Draft Comparative Effectiveness Review

Number XX (Provided by AHRQ)

Comparative Effectiveness of Medications in Patients with Epilepsy

For Peer Review

Prepared for:
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Contract No.

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AHRQ Publication No. XX-E0XX (Provided by AHRQ)
Publication Month and Year (Provided by AHRQ)

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested Citation: AHRQ Publication No. XX-E0XX. Rockville, MD: Agency for Healthcare Research and Quality. Month Year.

Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. 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 e-mail to **epc@ahrq.gov.**

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Structured Abstract

Objectives: This is an evidence report prepared by the XXX 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 2010.

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 pre-specified 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 (RR) and for continuous endpoints we used weighted mean differences (WMD) or standardized mean differences (SMD). Both were calculated using a DerSimonian and Laird random effects model and reported with 95 percent confidence intervals (CIs). When mean change scores from baseline for each group were not reported, the difference between the mean baseline and mean follow-up scores for each group and the standard deviations (SDs) of the change scores were calculated. I^2 was used to detect statistical heterogeneity and Egger's weighted regression statistics were used to assess for publication bias. The strength of evidence (SOE) and applicability of evidence (AOE) for each outcome was rated as insufficient (I), low (L), moderate (M), or high (H).

Results: When newer antiepileptic medications were compared against carbamazepine, there was a lower risk of being seizure free for 6-12 months [RR 0.81 (0.67, 0.99, NNT 9, SOE: L, AOE: M] or 24 months [RR 0.82 (0.72, 0.94), NNT 13, SOE: M, AOE: M] and a greater risk of withdrawing due to a lack of efficacy [RR 1.59 (1.25, 2.02), NNT 50, SOE: L, AOE: M]. The risk of withdrawing due to adverse events [RR 0.62 (0.53, 0.73), NNT 13, SOE: M, AOE: M] and the risk of several adverse events including fatigue [RR 0.57 (0.41, 0.80), NNT 11, SOE: L, AOE: M], somnolence [RR 0.47 (0.36, 0.61), NNT 14, SOE: M, AOE M], dizziness [RR 0.78 (0.67, 0.91), NNT 50, SOE: M, AOE: M], and skin rash [RR 0.52 (0.39, 0.69), NNT 24, SOE: M, AOE: M] were significantly reduced but the risk of withdrawing for any reason was not significantly impacted [RR 0.90 (0.82, 1.00), SOE: L, AOE: M]. Similarly, when newer antiepileptic medications were compared to carbamazepine sustained or controlled release (SR/CR) products their was a greater risk of withdrawing due to a lack of efficacy [RR 2.42 (1.32, 4.52), NNT 16] but a reduced risk of withdrawing due to adverse events [RR 0.69 (0.50, 0.95), NNT 16, SOE: M, AOE: L] and skin rash [RR 0.47 (0.25, 0.89), NNT 27, SOE: L, AOE: M]. The risk of withdrawing for any reason was not significantly impacted [RR 0.96 (0.78, 1.18), SOE: L, AOE: L].

There was no significant difference in the risk of being seizure free for the study duration when newer antiepileptic medications were compared against phenytoin [RR 0.92 (0.85, 1.00), SOE: M, AOE: M] or valproic acid [RR 0.97 (0.87, 1.08), SOE: M, AOE: M], or the risk of

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being seizure free at 6-12 [RR 0.97 (0.89, 1.06), SOE: M, AOE: M] or 24 months [RR 0.85 (0.73, 1.00), SOE: M, AOE: M] for valproic acid. No significant differences were seen for newer antiepileptic medications versus either phenytoin or valproic acid for withdrawals for any reason [phenytoin: RR 0.91 90.76, 1.09), SOE: L, AOE: M] [valproic acid: RR 0.96 (0.85, 1.09), SOE: L, AOE: M], withdrawals due to lack of efficacy [phenytoin: RR 1.03 (0.33, 3.23). SOE: L, AOE: L] [valproic acid: RR 1.10 (0.77, 1.56), SOE: L, AOE: M], or withdrawals due to adverse events [phenytoin: RR 0.38 (0.14, 1.03), SOE: I, AOE: M] [valproic acid: RR 0.90 (0.75, 1.08), SOE: L, AOE: M]. The risk of certain adverse events including fatigue [RR 0.61 (0.44, 0.85, NNT 23, SOE: M, AOE: M], somnolence [RR 0.65 (0.43, 0.98), NNT 25, SOE: M, AOE: M], nausea [RR 0.56 (0.41, 0.77), NTT 31, SOE: M, AOE: M], and alopecia [RR 0.18 (0.10, 0.31), NNT 10, SOE: M, AOE: M] were significantly lower for newer antiepileptic medications versus valproic acid. The risk of vomiting [RR 0.09 (0.01, 0.89), NNT 19, SOE: I, AOE: L] and gum hyperplasia [RR 0.10 (0.04, 0.27), NNT 6, SOE: H, AOE: L] 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 [RR 0.87 (0.64, 1.18), SOE: L, AOE: L], seizure frequency [SMD 0.03 (-0.08, 0.14), SOE: L, AOE: L], total withdrawals [RR 0.90 (0.39, 2.08), SOE: L, AOE: M], withdrawals due to lack of efficacy [RR 1.02 (0.41, 2.54), SOE: L, AOE: M], or withdrawals due to adverse events [RR 0.79 (0.28, 2.20), SOE: L, AOE: M] 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 [qualitiatively evaluated, SOE: L, AOE: M], hospital stay duration [qualitiatively evaluated, SOE: L, AOE: M], and the composite of medical service utilization [qualitiatively evaluated, SOE: I, AOE: M] but may not increase outpatient service utilization [qualitiatively evaluated, SOE: L, AOE: M].

Conclusions: Carbamazepine had advantages in epilepsy control over newer antiepileptic medications as a class but had more adverse effects. Valproic acid and phenytoin provided similar epilepsy control as 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. 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. We had insufficient to low strength of evidence for these conclusions.

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Appendices and Evidence Tables for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/XXX/XXX.pdf.

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Effective Health Care

Comparative Effectiveness of Medications in Patients with Epilepsy

Executive Summary

Effective Health Care Program

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov. Ahrq.gov/reports/final.cfm

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Background

Epilepsy is a clinical phenomenon in which a person has recurrent seizures due to a chronic underlying process.[1,2] Approximately 1-3 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 nine 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]

Over the last decade there have been newer antiepileptic drugs that have been approved for use by the FDA in the treatment of epilepsy.[6] The comparative benefits and harms of older versus newer antiepileptic drugs have been assessed in numerous randomized controlled trials (RCT) with varying results.[1,7,8]

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.[9,10] The Italian 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.[11] The Food and Drug Administration (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 of the benefits and harms associated with newer versus older and innovator versus generic antiepileptic treatments is needed to clarify these issues.

Objectives

This comparative effectiveness review utilized data on benefits and harms from direct comparative studies of newer versus older or innovator versus generic antiepileptic medications in patients with epilepsy.

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 drivers license, and loss of employment?

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?

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?

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.

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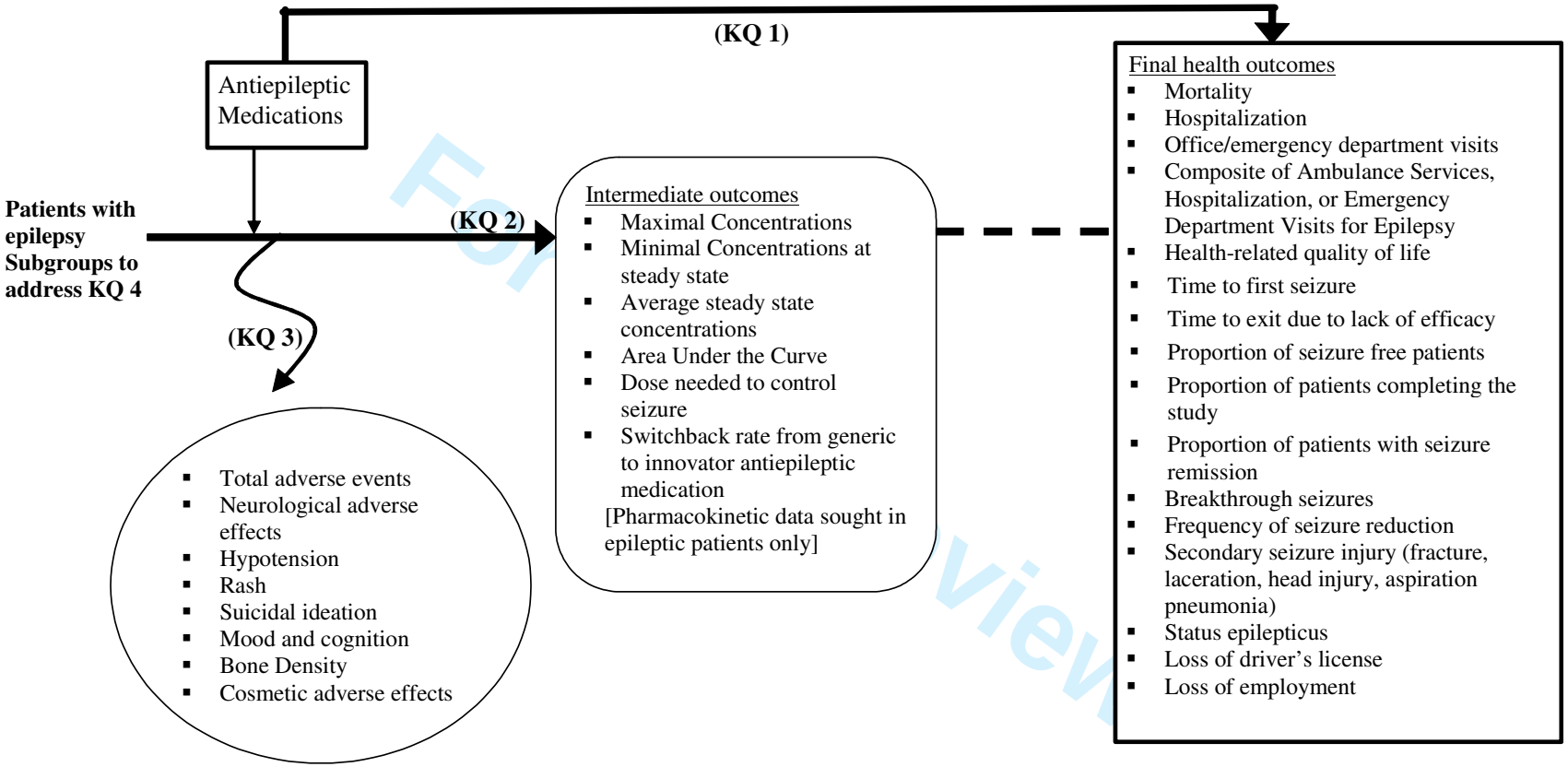
Figure ES- 1. Analytic Framework for the Evaluation of Effectiveness and Safety of Antiepileptic Medication in Patients With Epilepsy



Legend: KQ=key question

Methods

Input from Stakeholders:

TheEvidenc Based Practice Center (EPC) drafted a topic refinement document with proposed key questions after consult 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, proposed revisions to the key questions, and a preliminary protocol was generated and reviewed with the Technical Expert Panel. Our 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 will undergo peer review and public commentary and revisions will be made before being finalized.

Data Sources and Selection:

Two independent investigators conducted systematic literature searches of MEDLINE (from 1950 to the present), Web of Science from the earliest possible date through March 2, 2010, and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews from the earliest possible date through March 2, 2010. A separate search strategy was employed for each evaluation. The search for the older versus newer antiepileptic medication evaluation was used to identify direct comparative trials and studies explicitly evaluating older versus newer antiepileptic medications and providing data on intermediate or final health outcomes of interest. For the search, we utilized Cochrane's Highly Sensitive Search Strategy (Sensitivity Maximizing Version 2008) to limit to randomized controlled trials and the Scottish Intercollegiate Guidelines Network Observational Study Search Filter to limit 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 vs. its generic, or for healthcare utilization a generic to innovator, innovator to generic, or generic to generic). We did not limit the search to "A" rated version 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.

Studies were included in the evaluation of key questions if they: (1) compared older antiepileptic medications (phenytoin, carbamazepine, carbamazepine sustained release (SR) or controlled release (CR), valproic acid, clonazepam, phenobarbital, ethosuximimide, primidone) to newer antiepileptic medications or compared innovator antiepileptic medications to generic antiepileptic medications; (2) are conducted in patients with epilepsy; and (3) reported data on pre-specified clinical or humanistic outcomes.

Data Extraction and Quality Assessment:

Through the use of 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 follow-up), 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, BCS class], co-morbidities, and use of concurrent standard medical therapies. Intermediate, 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 assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of subjects, blinding of outcome assessors, intent-to-treat analysis, description of participant withdrawals, and potential conflict of interest. Additionally, RCTs were assessed for randomization technique and

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allocation concealment. Observational studies were assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies were then given an overall score of good, fair, or poor.

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 to 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 were those where therapy was compared against a comparator and the investigators had control over the determination of therapy. These controlled trials could be crossover or parallel trials but may or may not be randomized. Controlled observational studies were cohort or case control studies, had to have a control group, and the investigators did not determine who would receive which therapy. 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 (WMD) 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 (SMD) (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 was not reported, we calculated the difference between the mean baseline and mean follow-up 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: SDbaseline-followup=sqrt(SD2baseline + SD2followup – 2*(correlation coefficient)SDbaseline*SDfollowup). A correlation coefficient of 0.5 proposed by Follman and colleagues was used.[18] 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 confidence intervals (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 addressed using the I^2 statistic which assesses the degree of inconsistency not due to chance across studies and ranges from 0-100 percent with values of >50 percent representing important statistical heterogeneity. Cochrane Q statistics were provided for completeness sake. 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, data was available as incidence rate ratios in the individual observational studies, were described but were not pooled. For the section on time to first seizure, data was expressed in the trials as hazard ratios and are reported and pooled.

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, where evidence existed, for 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

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medications within a Biopharmaceutics Classification System (BCS) class (I, II, or III) were compared to their corresponding generic medications within that same class.

Results

For the newer versus older antiepileptic medication literature search, 5463 nonduplicative citations were identified. After title and abstract screening and full text review, 5064 and 186 citations were excluded, respectively. Sixty-three and 48 studies were available for qualitative and quantitative synthesis respectively. Newer versus older comparisons were largely limited to studies using carmbamazepine or valproic acid and to a lesser extent phenytoin and sustained/controlled release carbamazepine. Comparisons versus clonazepam, phenobarbital, ethosuximide, or primidone are very limited or not conducted at all. The newer antiepileptic medications compared versus each older agent varied in the comparisons.

For the innovator versus generic antiepileptic medication literature search, 332 nonduplicative citations were identified. After title and abstract screening and full text review, 240 and 11 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 and applicability of evidence for all key questions can be found in Table ES-1. 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 in fully understanding the topic area.

<u>Key Question 1:</u>

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. These studies compared the use of long tolerated innovator antiepileptic medication use with short term results yielded after switching. The controlled observational studies did not state that they were limited to “A” rated products. If generic versions do not meet the FDA guidance for an “A” rated generic, the differences between the innovator and generic groups may be greater than when limited to “A” rated versions. The switch was not blinded so patient and clinician 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 well conducted controlled observational studies assessed a composite endpoint of medical service utilization.[33-35] They did not compare innovator to 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 could not control for co-morbidities 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 [OR 1.51 (1.29, 1.76)] but no significant difference was found

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after adjusting for confounders [OR 1.08 (0.91, 1.29)], although the direction of effect was the same. Unlike the other two trials, this study authors controlled for 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, the three observational studies suggest that switching from an antipeilpetic medication to an "A" rated version of the product may increase the utilization of a composite of medical services (hospitalization, emergency department visit, with or without utilizing ambulance services for epilepsy).[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 seizure freedom 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 to their respective generic versions we found that seizure occurrence and frequency was 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, 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 they were comparing two established versions of a sustained release carbamazepine product versus a new version which 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 was 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 Cmax, Cmin, Css, Tmax, and AUC values from a population of patients receiving innovator antiepileptic medications are not significantly different from that of their generic versions. A population of patients should derive similar concentrations on an innovator as they would using generic antiepileptic medications. However, our data do not allow us to determine if an individual patient or

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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 percent 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. What this data does show is that a number of neurologists and patients with epilepsy have concerns about switching between versions of antiepileptic medications.

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 was limited mostly to partial epilepsy, 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. 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 generally followed those in the base case evaluations although 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, 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 to 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 to older patients [HR 0.993 (0.988 to 0.997); p=0.002].

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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.

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Table ES- 1. Summary of results.

