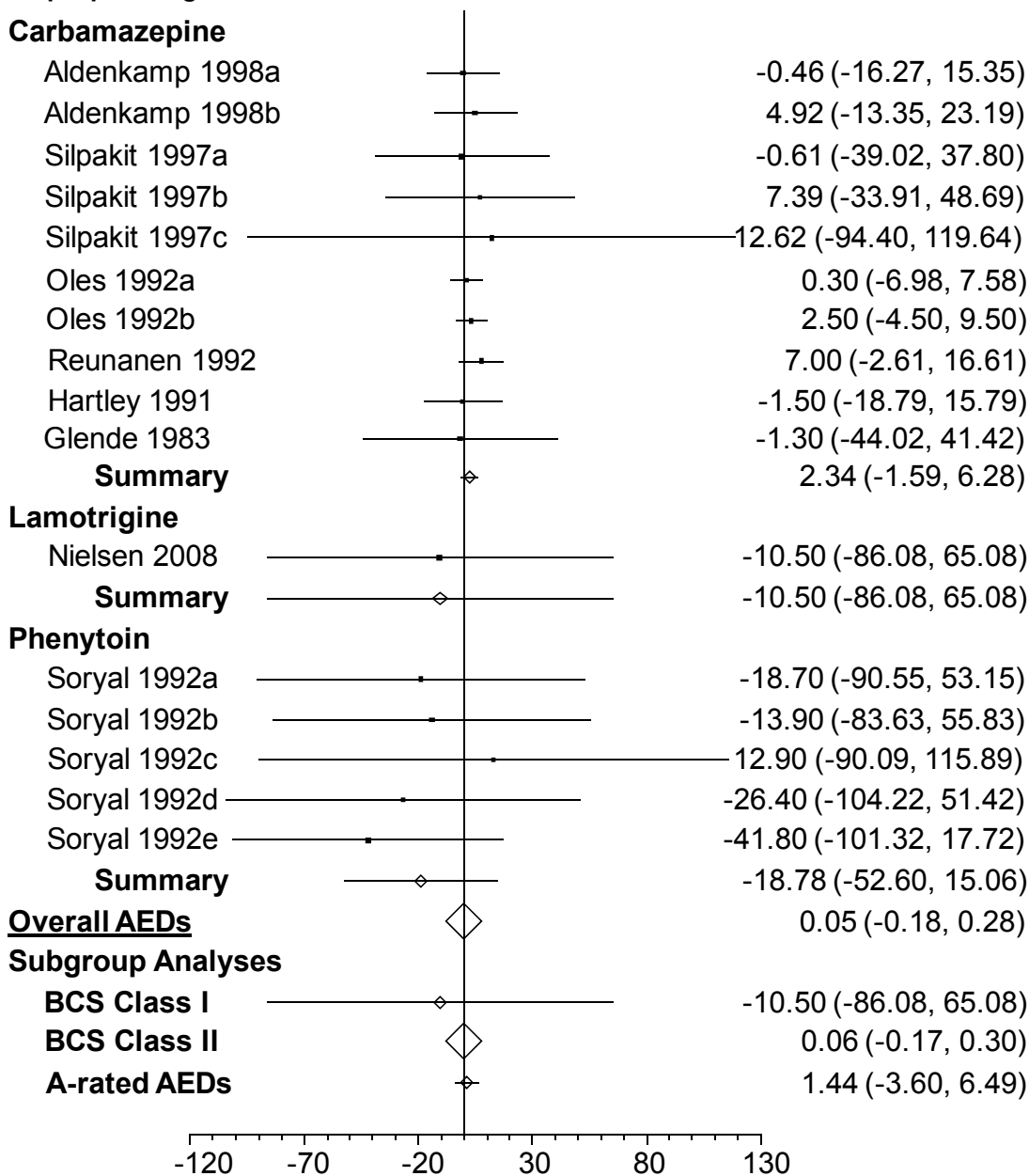


Mean Difference (95% Confidence Interval)

AEDs = antiepileptic drugs; BCS = biopharmaceutics classification system; Tmax = time to maximum concentration.

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure J-36. Composite forest plot of meta-analysis of area under the curve (AUC) in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug

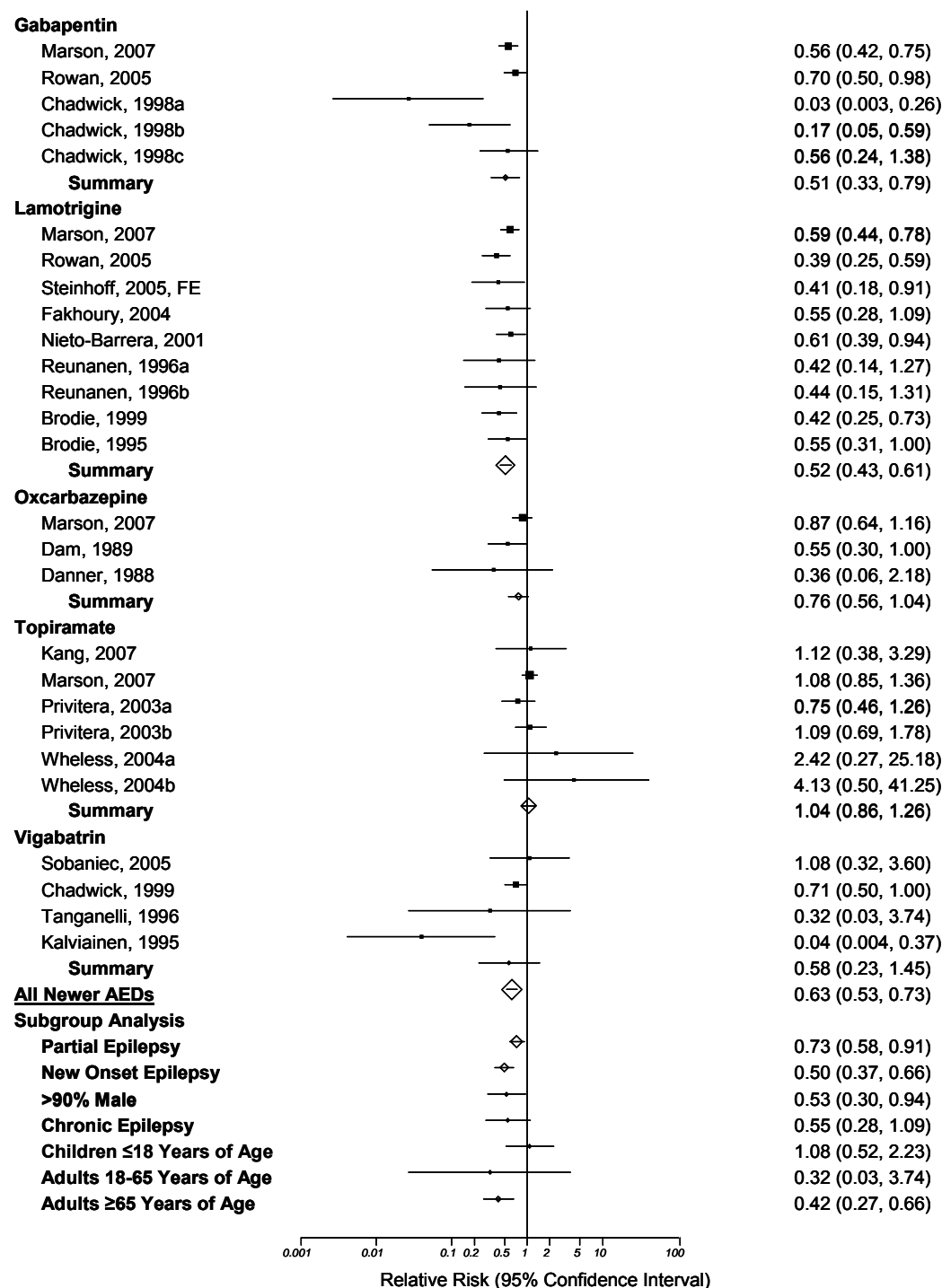


Mean Difference (95% Confidence Interval)

AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; AUC=area under the curve

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

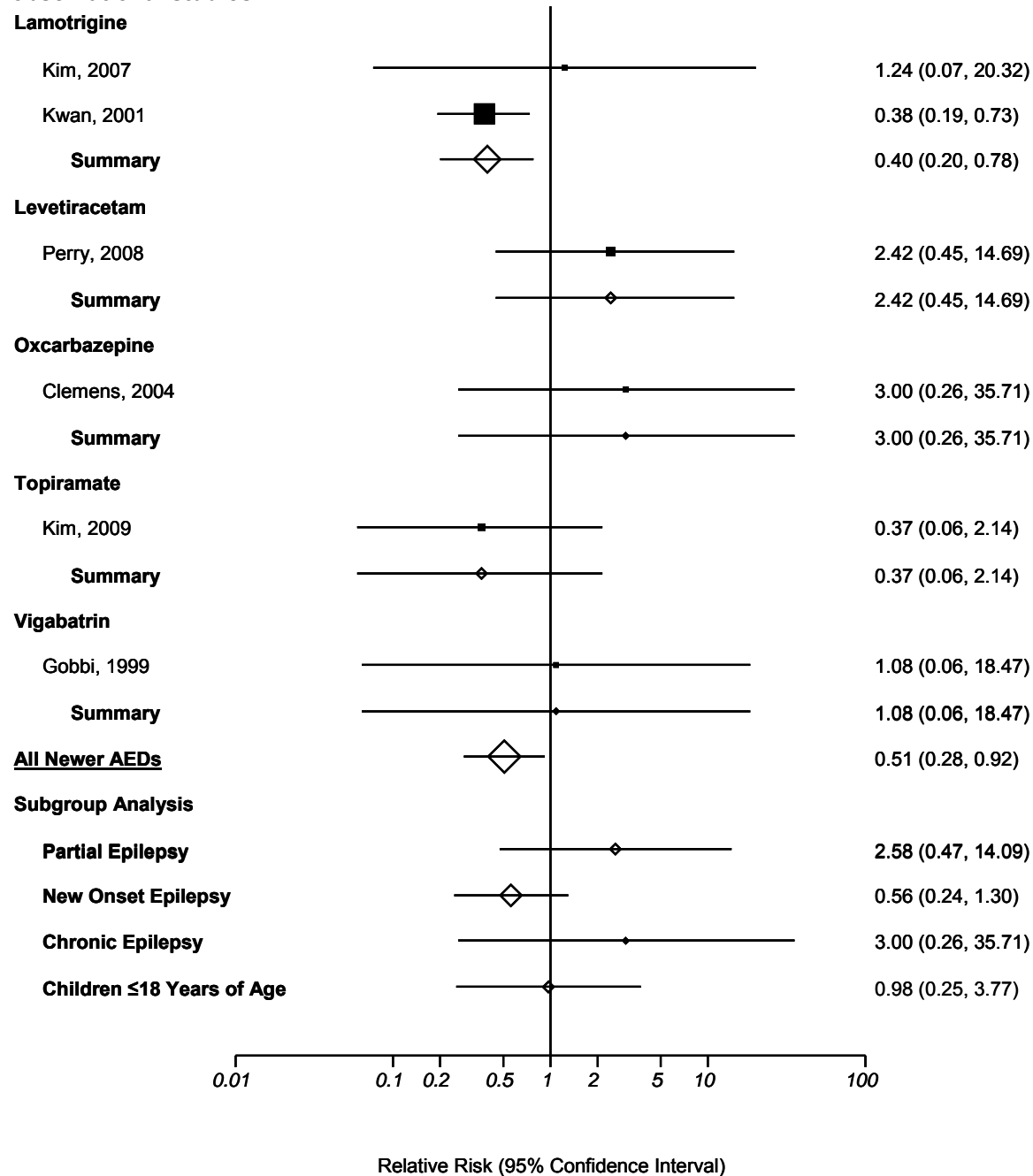
Figure J-37. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs; FE = focalized epilepsy

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

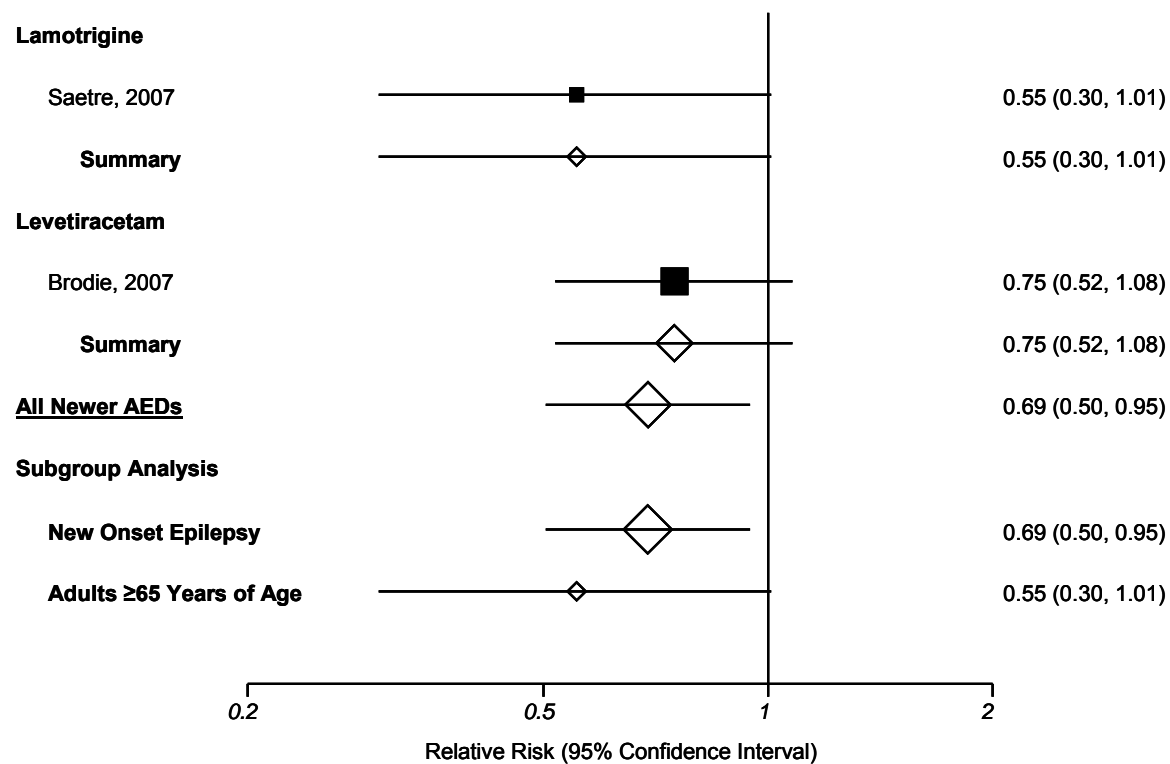
Figure J-38. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

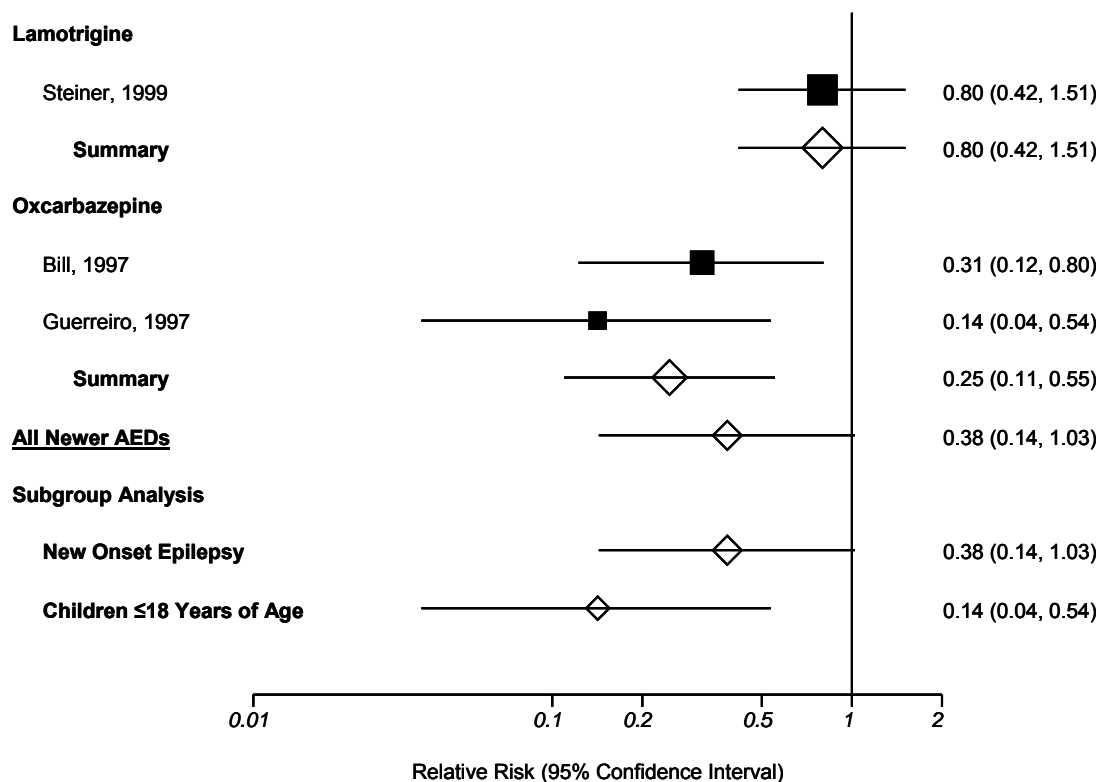
Figure J-39. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared with controlled or sustained release carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