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
KEY QUESTION 1 ENDPOINTS					
MORTALITY:					
Newer vs. Carbamazepine	6 RCT	Yes	No effect, RR 0.75 (0.51, 1.12)	SOE: L	AOE: M
Newer vs. Phenytoin	3 RCT	Yes	No effect, RR 0.30 (0.05, 1.95)	SOE: L	AOE: M
Newer vs. Valproic Acid	3 RCT	Yes	No effect, RR 0.94 (0.31, 2.80)	SOE: L	AOE: M
OUTPATIENT SERVICE UTILIZATION:					
Innovator vs. Generic	4 OBS	No	Similar utilization of outpatient services during generic medication periods.	SOE: L	AOE: M
HOSPITALIZATIONS:					
Newer vs. Carbamazepine	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared to carbamazepine.	SOE: I	AOE: L
Newer vs. Valproic Acid	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared to valproic acid.	SOE: I	AOE: L
Newer vs. Ethosuximide	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared to ethosuximide.	SOE: I	AOE: L
Innovator vs. Generic	4 OBS	No	Increased risk of hospitalizations during generic medication periods.	SOE:L	AOE: M
HOSPITAL STAY DURATION:					
Innovator vs. Generic	4 OBS	No	Increased hospital stay during generic medication periods.	SOE:L	AOE: M
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	AOE: M

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Table ES-1. Summary of results. (continued)

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

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Table ES-1. Summary of results. (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Strength/ Applicability of Evidence
SEIZURE REMISSION:					
6 to 12-Month:					
Newer vs. Carbamazepine	2 RCT	Yes	Patients on newer antiepileptic medications less likely to have seizure remission vs. carbamazepine, [RR 0.81 (0.67, 0.99), NNT 9]	SOE:L	AOE: M
Newer vs. Valproic Acid	1 RCT	Yes	No effect, [RR 0.97 (0.89,1.06)]	SOE: M	AOE: M
24-Month:					
Newer vs. Carbamazepine	1 RCT	Yes	Patients on newer antiepileptic medication less likely to have seizure remission vs. carbamazepine, [RR 0.82 (0.72, 0.94), NNT 13]	SOE: M	AOE: M
Newer vs. Valproic Acid	1 RCT	Yes	No effect, [RR 0.85 (0.73,1.00)]	SOE: M	AOE: M
STATUS EPILEPTICUS, SECONDARY INJURY FROM SEIZURES, LOSS OF DRIVER'S LICENSE/EMPLOYMENT:					
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
TOTAL WITHDRAWALS:					
Newer vs. Carbamazepine	14 RCT	Yes	No effect, [RR 0.90 (0.82, 1.00)]	SOE: L	AOE: M
Newer vs. Carbamazepine CR/SR	2 RCT	Yes	No effect, [RR 0.96 (0.78, 1.18)]	SOE: L	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [RR 0.91 (0.76, 1.09)]	SOE: L	AOE: M
Newer vs. Valproic Acid	16 RCT	Yes	No effect, [RR 0.96 (0.85, 1.09)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.95 (0.53, 1.71)]	SOE: I	AOE: L
Innovator vs. Generic	9 RCT + 1 NRCT	Yes	No effect, [RR 0.90 (0.39, 2.08)]	SOE: L	AOE: M

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Table ES-1. Summary of results. (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
WITHDRAWALS DUE TO LACK OF EFFICACY:					
Newer vs. Carbamazepine	10 RCT	Yes	Withdrawals due to lack of efficacy increased with newer agents vs. carbamazepine, [RR 1.59 (1.25, 2.02), NNT 50]	SOE: L	AOE: M
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	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [RR 1.03 (0.33, 3.23)]	SOE: L	AOE: M
Newer vs. Valproic Acid	11 RCT	Yes	No effect, [RR 1.10 (0.77, 1.56)]	SOE: L	AOE: M
Innovator vs. Generic	9 RCT + 1 NRCT	Yes	No effect, [RR 1.02 (0.41, 2.54)]	SOE: L	AOE: M
KEY QUESTION 2 ENDPOINTS					
MAXIMUM CONCENTRATION: Innovator vs. Generic	7 RCT + 1 NRCT	Yes	No effect, [SMD 0.10 (-0.13, 0.32)]	SOE: L	AOE: M
MINIMUM CONCENTRATION: Innovator vs. Generic	5 RCT + 1 NRCT	Yes	No effect, [SMD 0.05 (-0.21, 0.31)]	SOE: L	AOE: L
STEADY STATE CONCENTRATION: Innovator vs. Generic	7 RCT	Yes	No effect, [SMD 0.18 (-0.09, 0.45)]	SOE: L	AOE: L
TIME TO MAXIMAL CONCENTRATION: Innovator vs. Generic	5 RCT	Yes	No effect, [WMD 0.00 (-0.43, 0.43)] (Note: a WMD was calculated vs. a SMD for Tmax because only carbamazepine trials made up this evaluation).	SOE: I	AOE: M
AREA UNDER THE CURVE: Innovator vs. Generic	7 RCT + 1 NRCT	Yes	No effect, [SMD 0.05 (-0.18, 0.28)]	SOE: L	AOE: M

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Table ES-1. Summary of results. (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidemce	Applicability of Evidence
DOSE REQUIREMENTS FOR SEIZURE CONTROL:					
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: 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	AOE: L
KEY QUESTION 3 ENDPOINTS					
WITHDRAWALS DUE TO ADVERSE EVENTS:					
Newer vs. Carbamazepine	18 RCT	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	AOE: M
Newer vs. Carbamazepine CR/SR	2 RCT	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	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [0.38 (0.14, 1.03)]	SOE: I	AOE: M
Newer vs. Valproic Acid	16 RCT	Yes	No effect, [RR 0.90 (0.75, 1.08)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.71 (0.45, 1.12)]	SOE: I	AOE: L
Innovator vs. Generic	9 RCT + 1 NRCT	Yes	No effect, [RR 0.79 (0.28, 2.20)	SOE: L	AOE: M
HEADACHE:					
Newer vs. Carbamazepine	15 RCT	Yes	No effect, [RR 0.92 (0.78, 1.08)]	SOE: L	AOE: M
Newer vs. Carbamazepine SR/CR	2 RCT	Yes	No effect, [RR 0.83 (0.63, 1.10)]	SOE: L	AOE: L
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.74(0.53, 1.02)]	SOE: L	AOE: M
Newer vs. Valproic Acid	15 RCT	Yes	No effect, [RR 0.90 (0.70, 1.16)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.66 (0.33, 1.29)]	SOE: I	AOE: L
Innovator vs. Generic	3 RCT	Yes	No effect, [RR 0.95 (0.55, 1.64)]	SOE: I	AOE: L

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Table ES-1. Summary of results. (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
FATIGUE:					
Newer vs. Carbamazepine	7 RCT	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. carbamazepine. [RR 0.57 (0.41, 0.80), NNT 11]	SOE: L	AOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	Yes	No effect, [RR 1.17 (0.80, 1.72)]	SOE: I	AOE: L
Newer vs. Phenytoin	1 RCT	No	No effect, [RR 1.05 (0.49, 2.25)]	SOE: I	AOE: L
Newer vs. Valproic Acid	8 RCT	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. valproic acid. [RR 0.61 (0.44, 0.85), NNT 23]	SOE: M	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.90 (0.45, 1.80)]	SOE: I	AOE: L
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
SOMNOLENCE:					
Newer vs. Carbamazepine	8 RCT	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. carbamazepine. [RR 0.47 (0.36, 0.61), NNT 14]	SOE: M	AOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	No	No effect, [RR 1.21 (0.75, 1.96)]	SOE: I	AOE: L
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.72 (0.44, 1.18)]	SOE: I	AOE: M
Newer vs. Valproic Acid	9 RCT	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. valproic acid. [RR 0.65 (0.43, 0.98), NNT 25]	SOE: M	AOE: 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	AOE: L
Innovator vs. Generic	2 RCT	Yes	No effect, [RR 0.90 (0.48, 1.70)]	SOE: L	AOE: L
DIZZINESS:					
Newer vs. Carbamazepine	16 RCT	Yes	Risk of dizziness reduced with newer antiepileptic medications vs. carbamazepine. [RR 0.78 (0.67, 0.91), NNT 50]	SOE: M	AOE: M
Newer vs. Carbamazepine SR/CR	2 RCT	Yes	No effect, [RR 3.26 (0.58, 18.52)]	SOE: L	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [RR 0.67 (0.43, 1.05)]	SOE: L	AOE: M
Newer vs. Valproic Acid	12 RCT	Yes	No effect, [RR 0.98 (0.71, 1.35)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.46 (0.15, 1.38)]	SOE: I	AOE: L
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I

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Table ES-1. Summary of results. (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability 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 1000 person years, 75.7 events per 1000 person years, p=NS	SOE: L	AOE: L
DIPLOPIA:					
Innovator vs. Generic	2 RCT	Yes	No effect, [1.28 (0.38, 4.31)]	SOE: L	AOE: L
HYPOTENSION, ASTHENIA, ATAXIA, NYSTAGMUS, TREMOR:					
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
NAUSEA:					
Newer vs. Carbamazepine	8 RCT	Yes	No effect, [RR 0.69 (0.46, 1.02)]	SOE: L	AOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	No	No effect, [RR 0.66 (0.39, 1.12)]	SOE: I	AOE: L
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.88 (0.56, 1.37)]	SOE: L	AOE: M
Newer vs. Valproic Acid	11 RCT	Yes	Risk of nausea reduced with newer antiepileptic medications vs. valproic acid. [RR 0.56 (0.41, 0.77), NNT 31]	SOE: M	AOE: M
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
VOMITING:					
Newer vs. Carbamazepine	3 RCT	Yes	No effect, [RR 1.25 (0.66, 2.35)]	SOE: L	AOE: M
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	AOE: L
Newer vs. Valproic Acid	5 RCT	Yes	No effect, [RR 0.69 (0.34, 1.42)]	SOE: L	AOE: M
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I

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Table ES-1. Summary of results. (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
SKIN RASH:					
Newer vs. Carbamazepine	13 RCT	Yes	Risk of skin rash was reduced with newer antiepileptic medications vs. carbamazepine [RR 0.52 (0.39, 0.69), NNT 24]	SOE: M	AOE: M
Newer vs. Carbamazepine SR/CR	2 RCT	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	AOE: M
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.76 (0.34, 1.66)]	SOE: I	AOE: M
Newer vs. Valproic Acid	10 RCT	Yes	No effect, [RR 1.17 (0.55, 2.48)]	SOE: L	AOE: M
Innovator vs. Generic	2 RCT	Yes	No effect, [RR 0.77 (0.17, 3.57)]	SOE: I	AOE: L
SUICIDAL IDEATION:					
Newer vs. Older	No data	No	No data	SOE: I	AOE: I
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
MOOD AND COGNITION:					
Newer vs. Carbamazepine	4 RCT	No	Different scales and subscales, data inconclusive	SOE: I	AOE: I
Newer vs. Phenytoin	1 RCT	No	No effect	SOE: I	AOE: I
Newer vs. Valproic Acid	5 RCT	No	Different scales and subscales, data inconclusive	SOE: I	AOE: 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	AOE: I
BONE DENSITY:					
Newer vs. Older	No data	No	No data	SOE: I	AOE: I
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
ALOPECIA:					
Newer vs. Carbamazepine	6 RCT	Yes	No effect, [RR 0.60 (0.23, 1.58)]	SOE: L	AOE: M
Newer vs. Valproic Acid	8 RCT	Yes	Risk of alopecia was reduced with newer antiepileptic medications vs. valproic acid [RR 0.18 (0.10, 0.31), NNT 10]	SOE: M	AOE: M
ACNE:					
Newer vs. Phenytoin	1 RCT	No	No effect, [RR 2.78 (0.82, 9.53)]	SOE: I	AOE: L
GUM HYPERPLASIA:					
Newer vs. Phenytoin	2 RCT	Yes	Risk of gum hyperplasia was reduced with newer antiepileptic medications vs. phenytoin [RR 0.10 (0.04, 0.27), NNT 6]	SOE: H	AOE: L

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Legend: AOE=Applicability of Evidence; CR=Controlled Release; H=High; I=Insufficient; L=Low; M=Moderate; MD=Mean Difference; SMD=Standardized Mean Difference; NRCT=Non-Randomized 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

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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 to 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 as 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 more 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. 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 antepileptic 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 evauation 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:

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

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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 evaluation of newer versus older antiepileptic medications provide population wide 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.

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 Food and Drug Administration. 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. Follow-up 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, healthcare 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.

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.

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).

Cmax: The maximal concentration of antiepileptic medication obtained after dosing.

Css: The concentration of antiepileptic medication obtained at steady state.

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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.

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).

I^2: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to100.

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 Analyses: 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

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Note: Other formulas also exist.

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

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

References

Please refer to the reference list in the full report for documentation of statements contained in the Executive Summary

Internet Citation

{Provided by AHRQ} Authoring EPC, Title, Comparative Effectiveness Review: Number ##. AHRQ Publication Number No. 0#-###, Month 200#. Agency for Healthcare Research and Quality, Rockville, MD. http://www.effectivehealthcare.ahrq.gov/xxxxxxx

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Evidence Report

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Chapter 1. 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 1000.[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 classify the three main types of seizures: partial, generalized, and unclassified and 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 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 MRI 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

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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 types[1]

Seizure Type	Subtypes
Partial Seizures	Simple partial seizures Complex partial seizues 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 nine 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 (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 (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]

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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 goal of antiepileptic therapy is 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.[1,2,38-40]

Table 3. Important characteristics of antiepileptic medications[1,2,38-40]

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Carbamazepine	Na^+ channel inhibition	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
Clonazepam	Potentiate GABA receptor function	Absence Atypical Absence Myoclonic	Neurological: ataxia, sedation, lethargy Non-Neurological: anorexia	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No

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Table 3. Important characteristics of antiepileptic medications[1,2,38-40] (Continued)

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Ethosuximide	T-type Ca^{2+} channel inhibition 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
Felbamate	NMDA receptor antagonist and increase 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	Na^{+} channel inhibition	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 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
Levetiracetam	Synaptic vesicle release modulation	Partial	Neurological: sedation, fatigue, incoordination, psychosis Non-Neurological: anemia, leucopenia	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	Yes

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Table 3. Important characteristics of antiepileptic medications[1,2,38-40] (Continued)

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Oxcarbazepine	Na^+ channel inhibition	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	Potentiate 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	Na^+ and Ca^{2+} channel inhibition	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, confusion Non-Neurological: gingival hyperplasia, peripheral neuropathy, lymphadeonopathy, 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
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
Rufinamide	Na^+ channel inhibition	Lennox-Gastaut	Neurological: headache, dizziness, fatigue, somnolence, convulsion, diplopia, tremor, nystagmus Non-Neurological: nausea, vomiting, nasopharyngitis, blurred vision	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No

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Table 3. Important characteristics of antiepileptic medications[1,2,38-40] (Continued)

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Tiagabine	Increase 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	Na^+ channel inhibition	Partial Tonic-Clonic Lennox-Gastaut	Neurological: psychomotor slowing, sedation, speech problems, fatigue, paresthesias Non-Neurological: kidney stones, glaucoma, weight loss, hypohydrosis	Enzyme Substrate: None Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Valproic Acid	T-type Ca++ channel inhibition in thalamus increase 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, inhibits 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
Zonisamide	Na^+ channel inhibition	Partial	Neurological: sedation, dizziness, confusion, headache, psychosis Non-Neurological: Anorexia, renal stones, hypohydrosis	Enzyme Substrate: CYP 2C19, 3A4 Enzyme Inducer: None Enzyme Inhibitor: None	Yes

* denotes skin rash risk (Steven's Johnson Syndrome and Toxic Epidermal Necrolysis) related to Human Leukocyte Antigen (HLA)-phenotype.
Legend: Ca^{2+} = calcium ion, CYP = cytochrome P enzyme, GABA = gamma amino butyric acid, Na^+ = sodium ion, NMDA= N-methyl D-aspartic acid.

Over the last decade there have been newer antiepileptic drugs that have been approved for use by the Food and Drug Administration (FDA) in the treatment of epilepsy. While most newer antiepileptic drugs are approved as second line agents for the treatment of refractory seizures;

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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).[41] 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°C.[42,43] A drug is considered to be highly permeable when the extent of absorption (bioavailability) is ≥ 90 percent.[42,43] 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.[44] The BCS classification for older and newer epilepsy medications is given in Table 4.[42,45-58]

Table 4. Biopharmaceutics Classification System of antiepileptic medications.[42,45-58]

AED	Solubility	Permeability	BCS class
Older Antiepileptic Medications			
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
Newer Antiepileptic Medications			
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

The comparative benefits and harms of older versus newer antiepileptic drugs have been assessed in numerous randomized controlled trials (RCT) 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 as compared to older antiepileptics.[7,8]

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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.[9,10] 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.[11] The Food and Drug Administration (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] 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.[12,59-62] 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".[62] 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 (AUC) 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.[12,63]

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.

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Objective

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.

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The Key Questions

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 drivers license, and loss of employment?

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?

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?

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))?

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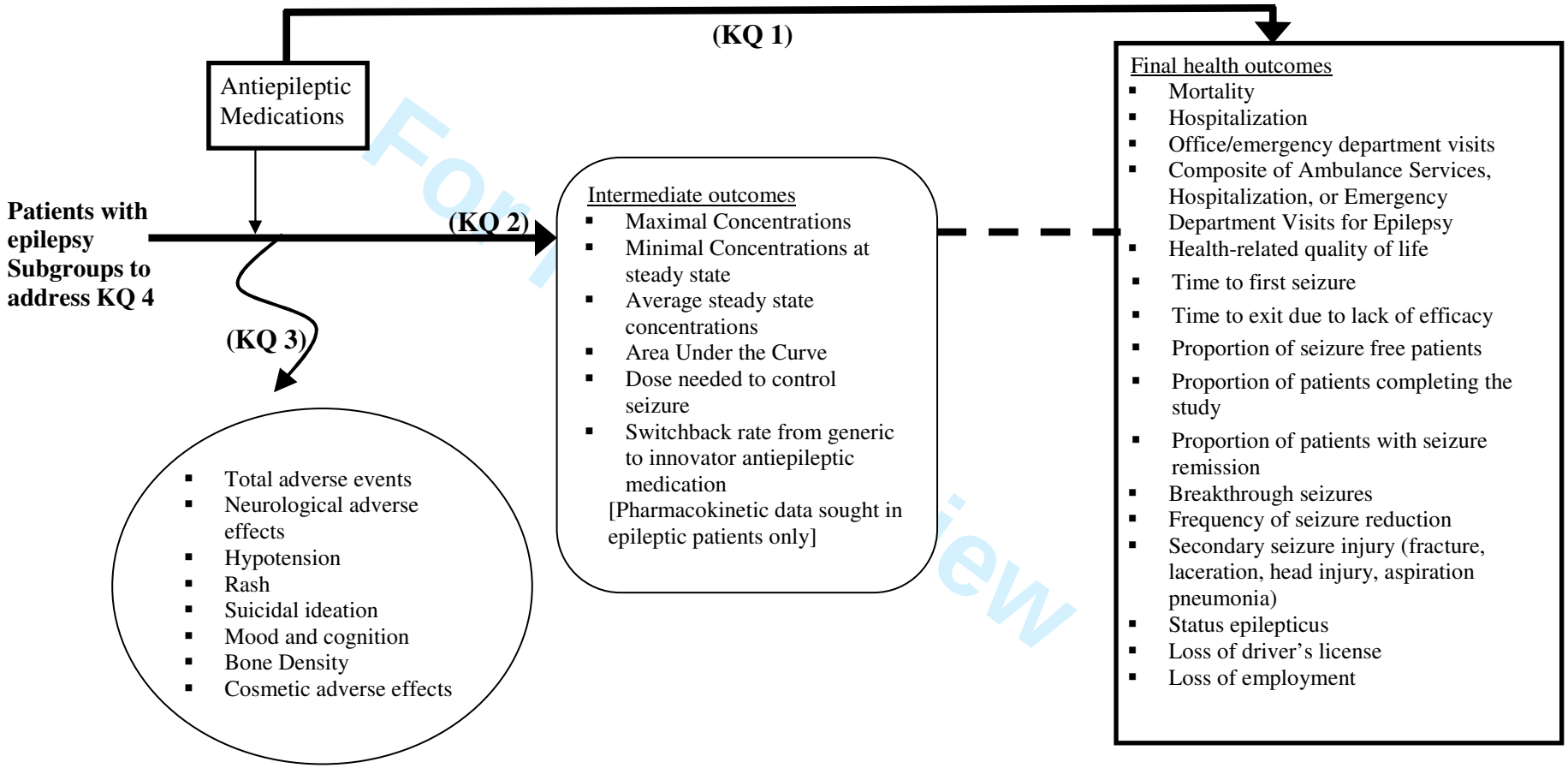
Analytic Framework

Figure 1. Analytic Framework for the Evaluation of Effectiveness and Safety of Antiepileptic Medication in Patients with Epilepsy



Legend: KQ=Key Question

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Chapter 2. 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 reviewing the public commentary, the key questions were finalized by EPC and approved by AHRQ.

Literature Search Strategy

Two independent investigators conducted systematic literature searches of MEDLINE (from 1950 to the present), Web of Science from the earliest possible date through the present, and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews from the earliest possible date through the present. Separate search strategy was employed for each evaluation. The search for the older versus newer antiepileptic medication evaluation was used to identify direct comparative trials and studies explicitly evaluating older versus newer antiepileptic medications and providing data on intermediate or final health outcomes of interest. For the search, we utilized Cochrane's Highly Sensitive Search Strategy (Sensitivity Maximizing Version 2008) to limit to randomized controlled trials and the Scottish Intercollegiate Guidelines Network Observational Study Search Filter to limit 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 healthcare utilization a generic to innovator, innovator to generic, or generic to generic). We did not limit the search to "A" rated version 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, ethosuximimide, primidone) to newer antiepileptic medications or compared innovator antiepileptic medications to generic antiepileptic medications (or in the case of healthcare utilization compared generic to innovator, innovator to generic, or generic to generic version of the same medication); (2) are conducted in patients with epilepsy; and (3) reported data on pre-specified 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 abstraction 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

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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 follow-up), 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], co-morbidities, and use of concurrent standard medical therapies. Intermediate, final health and harms outcomes were collected where applicable. Authors were contacted for clarification or to provide additional data, where applicable.

We differentiated the outcomes based on the following scheme:

- ➢ Outcome for older and newer antiepileptic evaluation
- • Outcome for innovator and generic antiepileptic evaluation
- ❖ Common outcome for both older/newer and innovator/generic antiepileptic evaluations

The outcomes for the Compartive Effectiveness Review are as follows:

Comparative pharmacokinetics in those receiving therapy for epilepsy:

- Maximum concentration (C_{max})
- Minimum concentration (C_{min})
- Average Steady-state concentration (C_{ss})
- Area under the curve (AUC)
- Time to maximum concentration (T_{max})

Comparative Efficacy:

- ➢ Time to first seizure
- ➢ Time to study exit due to lack of efficacy
- ➢ Proportion of seizure free patients
- ➢ Proportion of patients completing the study
- ➢ Proportion of patients achieving seizure remission
- ❖ Seizure frequency
- • Incidence of breakthrough seizure
- • Incidence of status epilepticus
- • Dose needed to control seizures after switching from an innovator antiepileptic to its generic counterpart
- • Secondary seizure injury (fracture, laceration, head trauma, aspiration pneumonia)

General Measures of Comparative Tolerance and Harms:

- ➢ Proportion of patients withdrawn due to adverse effects
- ➢ Cosmetic adverse events
- ❖ Incidence of adverse events
- ❖ Incidence of individual adverse events
- ❖ Incidence of adverse events resulting in therapy withdrawal
- ❖ Incidence of adverse events not resulting in therapy withdrawal
- ❖ Skin rash
- ❖ Neurological adverse events
- ❖ Suicidal ideation
- ❖ Health-related quality-of-life
- ❖ Mortality

- Medical service utilization
  - Office/emergency department visits
  - Hospitalizations
- Hypotension
- Harms specific to that particular antiepileptic medication
- Hospital stay duration
- Loss of drivers license
- Loss of employment
- Rates of switching from generic back to innovator medication for any reason

Validity Assessment

Validity assessment was performed using the recommendations in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[16] Each study was assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of subjects, blinding of outcome assessors, intent-to-treat analysis, description of participant withdrawals, and potential conflict of interest. Additionally, randomized controlled trials (RCTs) were assessed for randomization technique and allocation concealment. Observational studies were assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies were then given an overall score of good, fair, or poor (Table 5). 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 criteria as a "fair" observational study. Both study design and quality rating were considered when interpreting the methodological quality of a study.

Table 5. 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 to its corresponding generic medication separately as part of a

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direct comparative study. Single-arm observational studies, case series, or case reports were termed descriptive studies and were only described qualitatively. Comparative trials or studies could be qualitatively described or quantitatively synthesized.

Quantitative Analysis

Controlled clinical trials were those where therapy was compared against a comparator and the investigators had control over the determination of therapy. These controlled trials could be crossover or parallel trials but may or may not be randomized. Controlled observational studies were cohort or case control studies, had to have a control group, and the investigators did not determine who would receive which therapy. 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 (WMD) 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 AEDs together for continuous endpoints, we used an inverse variance weighting approach as standardized mean difference (SMD) (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 was not reported, we calculated the difference between the mean baseline and mean follow-up 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: $SD_{baseline\text{-}followup}=sqrt(SD^2_{baseline} + SD^2_{followup} - 2*(\text{correlation coefficient})SD_{baseline}*SD_{followup})$. A correlation coefficient of 0.5 proposed by Follman and colleagues was used.[18] 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 confidence intervals. 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 addressed using the I^2 statistic which assesses the degree of inconsistency not due to chance across studies and ranges from 0-100 percent with values of >50 percent representing important statistical heterogeneity, respectively. Cochrane Q statistics were provided for completeness sake. 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, data was available as incidence rate ratios in the individual observational studies, were described but were 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

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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 to 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.[64] 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 6). 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 6. 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

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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 an 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 applicability are identified in Table 7; those factors that were extracted into evidence tables for every study. 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 7. 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

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Chapter 3. 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 5454 unique citations and another 7 citations were identified from other sources. Five thousand two hundred and fourteen articles were excluded during the title and abstract review and 186 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 63 articles were found to match our inclusion criteria.

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 313 unique citations and another 9 citations were identified from other sources. Two hundred and forty articles were excluded during the title and abstract review and eleven 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 seventy one articles were found to match our inclusion criteria.

General Overview of Results

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Table 8 delineates the results of the CER with a rating of the strength and applicability of evidence. The subchapters that follow provide much more detail into the analyses conducted and the nuances necessary to understand the analyses and how they apply to healthcare decisionmakers, clinicians, and patients

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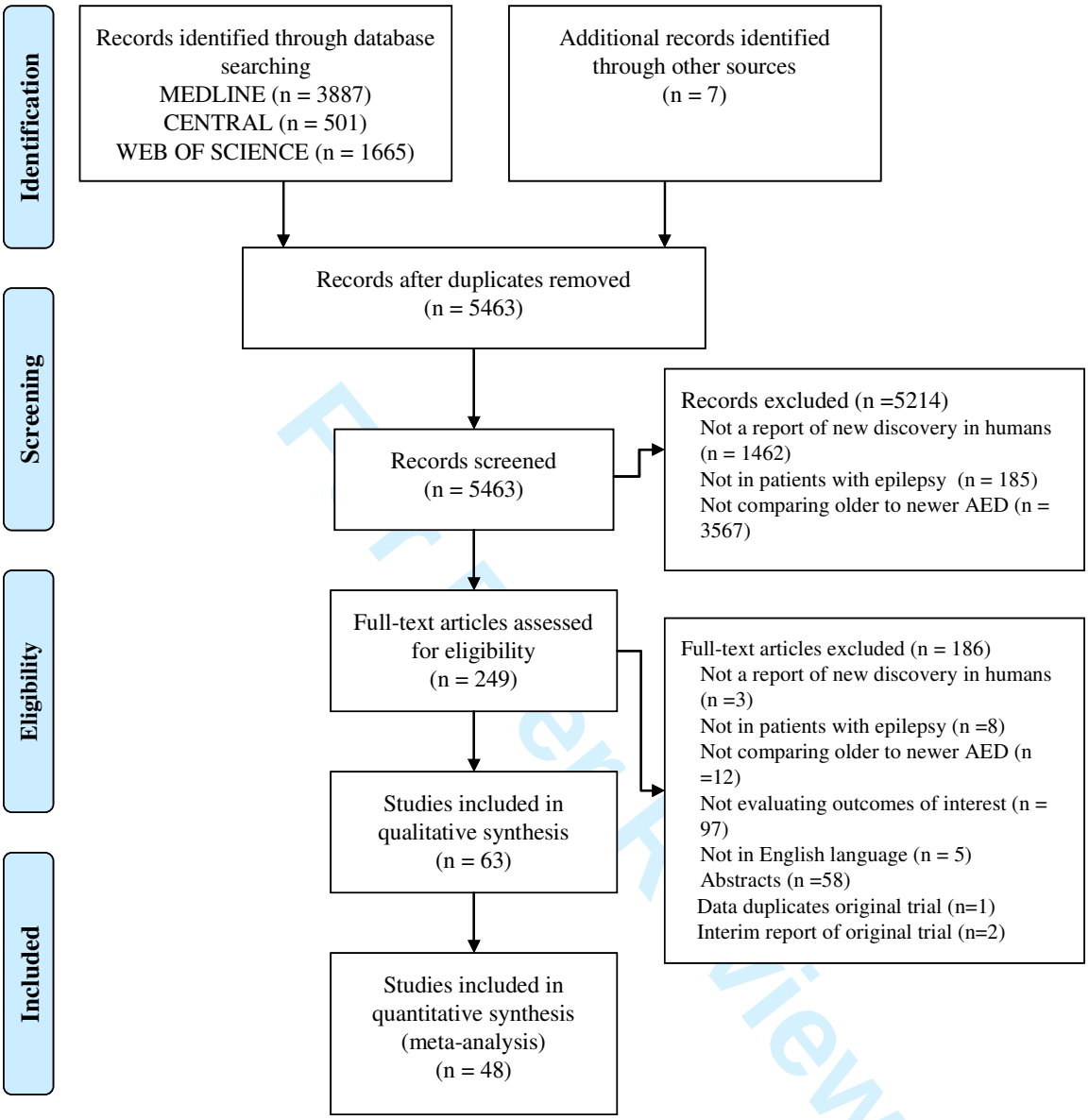
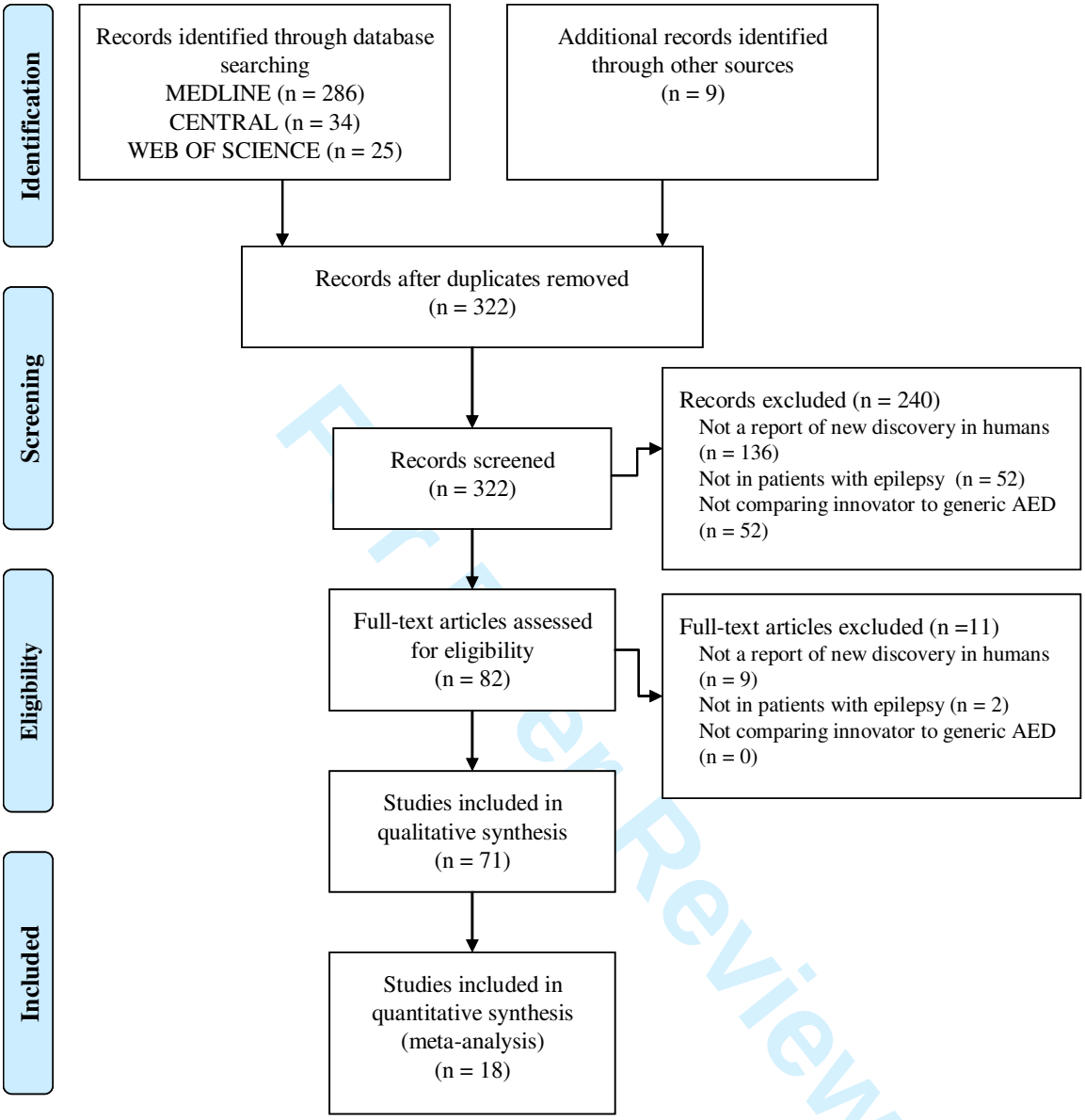
Figure 2. PRISMA flow diagram of citations identified and evaluated in the older versus newer search.



Legend: 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.



Legend: 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 drivers license, and loss of employment?

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Key Points

- There was no difference observed in the risk of mortality when newer antiepileptic medications were compared to 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 being seizure free for either 12 or 24 months was significantly lower for newer antiepileptic agents versus carbamazepine. In individual newer antiepileptic medication versus carbamazepine analyses, the risk of being seizure free was significantly reduced by gabapentin or oxcarbazepine versus carbamazepine at 12 and 24 months and for topiramate versus carbamazepine at 12 months. No differences in 12 or 24 month seizure freedom were seen for newer antiepleptic medications versus valproic acid although this was based on a single controlled clinical trial. No trials were available evaluating newer antiepileptic medications versus controlled/sustained release carbamazepine or phenytoin.
- 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.
- Four instruments were used to assess for health related quality of life in the newer versus older antiepileptic medication evaluation and the instruments have differences in the importance of subscales or which areas are evaluated.
    - In a direct comparative trial, gabapentin, lamotrigine, oxcarbazepine and topiramate similarly impacted health rated quality of life versus carbamazepine. Tiagibine 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 a direct comparative trial, lamotrigine had a greater positive impact on health rated quality of life versus phenytoin. Tiagibine 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 as 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 1 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 where 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).[20-29,65-80,80-101]

Twenty-four reports were funded by the pharmaceutical industry[22,23,26,28,29,67,69,70,75,76,78-81,83-86,88,90-93,95,101] five reports were funded by government or foundation funding[24,26,98-100] and funding was not reported for 19 reports.[20,21,25,27,65,66,68,71,73,74,77,78,82,87,94,96,102]

Thirteen reports were conducted in the United States,[23,26,29,68,69,78,80,81,83,84,94,98,101] two reports were conducted in China,[100,102] two reports were conducted in Finland,[65,71] one report was conducted in Germany,[90] three reports were conducted in the United Kingdom,[20,24,96] three reports were conducted in Italy,[73,87,99] one report was conducted in Korea,[93] one report was conducted in the Netherlands,[77] eight multinational report conducted in Europe[22,28,67,70,79,82,92,95] one multinational report were conducted in Asia, Europe, North America and South Ameriaca,[97] one multinational report was conduced in Australia and Europe,[25] one multinational report was

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conducted Australia, Europe and South Africa,[21] one multinational report was conducted in Australia, Europe, South Africa, the United States and South America[86] and one multinational report was conducted in Europe and South Africa[91] and three reports did report any country.[66,85,88]

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 fifteen trials that reported it.[20,26,27,29,67,69,73-75,77,82,84,91,93,95,97] Ethnicity was reported by ten trials,[26,27,29,69,75,80,84,91,97,98] the percentage of Caucasian participants ranged from 47 to 92.1 in the ten trials that reported the percentage of Caucasian particiapants,[26,27,29,69,75,80,84,91,97,98] the percentage of Black patients ranged from 3 to 27.6 in the ten trials that reported the percentage of Black particiapants,[26,27,29,69,75,80,84,91,97,98] the percentage of Asian participants ranged from 0 to 11 in the four trials that reported the percentage of Asian participants,[29,80,84,91] the percentage of Hispanic participants ranged from 0 to 8 in the four trials that reported the percentage of Hispanic participants[26,80,84,97] and the percentage of participants with an other ethnicity ranged from 1.5 to 34 in the seven trials that reported participants with an other ethnicity.[26,27,29,69,75,91,98]

Epilepsy history was only reported by 23 trials,[21,23-25,27,29,68,69,74-77,80-82,84,87,90,92,93,95,97,98] and only thirty trials reported seizure type.[22-24,26-29,65,67,69-71,73-76,80-82,84,86-88,90-92,94,97,98,102]

Fourteen trials reported the number of patients that were untreated with antiepileptic agents prior to enrollment.[22,24,26-28,70,71,73,82,84,86,92,94,97]Prior or concurrent use of carbamazepine, phenytoin, valproic acid, phenobarbital, gabapentin, lorazepam or other therapy was reported in ten trials.[21,23,24,65,80,81,84,94,97,103].

Fifteen observational reports (n=2469) evaluated older versus newer antiepileptic medication comparisons and were eligible for inclusion (Appendix F Table 5).[72,72,89,103-114] Three reports were funded by pharmaceutical companies,[104,105,111] five reports were funded by government or foundations and[72,110,113,114] seven reports did not report the role of funding.[89,103,106-109,112] Three reports were conducted in the United States,[104,105,110,111] one report was conducted in Denmark,[72] one report was conducted in Italy,[106] one report was conducted in Scotland,[107] one report was conducted in Hungary,[103] one report was conducted in Poland,[89] one report was conducted in Turkey,[108] two reports were conducted in Korea,[109,112] one report was conducted in China,[113] and one report was conducted in Brazil.[114] (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[108,110] and the percentage of Caucasian participants ranged from 61 to 76 in the study that reported the percentage of Caucasian participants (Appendix F Table 7).[110] Epilepsy history was reported in two observational studies.[107,110] and only three of the studies reported the seizure type (Appendix F Table 8).[89,106,108]

Four studies reported the number of patients that were untreated with antiepileptic agents prior to enrollment.[72,106,107,109] 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).[89,103,108,110]

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

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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).[115-131] Two phenytoin trials that appeared otherwise eligible for our analyses were excluded upon detailed evaluation.[132,133] 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 to each other and the generic versions were not of the same salt form (Appendix C Table 1).[132,133]

Only one of the seventeen reports specified that they were limited to "A" rated versions of the generic medications.[120] Four were funded by the pharmaceutical industry,[115,118,120,127] and funding was not known for eight studies.[119,121,123,124,126,128-130] Multiple studies were included in one of the reports.[120] Four reports were conducted in the United States,[117,120,129,131] five were conducted in the United Kingdom,[118,119,126,127,130] two in Finland[115,121] and one each in Germany, Thailand, Netherlands, Denmark, Sweden and India (Appendix F Table 1).[116,122-125,128]

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 and 100 percent. Body weight ranged between 35.8 and 59.6 kg within the six studies that reported it.[116,118,122,128,130,131] 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)[118,123,128] and only six of the studies reported the seizure type (Appendix F Table 3).[118,121-124,127]

Patients in these trials had been previously treated with antiepileptic medications. Prior or concurrent use of carbamazepine, phenytoin, or valproic acid was reported in eleven out of sixteen trials (Appendix F Table 4).[115-118,120-124,126,129] The use of combination therapy was reported in eight[115-117,120,122-124,129] of the seventeen 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).[12,30-36,134] Only three of the eight reports specified that they were limited to "A" rated versions of the generic medications.[33-35] All of the reports were funded by the pharmaceutical industry.[12,30-36,134] Multiple studies were included in three of the reports.[12,30,134] Five reports were conducted in the United States[30,33-36] and the other four in Canada appendix table 1 (Appendix F Table 1).[12,31,32,134]

Baseline characteristics are elucidated in appendix tables 2 and 3 (Appendix F Table 2-3). 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).[33-35]

Patients in observational studies had been previously treated with antiepileptic medications (Appendix F Table 4).[12,30-36,134] Prior or concurrent use of carbamazepine, phenytoin, or valproic acid was not reported. The use of combination therapy was reported in four[12,31,32,134] of the eight trials and the percent of patients on combination treatment ranged between 52 and 94 percent.