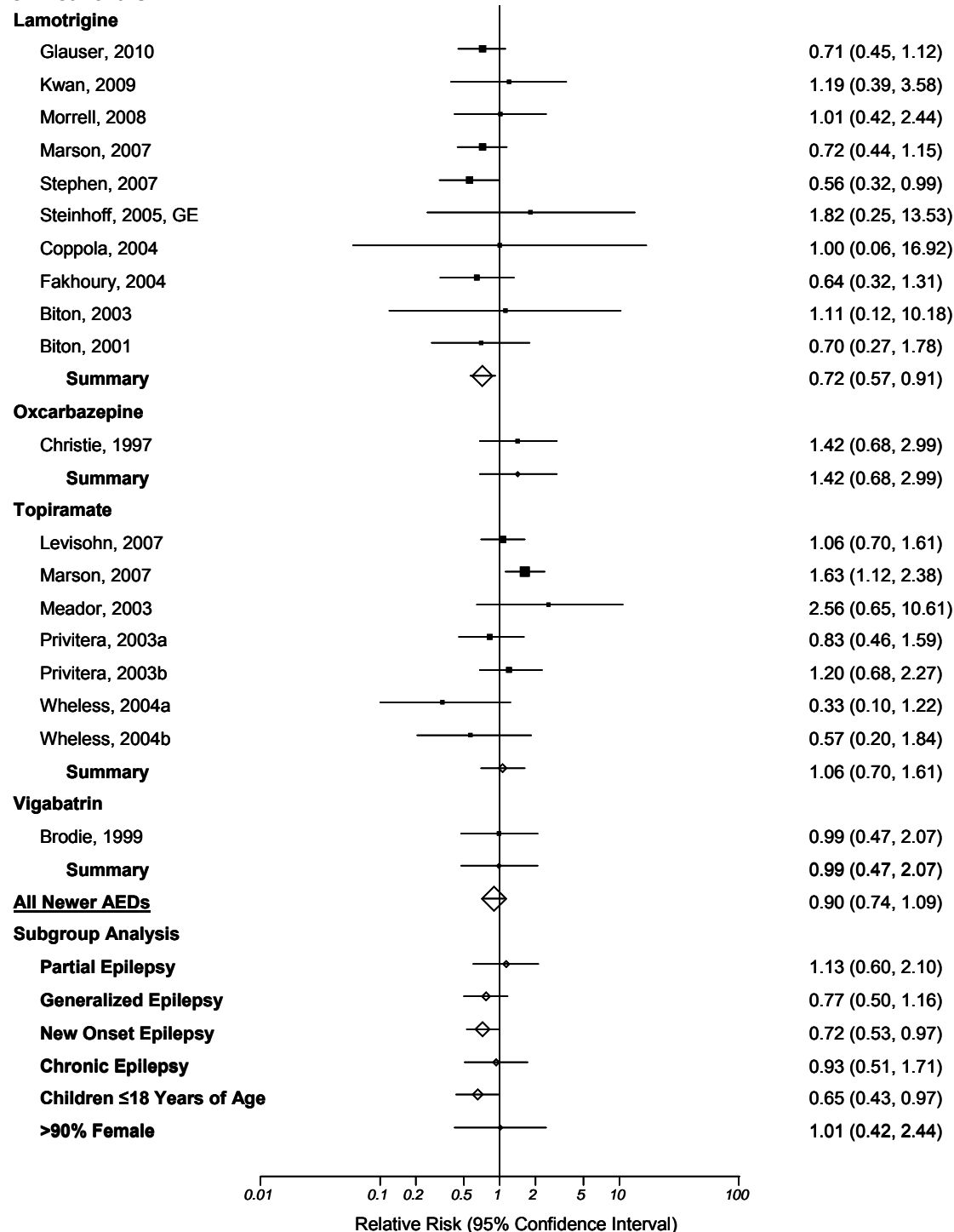
Figure J-40. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

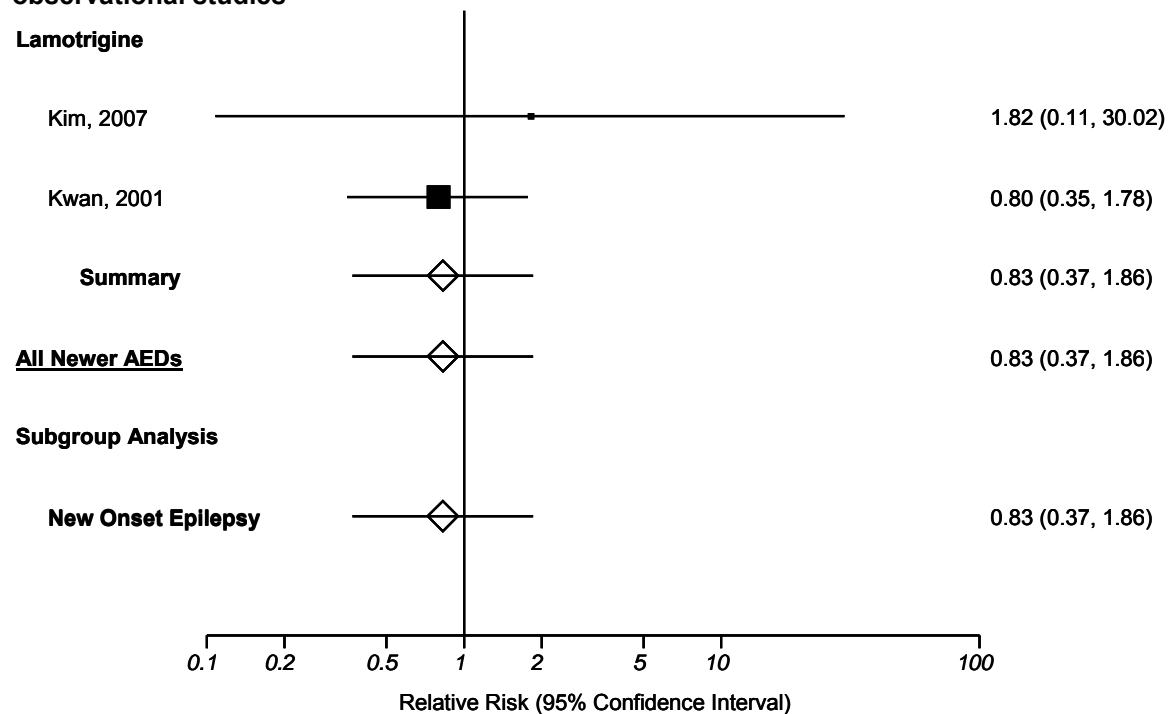
Figure J-41. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs; GE = generalized epilepsy

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

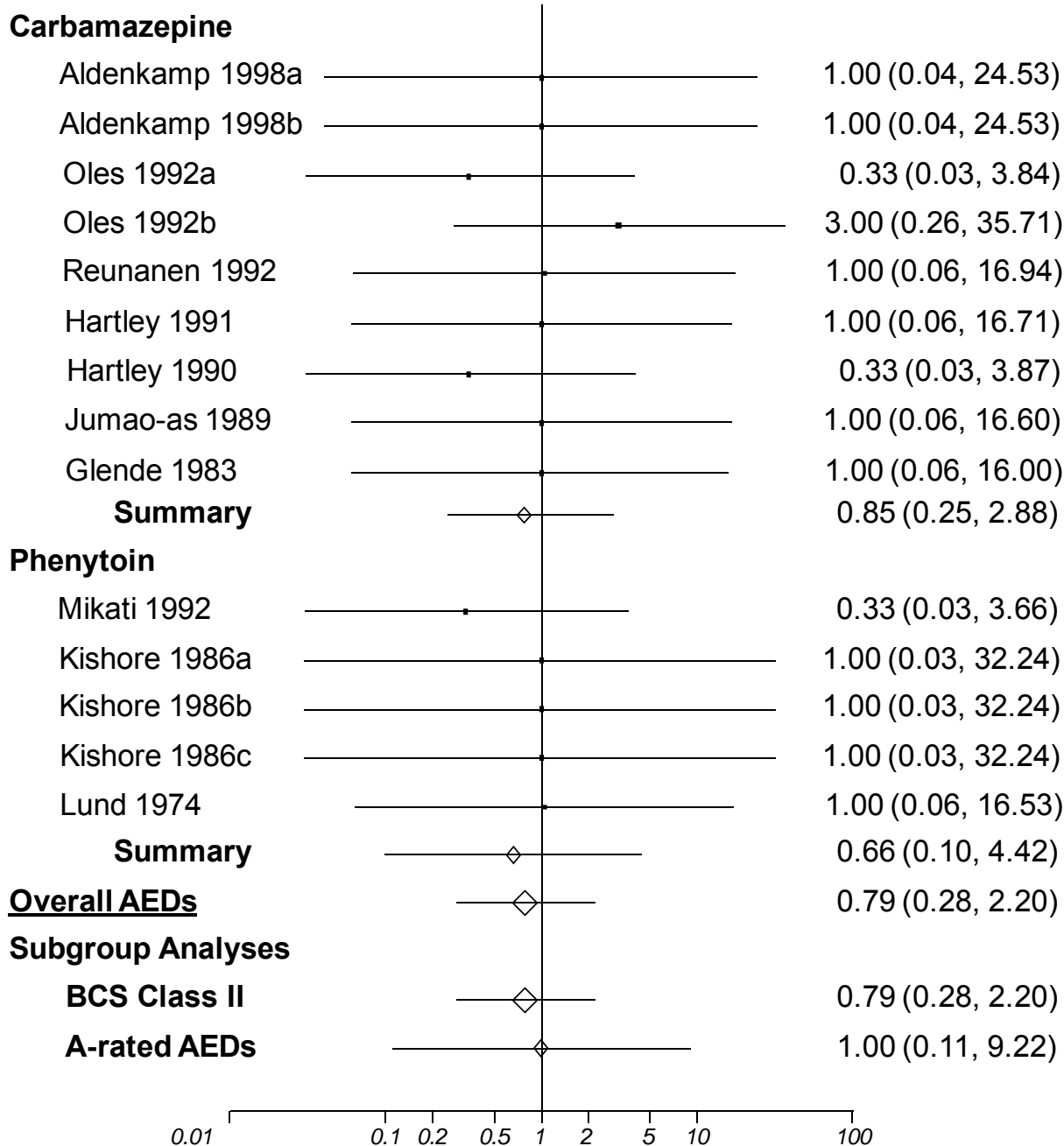
Figure J-42. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure J-43. Composite forest plot of meta-analysis of withdrawals due to adverse events in patients with epilepsy taking generic antiepileptic drugs compared with the corresponding innovator antiepileptic drug

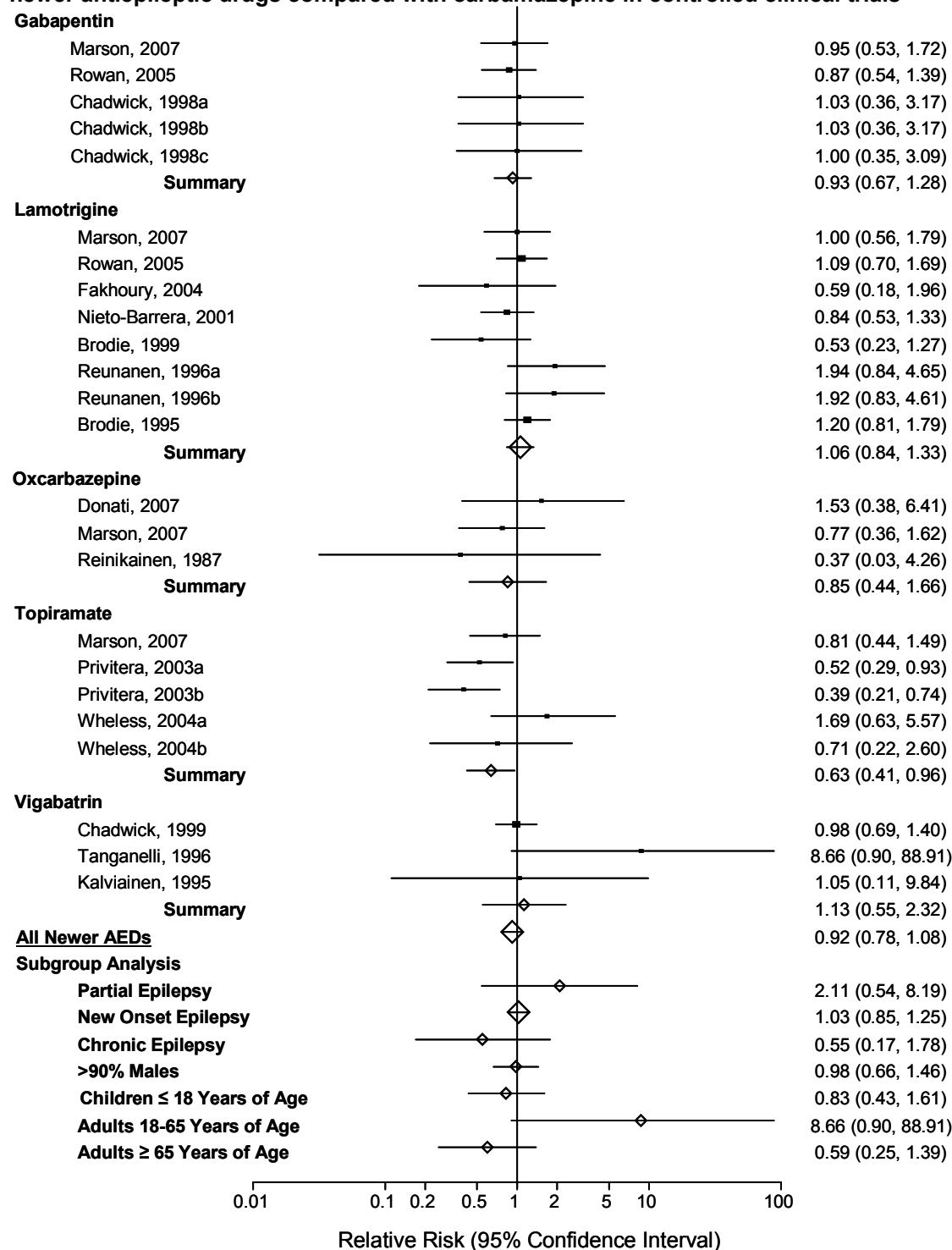


Relative Risk (95% Confidence Interval)

AEDs = antiepileptic drugs; BCS = biopharmaceutics classification system

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

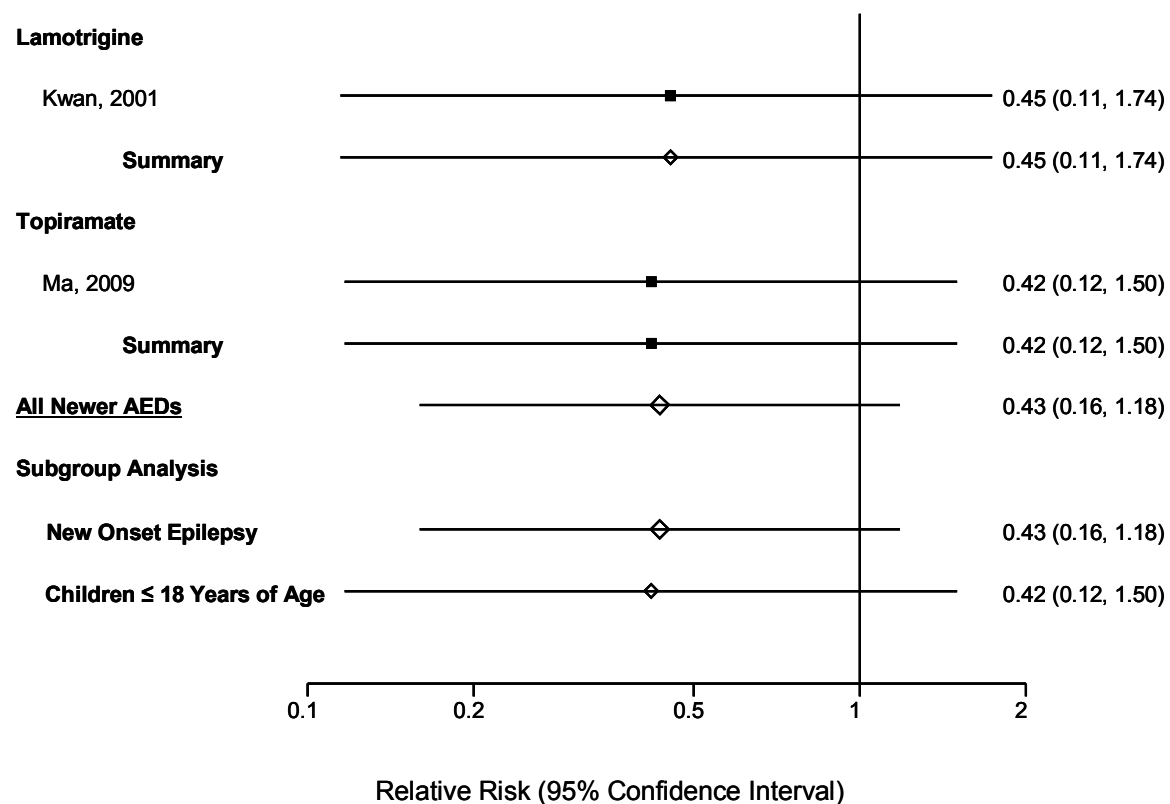
Figure J-44. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

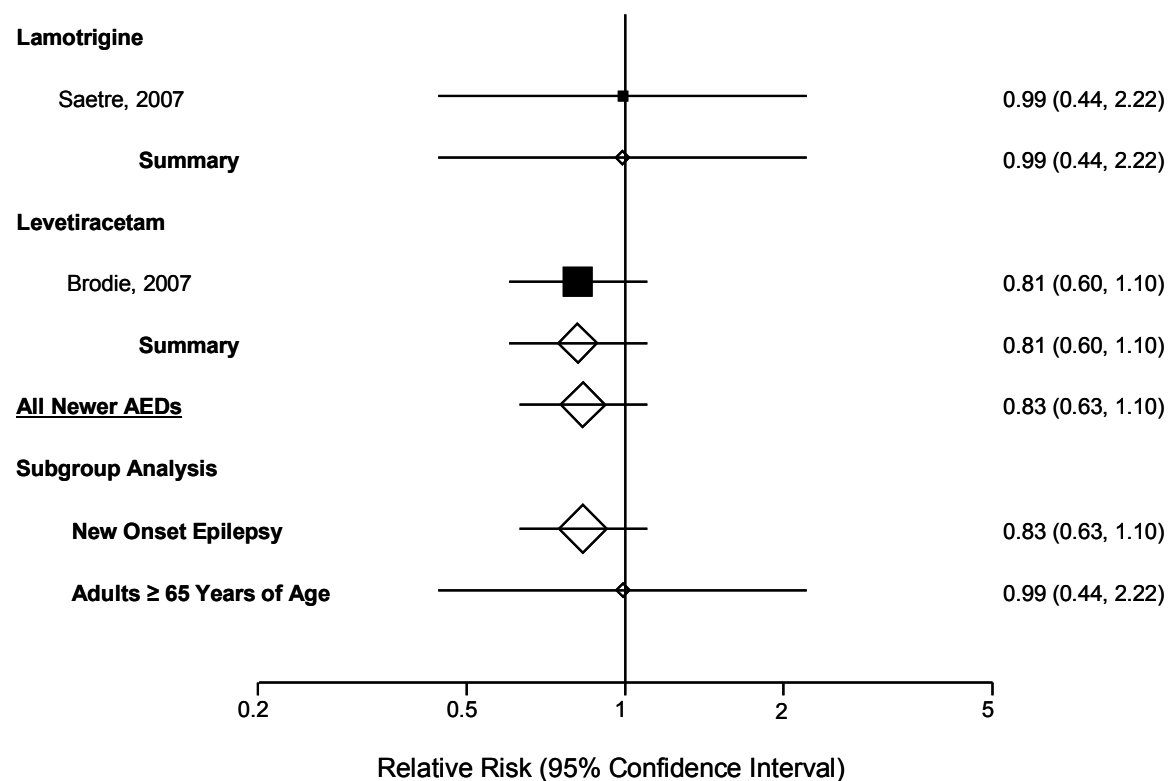
Figure J-45. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

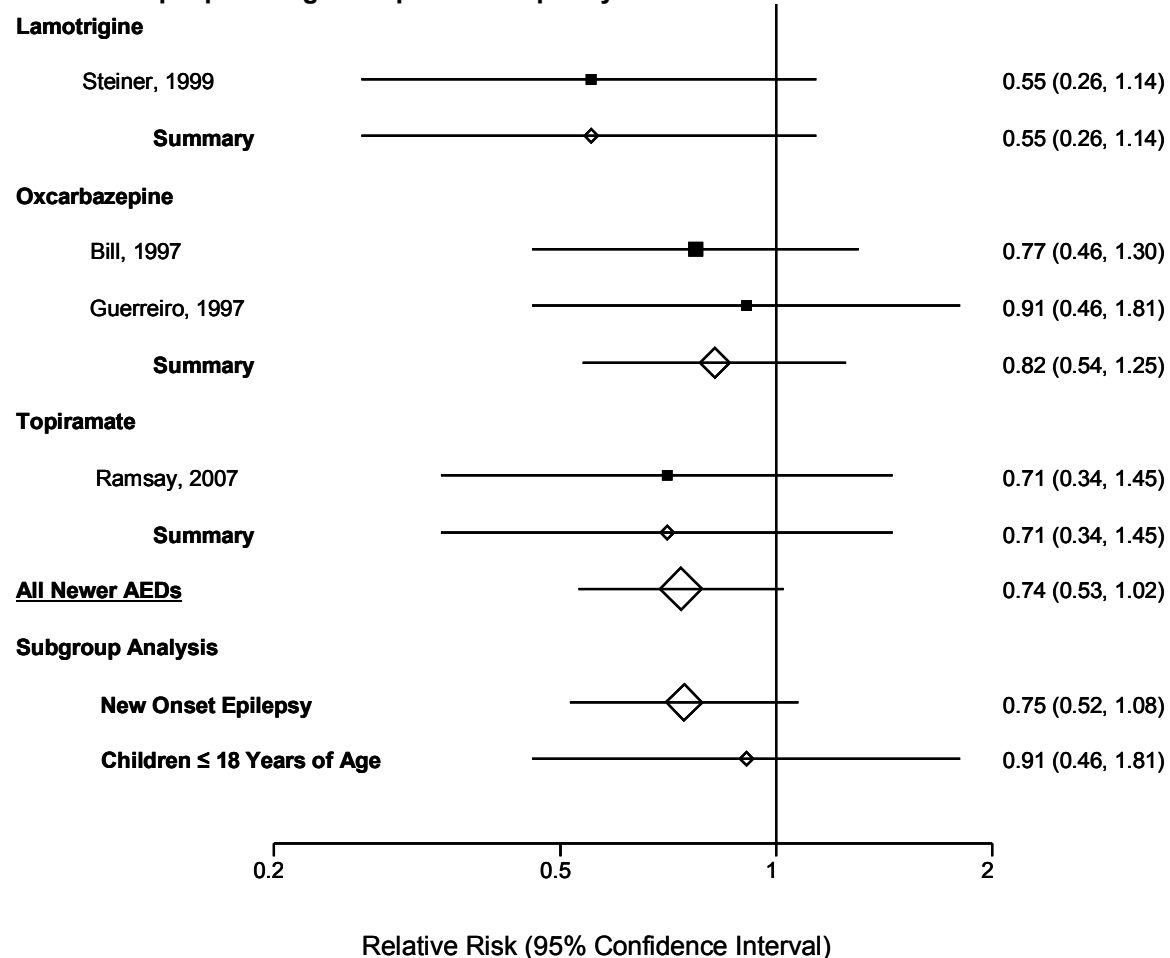
Figure J-46. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared with controlled or sustained release carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

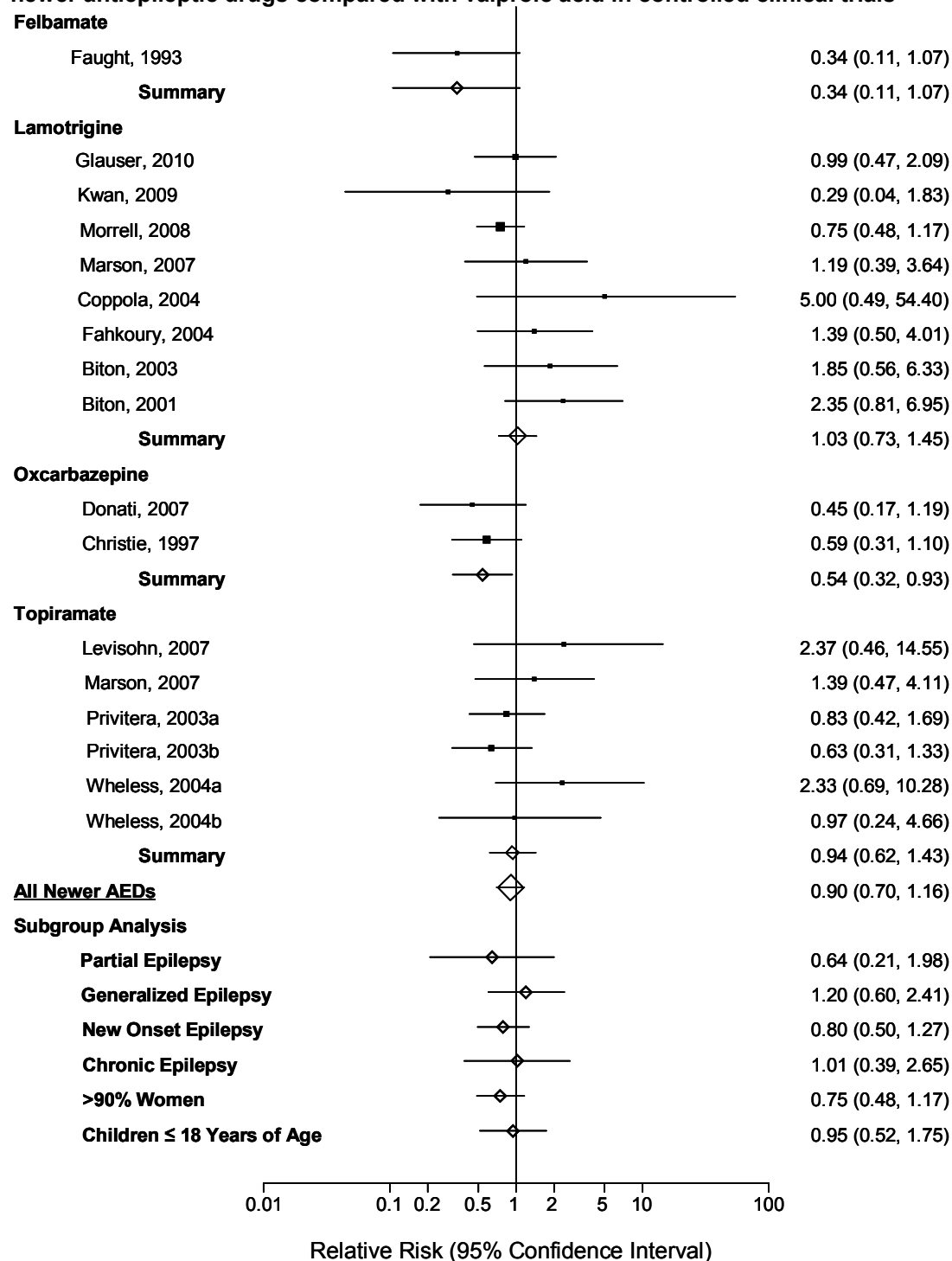
Figure J-47. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

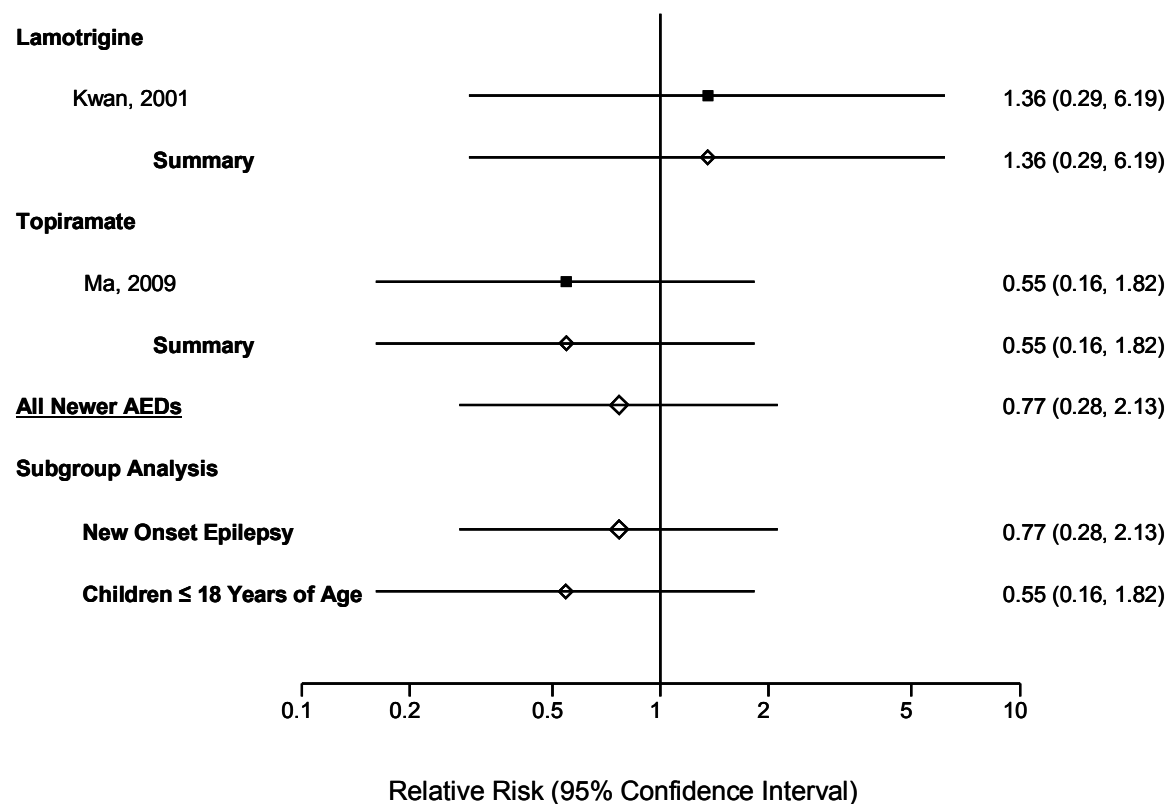
Figure J-48. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

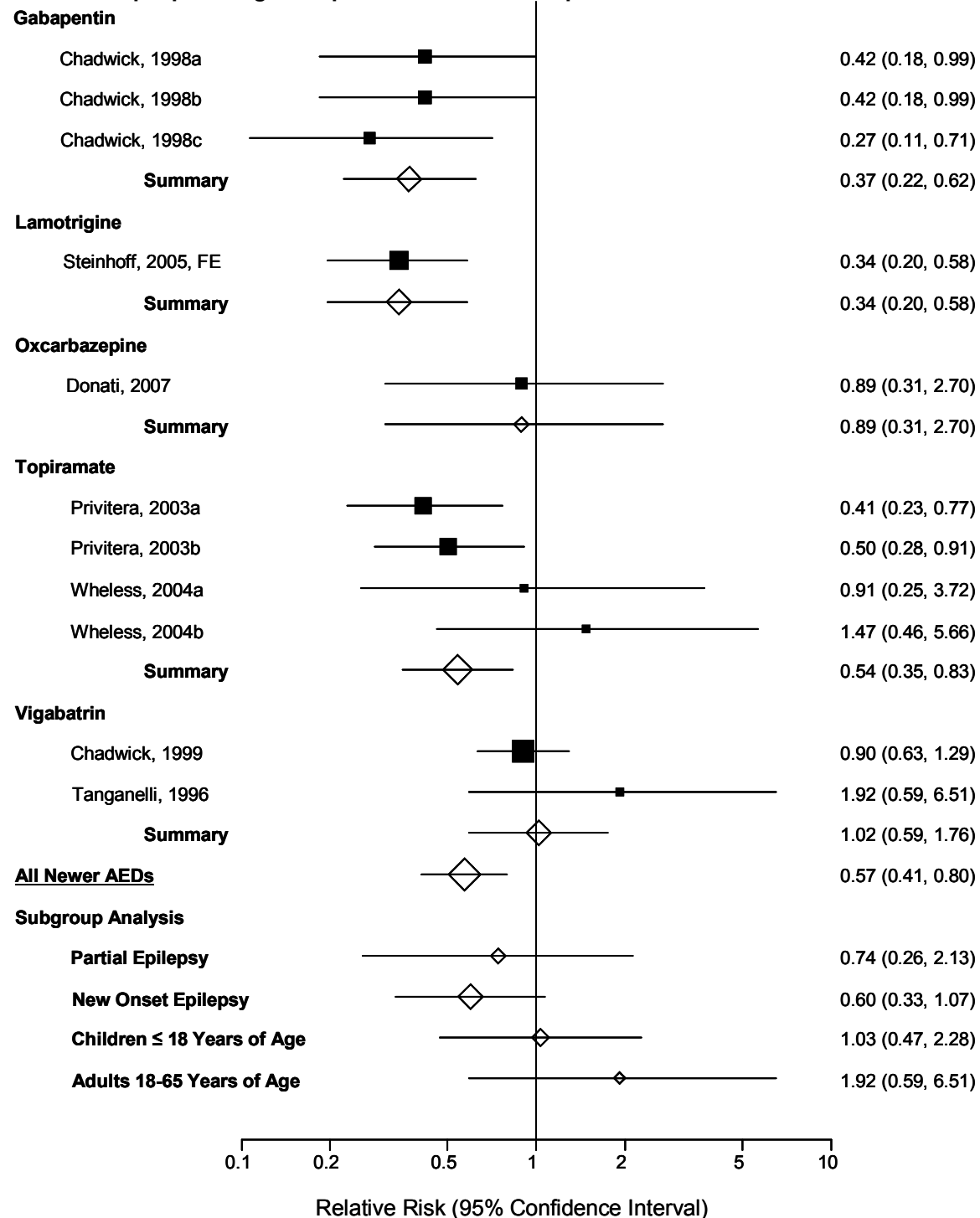
Figure J-49. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

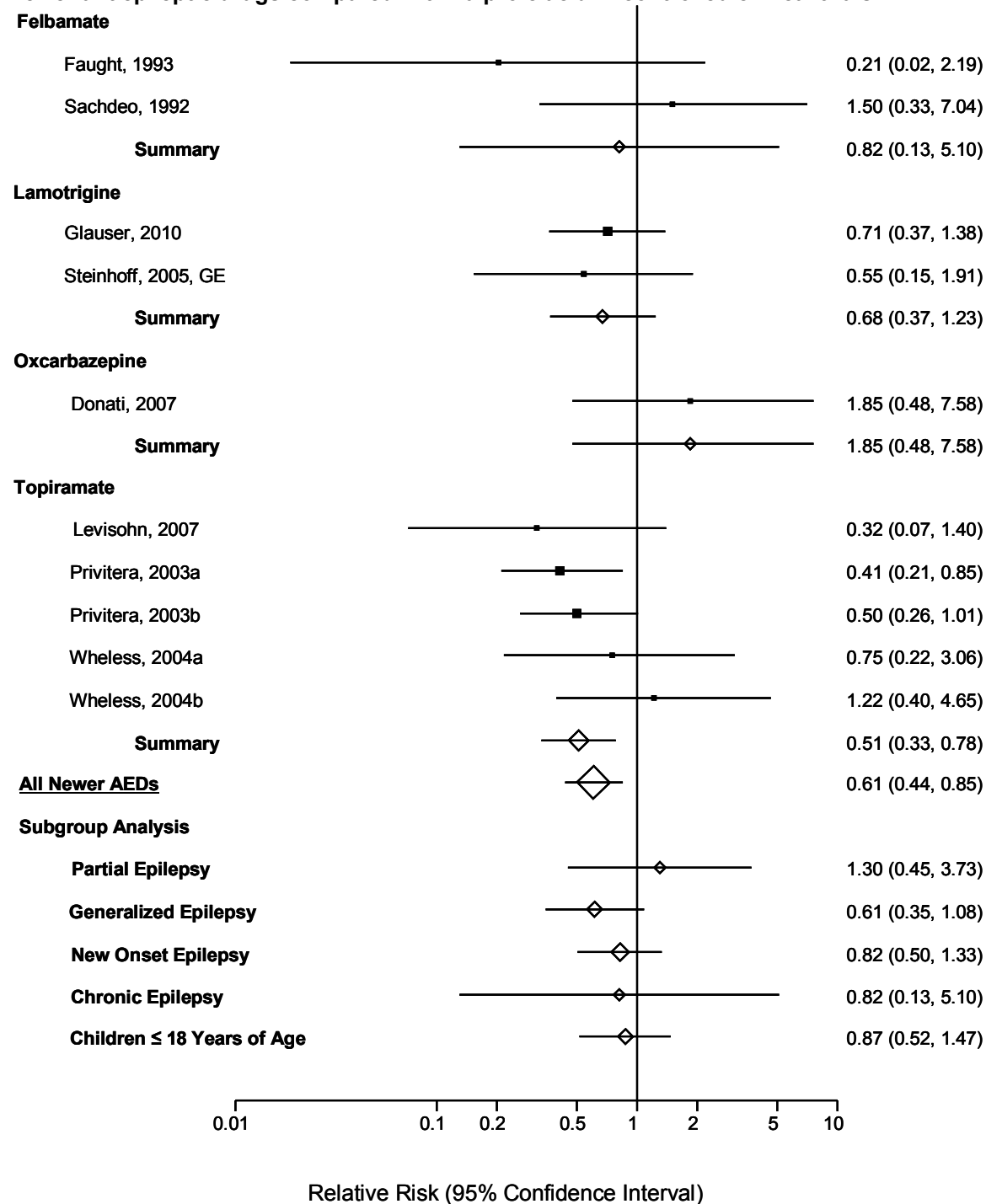
Figure J-50. Composite forest plot of meta-analysis of fatigue in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