Twenty-nine descriptive reports (n=2190) 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 7 were other designs where patients were described but not compared to a control group.

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Four of the reports were funded by the pharmaceutical industry,[135-138] two of the reports were funded by the National Institute of Health,[139,140] and funding for all the other reports was not specified.[124,141-162] Multiple descriptive studies were included in ten of the reports.[135-137,139,141-146] Fifteen reports were conducted in the United States,[136,137,139,140,142,144-150,156,159,160] two reports were conducted in the United Kingdom,[135,141] two reports were conducted in Poland,[143,157] two reports were conducted in Germany[154,158] and one report each was conducted in Switzerland, Italy, Canada and Denmark.[124,138,151,153] Study location for four other reports was unknown (Appendix F Table 1).[152,155,161,162]

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 and 100 percent. Body weight and ethnicity were not reported in these reports (Appendix F Table 2). Epilepsy history was only reported by five studies.[146,148-150,159] Epilepsy duration ranged from 1 to 16 years.[146,150,159] Four studies reported chronic onset of epilepsy which was either at birth or 1 year of age.[148-150,159] 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).[124,137,141,144,147-149,151,157,159,161,162]

Patients in fourteen studies had been previously treated with antiepileptic medications (Table 4).[124,144,146-153,157-159,161] Prior or concurrent use of carbamazepine, phenytoin, or valproic acid was reported in eight studies.[124,147-151,153,161] The use of combination therapy was reported in twelve of these trials[124,144,146,148-153,157-159] 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. However, the descriptive studies suggest a general anxiety amongst a sizeable number of neurologists and patients with epilepsy over automatic generic substitution of antiepileptic medications.

Outcome Evaluations

Mortality

Older versus Newer Antiepileptic Drug Evaluation

Carbamazepine versus Newer

Six randomized controlled trials reported the number of patients that died when receiving a newer antiepileptic compared to carbamazepine and all 6 were amenable for pooling.[21-26]

Two randomized controlled trials reported the number of patients that died when gabapentin was compared to carbamazepine and both were amenable for pooling.[24,26] The risk of death was nonsignificantly decreased by 8 percent when gabapentin was compared to carbamazepine [RR 0.92 (0.57 to 1.48)] (Appendix J Figure 1).

Five randomized controlled trials reported the number of patients that died when lamotrigine was compared to carbamazepine and all five were amenable for pooling.[21,23-26] The risk of death was nonsignificantly decreased by 37 percent when lamotrigine was compared to 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 that died when oxcarbazepine was compared to carbamazepine.[24] The risk of death was nonsignificantly

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decreased by 50 percent when oxcarbazepine was compared to carbamazepine [RR 0.50 (0.19 to 1.27)] (Appendix J Figure 1).

One randomized controlled trial reported the number of patients that died when topiramate was compared to carbamazepine.[24] The risk of death was nonsignificantly decreased by 6 percent when topiramate was compared to carbamazepine [RR 0.94 (0.50 to 1.78)] (Appendix J Figure 1).

One randomized controlled trial reported the number of patients that died when vigabatrin was compared to carbamazepine.[22] The risk of death was nonsignificantly increased by 2.0-fold when vigabatrin was compared to carbamazepine [RR 2.01 (0.26 to 15.27)] (Appendix J Figure 1).

Six randomized controlled trials reported the number of patients that died when either gabapentin, lamotrigine, oxcarbazepine or topiramate was compared to carbamazepine and all six were amenable for pooling.[21-26] The risk of death was nonsignificantly decreased by 25 percent when all newer antiepileptics were compared to 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 to phenytoin and all three were amenable for pooling.[27,29]

One randomized controlled trial reported the number of patients who died when lamotrigine was compared to phenytoin.[28] The risk of death was nonsignificantly decreased by 78 percent when lamotrigine was compared to 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 to phenytoin.[27] The risk of death was nonsignificantly decreased by 80 percent when oxcarbazepine was compared to 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 to phenytoin.[29] The risk of death was nonsignificantly decreased by 4 percent when topiramate was compared to 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 were compared to phenytoin and all three were amenable for pooling.[27,28] The risk of death was nonsignificantly decreased by 70 percent when the newer agents were compared to 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 to valproic acid and all three were amenable for pooling.[20,23,24]

Two randomized controlled trials reported the number of patients who died when lamotrigine was compared to valproic acid and both were amenable for pooling.[23,24] The risk of death was nonsignificantly increased by 6 percent when lamotrigine was compared to valproic acid [RR 1.06 (0.30 to 3.76)] (Appendix J Figure 3).

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One randomized controlled trial reported the number of patients who died when topiramate was compared to valproic acid.[24] The risk of death was nonsignificantly decreased by 25 percent when topiramate was compared to valproic acid [RR 0.75 (0.19 to 2.95)] (Appendix J Figure 3).

One randomized controlled trial reported the number of patients that died when vigabatrin was compared to valproic acid.[21] The risk of death was nonsignificantly decreased by 1 percent when vigabatrin was compared to 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 to valproic acid and all three were amenable for pooling.[21,23,24] The risk of death was nonsignificantly decreased by 6 percent when newer agents were compared to 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 F Table 12).[12,30-32] None of the four reports specified that they were limited to "A" rated versions of the generic medications. All of the reports were funded by the pharmaceutical industry.[12,30-32] Multiple studies were included in two of the reports.[12,30] One report was conducted in the United States[30] and the other three in Canada (Appendix F Table 12).[12,31,32]

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 and 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).[12,30-32] Prior or concurrent use of carbamazepine, phenytoin, or valproic

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acid was not well reported. The use of combination therapy was reported in three[12,31,32] of the four trials and ranged between 70 and 94 percent.

No controlled clinical trials and three controlled observational reports (n=17424) 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.[33-35] 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 tables 2 and 3 (Appendix F Table 2, Appendix F Table 3). The average age ranged between 35.6 and 44 years and the percentage of male participants ranged from 43.9 and 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[12,30,32] on office or emergency room visits. One was conducted in United States and the other three studies were conducted in Canada. Two of the studies were supported by GlaxoSmithKline[12,30] and the other two studies were supported by Ortho-McNeil-Janssen.[31,32] 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.[30] 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 outpatients 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.[12] 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

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dispensations, the dispensation length was set to 28 days. Outpatient visits were more frequent during the generic period compared to 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.[31] 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.[32] 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 incidence rate ratios (IRR). 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[12,30-32] on hospitalizations. One study[30] was conducted in United States and the other three studies were conducted in Canada. Two of the studies were supported by GlaxoSmithKline[12,30] and the other two studies were supported by Ortho-McNeil-Janssen.[31,32] 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 2 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.[30] 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)

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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.[12] 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.[31] 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 incidence rate ratios (IRR). 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.[32] 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 innovatored versus generic use of topiramate using incidence rate ratios (IRR). 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 to 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

<u>Innovator versus Generic Antiepileptic Drug Evaluation</u>

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[12,30,32,163] on office or emergency room visits. One study[30] was conducted in United States and the other three studies were conducted in Canada. Two of the studies were supported by GlaxoSmithKline[12,30] and the other two studies were supported by Ortho-McNeil-Janssen.[31,32] 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

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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.[30] 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 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 innovatored versus generic use of lamotrigine,[12] 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 to 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 innovatored topiramate only, single-generic topiramate use, and multiple-generic topiramate use.[31] Incidence rates of length of hospital stay was calculated and compared between periods of innovatored 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 incidence rate ratios (IRR). Longer mean hospital lengths of stay were observed for multiple-generic period and for single-generic period than for innovatored 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.[32] 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 innovatored versus generic use of topiramate using incidence rate ratios (IRR). The days of drug supplied were harmonized to 28 days to enable incidence rate comparisons. Longer average length of hospital stays were observed during generic period compared to innovator period (2.4 [innovator] versus 3.1 [generic] days per person per year; adjusted IRR 1.21 (1.15 to 1.28)).

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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.[33-35] 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[33,34] while the last was supported by the pharmacy benefit managing company Express Scripts, Inc.[35]

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.[33] 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 more likely to have undergone a switch from one "A" rated antiepileptic medication to another "A" rated version of the medication in the base case analysis [OR 1.81 (1.25, 2.63), 11.3 percent versus 6.5 percent], the analysis excluding patients with a concurrent change in dosage [OR 2.01 (1.19, 3.40), 9.7 percent versus 5.1 percent], and the analysis excluding patients with Medicaid coverage [OR 1.86 (1.26, 2.73), 11.3 percent versus 6.4 percent].

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.[34] 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 were different. The cases were more likely to have undergone a switch from one "A" rated antiepileptic medication to another "A" rated version of the medication in the base case analysis [OR 1.84 (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 follow-up time since January 1, 2006.[35] The

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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 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 was 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 1286. Upon re-analysis, the adjusted odds ratio of acute epilepsy exacerbations increased to 1.14 (0.99–1.31).

Health-Related Quality-of-Life

Older versus Newer Antiepileptic Drug Evaluation

Four instruments, Quality of Life in Epilepsy-89(QOLIE-89), Side Effect and Life Satisfaction Inventory (SEALS Inventory), Newly Diagnosed Epilepsy Quality of Life (NEWQOL) and European Descriptive Health Related Quality of Life States (EQ-5D) were employed to evaluate health related quality of life (HRQoL) when newer antiepileptic drugs were compared to 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, 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 5 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 and 81 of the items comprise 8 multi-item subscales that measure anxiety, depression, social activities, symptoms, locus of control/mastery, neuropsychological problems, social stigma, worry and work. The remaining items are single-item subscales 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 5 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.

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Carbamazepine versus Newer

Three randomized controlled trials reported information regarding HRQoL when newer antiepileptic drugs were compared to carbamazepine using the QOLIE-89, SEALS Inventory and NEWQOL and EQ-5D instruments (Appendix G Table 23).[7,79,81]

One trial reported information regarding HRQoL using the QOLIE-89 instrument when patients were receiving carbamzaepine or tiagabine in addition to baseline phenytoin therapy.[81] 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.

One trial reported information regarding HRQoL versus baseline using the SEALS Inventory when patients received lamotrigine or carbamazepine.[79] The 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).

One trial reported information regarding HRQol using the NEWQOL (Newly Diagnosed Epilepsy Quality of Life) and EQ-5D (Descriptive Health Related Quality of Life States) inventories when newer antiepileptics, gabapentin, lamotrigine, oxcarbazepine and topiramate were compared to carbamazepine.[7] 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 to carbamazepine using the EQ-5D.

Phenytoin versus Newer

Two randomized controlled trials reported information regarding HRQoL when newer antiepileptic drugs were compared to phenytoin using the QOLIE-89 scale the SEALS Inventory instruments (Appendix G Table 23).[28,81]

One trial reported information regarding HRQoL using the QOLIE-89 instrument when patients were receiving phenytoin or tiagabine in addition to baseline carbamazepine therapy.[81] 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 to phenytoin.[28] This trial reported the mean total SEALS Inventory scores by visit and the estimated difference between treatments in the overall change

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from baseline. The estimated difference between treatments in the overall change from baseline was 4.0 points greater for the lamotrigine group compared to the phenytoin group (p=0.02).

Valproic Acid versus Newer

Three randomized controlled trials reported information regarding HRQoL when newer antiepileptic drugs were compared to valproic acid using the QOLIE-89, NEWQOL and EQ-5D instruments (Appendix G Table 23).[8]

One trial reported information regarding HRQol using the NEWQOL and EQ-5D inventories when the newer antiepileptic drugs lamotrigine and topiramate were compared to valproic acid.[7] 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 to 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 to valproic acid using results from the EQ-5D.

One trial reported information regarding HRQoL using the QOLIE-89 inventory when topiramate was compared to valproic acid.[85] 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 to valproic acid [WMD -2 (-1 to -3)].

One trial reported information regarding HRQoL using the QOLIE-89 inventory when lamotrigine was compared to valproic acid.[83] The trial reported the likelihood that patients would have an improvement in HRQoL when lamotrigine was compared to 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 to 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.

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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 to carbamazepine[22,24,25,70,86,88] and four trials were amenable for pooling.[22,24,25,70]

One randomized controlled trial reported the time to first seizure when gabapentin was compared to carbamazepine.[24] The time to first seizure was significantly increased when gabapentin was compared to 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 to carbamazepine and all three were amenable for pooling.[24,25,70] The time to first seizure was nonsignificantly decreased when lamotrigine was compared to 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 to carbamazepine.[24] The time to first seizure was nonsignificantly increased when oxcarbazepine was compared to 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 to carbamazepine.[24] The time to first seizure was nonsignificantly increased when topiramate was compared to 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 to carbamazepine.[22] The time to first seizure was significantly increased when vigabatrin was compared to 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 to carbamazepine and all four trials were amenable for pooling.[24,25,70,76] The time to first seizure was nonsignificantly increased when either newer agent was compared to 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 non-significant difference in the time to first seizure when topiramate was compared to carbamazepine was reported in these two trials (Appendix G Table 19).[86,88]

Phenytoin versus Newer

Two randomized controlled trials reported time to first seizure when newer antiepileptics were compared to phenytoin and both were amenable for pooling.[28,29]

One randomized controlled trial reported time to first seizure when lamotrigine was compared to phenytoin.[28] The time to first seizure was nonsignificantly increased when lamotrigine was compared to 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.

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One randomized controlled trial reported time to first seizure when topiramate was compared to phenytoin.[29] The time to first seizure was nonsignificantly increased when topiramate was compared to 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 to phenytoin and both were amenable for pooling.[28,29] Time to first seizure was significantly increased when either newer agent was compared to 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 to valproic acid.[24,86,88]

One randomized controlled trial reported time to first seizure when lamotrigine was compared to valproic acid.[24] The time to first seizure was significantly decreased when lamotrigine was compared to 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 to valproic acid.[24] The time to first seizure was nonsignificantly decreased when topiramate was compared to 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 to valproic acid.[24] The time to first seizure was nonsignificantly decreased when either newer agent was compared to 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 non-significant difference in the time to first seizure was reported when topiramate was compared to valproic acid in these two trials.[86,88]

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[117,118,120,122,123,128,131] (Appendix J Figure 7).

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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.[117,118,120,122,123] Only one of the trials[120] 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 phenytoin[128] 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 acid[131] 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.[117,118,120,122,123,128,131] 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 6 trials comparing innovator and generic versions of carbamazepine and phenytoin.[117,118,120,122,123,128] 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.[120] 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 to carbamazepine.[67] Seizure frequency was nonsignificantly decreased from baseline when oxcarbazepine was compared to 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 to carbamzepine.[93] 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 to phenytoin.[27,75] 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 to valproic acid.[74] 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.[117,120,131]

Two trials reported data on seizure frequency in patients receiving innovator carbamazepine versus a generic version and were both amenable to pooling.[117,120] Only one of the trials utilized a discernable Food and Drug Administration (FDA) "A" rated generic carbamazepine product.[120] 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.[131] 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.[117,120,131] (Appendix J Figure 8) The seizure frequency is nonsignificantly higher in the generic antiepileptic medication group versus the innovator group [SMD 0.03 (-0.08 to 0.14) seizures over the evaluative period]. No statistical heterogeneity was detected (I^2: 0 percent) but 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.[120] 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].

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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 to carbamazepine.[21-26,65,70,71,76,82,86,88-90,93,106,107,109,111,112]

Sixteen randomized controlled trials reported data on withdrawals for any reason when newer antiepileptics were compared versus carbamazepine[21-26,65,70,71,76,82,86,88-90,93] and 14 were all amenable to pooling.[21-26,70,71,76,82,86,89,90,93]

Three randomized controlled trials reported data on withdrawals for any reason when gabapentin was compared versus carbamazepine and all three were amenable for pooling.[24,26,76] 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.[21,23-26,70,82,90] 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 -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.[24] 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.[24,86,93] 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 were 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.[22,71,89] 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 to carbamazepine.[21-26,70,71,76,82,86,89,90,93] 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).

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Two randomized controlled trials reported data on withdrawals for any reason when the newer antiepileptics gabapentin, lamotrigine and topiramate were compared to 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 21).[65,88]

Two observational studies reported withdrawals for any reason when lamotrigine was compared versus carbamazepine.[107,109] The risk of withdrawal was significantly decreased by 44 percent when lamotrigine was compared versus carbamazepine [RR 0.66 (0.49 to 0.89)] (Appendix J Figure 10). Given the risk difference, [RD -0.11 (-0.33, 0.12)], for every 10 patients treated with lamotrigine, 1 less patient would withdraw compared to 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.[111] 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.[112] 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.[106] 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 risk difference, [RD 0.24 (0.10 to 0.38)], for every five patients treated with vigabatrin, one additional patient would withdraw compared to those treated with carbamazepine.

Five observational studies reported withdrawals for any reason when lamotrigine, levetiracetam or vigabatrin was compared to carbamazepine.[106,107,109,111,112] 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 occurred (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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95]

One randomized controlled trial reported withdrawals for any reason when lamotrigine was compared to sustained release carbamazepine.[95] 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 to controlled release carbamazepine.[91] There was no significant difference in the risk of withdrawal when lamotrigine 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95] The risk of withdrawal was nonsignificantly decreased by 4 percent

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when either newer agent was compared to 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 to phenytoin and all were amenable for pooling.[27,28,75]

One randomized controlled trial reported data on withdrawals for any reason when lamotrigine was compared to phenytoin.[28] 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 to phenytoin and were amenable for pooling.[27,75] 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.[27,75] 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 to valproic acid.[20,23,24,68,74,77,80,84-88,90,96-98,102,107,109]

Seventeen randomized controlled trials reported data on withdrawals for any reason when newer antiepileptics were compared versus valproic acid[20,23,24,68,74,77,80,84-88,90,96-98,102] and sixteen were amenable for pooling.[20,23,24,68,74,77,80,84-87,90,96-98,102]

One randomized controlled trial reported data on withdrawals for any reason when felbamate was compared versus valproic acid.[68] 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.[23,24,80,84,87,90,96-98,102] The risk of withdrawal was nonsignificantly 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.[74] 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.[24,77,85,86] The risk

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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.[20] 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.[20,23,24,68,74,77,80,84-87,90,96-98,102] 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 to 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 21).[88]

Two observational studies reported withdrawals for any reason while patients were receiving newer antiepileptic medications compared to valproic acid and both were amenable for pooling.[107,109]

Two observational studies reported withdrawals for any reason when lamotrigine was compared to valproic acid and were amenable for pooling.[107,109] 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 to ethosuximide.[98] The risk of overall withdrawal was nonsignificantly decreased by 5 percent when lamtrigine 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.[36,116-121,123,125,128,129]

Seven randomized controlled trials reported data on withdrawals for any reason for innovator versus one or more generic versions of carbamazepine[116-121,123] and were all amenable to pooling. Only one trial[120] 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 (Garnett 2005). The

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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[128,129]and one prospective nonrandomized trial.[125] 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 is 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[116-121,123,128,129] and one prospective nonrandomized trial.[125]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.[120] 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 to carbamazepine.[21,22,24-26,67,70,71,86,88,90,106,107,109,112,113]

Eleven randomized controlled trials reported data on withdrawals due to lack of efficacy when newer antiepileptics were compared versus valporic acid.[21,22,24-26,67,70,71,86,88,90] and 10 were amenable for pooling.[21,22,24-26,67,70,71,86,90]

Two randomized controlled trials reported data on withdrawals due to lack of efficacy when gabapentin was compared versus carbamazepine and were amenable for pooling.[24,26] 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 risk difference [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 to those treated with carbamazepine. Since

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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.[21,24-26,70,90] 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 risk difference, [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 to 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.[24,67] 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.[24,86] 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.[22,71] 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 risk difference [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 to 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 either gabapentin, lamotrigine, oxcarbazepine, topiramate or vigabatrin was compared versus carbamazepine and were amenable for pooling.[21,22,24-26,67,70,71,86,90] 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 risk difference [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 to those treated with carbamazepine. No statistical heterogeneity (I^2: 0 percent) or publication bias were 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.[88] 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 to carbamazepine and all five were amenable for pooling.[106,107,109,112,113]

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Two observational studies reported withdrawals due to lack of efficacy when lamotrigine was compared versus carbamazepine and were amenable for pooling.[107,109] 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.[112,113] 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.[106] 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 risk difference, [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 to 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 viagbatrin was compared to carbamazepine.[106,107,109,112,113] 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) and 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 to controlled release carbamazepine.[91] 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 risk difference, [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 to 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.[27,28,75]

One randomized controlled trial reported data on withdrawal due to lack of efficacy when lamotrigine was compared versus phenytoin.[28] 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.[27,75] The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 24 percent when

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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.[27,28,75] 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 to valproic acid.[20,24,74,77,86-88,90,94,96,97,102,107,109,113]

Twelve randomized controlled trials reported data on withdrawals due lack of efficacy when newer antiepileptics were compared versus valproic acid[20,24,74,77,86-88,90,94,96,97,102] and eleven were amenable for pooling.[20,24,74,77,86,87,90,94,96,97,102]

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.[24,87,90,96,97,102] 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.[74] 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.[24,77,86,94] 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.[20] 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.[7,20,74,77,86,87,90,94,96,97,102] 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

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analysis because withdrawals were reported for the whole patient population and not per treatment group (Appendix G Table 19).[88]

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.[107,109]

Two observational studies reported data on withdrawals due to lack of efficacy when lamotrigine was compared versus valproic acid and were amenable for pooling.[107,109] 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.[113] 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.[107,109,113] 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.

<u>Innovator versus Generic Antiepileptic Drug Evaluation</u>

Ten trials (nine randomized controlled trials[116-121,123,128,129] and one prospective nonrandomized trial[125] 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[116-121,123] and they were all suitable for meta-analysis. Only one of the trials utilized a discernable FDA "A" rated generic carbamazepine product.[120] 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[128,129] and one prospective nonrandomized trial[125] 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[116-121,123,128,129] and one prospective nonrandomized trial[125] 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

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[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.[120] 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 to carbamazepine.[7,22]

One randomized controlled trial reported the number of patients who achieved 12 month seizure remission when gabapentin was compared to carbamazepine.[7] The risk of achieving 12 month seizure remission was significantly decreased by 15 percent when gabapentin was compared to carbamazepine [RR 0.85 (0.76 to 0.95)] (Appendix J Figure 22). Given the risk difference [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 to carbamazepine.[7] The risk of achieving 12 month seizure remission was nonsignificantly decreased by 4 percent when lamotrigine was compared to 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 to carbamazepine.[7] The risk of achieving 12 month seizure remission was significantly decreased by 52 percent when oxcarbazepine was compared to carbamazepine [RR 0.48 (0.39 to 0.59)] (Appendix J Figure 22). Given the risk difference [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 to carbamazepine.[7] The risk of achieving 12 month seizure remission was significantly decreased by 10 percent when topiramate was compared to carbamazepine [RR 0.90 (0.81 to 0.99)] (Appendix J Figure 22). Given the risk difference [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 to carbamazepine.[22] The risk of achieving 12 month seizure remission was nonsignificantly decreased by 5 percent when vigabatrin was compared to 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 to carbamazepine and were amenable for pooling.[7,22] The risk of achieving 12 month

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seizure remission was significantly decreased by 19 percent when newer agents were compared to carbamazepine [RR 0.81 (0.67 to 0.99)] (Appendix J Figure 22). Given the risk difference [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 to carbamazepine.[7] This randomized controlled trial reported the number of patients who achieved 24 month seizure remission when gabapentin was compared to carbamazepine.[7] The risk of achieving 24 month seizure remission was significantly decreased by 21 percent when gabapentin was compared to carbamazepine [RR 0.79 (0.66 to 0.94)] (Appendix J Figure 23). Given the risk difference [RD -0.10 (-0.17 to -0.02)], for every 10 patients treated with 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 24 month seizure remission when lamotrigine was compared to carbamazepine.[7] The risk of achieving 24 month seizure remission was nonsignificantly decreased by 8 percent when lamotrigine was compared to carbamazepine [RR 0.92 (0.78 to 1.08)] (Appendix J Figure 23).

One randomized controlled trial reported the number of patients who achieved 24 month seizure remission when oxcarbazepine was compared to carbamazepine.[7] The risk of achieving 24 month seizure remission was significantly decreased by 27 percent when oxcarbazepine was compared to carbamazepine [RR 0.73 (0.58 to 0.91)] (Appendix J Figure 23). Given the risk difference [RD -0.12 (-0.21 to -0.04)], for every nine patients treated with 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 24 month seizure remission when topiramate was compared to carbamazepine.[7] The risk of achieving 24 month seizure remission was significantly decreased by 16 percent when topiramate was compared to carbamazepine [RR 0.84 (0.71 to 0.94)] (Appendix J Figure 23). Given the risk difference [RD -0.07 (-0.15 to -0.001)], for every 15 patients treated with 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 24 month seizure remission when gabapentin, lamotrigine, oxcarbazepine or topiramate was compared to carbamazepine.[7] The risk of achieving 24 month seizure remission was significantly decreased by 18 percent when these newer antiepileptic medications was compared to carbamazepine [RR 0.82 (0.72 to 0.94)] (Appendix J Figure 23). Given the risk difference [RD -0.08 (-0.14 to -0.02)], for every 13 patients treated with 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 to valproic acid.[8]

One randomized controlled trial reported the number of patients who achieved 12 month seizure remission when lamotrigine was compared to valproic acid.[8] The risk of achieving 12 month seizure remission was nonsignificantly decreased by 6 percent when lamotrigine was

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compared to 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 to valproic acid.[8] The risk of achieving 12 month seizure remission remained the same when topiramate was compared to 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 to valproic acid.[8] The risk of achieving 12 month seizure remission was nonsignificantly decreased when either newer agent was compared to 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 to valproic acid.[24]

One randomized controlled trial reported the number of patients who achieved 24 month seizure remission when lamotrigine was compared to valproic acid.[24] The risk of achieving 24 month seizure remission was nonsignificantly decreased by 17 percent when lamotrigine was compared to 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 to valproic acid.[24] The risk of achieving 24 month seizure remission was nonsignificantly decreased by 12 percent when topiramate was compared to 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 to valproic acid.[24] The risk of achieving 24 month seizure remission was nonsignificantly decreased by 15 percent when either newer antiepileptic was compared to valproic acid [RR 0.85 (0.73 to 1.00)] (Appendix J Figure 25).

<u>Innovator versus Generic Antiepileptic Drug Evaluation</u>

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

Seizure Freedom For Study Duration

<u>Older versus Newer Antiepileptic Drug Evaluation</u>

<u>Carbamazepine versus Newer</u>

Twenty studies (15 randomized controlled trials and 5 observational studies) reported data on seizure freedom for duration of study while receiving a newer antiepileptic medications compared to carbamazepine.[21,23,25,26,66,67,70-73,82,86,88,90,92,93,106,107,111,113]

Fifteen randomized controlled trials reported data on seizure freedom for duration of study when newer antiepileptics were compared versus carbamazepine[21,23,25,26,66,67,70,71,73,82,86,88,90,92,93] and were all amenable to pooling.

One randomized controlled trial comparing gabapentin to carbamazepine reported data on seizure freedom for study duration.[26] 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 study duration.[21,23,25,26,70,82,90] The risk of remaining seizure free for duration

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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 study duration.[66,67,92] The risk of remaining seizure free for 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 study duration.[86,88,93] The risk of remaining seizure free for duration of study is nonsignificantly increased by 8 percent when topiramate is used versus carbamazepine [RR 1.08 (0.91 to 1.27)] (Appendix J Figure 26). 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 study duration.[71,73] The risk of remaining seizure free for duration of study is nonsignificantly decreased by 30 percent when vigabatrin is used versus carbamazepine [RR 0.70 (0.49 to 1.01)] (Appendix J Figure 26).

Fifteen randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration.[21,23,25,26,66,67,70,71,73,82,86,88,90,92,93] The risk of remaining seizure free for duration of study is nonsignificantly decreased by 6 percent when newer 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) but a trend towards publication bias was detected (Egger's p=0.054).

Five observational studies reported seizure freedom for study duration while patients were receiving newer antiepileptic medications compared to carbamazepine and all five were amenable for pooling.[72,106,107,111,113]

One observational study comparing lamotrigine to carbamazepine reported data on seizure freedom for study duration.[107] The risk of remaining seizure free for 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).

One observational study comparing levetiracetam to carbamazepine reported data on seizure freedom for study duration.[111] The risk of remaining seizure free for duration of study is nonsignificantly increased by 17 percent when levetiracetam is used versus carbamazepine [RR 1.17 (0.43 to 3.68)] (Appendix J Figure 27).

One observational study comparing oxcarbazepine to carbamazepine reported data on seizure freedom for study duration.[72] The risk of remaining seizure free for 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.[113] The risk of remaining seizure free for 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.[106] The risk of remaining seizure free for 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).

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Five observational studies comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration.[72,106,107,111,113] The risk of remaining seizure free for duration of study is nonsignificantly increased by 5 percent when newer antiepileptic medications are used versus carbamazepine [RR 1.05 (0.80 to 1.38)] (Appendix J Figure 27). A high level of statistical heterogeneity was detected (I^2: 63.6 percent) but publication bias was not detected (Egger's p=0.573).

Two randomized controlled trials reported data on seizure freedom for study duration when newer antiepileptics were compared to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95]

One randomized controlled trial reported data on seizure freedom for study duration when lamotrigine was compared to sustained release carbamazepine.[95] 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).

One randomized controlled trial reported data on seizure freedom for study duration when levetiracetam was compared to controlled release carbamazepine.[91] The risk of remaining seizure free for 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95] The risk of remaining seizure free for study duration was nonsignificantly decreased by 10 percent when either newer agent was compared to 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 to phenytoin[27-29,75] and were all amenable to pooling.

One randomized controlled trial comparing lamotrigine to phenytoin reported data on seizure freedom for study duration.[28] The risk of remaining seizure free for 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.[27,75] The risk of remaining seizure free for 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.[29] The risk of remaining seizure free for 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 risk difference [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.[27-29,75] The risk of remaining seizure free for 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).

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One observational study comparing oxcarbazepine to phenytoin reported data on seizure freedom on study duration.[72] The risk of remaining seizure free for 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 to valproic acid.[23,72,74,80,84,86,88,90,92,94,96,97,102,107,113]

Twelve randomized controlled trials reported data on seizure freedom for study duration when newer antiepileptics were compared versus valproic acid[23,74,80,84,86,88,90,92,94,96,97,102] and were all amenable to pooling.

Seven trials comparing lamotrigine to valproic acid reported data on seizure freedom for study duration.[23,84,90,96,97,102] The risk of remaining seizure free for 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.[74,92] The risk of remaining seizure free for 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.[86,88,94] The risk of remaining seizure free for 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) was detected.

Twelve trials comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration.[23,74,80,84,86,88,90,92,94,96,97,102] The risk of remaining seizure free for study duration is nonsignificantly decreased by 3 percent when newer antiepileptic medications are used versus valproic acid [RR 0.97 (0.87 to 1.08)] (Appendix J Figure 30). 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 to valproic acid and all were amenable for pooling.[72,107,113]

One observational study comparing lamotrigine to valproic acid reported data on seizure freedom for study duration.[107] 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.[72] The risk of remaining seizure free for 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.[113] The risk of remaining seizure free for 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.[72,107,113] 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 (0.72 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 antiepleptic medications versus valproic acid although this was based on a single controlled clinical trial.

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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.[37] 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)] is characteristically similar to that of the meta-analysis by Kesselheim 2010 [OR 1.1 (0.9 to 1.2)].

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. 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

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internal validity, even when sophisticated statistical methods are used to create more comparable control groups. Even under the best of circumstances, you 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, like 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[12,30] but two other trials focusing on topiramate did not.[32,163] 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. 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 versions of the same antiepileptic

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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.[35] 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,[33,34] this study authors controlled for person's risk of epilepsy exacerbation, change in disease severity, drug interactions, poor adherence, and change in patient diagnosis.[35] 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.[33-35] 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.

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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 (Cmax), minimum concentration (Cmin), time to maximum concentration (Tmax), 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 (Css) 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 Css 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.
- Some patients and clinicians are concerned over the switch 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 (Cmax) of patients receiving innovator and their associated generic antiepileptic medications.[118-124,130]

Six randomized controlled trials reported data on Cmax in patients receiving innovator carbamazepine versus generic versions and were all suitable for meta-analysis.[118-123] Only one of the trials utilized a discernable Food and Drug Administration (FDA) “A” rated generic

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carbamazepine product.[120] 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.[124] 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.[130] 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.[118-124,130] 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.[118-123,130] 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.[120] 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.

<u>Minimum Concentration</u>

Six trials (four randomized controlled trials, one prospective before and after non-blinded trial and one prospective nonrandomized trial) reported the minimal blood concentrations (Cmin) of patients receiving innovator and their associated generic antiepileptic medications.[115,118,121-124]

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.[115,118,121-123] 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).

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One prospective nonrandomized trial reported data on Cmin in patients receiving innovator lamotrigine versus a generic version but did not use a discernable FDA "A" rated generic.[124] 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[118,121-123] one prospective before and after nonblinded trial[115] and one prospective nonrandomized trial[124] reported data on Cmax 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 (Css) of patients receiving innovator and their associated generic antiepileptic medications.[116,117,119,121,126,128,129]

Four randomized controlled trials reported data on Css in patients receiving innovator carbamazepine versus generic versions and were all suitable for meta-analysis.[116,117,119,121] None of the trials utilized a discernable FDA "A" rated generic carbamazepine product. The weighted mean difference for Css 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 Css in patients receiving innovator phenytoin versus one or more generic versions of phenytoin.[126,128,129] 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.[116,117,119,121,126,128,129] 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 (Tmax) of patients receiving innovator and their associated generic antiepileptic medications.[119-123]

Five randomized controlled trials reported data on Tmax in patients receiving innovator carbamazepine versus generic versions and were all suitable for meta-analysis.[119-123] Only one of

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the trials utilized a discernable FDA "A" rated generic carbamazepine product.[120] 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 Biopharmaceutics Classification System (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.[120] The weighted mean difference in 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 trial and one prospective nonrandomized trial) reported area under the curve (AUC) of patients receiving innovator and their associated generic antiepileptic medications.[118-124,130]

Six randomized controlled trials reported data on AUC in patients receiving innovator carbamazepine to generic versions and were all suitable for meta-analysis.[116,119-123] Only one of the trials utilized a discernable FDA "A" rated generic carbamazepine product.[120] The weighted mean difference 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.[124] The weighted mean difference 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.[130] The weighted mean difference 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).

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Eight trials, seven randomized controlled trials[116,119-123,130] and one prospective nonrandomized trial[124] reported data on innovator versus generic versions of antiepileptic medication suitable for meta-analysis. The standardized mean difference 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 found 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.[118-123,130] 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) 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.[120] The weighted mean difference 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,[30] 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,[12,31] divalproex was 14 percent,[31] valproic acid was 20.9 percent and 23.9 percent,[31,134] clobazam was 20.5 percent, 44.1 percent and 23 percent,[12,134,163] gabapentin was 30.9 percent and 19.5 percent,[12,31] lamotrigine was 13 percent, 27.5 percent and 12.4 percent[12,31,134], and topiramate was 12.5 percent.[31]

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. As such, there is limited ability to extrapolate to all antiepileptic medications.

The average Cmax, Cmin, Tmax, 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 Css 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 Css with generic versus innovator phenytoin.

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

While 12 percent to 44 percent of patients in four observational studies switched back to innovator antiepileptics after taking a generic version of the medication, the main limitation of this type of data is that the patients and clinicians were not blinded. As such, the switchback from a generic to an innovator antiepileptic medication may or may not be due to real versus perceived differences in efficacy or adverse events. What this data does show is a number of neurologists and patients with epilepsy have concerns about switching between versions of antiepileptic medications.

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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 to 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 to 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 was 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 and 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

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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 carbamezepine 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 to valproic acid and when lamotrigine and topiramate were individually compared to 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 as 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 tiagibine had a similar impact on cognition.