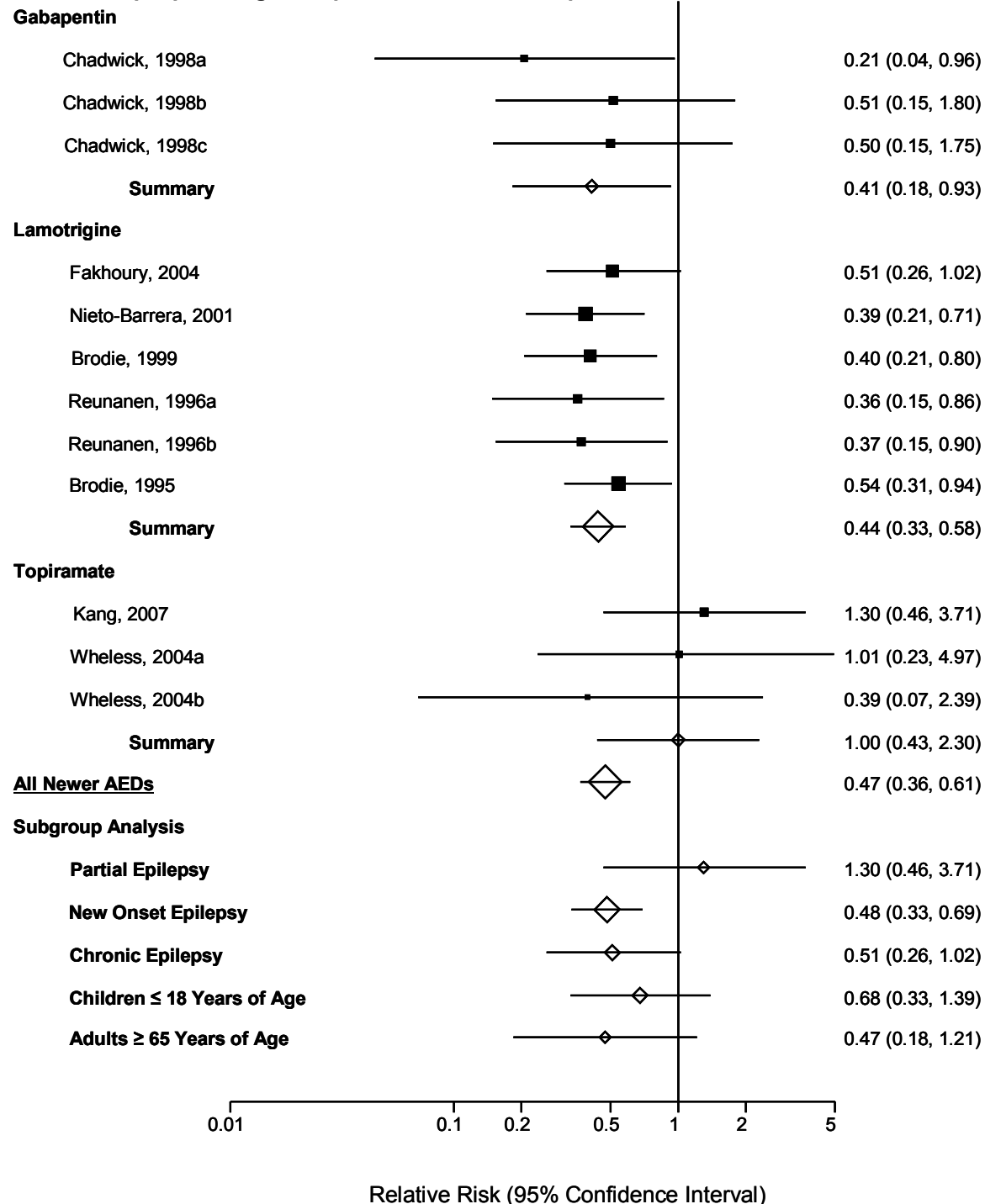
Figure J-51. Composite forest plot of meta-analysis of fatigue in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

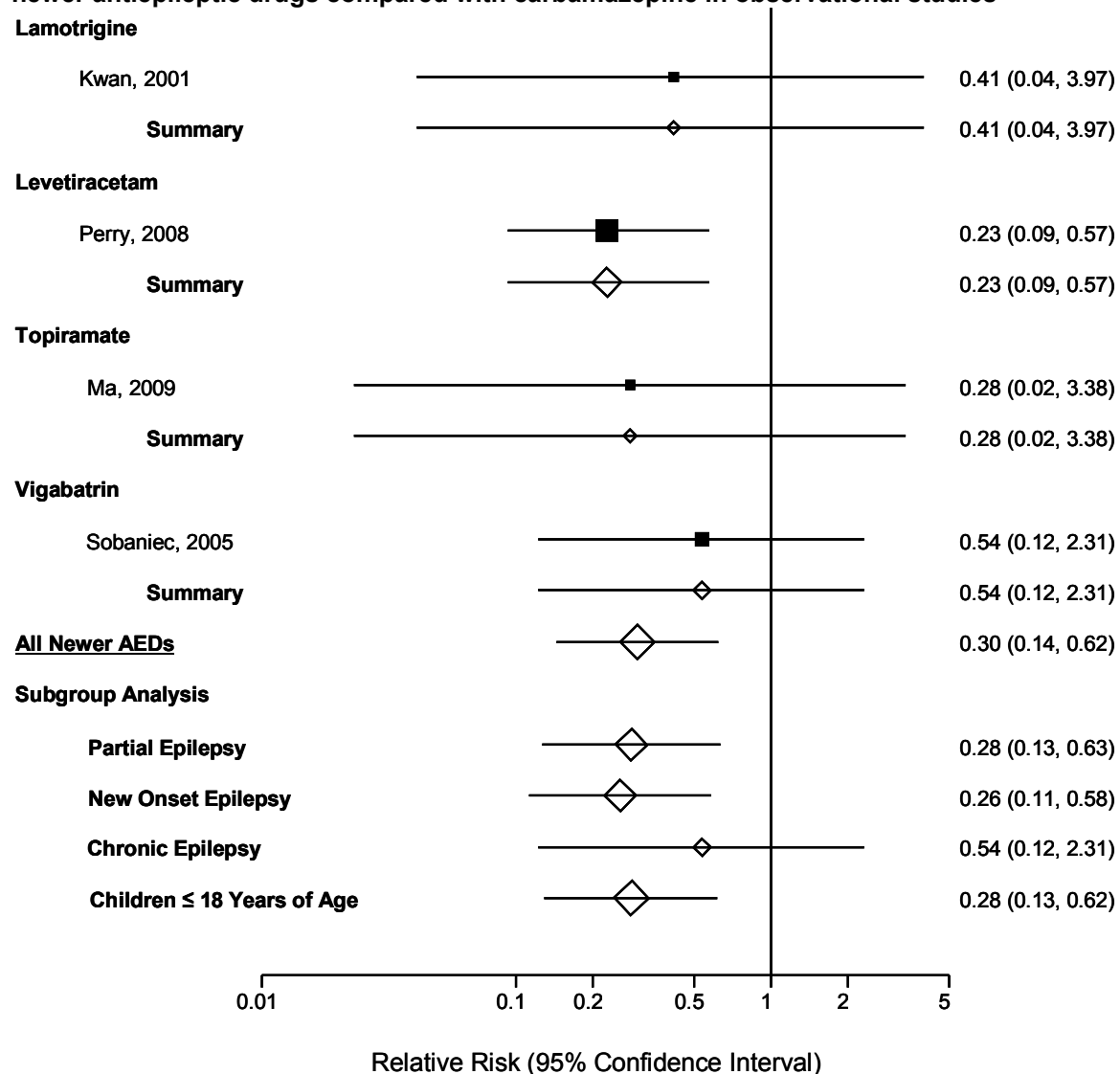
Figure J-52. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

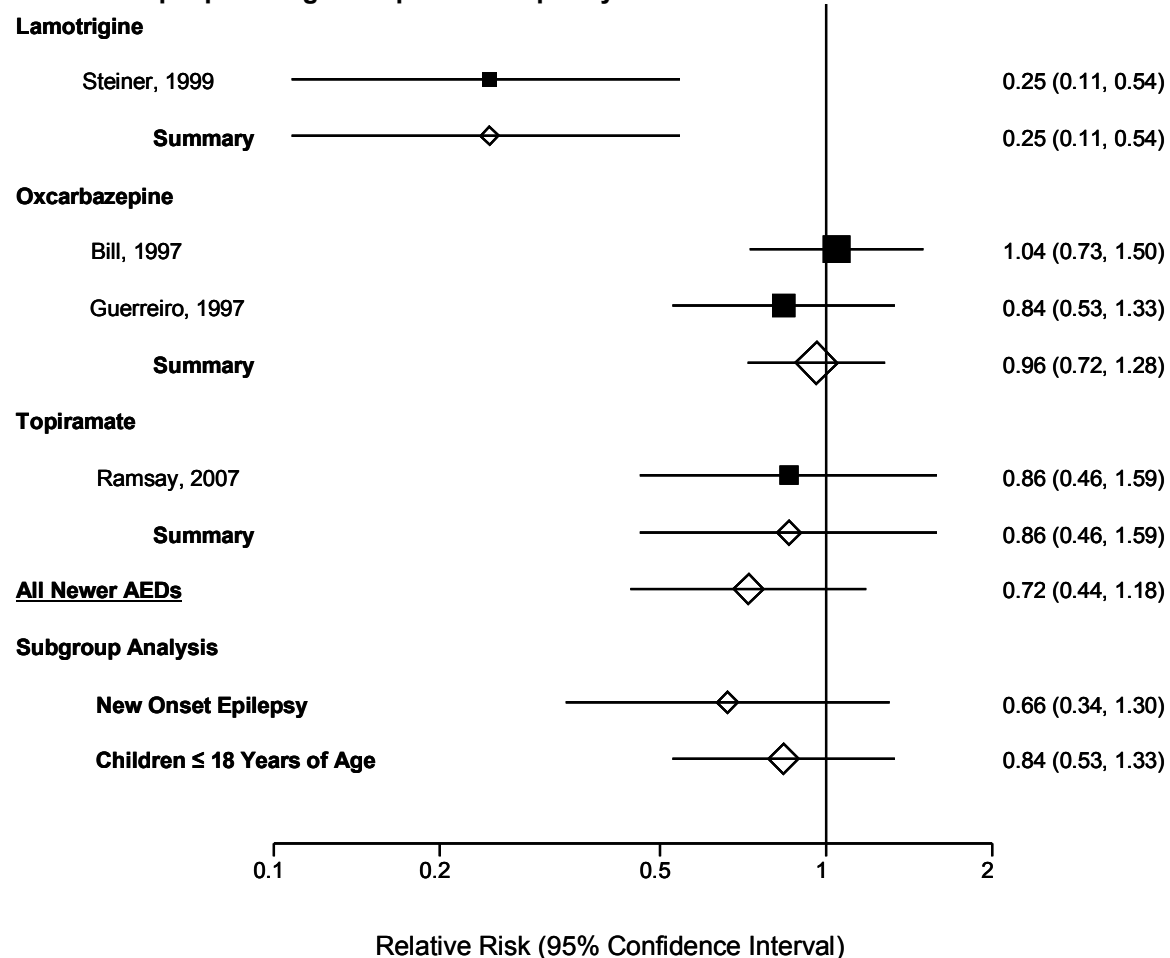
Figure J-53. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

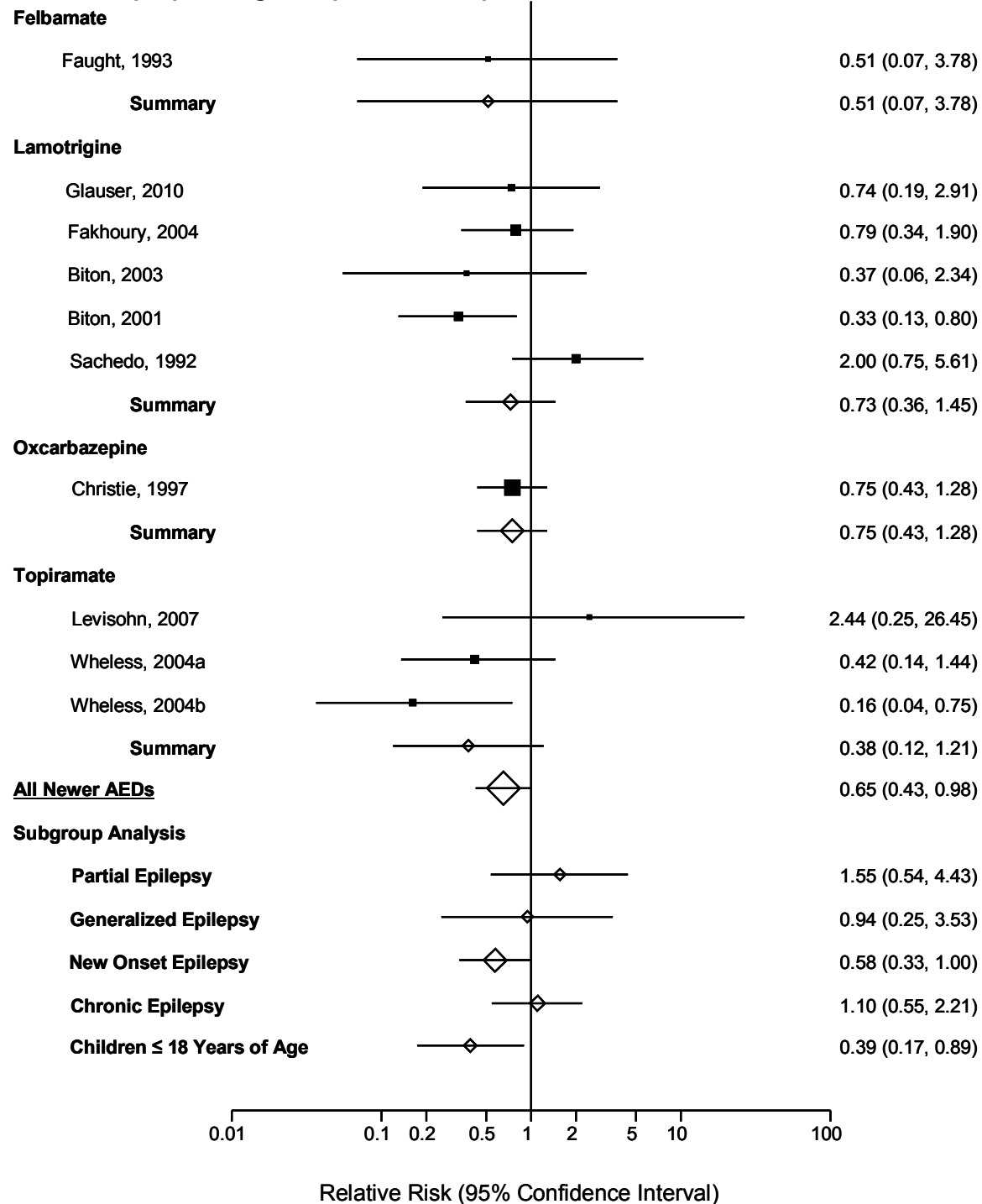
Figure J-54. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

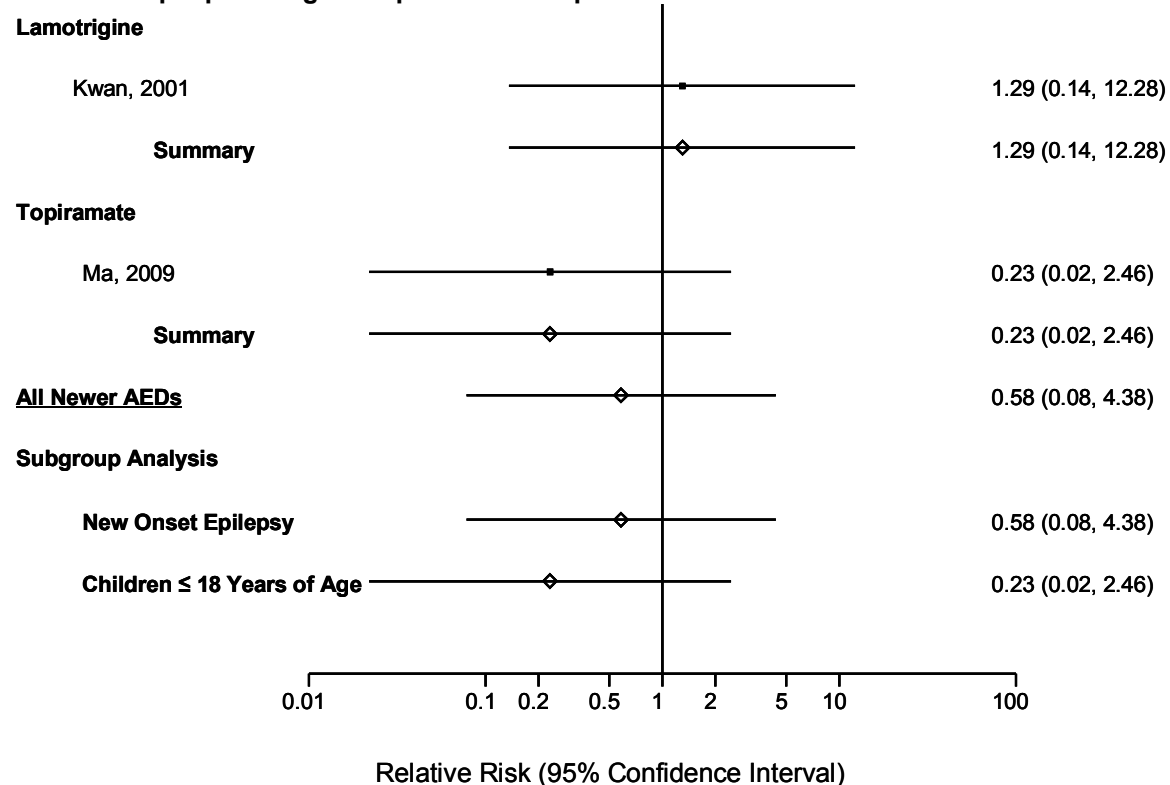
Figure J-55. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

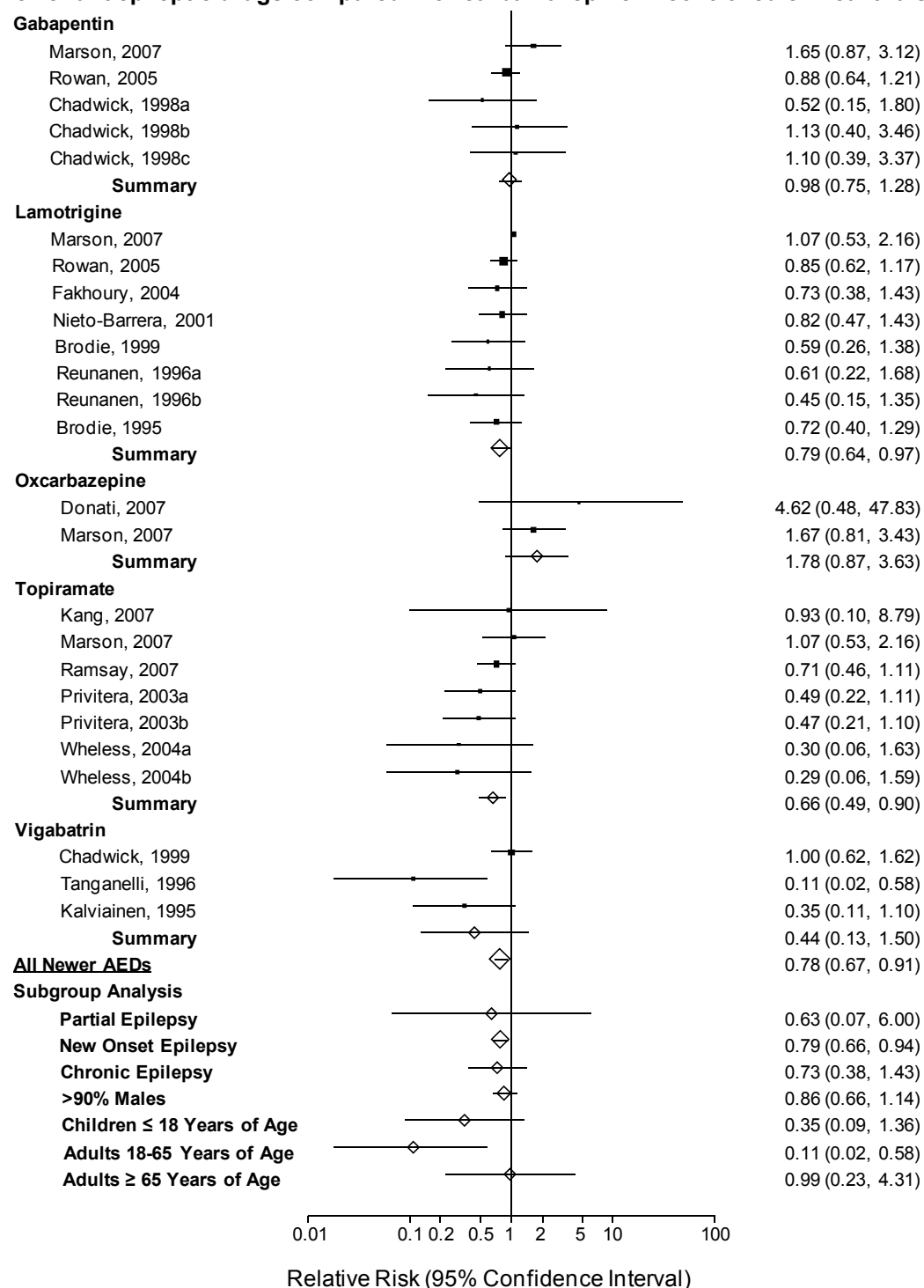
Figure J-56. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

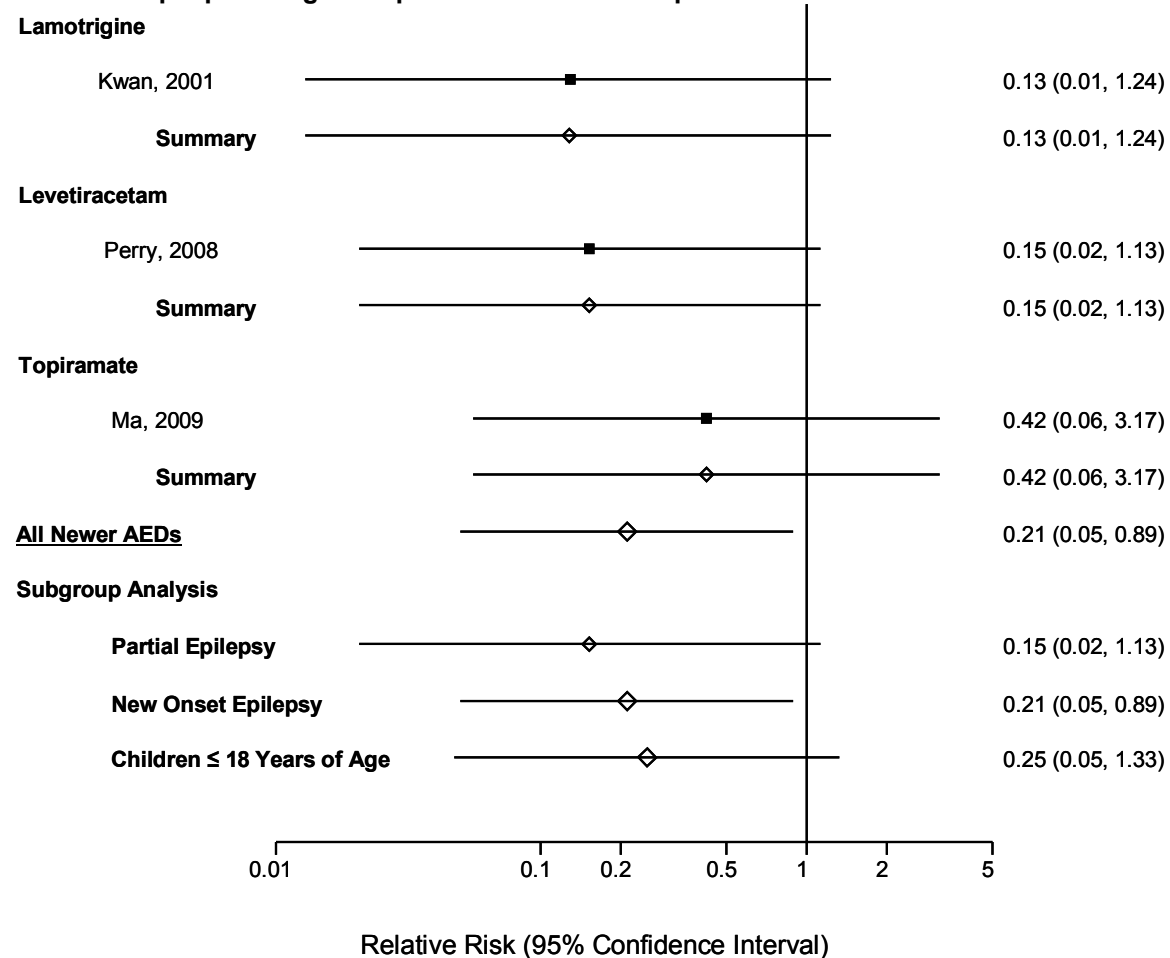
Figure J-57. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

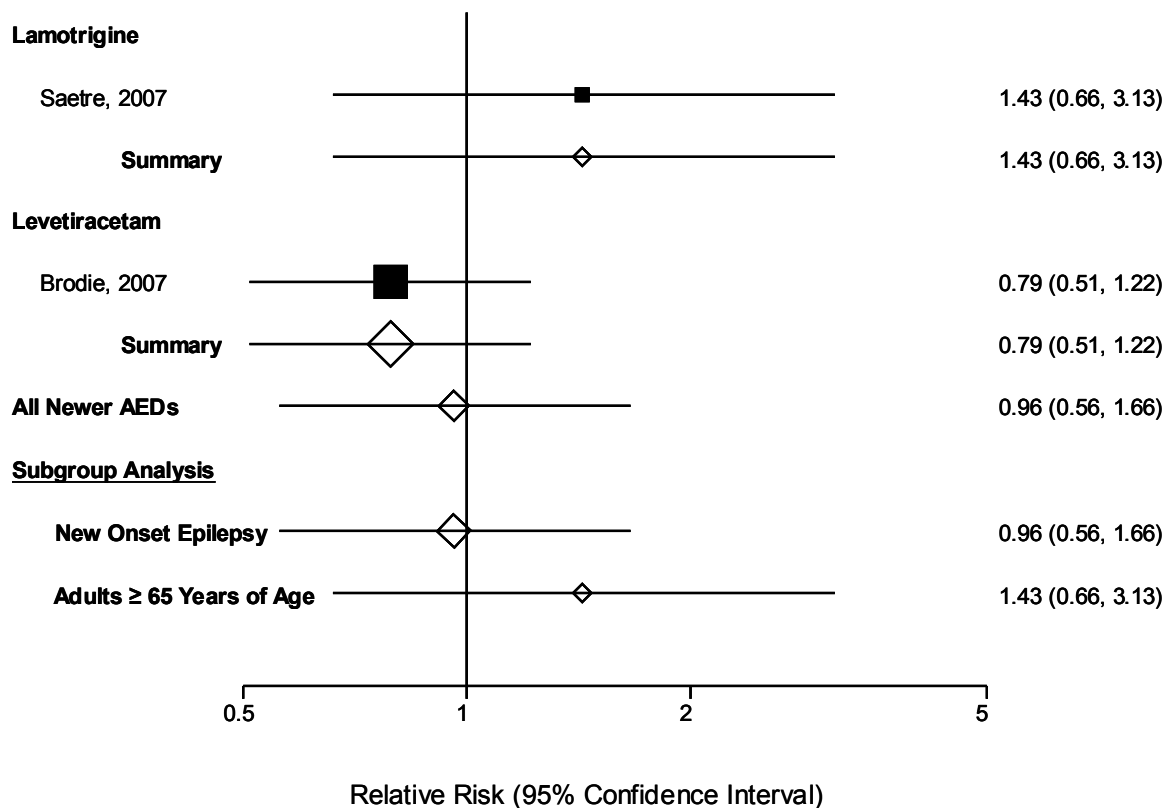
Figure J-58. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

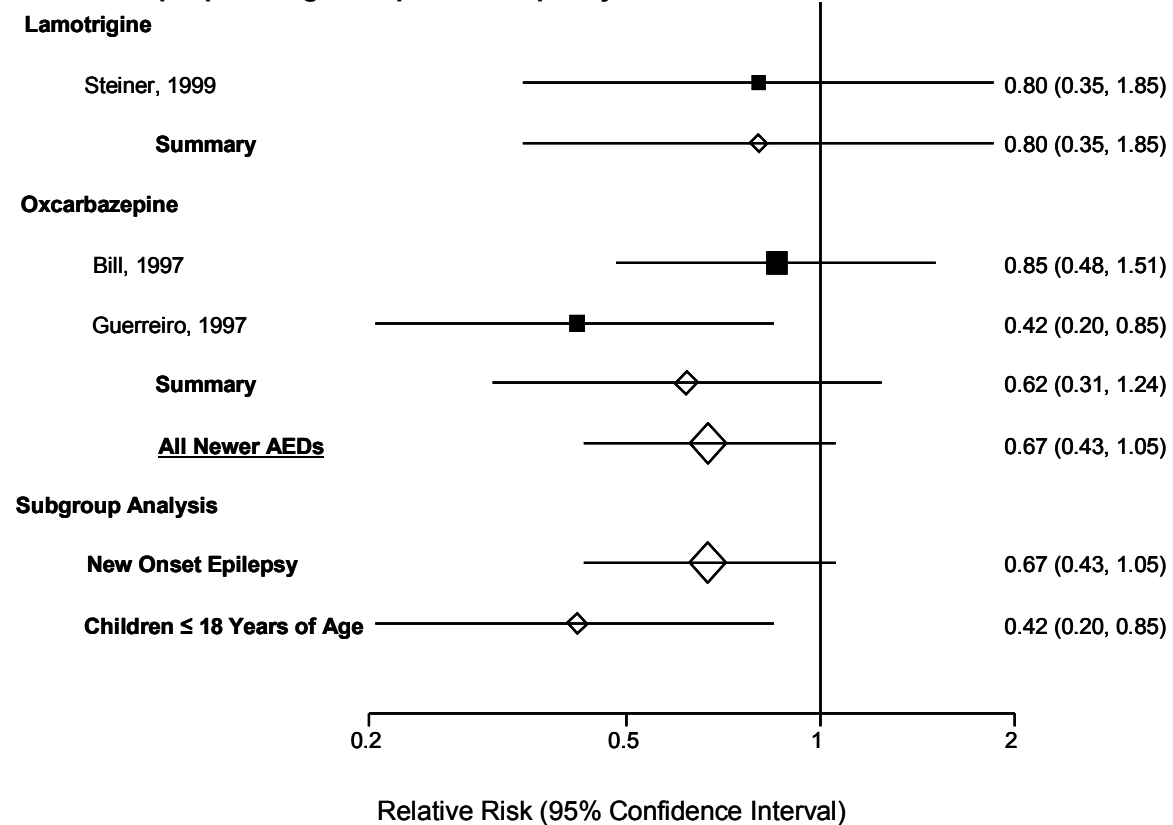
Figure J-59. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared with controlled or sustained-release carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

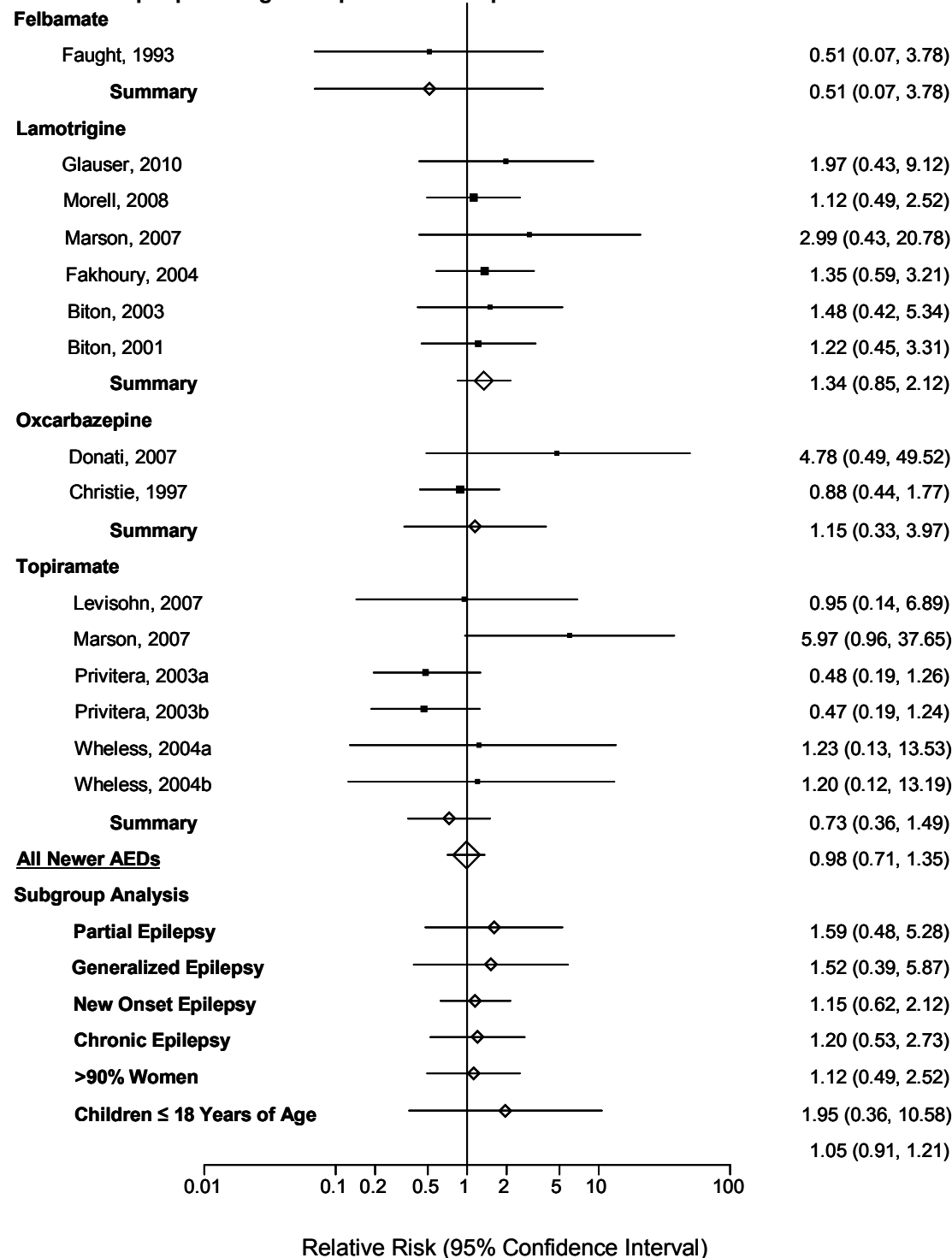
Figure J-60. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