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- Valproic acid has better effects in some measures of cognition versus topiramate but have 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 were 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 as topiramate but inferior effects on mood as lamotrigine.
  - Phenobarbital had inferior effects on mood as compared to 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.
  - Once 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 Table 24-28

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 14, 16-18

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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 to carbamazepine.[21-26,66,67,70,71,73,76,82,86,88-90,93,103,106,107,109,111,112]

Seventeen randomized controlled trials reported data on withdrawals due to adverse events when newer antiepileptics were compared versus carbamazepine and were amenable for pooling.[21-26,66,67,70,71,73,76,82,86,88-90,93]

Three randomized controlled trials reported data on withdrawals due to adverse events when gabapentin was compared versus carbamazepine and were amenable for pooling.[24,26,76] The risk of withdrawal was significantly decreased by 49 percent when topiramate was compared versus carbamazepine [RR 0.51 (0.33 to 0.79)] (Appendix J Figure 37). Given the risk difference, [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 to 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.[21,23-26,70,82,90] 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 risk difference [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 to those treated with carbamazepine. No statistical heterogeneity (I^2: 0 percent) or publication bias (Egger's: p=0.222) were detected.

Three randomized controlled trials reported data on withdrawal due to adverse events when oxcarbazepine was compared versus carbamazepine and were amenable for pooling.[24,66,67] 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.[24,86,88,93] 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 detected (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.[22,71,73,89] 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 eighteen randomized trials reporting data on withdrawals due to adverse events when either gabapentin, lamotrigine, oxcarbazepine, topiramate or vigabatrin

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were compared versus carbamazepine.[21-26,66,67,70,71,73,76,82,86,88-90,93] 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 risk difference [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 to 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 a newer antiepileptic medications compared to carbamazepine and all six were amenable for pooling.[103,106,107,109,111,112]

Two observational studies reported withdrawals due to adverse events when lamotrigine was compared versus carbamazepine and were amenable for pooling.[107,109] 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 risk difference, [RD -0.10 (-0.27 to 0.07)], for every 10 patients treated with lamotrigine, 1 less patient would withdraw compared to those treated with carbamazepine.

One observational study reported withdrawal due to adverse events when levetiracetam was compared versus carbamazepine.[111] 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.[103] 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.[112] 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.[106] The risk of withdrawal was nonsignificantly increased by 8 percent when topiramate 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.[103,106,107,109,111,112] 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 risk difference [RD -0.020 (-0.098 to 0.057)], for every 50 patients treated with a newer agent, 1 less patient would withdraw compared to 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95]

One randomized controlled trial reported withdrawals due to adverse events when lamotrigine was compared to sustained release carbamazepine.[95] The risk of withdrawal was

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nonsignificantly decreased by 45 percent when lamotrigine was compared to 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.[91] The risk of withdrawal was nonsignificantly decreased by 25 percent when lamotrigine was compared to 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95] The risk of withdrawal was significantly decreased by 31 percent when either newer agent was compared to controlled or sustained release carbamazepine [RR 0.69 (0.50 to 0.95)] (Appendix J Figure 39). Given the risk difference [RD -0.0063 (-0.012 to -0.0090], for every 159 patients treated with a newer agent, 1 less patient would withdraw compared to 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 to phenytoin and all three were amenable for pooling.[27,28,75]

One randomized controlled trial reported data on withdrawals due to adverse events when lamotrigine was compared to phenytoin.[28] 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 to phenytoin and were amenable for pooling.[27,75] 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 risk difference [RD -0.095 (-0.14 to -0.05)], for every 11 patients treated with oxcarbazepine 1 less would withdraw due to adverse events compared to 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.[27,28,75] 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 to valproic acid.[21,23,24,74,80,84-88,90,94,96-98,102,107,109]

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.[20,23,24,74,80,84-88,90,94,96-98,102]

Ten randomized controlled trials reported data on withdrawals due to adverse events when lamotrigine was compared versus valproic acid and were amenable for pooling.[23,24,80,84,87,90,96-98,102] 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 risk

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difference [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.[74] 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.[24,85,86,88,94] 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.[20] 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.[20,23,24,74,80,84-88,90,94,96-98,102] 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) or publication bias (Egger's: p=0.840) was detected.

Ethosuximide versus Newer

One randomized controlled trial reported withdrawals due to adverse events while patients were receiving lamotrigine compared to ethosuximide.[98] 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[116-118,120,121,123,128,129] and one prospective nonrandomized trial)[125] 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.[116-121,123] Only one of the trials utilized a discernable Food and Drug Administration (FDA) "A" rated generic carbamazepine product.[120] The risk of withdrawals due to adverse effects 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 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[128,129] and one prospective nonrandomized trial[125] 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

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(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[116-121,123,128,129] and one prospective nonrandomized trial[125] reported on withdrawals due to adverse events for any innovator versus generic versions of antiepileptic medication and the 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.[120] 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 to carbamazepine.[21-26,65,70,71,73,76,82,86,88,92,107,113]

Fifteen randomized controlled trials reported data on headache when newer antiepileptics were compared versus carbamazepine[21-26,65,70,71,73,76,82,86,88,92] and were all amenable to pooling.

Three trials comparing gabapentin to carbamazepine reported data on headache.[24,26,76] 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 seen (Egger's p=0.046).

Seven trials comparing lamotrigine to carbamazepine reported data on headache.[21,23-26,70,82] 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) and no publication bias was detected (Egger's p=0.880).

Three trials comparing oxcarbazepine to carbamazepine reported data on headache.[24,65,92] 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) but test for publication bias could not be performed.

Three trials comparing topiramate to carbamazepine reported data on headache.[24,86,88] 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 risk difference [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) but no publication bias was detected (Egger's p=0.308).

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Three trials comparing vigabatrin to carbamazepine reported data on headache.[22,71,73] 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 (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.[21-26,65,70,71,73,76,82,86,88,92] 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 (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 medications compared to carbamazepine and all five were amenable for pooling.[103,107,111-113]

One observational study comparing lamotrigine to carbamazepine reported data on headache.[107] 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.[113] 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.[107,113] 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95]

One randomized controlled trial reported data on headache when lamotrigine was compared to sustained release carbamazepine.[95] 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 to controlled release carbamazepine.[91] The risk of headache was nonsignificantly decreased by 19 percent when lamotrigine 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95] The risk of headache was nonsignificantly decreased by 17 percent when either newer agent was compared to 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 to phenytoin[27-29,75] and were all amenable to pooling.

One trial comparing lamotrigine to phenytoin reported data on headache.[28] 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).

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Two trials comparing oxcarbazepine to phenytoin reported data on headache.[27,75] 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.[29] 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.[27-29,75] 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 to valproic acid.[23,24,68,69,74,80,84,86-88,92,94,97,98,102,107,113]

Fifteen trials reported data on headache when newer antiepileptics were compared versus valproic acid[23,24,68,69,74,80,84,86-88,92,94,97,98,102] and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on headache.[69] 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.[23,24,80,84,87,97,98,102] 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 (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.[74,92] Risk of headache is significantly increased by 46 percent when oxcarbazepine is used versus valproic acid [RR 0.54 (0.32 to 0.93)] (Appendix J Figure 48). Given the risk difference [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.[24,86,88,94] 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 (I^2: 0 percent) but statistically significant publication bias was detected (Egger's p=0.048). Given the risk difference [0.004 (-0.024 to 0.0310], for every 250 patients treated with topiramate, 1 more patient would with experience headache compared to those treated with valproic acid.

Fifteen trials comparing newer antiepileptic medications to valproic acid reported data on headache.[23,24,68,69,74,80,84,86-88,92,94,97,98,102] 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 medications compared to valproic acid and all were amenable for pooling.[107,113]

One observational study comparing lamotrigine to valproic acid reported data on headache.[107] 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).

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One observational study comparing topiramate to valproic acid reported data on headache.[113] 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.[107,113] 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 to ethosuximide.[98] 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

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)]. Biopharmaceutical Classification System (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[22,73,76,86,88,90,92] and were all amenable to pooling.

One trial comparing gabapentin to carbamazepine reported data on fatigue.[76] 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 risk difference [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.[90] 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 risk difference [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.[92] 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.[86,88] 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 risk difference [RD -0.099 (-0.172 to -0.027)], for every 11 patients treated, 1 less patient would develop fatigue from treatment with

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topiramate than with carbamazepine. A low level of statistical heterogeneity (I^2: 10.5 percent) and no significant publication bias was detected (Egger's p=0.092).

Two trials comparing vigabatrin to carbamazepine reported data on fatigue.[22,73] 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.[22,73,76,86,88,90,92] 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 risk difference [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 to controlled release carbamazepine.[91] Risk of fatigue is nonsignificantly increased by 17 percent when levetiracetam is used versus carbamazepine-CR [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 to phenytoin.[29] 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[68,69,86,88,90,92,94,98] and were all amenable to pooling.

Two trials comparing felbamate to valproic acid reported data on fatigue.[68,69] 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.[90,98] 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.[92] Risk of fatigue is nonsignificantly increased by 85 percent when topiramate 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.[86,88,94] 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 risk difference [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.[68,69,86,88,90,92,94,98] 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 risk difference [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

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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 to ethosuximide.[98] 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 to carbamazepine.[21,23,25,70,76,82,88,89,93,107,111,113]

Eight trials reported data on somnolence when newer antiepileptics were compared versus carbamazepine[21,23,25,70,76,82,88,93] and were all amenable to pooling.

One trial comparing gabapentin to carbamazepine reported data on somnolence.[76] 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 risk difference [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.[21,23,25,70,82] Risk of somnolence is significantly decreased by 54 percent when lamotrigine is used versus carbamazepine [RR 0.44 (0.33 to 0.58)] (Appendix J Figure 52). Given the risk difference [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.[88,93] 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.[21,23,25,70,76,82,88,93] 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 risk difference [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 medications compared to carbamazepine and all were amenable for pooling.[89,107,111,113]

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One observational study comparing lamotrigine to carbamazepine reported data on somnolence.[107] 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.[111] 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 risk difference [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.[113] 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.[89] 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.[89,107,111,113] 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 risk difference [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) and no publication bias was detected (Egger's p=0.409).

One randomized controlled trial reported data on somnolence while patients were receiving levetiracetam compared to controlled release carbamazepine.[21] 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 to phenytoin[27-29,75] and were all amenable to pooling.

One trial comparing lamotrigine to phenytoin reported data on somnolence.[28] 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 risk difference [RD -0.21 (-0.32 to -0.11)], for every five patients treated with lamotrigine, one less patient would develop somnolence compared to those treated with phenytoin.

Two trials comparing oxcarbazepine to phenytoin reported data on somnolence.[27,75] 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.[29] 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.[27-29,75] 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).

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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 to valproic acid.[23,68,69,74,80,84,88,94,98,107,113]

Nine randomized controlled trials reported data on somnolence when newer antiepileptics were compared versus valproic acid.[23,68,69,74,80,84,88,94,98] and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on somnolence.[69] 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.[23,68,80,84,98] 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.[74] Risk of somnolence is nonsignificantly decreased by 25 percent when topiramate 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.[88,94] Risk of somnolence is nonsignificantly decreased by 35 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 (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.[23,68,69,74,80,84,88,94,98] 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 risk difference [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 medications compared to valproic acid and both were amenable for pooling.[107,113]

One observational study comparing lamotrigine to valproic acid reported data on somnolence.[107] 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.[113] 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.[107,113] 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 to ethosuximide.[98] The risk of somnolence was significantly decreased by 78 percent when lamotrigine was compared versus ethosuximide [RR 0.22 (0.07 to 0.70)].

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Given the risk difference [-0.07 (-0.12 to -0.020], for every 15 patients treated with lamotrigine, 1 less patient would develop somnolence compared to 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 to carbamazepine.[21-26,29,70,71,73,76,82,86,88,92,93,107,111,113]

Sixteen randomized controlled trials reported data on dizziness when newer antiepileptics were compared versus carbamazepine[21-26,29,70,71,73,76,82,86,88,92,93] and were all amenable to pooling.

Three trials comparing gabapentin to carbamazepine reported data on dizziness.[24,26,76] 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.[21,23-26,70,82] 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 risk difference [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.[24,92] 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.[24,29,86,88,93] 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 risk difference [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.[22,71,73] 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.[21-26,29,70,71,73,76,82,86,88,92,93] 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 risk difference [RD -0.020 (-0.041 to -0.0001)], for every 50

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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 medications compared to carbamazepine and all were amenable for pooling.[107,111,113]

One observational study comparing lamotrigine to carbamazepine reported data on dizziness.[107] 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.[113] 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.[107,111,113] 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 risk difference [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 studies comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients with new partial epilepsy.[111] 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95]

One randomized controlled trial reported data on dizziness when lamotrigine was compared to sustained release carbamazepine.[95] 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 to controlled release carbamazepine.[91] The risk of dizziness was significantly increased by 7.9-fold when levetiracetam is used versus carbamazepine-CR [RR 7.91 (2.97 to 21.31)] (Appendix J Figure 59).

Two randomized controlled trials reported data on dizziness when lamotrigine or levetiracetam were compared to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95] The risk of dizziness was nonsignificantly increased by 3.3-fold when either newer agent was compared to controlled or sustained release carbamazepine [RR 3.26 (0.58 to 18.52)] (Appendix J Figure 59).

Phenytoin versus Newer

Three randomized controlled trials reported dizziness while patients were receiving newer antiepileptic medications compared to phenytoin[27,28,75] and were all amenable to pooling.

One trial comparing lamotrigine to phenytoin reported data on dizziness.[28] 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).

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Two trials comparing oxcarbazepine to phenytoin reported data on dizziness.[27,75] 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.[27,28,75] 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.[75] 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 risk difference [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 to valproic acid.[23,24,69,74,80,84,86,88,92,94,97,98,107,113]

Twelve randomized controlled trials reported data on dizziness when newer antiepileptics were compared versus valproic acid[23,24,69,74,80,84,86,88,92,94,97,98] and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on dizziness.[69] 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.[23,24,80,84,97,98] 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.[74,92] Risk of dizziness is nonsignificantly increased by 15 percent when topiramate 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.[24,86,88,94] 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) but no publication bias was detected (Egger's p=0.113).

Twelve trials comparing newer antiepileptic medications to valproic acid reported data on dizziness.[23,24,69,74,80,84,86,88,92,94,97,98] 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 (I2: 0 percent) or publication bias was detected (Egger's p=0.111).

Two observational studies reported dizziness while patients were receiving a newer antiepileptic medications compared to carbamazepine and both were amenable for pooling.[107,113]

One observational study comparing lamotrigine to valproic acid reported data on dizziness.[107] 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).

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One observational study comparing topiramate to valproic acid reported data on dizziness.[113] 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.[107,113] 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 to ethosuximide.[98] 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. 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 trial[118] and one controlled observational study[36]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 1000 person-years (percent) for innovator and generic carbamazepine. In the generic group (n=705), there were 145.7 events per 1000 person-years (percent), whereas in the innovator group (n=275), there were 75.7 events per 1000 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 is the same as carbamazepine results given above. Data on BCS Class I antiepileptic medications was not available.

Three controlled clinical trials[117,118,127] 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,[117,118] whereas dizziness was reported by only one trial.[117] None of the trials used discernable FDA “A” rated generics.

Diplopia is 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.

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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[23-25,65,70,73,86,88] and were all amenable to pooling.

One trial comparing gabapentin to carbamazepine reported data on nausea.[24] Risk of nausea is nonsignificantly decreased by 22 percent when gabapentin is used versus carbamazepine [RR 0.78 (0.30to 2.00)] (Appendix J Figure 63).

Four trials comparing lamotrigine to carbamazepine reported data on nausea.[23-25,70] 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.[24,65] 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.[24,86,88] 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 risk difference [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.[73] 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.[23-25,65,70,73,86,88] 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 (I^2: 32.7 percent) and no publication bias was detected (Egger's p=0.218).

One randomized controlled trial reported data on nausea while patients were receiving levetiracetam compared to controlled release carbamazepine.[21] Risk of nausea is nonsignificantly decreased by 34 percent when levetiracetam is used versus carbamazepine-CR [RR 0.66 (0.39 to 1.12)].

Phenytoin versus Newer

Four randomized controlled trials reported nausea while patients were receiving a newer antiepileptic medications compared to phenytoin[27-29,75] and were all amenable to pooling.

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One trial comparing lamotrigine to phenytoin reported data on nausea.[28] 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.[27,75] 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.[29] 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.[27-29,75] 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) and no 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[23,24,69,74,80,84,86,88,94,97,98] and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on nausea.[69] 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.[23,24,80,84,97,98] 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 risk difference [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.[74] 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.[24,86,88,94] 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) was detected.

Eleven trials comparing newer antiepileptic medications to valproic acid reported data on nausea.[23,24,69,74,80,84,86,88,94,97,98] 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 risk difference [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.

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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.[21,70,88] and were all amenable to pooling.

Two trials comparing lamotrigine to carbamazepine reported data on vomiting.[21,70] 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.[88] 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.[21,70,88] 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.[21,70,88] 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 to phenytoin.[75] 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 risk difference [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 to valproic acid.[69,84,84,88,97]

One trial comparing felbamate to valproic acid reported data on vomiting.[23] 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.[80,84,97] Risk of vomiting is nonsignificantly decreased by 34 percent when lamotrigine is used versus valporic 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.[88] 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.[69,80,84,88,97]. 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 (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 to carbamazepine.[21,22,24-26,70,71,73,82,86,90,92,93,103,107,111-113]

Thirteen randomized controlled trials reported data on skin rash when newer antiepilpetics were compared versus carbamazepine[21,22,24-26,70,71,73,82,86,90,92,93] and were all amenable to pooling.

Two randomized controlled trials comparing gabapentin to carbamazepine reported data on skin rash and were amenable for pooling.[24,26] 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 risk difference [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.[21,24-26,70,82,90] 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 risk difference [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.[24,92] 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.[24,86,93] 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 risk difference [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.[22,71,73] 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 risk difference [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 (I^2: 0 percent) but tests for publication bias could not be performed.

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Thirteen randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on skin rash.[21,22,24-26,70,71,73,82,86,90,92,93] 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 risk difference [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 publication bias was also detected (Egger's p=0.001).

Five observational studies reported data on skin rash while patients were receiving a newer antiepileptic medications compared to carbamazepine and all five were amenable for pooling.[103,107,111-113]

One observational trial comparing lamotrigine to carbamazepine reported data on skin rash.[107] 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.[111] 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.[103] 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.[112,113] 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 risk difference [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.[103,107,111-113] 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 to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95]

One randomized controlled trial reported data on skin rash when lamotrigine was compared to sustained release carbamazepine.[95] 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 70).

One randomized controlled trial reported data on skin rash when levetiracetam was compared to controlled release carbamazepine.[91] The risk of skin rash was nonsignificantly decreased by 49 percent when levetiracetam is used versus carbamazepine-CR [RR 0.51 (0.23 to 1.15)] (Appendix J Figure 70).

Two randomized controlled trials reported data on skin rash when lamotrigine or levetiracetam were compared to controlled or sustained release carbamazepine and both were amenable for pooling.[91,95] The risk of skin rash was significantly decreased by 53 percent when either newer agent was compared to controlled or sustained release carbamazepine [RR 0.47 (0.25 to 0.89)] (Appendix J Figure 71). Given the risk difference [RD (-0.038 (-0.081 to 0.005)],

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for every 27 patients treated with a newer agent, 1 less patient would develop skin rash compared to 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 medications compared to phenytoin[27-29,75] and were all amenable to pooling.

One randomized controlled trial comparing lamotrigine to phenytoin reported data on skin rash.[28] 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.[27,75] 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.[29] 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 risk difference [RD -0.071 (-0.120 to -0.022)], for every 15 patients treated, 1 less patient would develop skin rash from treatment with topirmate than with pheytoin.

Four trials comparing newer antiepileptic medications to phenytoin reported data on skin rash.[27-29,75] 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 to valproic acid.[24,69,84,86,87,90,92,94,97,102,107,113]

Ten randomized controlled trials reported data on skin rash when newer antiepilpetics were compared versus valproic acid.[24,69,84,86,87,90,92,94,97,102] and were all amenable to pooling.

One trial comparing felbamate to valproic acid reported data on skin rash[69] 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 risk difference [RD 0.001 (-0.070 to 0.072)], for every 1000 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.[24,84,87,90,97,102] Risk of skin rash is significantly increased over 2.7-fold when lamotrigine is used versus valporic acid [RR 2.69 (1.07 to 6.77)] (Appendix J Figure 73). Given the risk difference [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.[92] 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.[24,86,94] 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 risk difference [RD -0.035 (-0.104 to

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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.[24,69,84,86,87,90,92,94,97,102] 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 medications compared to valproic acid and both were amenable for pooling.[107,113]

One observational study comparing lamotrigine to valproic acid reported data on skin rash.[107] 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.[113] 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 study comparing newer antiepileptic medications to valproic acid reported data on skin rash.[107,113] 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.[117,118] Incidence of skin rash is nonsignificantly decreased by 23 percent when generic carbamazepine was 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

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

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 four studies evaluated the impact of newer antiepileptic medications on cognition as compared with carbamazepine, one in an adult population.[71] and three in pediatric/adolescent populations.[78,92,93] One randomized controlled clinical trial evaluated the impact of newer antiepileptic medications on mood as compared with carbamzaepine.[78] A randomized,

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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).[71] Those that 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 phenytoin[78] 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 therapy in a pediatric population with partial seizures.[92] 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 follow up period. The last 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.[93] 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).

Phenytoin versus Newer

A single study evaluated the impact of tiagabine on mood and cognition as compared with phenytoin for adjunctive therapy.[78] 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 to 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 five studies evaluated the impact of newer antiepileptic medications on cognition as compared with valproic acid.[77,85,92,100,114] Four of these studies used the newer agent topiramate as the comparator.[77,85,100,114] Three randomized controlled clinical trials evaluated the impact of newer antiepileptic medications on mood compared to valproic acid.[77,85,101] 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.[77] By in 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

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0.08). The Rev 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.[85] 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 follow up 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.[114] 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.[100] 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 deceased 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 single study evaluated the impact of oxcarbazepine on cognition as compared with valproic acid.[92] 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 follow up period. One randomized controlled trial evaluated mood when lamotrigine was compared to valproic acid using the Beck Depression Inventory, Cornell Dysthymia Rating Scale and the POMS scale.[101] The trial reported a greater improvement in Beck Depression Inventory and Cornell Dysthymia Scales from baseline after 32 weeks of therapy when lamotrigine was compared to 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.[99] 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 follow up period. They found that the effects of phenobarbital on the Mini Mental State Exam (MMSE) from baseline to 12 months were better than lamotrigine (p<0.05) but worse than levetiracetam (p<0.05). Phenobarbital was shown to be inferior to levetiracetam (p<0.05) on the Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog) and similar to lamotrigine (p=NS). Patients treated with lamotrigine

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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.

Multiple Older AEDs versus Newer

A total of three studies evaluated the impact of newer AEDs on cognition as compared with various older antiepileptic drugs.[72,104,105] Sabers et al evaluated the impact of AEDs on cognitive function in 87 patients with various epilepsy types over a 4 month period.[72] 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.[105] Cognitive Side Effects 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=1189), 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.[104] A cognitive adverse event was defined as it was in the last study.[105] The incidence of adverse events leading to either dose changes and/or treatment discontinuation was reported as ranges and indicated with (+) signs as follows: (+) 2-4.9 percent, (++) 5-9.9 percent, (+++) 10-19.9 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 (+++), levatiracetam (++), 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.[123] 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 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 innovatored 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 difference 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 27).[108] 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 to 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 to older antiepileptic medications (carbamazepine, phenytoin and valproic acid) (Appendix G Table 27).[110] 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 to these older agent after 1 year of treatment. However, comparisons of lamotrigine versus each individual older agent was 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 28).[109] The study reported that bone mineral density was significantly decreased in patients that 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.[23,67,71,86,88,92] and were all amenable to pooling.

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One trial comparing lamotrigine to carbamazepine reported data on alopecia.[23] 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.[67,92] 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.[86,88] 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 (I^2: 0 percent) and no significant publication bias was detected (Egger's p=0.009).

One trial comparing vigabatrin to carbamazepine reported data on alopecia.[71] 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.[23,67,71,86,88,92] 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.[27] 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.[27,75] and were all amenable to pooling.

Two trials comparing oxcarbazepine to phenytoin reported data on gum hyperplasia in patients with new onset epilepsy.[27,75] 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 risk difference [RD -0.17 (-0.29 to -0.04)], for every six patients treated with oxcarbazepine, one less patient would develop gum hyperplasia compared to those treated with phenytoin.

Valproic Acid versus Newer

Eight randomized controlled trials reported data on alopecia when newer antiepileptics were compared versus valproic acid.[23,74,80,84,86,88,92,94] and were all amenable to pooling.

Three trials comparing lamotrigine to valproic acid reported data on alopecia.[23,80,84] 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 risk difference [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) but tests for publication bias could not be performed.

Two trials comparing oxcarbazepine to valproic acid reported data on alopecia.[74,92] 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.[86,88,94] 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 risk difference [RD -0.162 (-0.236 to

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-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.[23,74,80,84,86,88,92,94] 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 risk difference [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 also 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 to 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 was 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 were 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 found 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.

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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 to 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 carbamezepine 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 tiagibine 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 levatiracetam 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 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 carbamazeine 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 carbamazepine or phenytoin. Data on dizziness, somnolence and

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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 was only available for carbamazepine, which showed no statistically significant difference between the innovator and generic version of carbamazepine.

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

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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 (Biopharmaceiticals Classification System (BCS) class II - IV).

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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 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 was 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.[12] Results showed that women compared to men were more likely to switch from innovator to generic [Hazard Ratio (HR) 0.95 (95 percent CI 0.91 to 0.99); p=0.0057] and there was no statistically significant difference in women compared to 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.[12] Results showed that younger patients were more likely to require a switchback to innovator medication compared to 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.[12] 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.

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 diminish the ability to identify useful information.

Seizure Etiology

Older versus Newer Antiepileptic Drug Evaluation

Carbamazepine versus Newer

Efficacy

Partial Epilepsy

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One randomized controlled trial reported the time to first seizure when vigabatrin was compared to carbamazepine in patients with partial epilepsy.[22] The time to first seizure was significantly increased when vigabatrin was compared to 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.[22,89,90,93] 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 to carbamazepine in patients with partial epilepsy.[106,111] 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 were compared versus carbamazepine.[22,90] 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 risk difference [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 to those treated with carbamazepine.

One observational study reported withdrawal due to lack of efficacy when vigababtrin was compared to carbamazepine in patients with partial epilepsy.[106] 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 risk difference, [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 to 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.[70,73,86,90,92,93] 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.[106,111] 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 to carbamazepine in patients with partial epilepsy.[22] The risk of achieving 12 month seizure remission was nonsignificantly decreased by 5 percent when vigabatrin was compared to carbamazepine in patients with partial epilepsy [RR 0.95 (0.79 to 1.14)] (Appendix J Figure 22).

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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.[70,86] 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 test 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.[22,73,82,89,90,93] 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 risk difference [RD -0.051 (-0.088 to -0.014)], for every 20 patients treated with lamotrigine, topiramate or vigabatrin, 1 less patient would withdraw compared to those treated with carbamazepine. No statistical heterogeneity (I^2: 0 percent) or publication bias (Egger's: p=0.629) were detected.

Two observational studies reported withdrawals due to adverse events when levetiracetam or oxcarbazepine was compared to carbamazepine in patients with partial epilepsy and were amenable for pooling.[103,111] 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.[73,92] 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.[73,90,92] 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.[93] 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.[111] 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 risk difference [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.[73,92,93] Risk of dizziness is nonsignificantly decreased by 37 percent when newer antiepileptic medications are used versus carbamazepine [RR 0.63

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(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.[111] 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.[73] 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.[73,90,92,93] 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.[92] 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 to phenytoin in patients with partial epilepsy.[28] The time to first seizure was not altered when lamotrigine was compared to 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.[27,28,75] 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.[20,68,77,85] 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 no publication bias was detected (Egger's: p=0.310).

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Three trials comparing newer antiepileptic medications to valproic acid reported data on seizure freedom for study duration in patients with partial epilepsy.[74,86,92] 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 was detected (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.[20,77] 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.[87,90,98] 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.[87,90,94] 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 seen 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.[74,86,90,94] 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 were compared versus valproic acid and were amenable for pooling.[20,85] 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.[68,69,92] 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.

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Three trials comparing newer antiepileptic medications to valproic acid reported data on fatigue in patients with partial epilepsy.[68,69,92] 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 was could not be performed.

Two trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with partial epilepsy.[68,69] 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.[68,69,92] 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 was could not be performed.

One trial comparing newer antiepileptic medications to valproic acid reported data on nausea in patients with partial epilepsy.[69] 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.[69] 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.[69,92] 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.[92] 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 risk difference [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.[87,90,94,98] 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.[87,94,98] 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 test for publication bias was could not be performed.

Three trials comparing newer antiepileptic medications to valproic acid reported data on fatigue in patients with generalized epilepsy.[90,94,98] 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 was could not be performed.

Two trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with generalized epilepsy.[94,98] 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.[94,98] 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.[94,98] 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 risk difference [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.[87,90,94] 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.[94] 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 to ethosuximide.[98] This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤18 years of age.[98] 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 to ethosuximide.[98] 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 to ethosuximide.[98] This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤18 years of age.[98] The risk of headache was nonsignificantly decreased by 34 percent when lamotrigine was compared versus ethosuximide

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[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 risk difference [RD -0.04 (-0.11 to 0.03)], for every 25 patients treated with lamotrigine, 1 less patients 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 to carbamazepine and all 3 were amenable for pooling.[21,22,26] The risk of death was nonsignificantly decreased by 37 percent when all newer antiepileptics were compared to 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 to carbamazepine in patients with new onset epilepsy.[22,70] The time to first seizure was nonsignificantly increased when either newer agent was compared to 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.[21,22,26,70,71,76,90] 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 risk difference 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 to 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 to carbamazepine in patients with new onset epilepsy.[106,107,109,111] 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

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versus carbamazepine.[21,22,26,70,71,90] 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 risk difference [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 to 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 viagbatrin were compared to carbamazepine in patients with new onset epilepsy.[106,107,109,112,113] The risk of withdrawal due to lack of efficacy was nonsignificantly decreased by 3 percent when either newer agent was compared to 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) and 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.[21,26,71,82,86] 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.[106,107,111,113] 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 to controlled or sustained release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.[91,95] The risk of withdrawal was nonsignificantly decreased by 4 percent when either newer agent was compared to 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 to controlled release carbamazepine.[91] 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 risk difference, [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 to those treated with carbamazepine.

Two randomized controlled trials reported data on seizure freedom for study duration when lamotrigine or levetiracetam were compared to controlled or sustained release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.[91,95] The risk of remaining seizure free for study duration was nonsignificantly decreased by 10 percent when either newer agent was compared to controlled or sustained release carbamazepine [RR 0.90 (0.79 to 1.02)] (Appendix J Figure 28).

Chronic Epilepsy

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One randomized controlled trial reported the number of patients with chronic epilepsy who died when lamotrigine was compared to carbamazepine.[23] The risk of death was nonsignificantly increased by 2.4-fold when lamotrigine was compared to 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.[23,89] 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.[23] 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.[21,22,26,66,70,71,73,76,88,90] 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 risk difference was [RD -0.11 (-0.16 to -0.06)], for every 10 patients treated with gabapentin, lamotrigine or vigabatrin, 1 less patient would withdraw compared to 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 to carbamazepine in patients with new onset epilepsy and were amenable for pooling.[106,107,109,111] 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.[107,113] 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.[21,70,76,88] 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 risk difference [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.[107,111,113] Risk of somnolence is significantly decreased by 74 percent when newer antiepileptic medications are used versus

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carbamazepine [RR 0.26 (0.11 to 0.58)] (Appendix J Figure 53). Given the risk difference [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.[21,22,26,29,70,71,73,88,92] 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 risk difference [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.[107,111,113] 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 risk difference [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.[70,73,88] 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) but 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.[21,22,26,70,71,73,90,92] 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 risk difference [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.[107,111,113] 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 test 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.[88,92] 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 to controlled or sustained release carbamazepine in patients with new onset epilepsy and both were amenable for pooling.[91,95] The risk of withdrawal was significantly decreased by 31 percent when either newer antiepileptic medications were compared to controlled or sustained release carbamazepine in patients with new onset epilepsy

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[RR 0.69 (0.50 to 0.95)] (Appendix J Figure 39). Given the risk difference [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 to 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.[21,22,26,70,71,73,76,88,92] 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 to controlled or sustained release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.[21,95] The risk of headache was nonsignificantly decreased by 17 percent when either newer agent was compared to 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 to controlled release carbamazepine in a population of patients with new onset epilepsy.[91] Risk of somnolence is nonsignificantly increased by 21 percent when levetiracetam is used versus carbamazepine-CR [RR 1.21 (0.75 to 1.96)].

Two randomized controlled trials reported data on dizziness when lamotrigine or levetiracetam were compared to controlled or sustained release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.[91,95] The risk of dizziness was nonsignificantly increased by 3.3-fold when either newer agent was compared to controlled or sustained release carbamazepine [RR 3.26 (0.58 to 18.52)] (Appendix J Figure 59).

One randomized controlled trial reported data on nausea while patients were receiving levetiracetam compared to controlled release carbamazepine in a population of patients with new onset epilepsy.[91] Risk of nausea is nonsignificantly decreased by 34 percent when levetiracetam is used versus carbamazepine-CR [RR 0.66 (0.39 to 1.12)].

Two randomized controlled trials reported data on skin rash when lamotrigine or levetiracetam were compared to controlled or sustained release carbamazepine and both were amenable for pooling in patients with new onset epilepsy.[91,95] The risk of skin rash was significantly decreased by 53 percent when either newer agent was compared to controlled or sustained release carbamazepine [RR 0.47 (0.25 to 0.89)] (Appendix J Figure 71).

Chronic Epilepsy

One randomized controlled trials reported data on withdrawals due to adverse events in patients with chronic epilepsy when lamotrigine was compared versus carbamazepine.[23] 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.[103] 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.[23,65] 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).

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One trial comparing newer antiepileptic medications to carbamazepine reported data on somnolence in patients with chronic epilepsy.[23] 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.[89] 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.[23] 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.[23,65] 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.[23,71] 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 to phenytoin.[27,28] The risk of death was nonsignificantly decreased by 79 percent when either newer agent was compared to 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 to phenytoin in patients with new onset epilepsy.[28] The time to first seizure was nonsignificantly increased when lamotrigine was compared to 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.[27,28,75] 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 either lamotrigine or oxcarbazepine were compared versus phenytoin in patients with new onset epilepsy and were amenable for pooling.[27,28,75] 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 19). No

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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.[27,28,75] 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.[27,28,75] 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.[27,28,75] 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.[27,28,75] 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.[27,28,75] 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.[27,28,75] 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.[74,87,90,96,98] The risk of withdrawal was nonsignificantly increased

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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 to valproic acid in patients with new onset epilepsy and were amenable for pooling.[107,109] 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.[74,87,90,96] 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 were compared versus valproic acid and were amenable for pooling.[107,109,113] 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.[74,88,90,92,96] 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.[107,113] 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 to valproic acid in patients with chronic epilepsy and both were amenable for pooling.[20,23] The risk of death was nonsignificantly increased by 28 percent when either newer agent was compared to 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.[20,23,68,85] 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 were compared versus valproic acid

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and were amenable for pooling.[20,77] 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.[23] 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.[74,87,88,90,96,98] 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 risk difference [RD -0.03 (-0.09 to 0.03)], for every 33 patients treated with either newer agent, 1 less patient would withdraw compared to those treated with valproic acid. No statistical heterogeneity was detected (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.[107,109] 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.[74,87,88,92,98] 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). 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.[107,113] 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.[88,90,92,98] 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.[74,88,98] 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 risk difference [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 (I2: 13.5 percent) but publication bias was not detected (Egger's p=0.257).

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Four trials comparing newer antiepileptic medications to valproic acid reported data on dizziness in patients with new onset epilepsy.[74,88,92,98] 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 (I2: 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.[107,113] 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.[74,88,98] 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 (I2: 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.[88] 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.[107,113] 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[87,90,92] 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) but 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.[74,88,92] 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 risk difference [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 were compared versus valproic acid and were amenable for pooling.[20,23,85] 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.[23,68,69] Risk of headache is nonsignificantly increased by 23 percent when newer antiepileptic medications are used versus valproic acid [RR 0.77 (0.28

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to 2.13)] (Appendix J Figure 49). A high level of statistical heterogeneity was detected (I^2: 58.5 percent) but 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.[68,69] 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).

Three trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in patients with chronic epilepsy.[68,69] 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) but 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.[23,69] 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.[23,69] 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.[69] 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 71).

One trial comparing newer antiepileptic medications to valproic acid reported data on alopecia in patients with chronic epilepsy.[23] 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 risk difference [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 to ethosuximide.[98] This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤18 years of age.[98] 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

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One randomized controlled trial reported data on headache while patients were receiving lamotrigine compared to ethosuximide.[98] This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤18 years of age.[98] 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 risk difference [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.[26] While the impact was not broken out in males alone, the risk death was nonsignificantly decreased by 36 percent when gabapentin or lamotrigine was used versus carbamazepine in the mixed population comprised of 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 comprised of 96 percent men [RR 0.74 (0.64 to 0.86)] (Appendix J Figure 9). Given the risk difference [RD -0.17 (-0.25 to -0.08)], for every 6 patients treated with gabapentin or lamotrigine, 1 less patient would withdraw compared to 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 comprised of >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 comprised of more than 90 percent men (96 percent of the patients enrolled in the trial were male) and compared gabapentin or lamotrigine to carbamazepine.[26] 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 to carbamazepine in this mixed population [RR 0.53 (0.30 to 0.94)] (Appendix J Figure 37). Given the risk difference

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[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 to carbamazepine. In this trial, risk of headache is nonsignificantly decreased by 2 percent when newer antiepileptic medications are used versus carbamzepine [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 carbamzepine [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 risk difference [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).[97] The risk of withdrawal was nonsignificantly decreased by 4 percent when lamotringe 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 to 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 comprised of more than 90 percent women (100 percent of the patients enrolled in the trial were women) and compared lamotrigine to valproic acid.[97] 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 49). 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 risk difference [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 risk difference [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

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percent when newer antiepileptic medications are used versus valproic acid [RR 1.13 (0.48 to 2.65)] (Appendix J Figure 76).