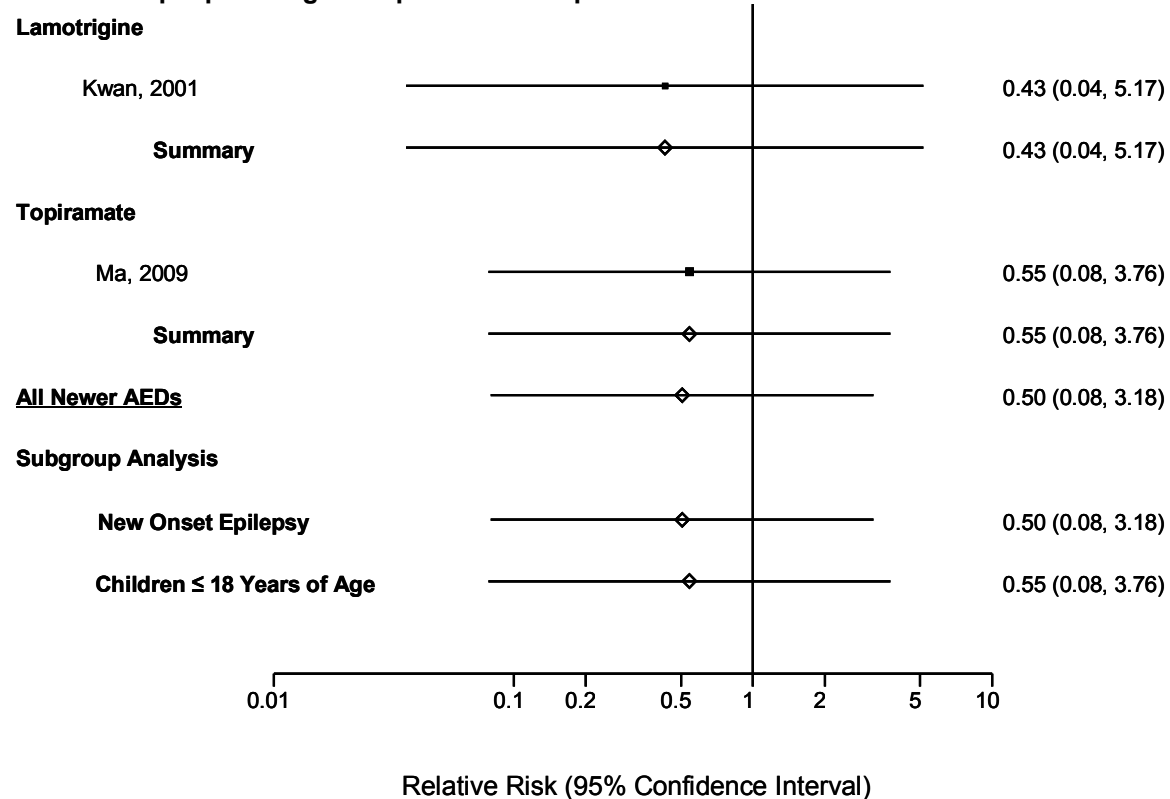
Figure J-61. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

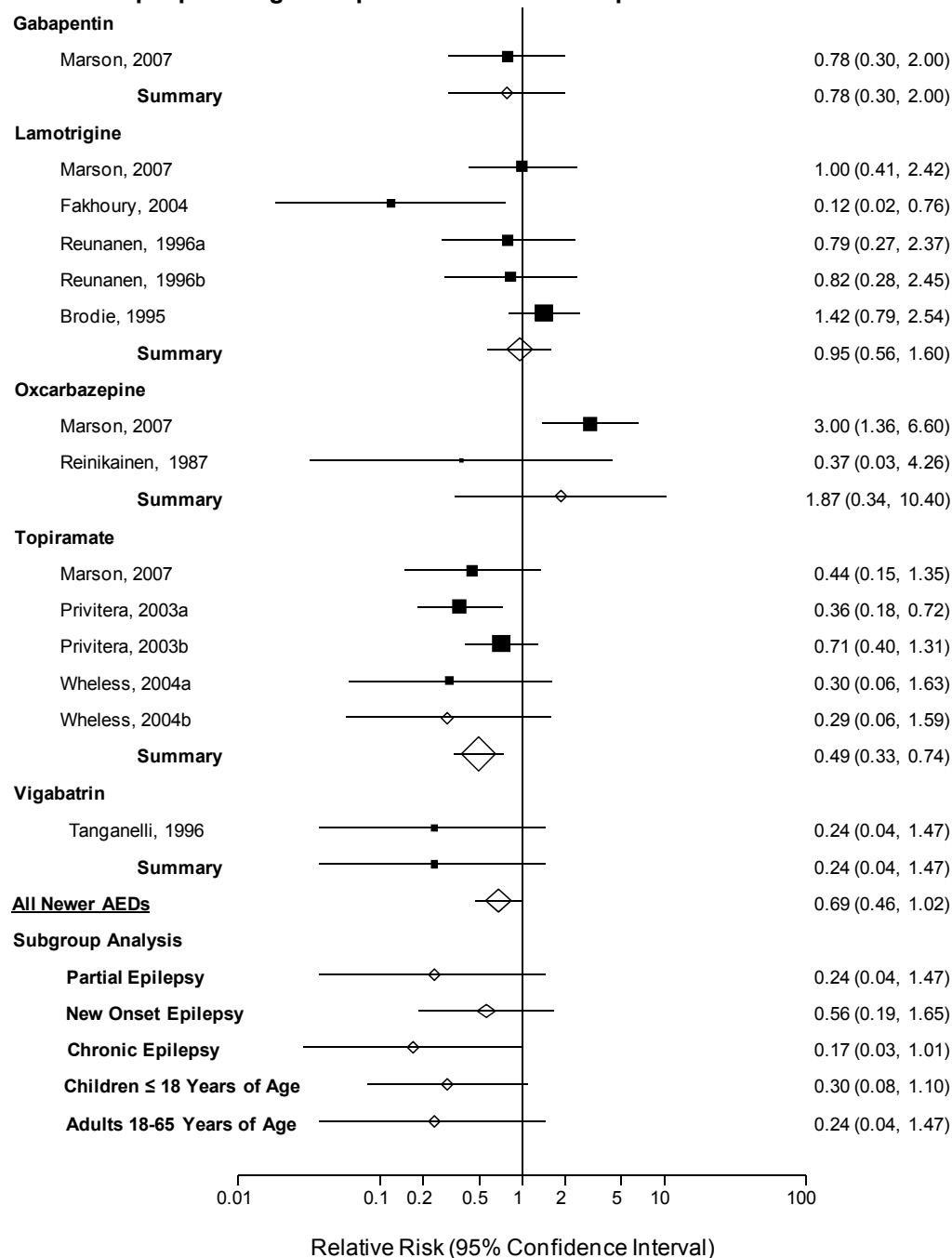
Figure J-62. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

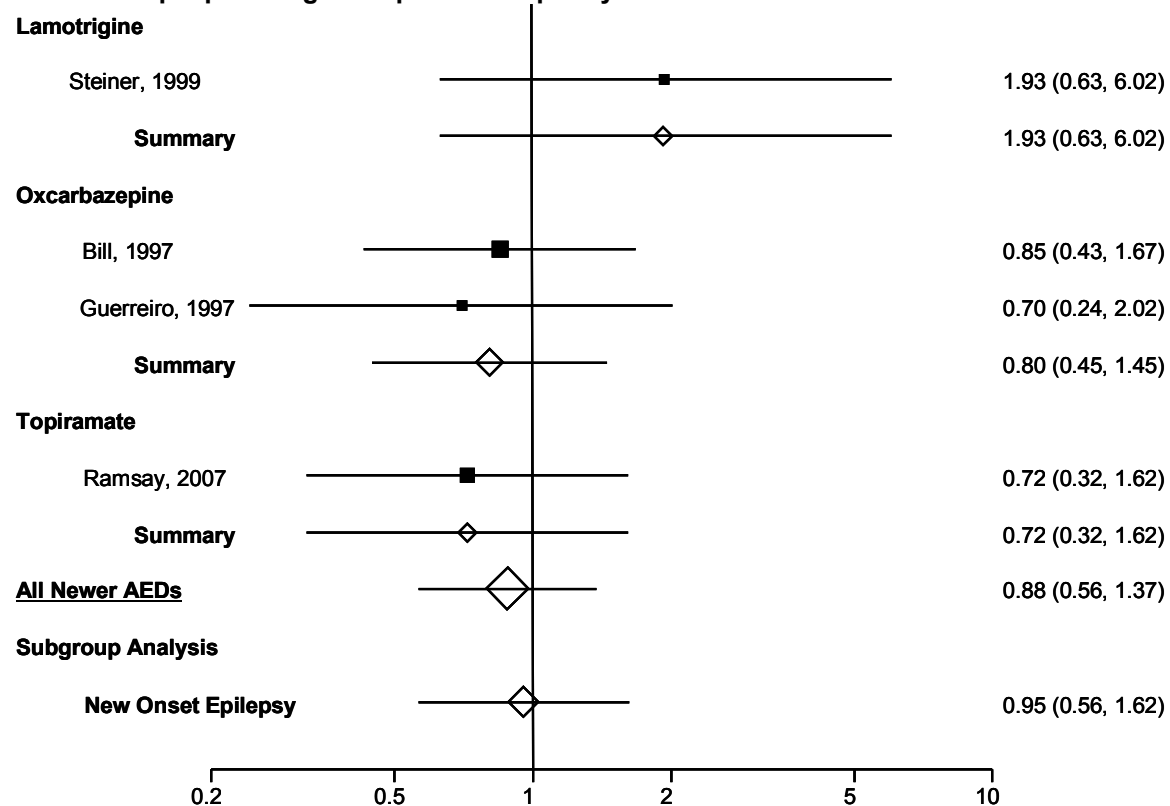
Figure J-63. Composite forest plot of meta-analysis of nausea in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure J-64. Composite forest plot of meta-analysis of nausea in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials

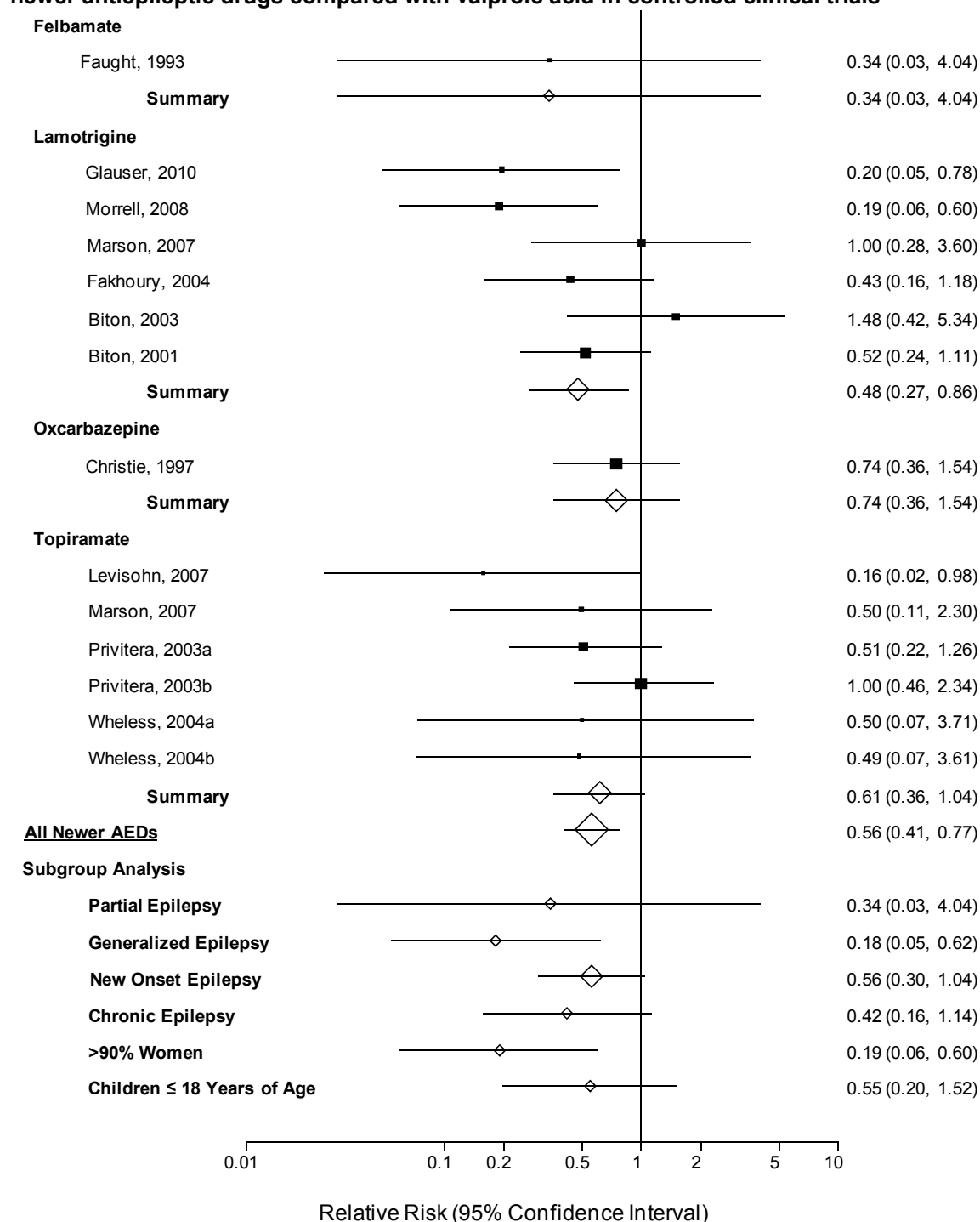


Relative Risk (95% Confidence Interval)

AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

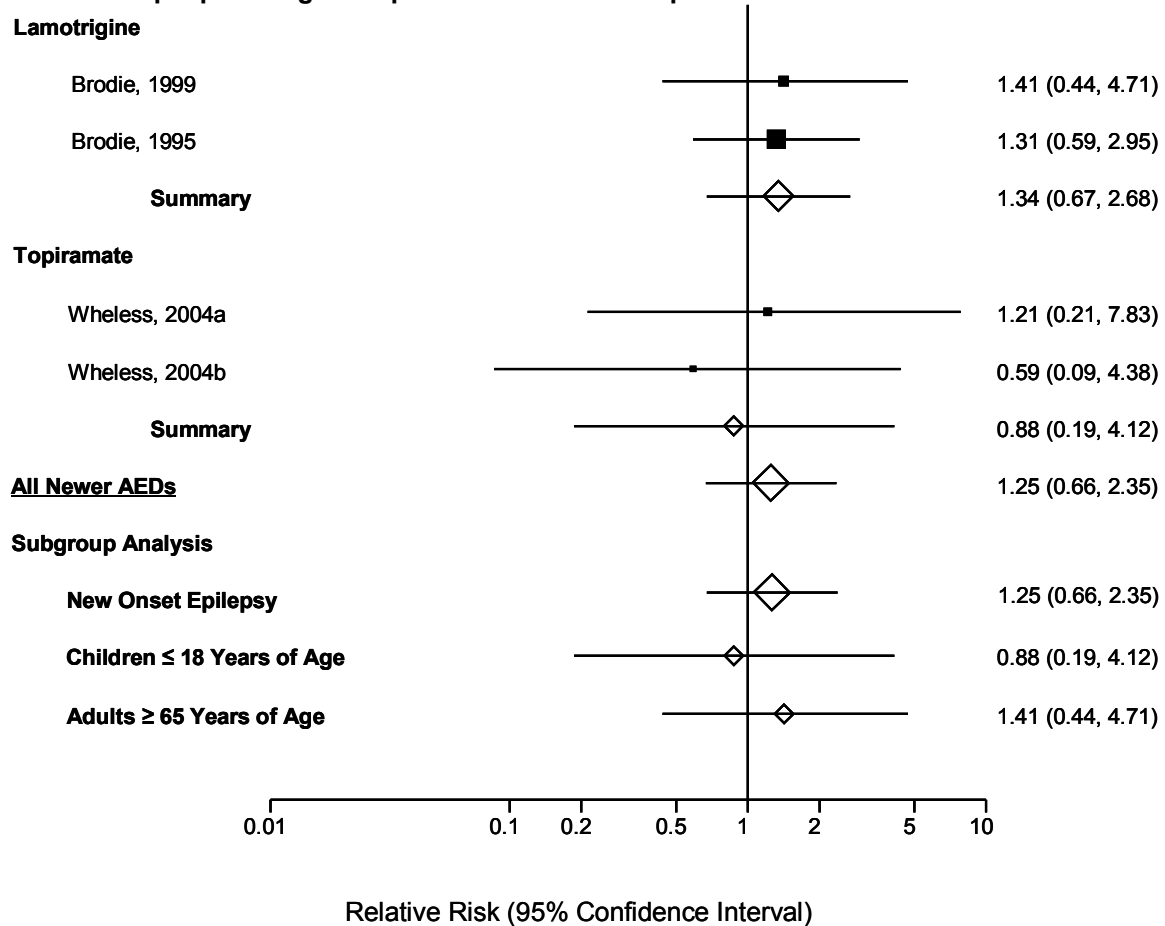
Figure J-65. Composite forest plot of meta-analysis of nausea in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

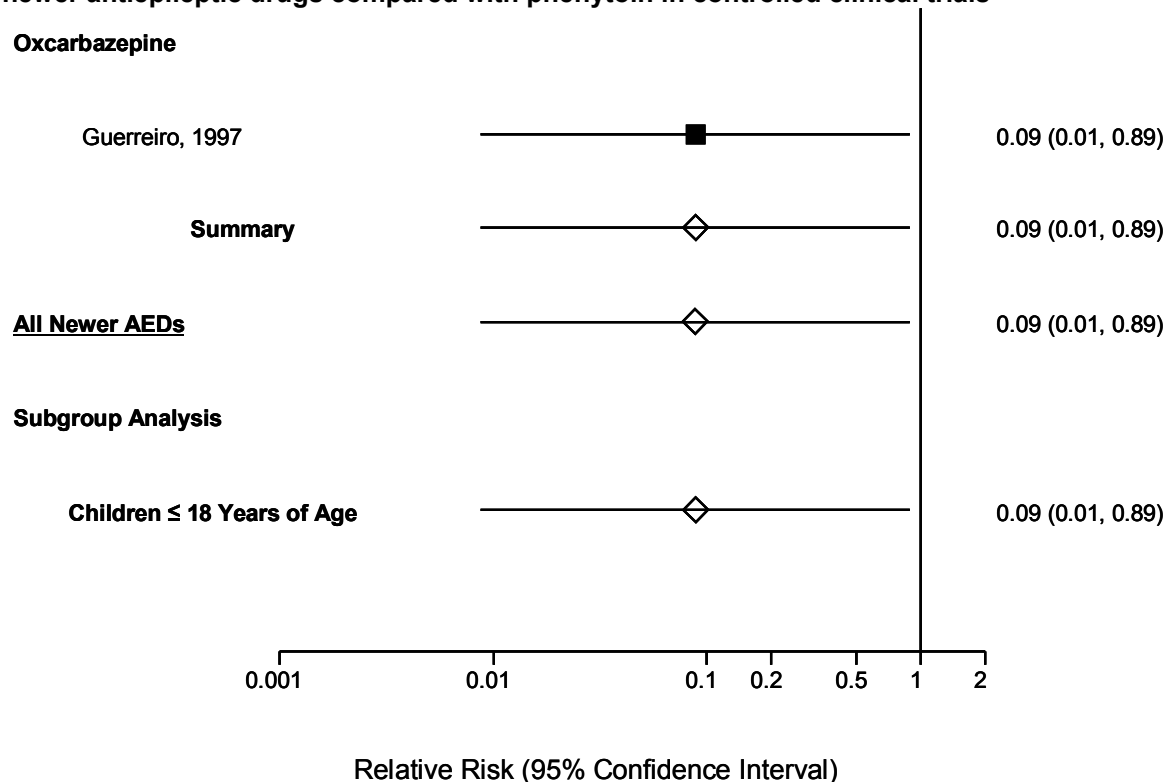
Figure J-66. Composite forest plot of meta-analysis of vomiting in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

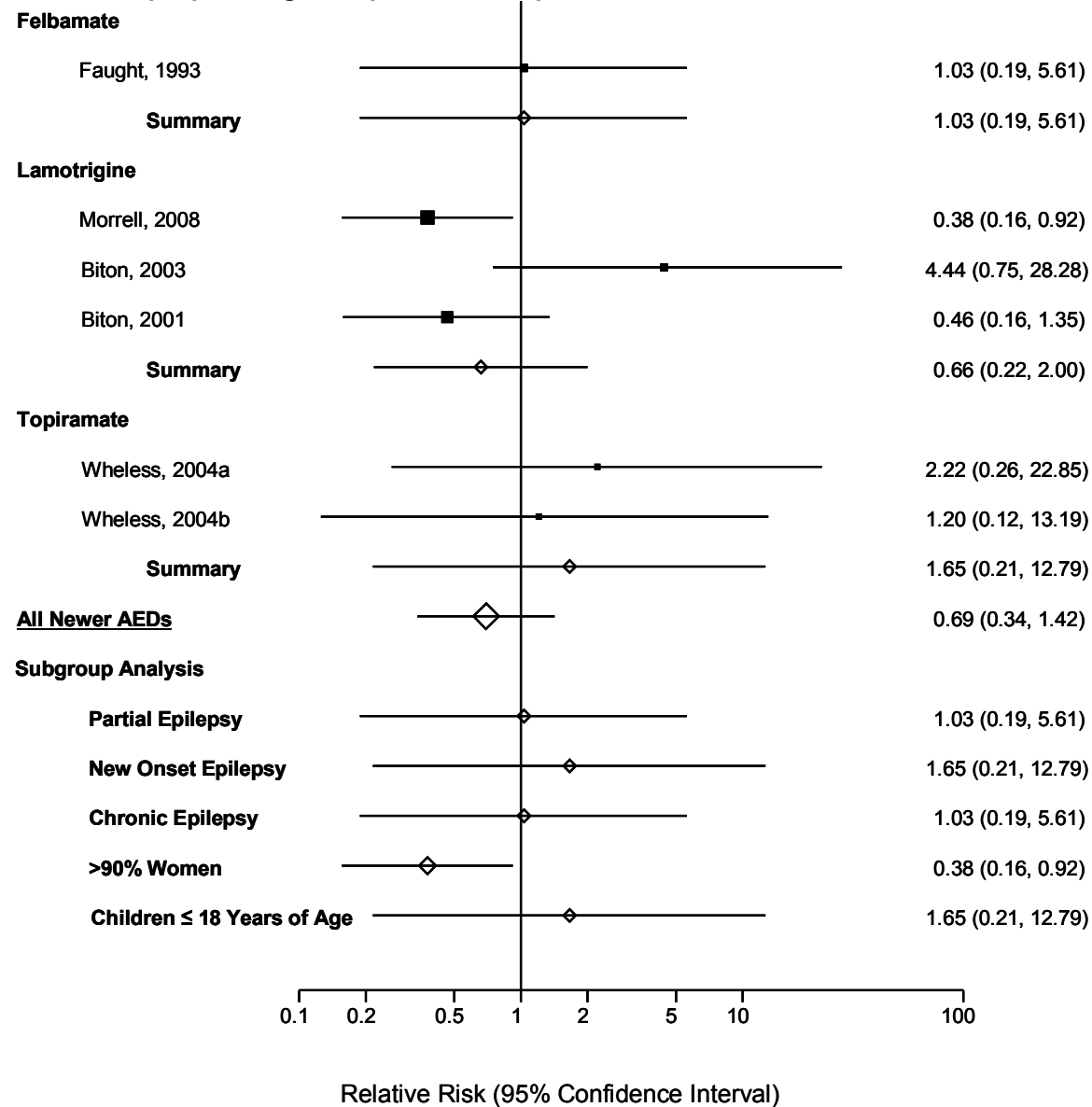
Figure J-67. Composite forest plot of meta-analysis of vomiting in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

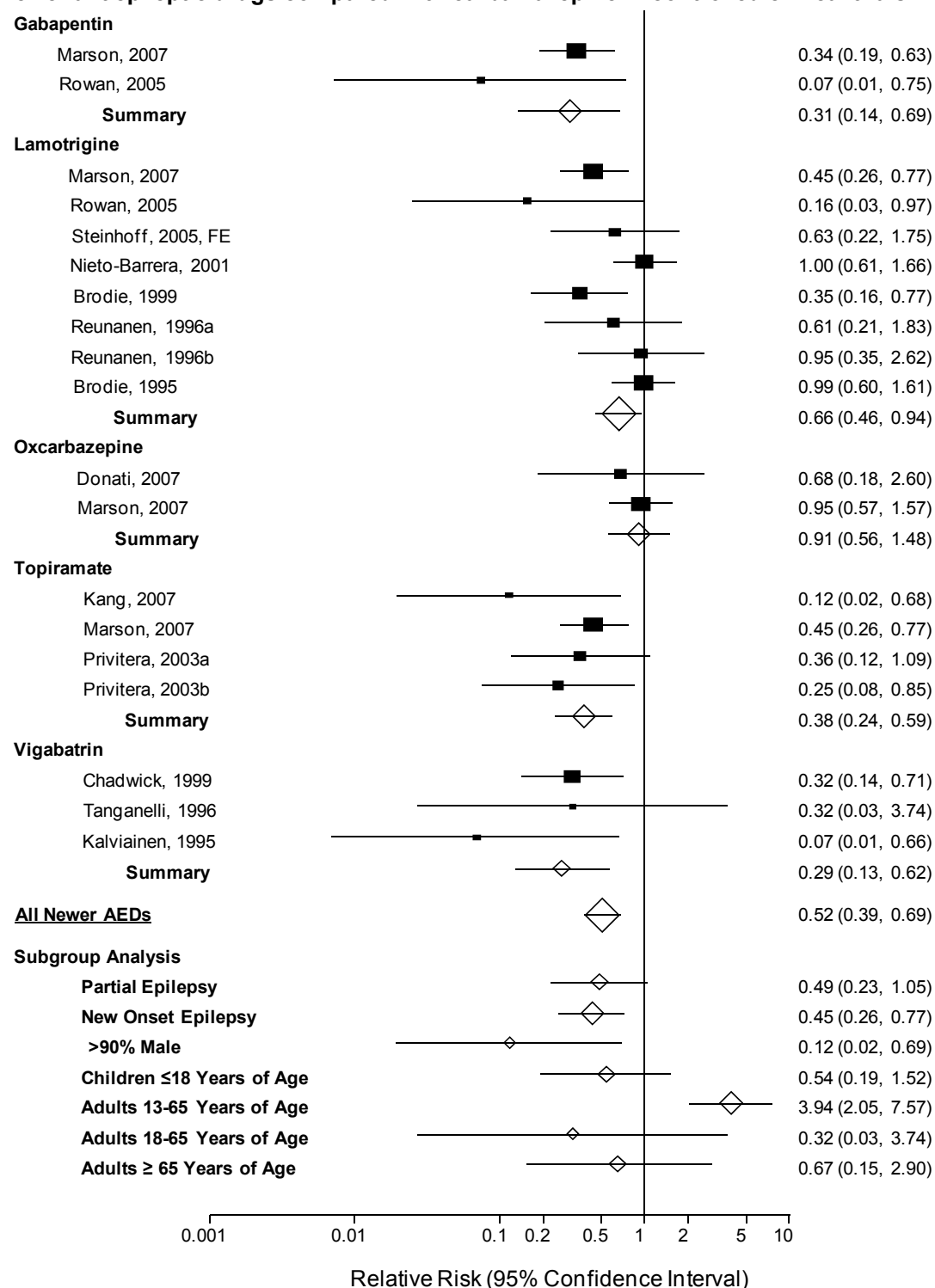
Figure J-68. Composite forest plot of meta-analysis of vomiting in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

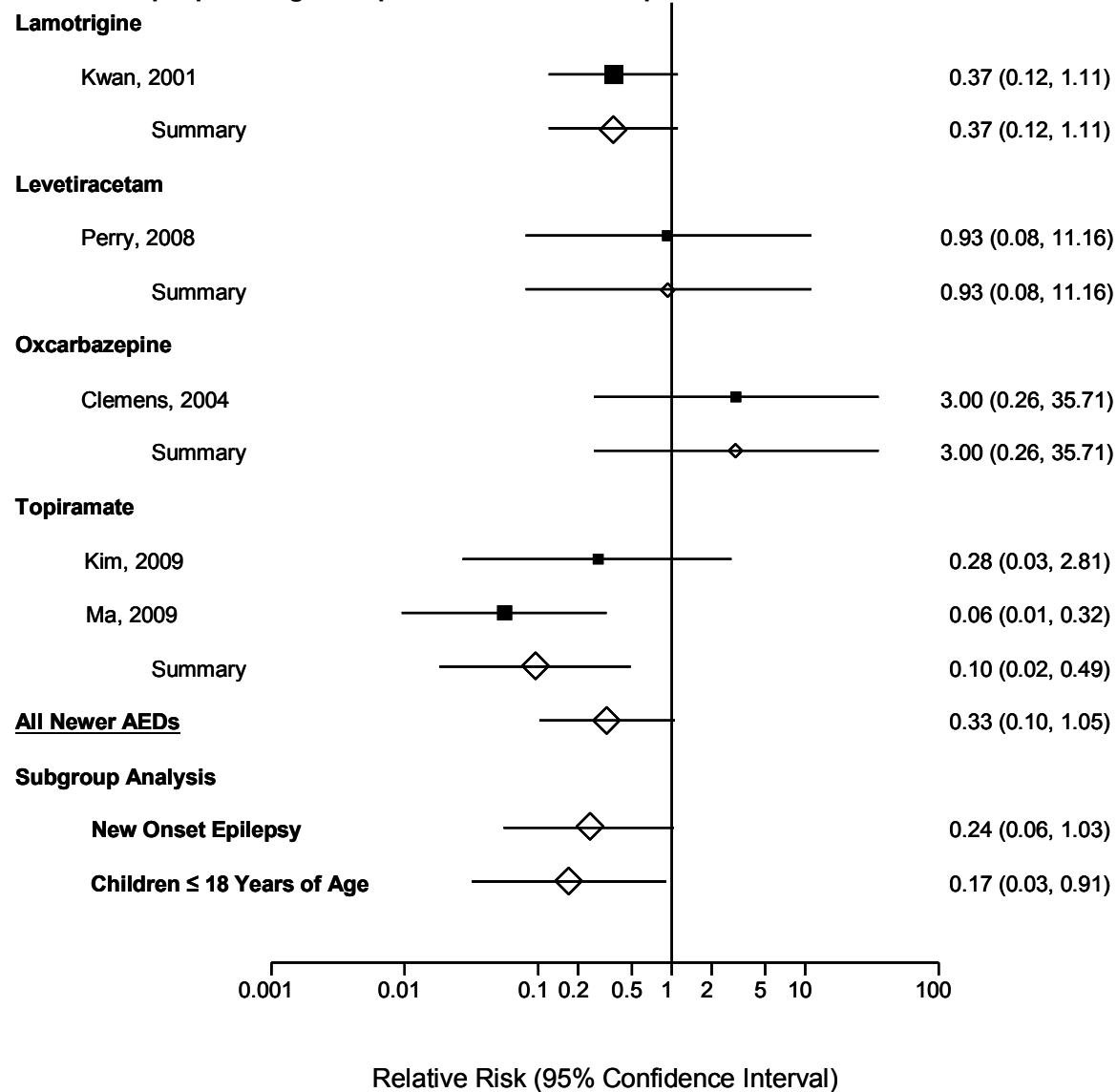
Figure J-69. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

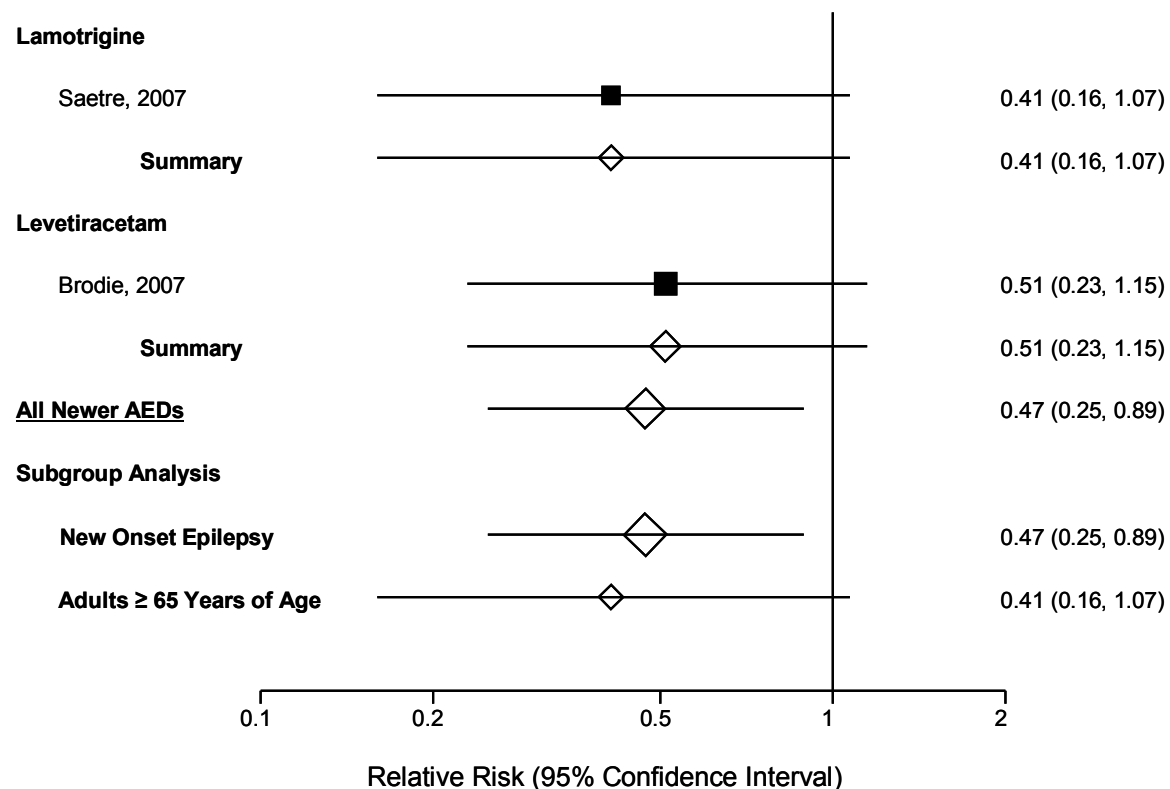
Figure J-70. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in observational studies



AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

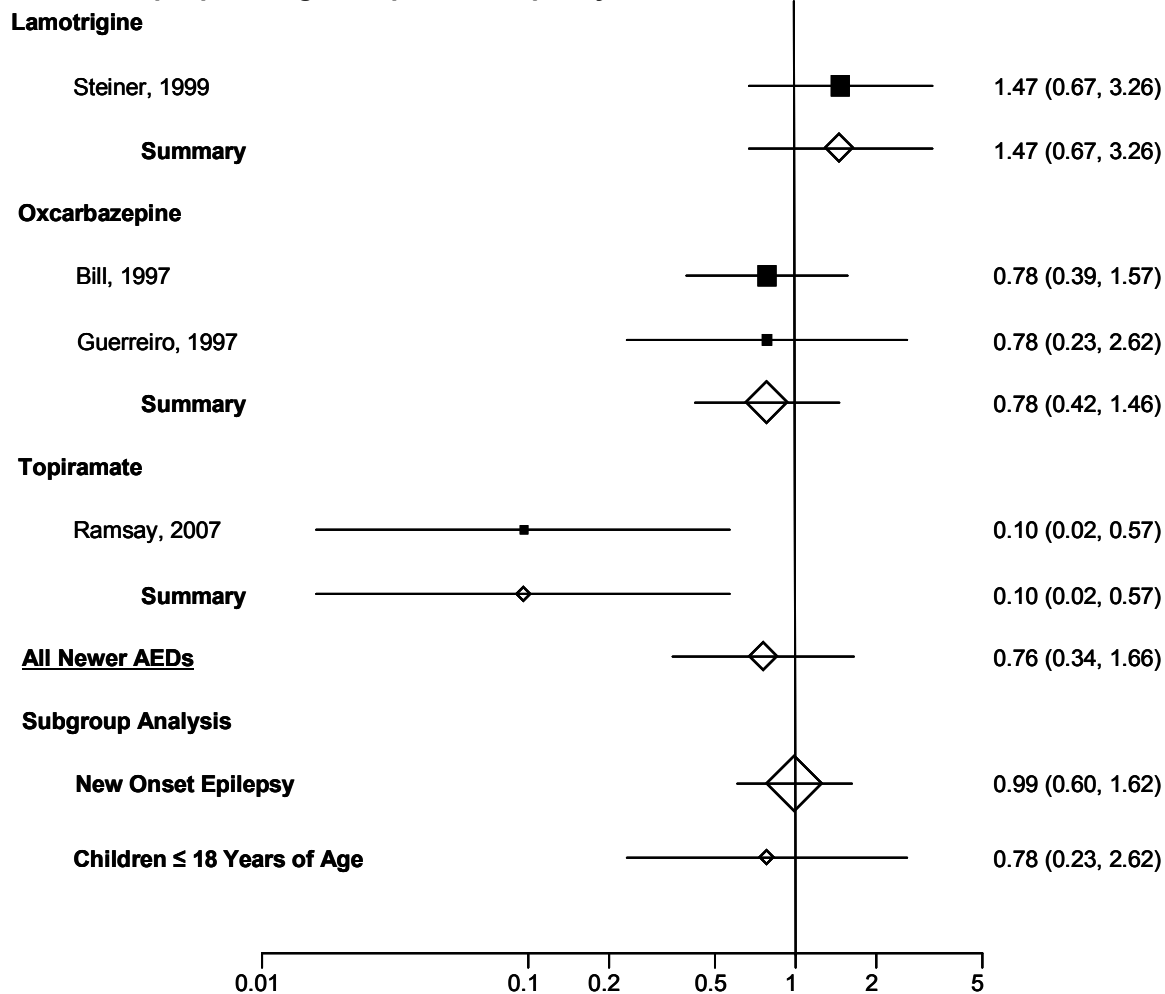
Figure J-71. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared with controlled- or sustained-release carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure J-72. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared with phenytoin in controlled clinical trials

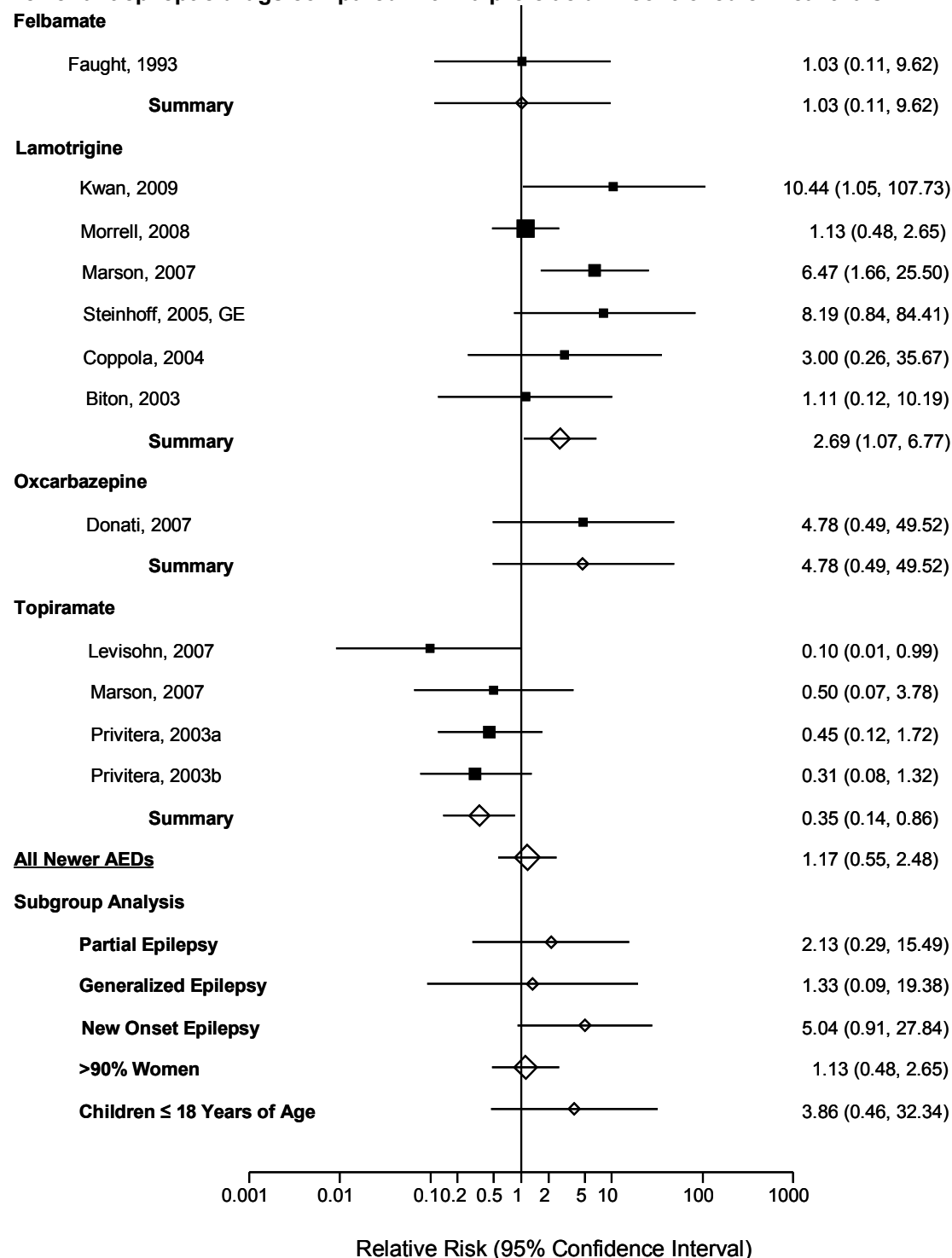


Relative Risk (95% Confidence Interval)

AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

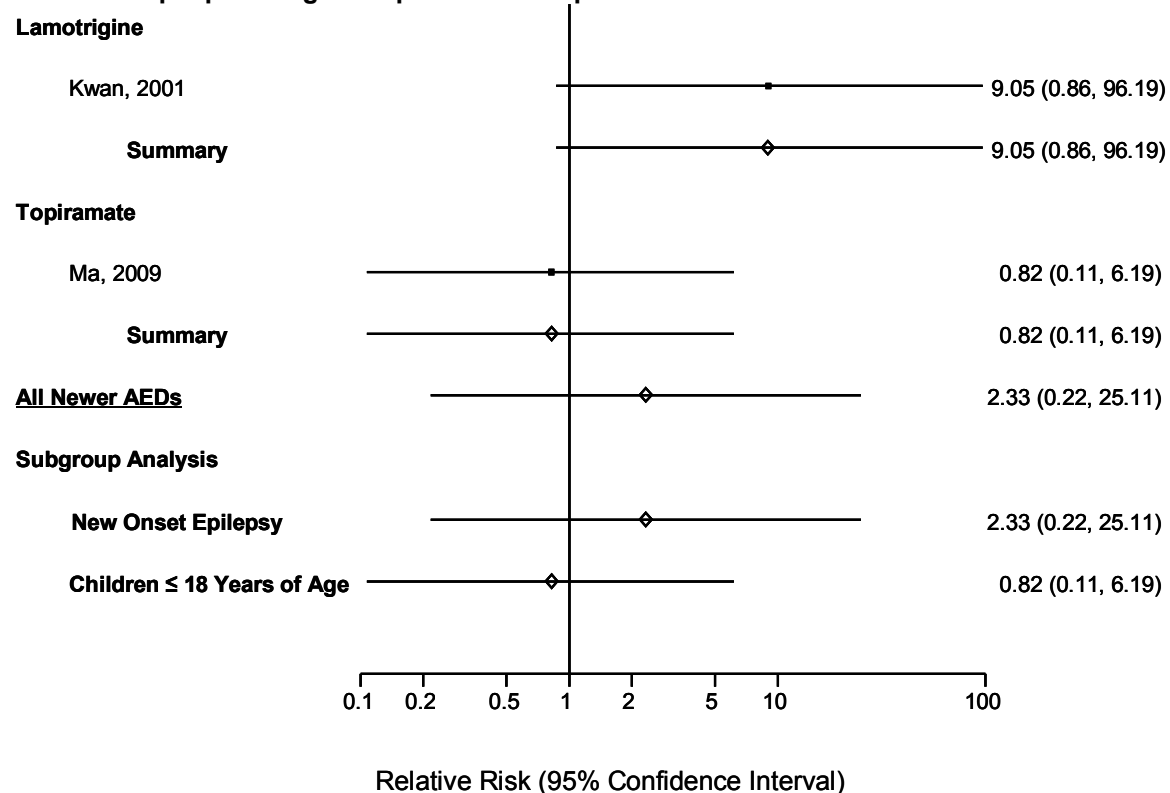
Figure J-73. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

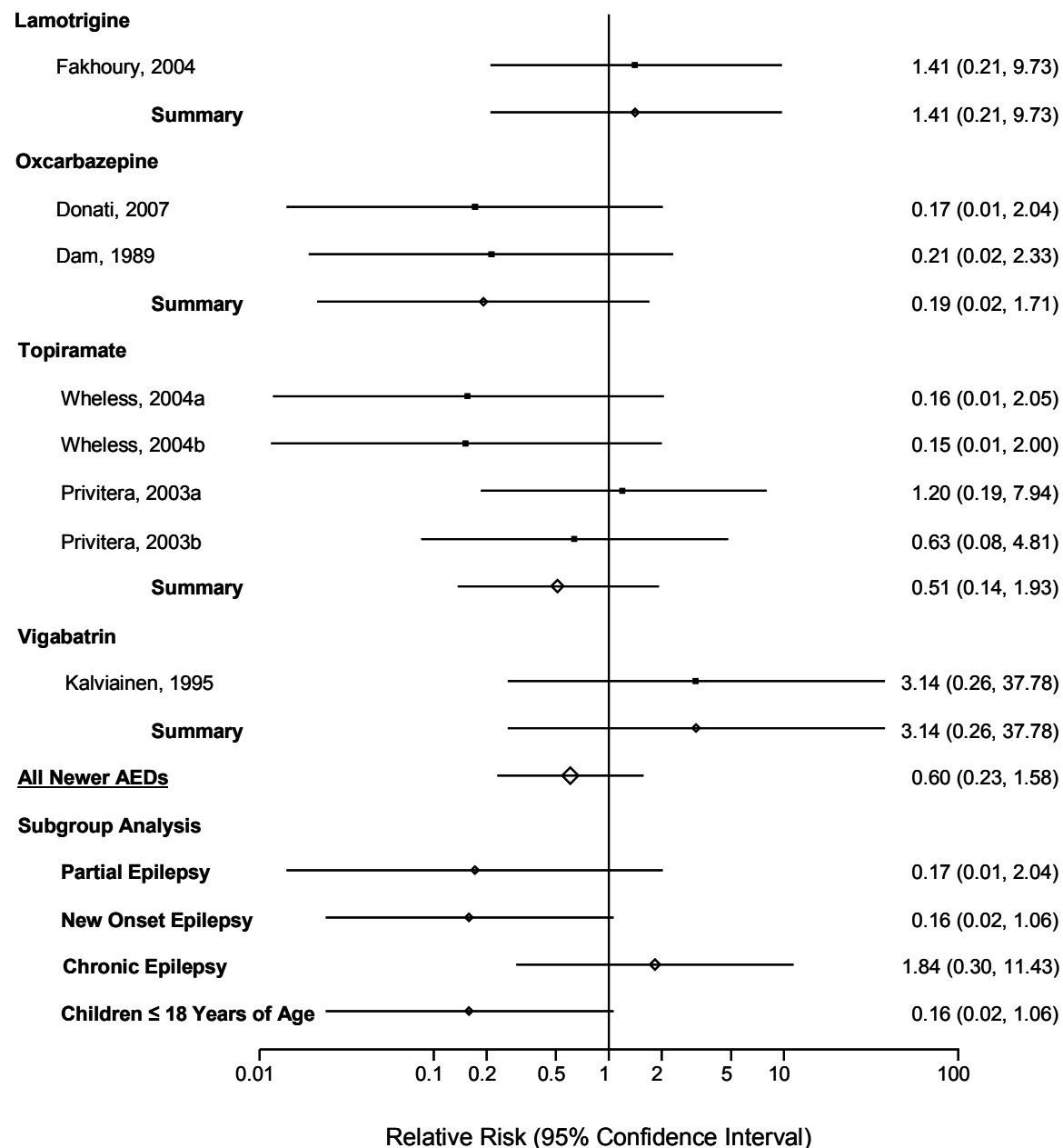
Figure J-74. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in observational studies



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

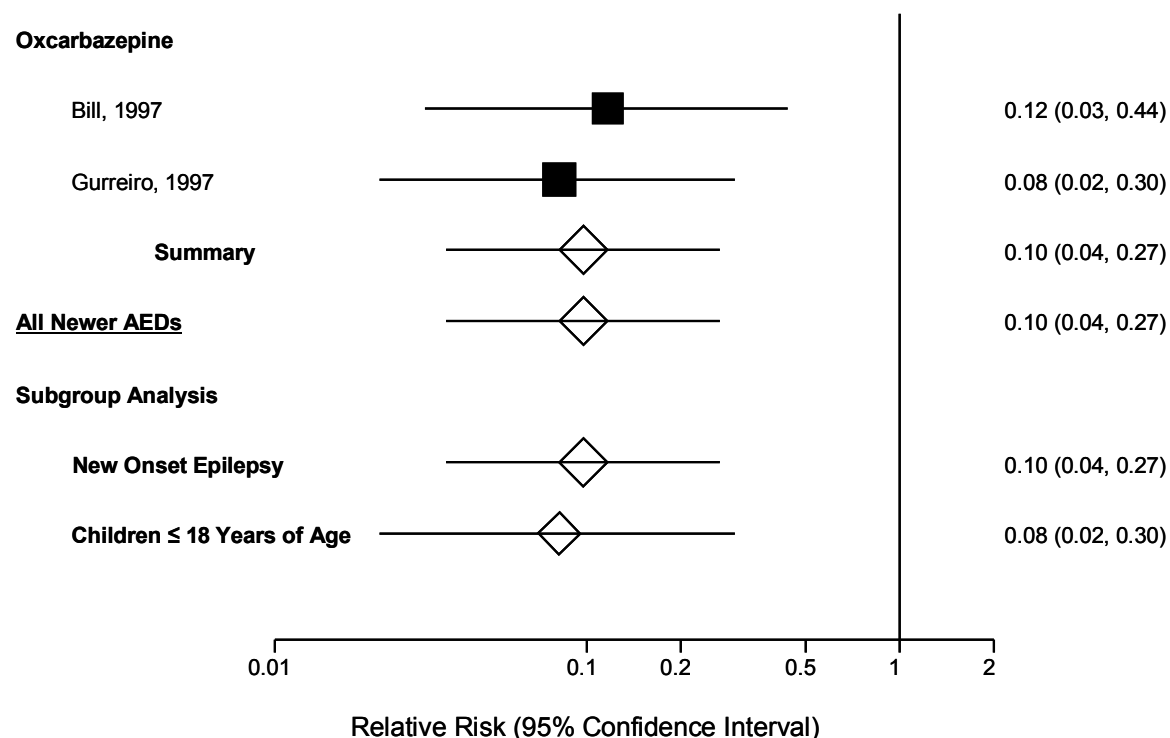
Figure J-75. Composite forest plot of meta-analysis of alopecia in patients with epilepsy taking newer antiepileptic drugs compared with carbamazepine in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

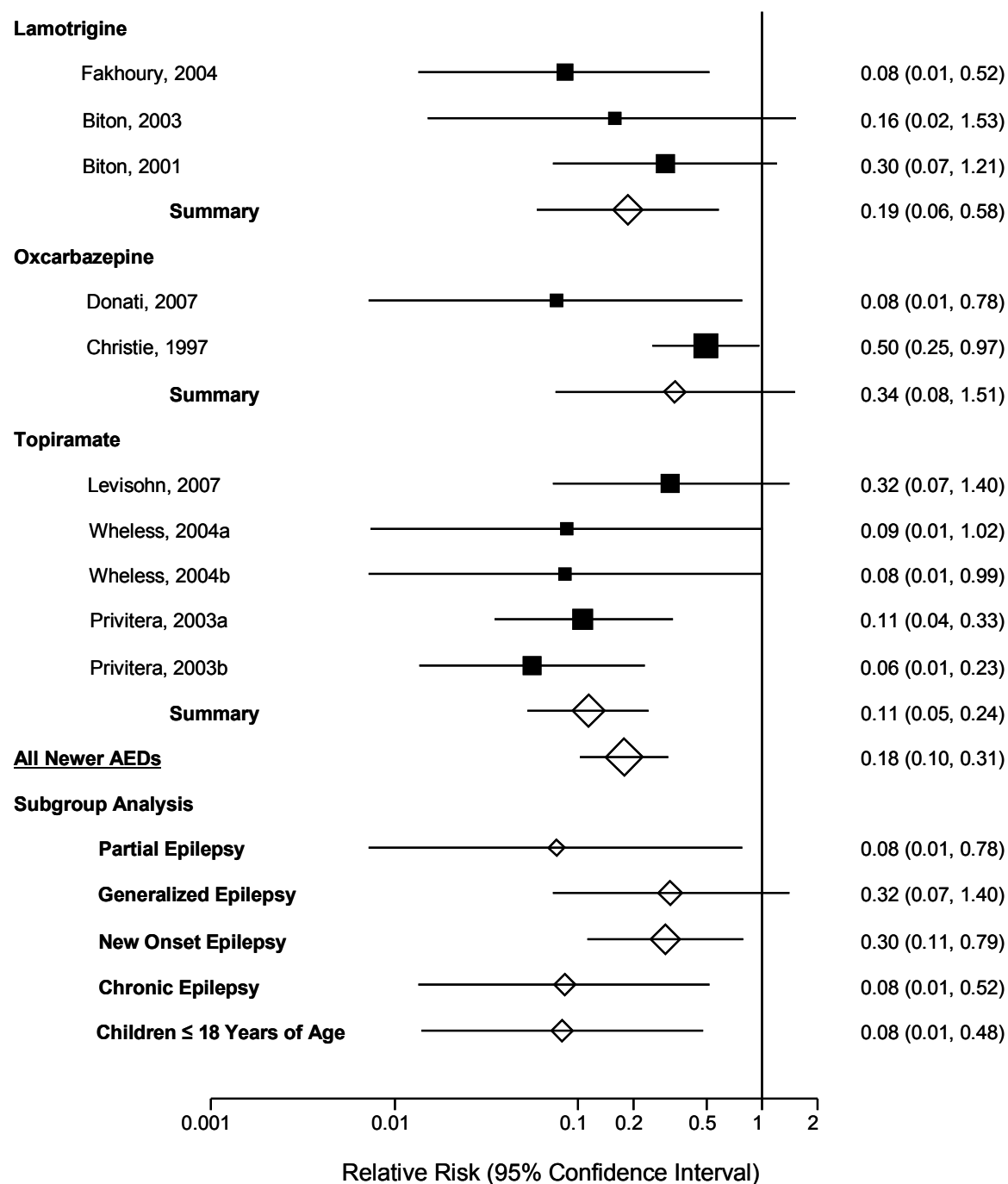
Figure J-76. Composite forest plot of meta-analysis of gum hyperplasia in patients with epilepsy taking oxcarbazepine compared with phenytoin in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure J-77. Composite forest plot of meta-analysis of alopecia in patients with epilepsy taking newer antiepileptic drugs compared with valproic acid in controlled clinical trials



AEDs = antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.