Innovator versus Generic Antiepileptic Drug Evaluation

No controlled clinical trial and one observational trial reported data on gender differences.[12] Results showed that women compared to men were more likely to switch from innovator to generic [Hazard Ratio (HR) 0.95 (95 percent CI 0.91 to 0.99); p=0.0057] and there was no statistically significant difference in women compared to 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.[82,89,93] 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 to carbamazepine in children ≤18 years of age.[106,111,112] 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 viagbatrin were compared to carbamazepine in children ≤18 years of age.[106,112,113] The risk of withdrawal due to lack of efficacy was nonsignificantly increased by 8 percent when newer agents were compared versus carbamazepine in children less than or equal to 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.

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Five randomized controlled trials comparing newer antiepileptic medications to carbamazepine reported data on seizure freedom for study duration in children ≤18 years of age.[73,82,88,92,93] The risk of remaining seizure free for duration of study is non -significantly 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.[106,111,113] 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 medications to carbamazepine reported data on seizure freedom for study duration in patients 18-65 years of age.[73] 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.[20] 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.[21,82] 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.[21] The risk of withdrawal due to ineffective treatment was nonsignificantly decreased by 53 percent when newer agents were compared versus carbamazepine in a population comprised of ≥65 years of age [RR 0.47 (0.01 to 23.49)] (Appendix J Figure 13).

One randomized controlled trial comparing lamotrigine to carbamazepine reported data on seizure freedom for study duration in patients 65 years or older.[21] 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 to sustained release carbamazepine in patients ≥ 65 years of age.[95] The risk of withdrawal was nonsignificantly decreased by 18 percent when lamotrigine was compared versus sustained release carbamazepine in patients 65 years of age and older [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 to sustained release carbamazepine in patients ≥65 years of age and older.[95] The risk of remaining seizure free for study duration was nonsignificantly decreased by

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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.[82,88,93] 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 were (Egger's: p=0.091) detected.

Three nonrandomized trials reported withdrawals due to adverse events when levetiracetam, topiramate and vigabatrin were compared to carbamazepine in patients ≤18 years of age and were amenable for pooling.[106,111,112] 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.[82,88,92] 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 (I^2: 27.3 percent) but no publication bias was detected (Egger's p=0.211).

One observational studies comparing newer antiepileptic medications to carbamazepine reported data on headache in children ≤18 years of age.[113] 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.[88,92] 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) but 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.[82,88,93] 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.[89,111,113] 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 risk difference [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) but 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.[88] 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).

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One trial comparing newer antiepileptic medications to carbamazepine reported data on vomiting in children ≤18 years of age.[88] 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.[82,92,93] 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) but 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.[111-113] 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 risk difference [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) but 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.[88,92] 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.

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.[73] 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.[73] 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.[73] 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 18-65 years of age. [73] 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 18-65 years of age.[73] 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

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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.[21,76,82] 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.[21,82] 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.[21] 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 or older.[21,82] 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 to sustained release carbamazepine in patients 65 years of age and older.[95] 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 to phenytoin in children ≤18 years of age.[75] 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 to phenytoin in children ≤18 years of age.[75] 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 risk difference [RD -0.13 (-0.20 to -

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0.05)], for every eight patients treated with oxcarbazepine, one less would withdraw due to adverse events compared to 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.[82,88,92,93] 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 (I^2: 47.5 percent) 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.[111,113] 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 to phenytoin.[75] 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 risk difference [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 ≥65 Years of Age

One trial comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients 18-65 years of age.[73] 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 risk difference [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.

Two trials comparing newer antiepileptic medications to carbamazepine reported data on dizziness in patients 65 years or older.[21,82] 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).

<u>*Valproic Acid versus Newer*</u>

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.[87,98] The risk of withdrawal was nonsignificantly increased by 34 percent when

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lamotrigine was compared versus valproic acid in children less than or equal to 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.[87] 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 less than 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.[113] 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.[88,92] 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.[113] 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.[88,98] 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 risk difference [RD -0.50 (-0.12 to 0.02)], for every two patients treated with either newer agent, one less patient would withdraw compared to those treated with valproic acid. No statistical heterogeneity (I^2: 0 percent) or publication bias (Egger's p=0.540) was not detected.

Four trials comparing newer AEDs to valproic acid reported data on headache in children ≤18 years of age.[87,88,92,98] 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.[113] 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.[88,92,98] 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).

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Two trials comparing newer antiepileptic medications to valproic acid reported data on somnolence in children ≤18 years of age.[88,98] 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 risk difference [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.[113] 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.[88,92] 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.[113] 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.[84,88,98] 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 (I^2: 25 percent) and 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 or younger.[88] 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.[87,92] 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.[113] 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.[88,92] 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 risk difference [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 (I2: 0 percent) but tests for publication bias could not be performed.

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Ethosuximide versus Newer

Efficacy

Children ≤18 Years of Age

One randomized controlled trial reported withdrawals for any reason while patients were receiving lamotrigine compared to ethosuximide.[98] This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤18 years of age.[98] 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 to ethosuximide.[98] This trial included patients with new onset, generalized epilepsy or childhood absence epilepsy in children ≤18 years of age.[98] 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.[12] Results showed that younger patients were more likely to require a switchback to innovator medication compared to 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).

Pharamacogenetic 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.

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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.[12] 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 innovatored 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 was 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.[12] There was no statistically significant difference in women compared to 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 to 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.

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Chapter 4. Summary and Discussion

Our general results with strength of evidence rating are given in

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Table 8. 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 antepileptic 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 antiepleptic 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 to 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

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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 antiarrhythmic 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.

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 carbamazeine 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.

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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[12,30] but two other trials did not.[32,163] 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,[33,34] this study authors controlled for person's risk of epilepsy exacerbation, change in disease severity, drug interactions, poor adherence, and change in patient diagnosis.[35] 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.

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Table 8. Summary of results, strength of evidence and strength of applicability

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
KEY QUESTION 1 ENDPOINTS					
Mortality					
Newer versus Carbamazepine Newer vs. Phenytoin Newer vs. Valproic Acid	6 RCT 3 RCT 3 RCT	Yes Yes Yes	No effect, RR 0.75 (0.51, 1.12) No effect, RR 0.30 (0.05, 1.95) No effect, RR 0.94 (0.31, 2.80)	SOE: L SOE: L SOE: L	AOE: M AOE: M AOE: M
Outpatient Service Utilization					
Innovator vs. Generic	4 OBS	No	Similar utilization of outpatient services during generic medication periods.	SOE: L	AOE: M
Hospitalizations					
Newer vs. Carbamazepine	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared to carbamazepine.	SOE: I	AOE: L
Newer vs. Valproic Acid	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared to valproic acid.	SOE: I	AOE: L
Newer vs. Ethosuximide	1 RCT	No	Newer antiepileptic medications (lamotrigine) did not reduce the risk of hospitalization compared to ethosuximide.	SOE: I	AOE: L
Innovator vs. Generic	4 OBS	No	Increased risk of hospitalizations during generic medication periods..	SOE: L	AOE: M
Hospital Stay Duration					
Innovator vs. Generic	4 OBS	No	Increased hospital stay during generic medication periods.	SOE: L	AOE: M
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	AOE: M
Health Related Quality Of Life					

Table 8. Summary of results, strength of evidence and strength of applicability

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
Newer vs. Carbamazepine	3 RCT	No	Different scales and subscales, data inconclusive	SOE: I	AOE: L
Newer vs. Phenytoin	2 RCT	No	Different scales and subscales, data inconclusive	SOE: I	AOE: M
Newer vs. Valproic Acid	3 RCT	No	Different scales and subscales, data inconclusive	SOE: I	AOE: M
Time To First Seizure					
Newer vs. Carbamazepine	4 RCT	Yes	No effect, [HR 1.14 (0.98, 1.33)]	SOE: L	AOE: M
Newer vs. Phenytoin	2 RCT	Yes	Time to seizure increased for newer vs. phenytoin, [HR 1.59 (1.04, 2.43)]	SOE: L	AOE: M
Newer vs. Valproic Acid	1 RCT	Yes	No effect, [HR 0.8 (0.63, 1.02)]	SOE: L	AOE: M
Seizure Occurrence					
Innovator vs. Generic	7 RCT	Yes	No effect, [0.87 (0.64, 1.18)]	SOE: L	AOE: L
Seizure Freedom For Study Duration					
Newer vs. Carbamazepine	15 RCT	Yes	No effect, [RR 0.94 (0.87, 1.03)]	SOE: L	AOE: M
Newer vs. Carbamazepine CR/SR	2 RCT	Yes	No effect, [RR, 0.90 (0.79, 1.02)]	SOE: M	AOE: L
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.92 (0.85, 1.00)]	SOE: M	AOE: M
Newer vs. Valproic Acid	12 RCT	Yes	No effect, [RR 0.97 (0.87, 1.08)]	SOE: M	AOE: M
Seizure Frequency					
Newer vs. Carbamazepine	1 RCT	No	No effect, [MD -3 (-6.32, 0.32)]	SOE: I	AOE: M
Newer vs. Phenytoin	2 RCT	No	Not enough data to evaluate effect	SOE: M	AOE: L
Newer vs. Valproic Acid	1 RCT	No	Not enough data to evaluate effect	SOE: I	AOE: L
Innovator vs. Generic	3 RCT	Yes	No effect, [SMD 0.03 (-0.08, 0.14)]	SOE: L	AOE: L
Seizure Remission					
6 to 12-Month: Newer vs. Carbamazepine	2 RCT	Yes	Patients on newer antiepileptic medications less likely to have seizure remission vs. carbamazepine, [RR 0.81 (0.67, 0.99), NNT 9]	SOE: L	AOE: M
Newer vs. Valproic Acid	1 RCT	Yes	No effect, [RR 0.97 (0.89,1.06)]	SOE: M	AOE: M
24-Month: Newer vs. Carbamazepine	1 RCT	Yes	Patients on newer antiepileptic medication less likely to have seizure remission vs. carbamazepine, [RR 0.82 (0.72, 0.94), NNT 13]	SOE: M	AOE: M
Newer vs. Valproic Acid	1 RCT	Yes	No effect, [RR 0.85 (0.73,1.00)]	SOE: M	AOE: M

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Table 8. Summary of results, strength of evidence and strength of applicability (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
Status Epilepticus, Secondary Injury From Seizures, Loss Of Driver's License/Employment					
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
Total Withdrawals					
Newer vs. Carbamazepine	14 RCT	Yes	No effect, [RR 0.90 (0.82, 1.00)]	SOE: L	AOE: M
Newer vs. Carbamazepine CR/SR	2 RCT	Yes	No effect, [RR 0.96 (0.78, 1.18)]	SOE: L	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [RR 0.91 (0.76, 1.09)]	SOE: L	AOE: M
Newer vs. Valproic Acid	16 RCT	Yes	No effect, [RR 0.96 (0.85, 1.09)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.95 (0.53, 1.71)]	SOE: I	AOE: L
Innovator vs. Generic	9 RCT + 1 NRCT	Yes	No effect, [RR 0.90 (0.39, 2.08)]	SOE: L	AOE: M
Withdrawals Due To Lack Of Efficacy					
Newer vs. Carbamazepine	10 RCT	Yes	Withdrawals due to lack of efficacy increased with newer agents vs. carbamazepine, [RR 1.59 (1.25, 2.02), NNT 50]	SOE: L	AOE: M
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	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [RR 1.03 (0.33, 3.23)]	SOE: L	AOE: M
Newer vs. Valproic Acid	11 RCT	Yes	No effect, [RR 1.10 (0.77, 1.56)]	SOE: L	AOE: M
Innovator vs. Generic	9 RCT + 1 NRCT	Yes	No effect, [RR 1.02 (0.41, 2.54)]	SOE: L	AOE: M
KEY QUESTION 2 ENDPOINTS					
Maximum Concentration: Innovator vs. Generic	7 RCT + 1 NRCT	Yes	No effect, [SMD 0.10 (-0.13, 0.32)]	SOE: L	AOE: M
Minimum Concentration: Innovator vs. Generic	5 RCT + 1 NRCT	Yes	No effect, [SMD 0.05 (-0.21, 0.31)]	SOE: L	AOE: L
Steady State Concentration					

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Table 8. Summary of results, strength of evidence and strength of applicability (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
Innovator vs. Generic	7 RCT	Yes	No effect, [SMD 0.18 (-0.09, 0.45)]	SOE: L	AOE: L
Time To Maximal Concentration					
Innovator vs. Generic	5 RCT	Yes	No effect, [WMD 0.00 (-0.43, 0.43)] (Note: a WMD was calculated vs. a SMD for Tmax because only carbamazepine trials made up this evaluation).	SOE: I	AOE: M
Area Under The Curve					
Innovator vs. Generic	7 RCT + 1 NRCT	Yes	No effect, [SMD 0.05 (-0.18, 0.28)]	SOE: L	AOE: M
Dose Requirements For Seizure Control					
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: 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	AOE: L
KEY QUESTION 3 ENDPOINTS					
Withdrawals Due To Adverse Events					
Newer vs. Carbamazepine	18 RCT	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	AOE: M
Newer vs. Carbamazepine CR/SR	2 RCT	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	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [0.38 (0.14, 1.03)]	SOE: I	AOE: M
Newer vs. Valproic Acid	16 RCT	Yes	No effect, [RR 0.90 (0.75, 1.08)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.71 (0.45, 1.12)]	SOE: I	AOE: L
Innovator vs. Generic	9 RCT + 1 NRCT	Yes	No effect, [RR 0.79 (0.28, 2.20)	SOE: L	AOE: M
Headache					

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Table 8. Summary of results, strength of evidence and strength of applicability (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
Newer vs. Carbamazepine	15 RCT	Yes	No effect, [RR 0.92 (0.78, 1.08)]	SOE: L	AOE: M
Newer vs. Carbamazepine SR/CR	2 RCT	Yes	No effect, [RR 0.83 (0.63, 1.10)]	SOE: L	AOE: L
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.74(0.53, 1.02)]	SOE: L	AOE: M
Newer vs. Valproic Acid	15 RCT	Yes	No effect, [RR 0.90 (0.70, 1.16)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.66 (0.33, 1.29)]	SOE: I	AOE: L
Innovator vs. Generic	3 RCT	Yes	No effect, [RR 0.95 (0.55, 1.64)]	SOE: L	AOE: L
Fatigue					
Newer vs. Carbamazepine	7 RCT	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. carbamazepine. [RR 0.57 (0.41, 0.80), NNT 11]	SOE: L	AOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	Yes	No effect, [RR 1.17 (0.80, 1.72)]	SOE: I	AOE: L
Newer vs. Phenytoin	1 RCT	No	No effect, [RR 1.05 (0.49, 2.25)]	SOE: I	AOE: L
Newer vs. Valproic Acid	8 RCT	Yes	Risk of fatigue reduced with newer antiepileptic medications vs. valproic acid. [RR 0.61 (0.44, 0.85), NNT 23]	SOE: M	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.90 (0.45, 1.80)]	SOE: I	AOE: L
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
Somnolence					
Newer vs. Carbamazepine	8 RCT	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. carbamazepine. [RR 0.47 (0.36, 0.61), NNT 14]	SOE: M	AOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	No	No effect, [RR 1.21 (0.75, 1.96)]	SOE: I	AOE: L
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.72 (0.44, 1.18)]	SOE: I	AOE: M
Newer vs. Valproic Acid	9 RCT	Yes	Risk of somnolence reduced with newer antiepileptic medications vs. valproic acid. [RR 0.65 (0.43, 0.98), NNT 25]	SOE: M	AOE: 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	AOE: L
Innovator vs. Generic	2 RCT	Yes	No effect, [RR 0.90 (0.48, 1.70)]	SOE: L	AOE: L
Dizziness					

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Table 8. Summary of results, strength of evidence and strength of applicability (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
Newer vs. Carbamazepine	16 RCT	Yes	Risk of dizziness reduced with newer antiepileptic medications vs. carbamazepine. [RR 0.78 (0.67, 0.91), NNT 50]	SOE: M	AOE: M
Newer vs. Carbamazepine SR/CR	2 RCT	Yes	No effect, [RR 3.26 (0.58, 18.52)]	SOE: L	AOE: L
Newer vs. Phenytoin	3 RCT	Yes	No effect, [RR 0.67 (0.43, 1.05)]	SOE: L	AOE: M
Newer vs. Valproic Acid	12 RCT	Yes	No effect, [RR 0.98 (0.71, 1.35)]	SOE: L	AOE: M
Newer vs. Ethosuximide	1 RCT	No	No effect, [RR 0.46 (0.15, 1.38)]	SOE: I	AOE: L
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: 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 1000 person years, p=NS	SOE: L	AOE: L
Diplopia					
Innovator vs. Generic	2 RCT	Yes	No effect, [1.28 (0.38, 4.31)]	SOE: L	AOE: L
Hypotension, Asthenia, Ataxia, Nystagmus, Tremor					
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
Nausea					
Newer vs. Carbamazepine	8 RCT	Yes	No effect, [RR 0.69 (0.46, 1.02)]	SOE: L	AOE: M
Newer vs. Carbamazepine SR/CR	1 RCT	No	No effect, [RR 0.66 (0.39, 1.12)]	SOE: I	AOE: L
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.88 (0.56, 1.37)]	SOE: L	AOE: M
Newer vs. Valproic Acid	11 RCT	Yes	Risk of nausea reduced with newer antiepileptic medications vs. valproic acid. [RR 0.56 (0.41, 0.77), NNT 31]	SOE: M	AOE: M
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
Vomiting					
Newer vs. Carbamazepine	3 RCT	Yes	No effect, [RR 1.25 (0.66, 2.35)]	SOE: L	AOE: M
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	AOE: L
Newer vs. Valproic Acid	5 RCT	Yes	No effect, [RR 0.69 (0.34, 1.42)]	SOE: L	AOE: M
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
Skin Rash					

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Table 8. Summary of results, strength of evidence and strength of applicability (continued)

Outcome	Type and Number of Studies	Pooled	Result/Conclusion	Strength of Evidence	Applicability of Evidence
Newer vs. Carbamazepine	13 RCT	Yes	Risk of skin rash was reduced with newer antiepileptic medications vs. carbamazepine [RR 0.52 (0.39, 0.69), NNT 24]	SOE: M	AOE: M
Newer vs. Carbamazepine SR/CR	2 RCT	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	AOE: M
Newer vs. Phenytoin	4 RCT	Yes	No effect, [RR 0.76 (0.34, 1.66)]	SOE: I	AOE: M
Newer vs. Valproic Acid	10 RCT	Yes	No effect, [RR 1.17 (0.55, 2.48)]	SOE: L	AOE: M
Innovator vs. Generic	2 RCT	Yes	No effect, [RR 0.77 (0.17, 3.57)]	SOE: I	AOE: L
Suicidal Ideation					
Newer vs. Older	No data	No	No data	SOE: I	AOE: I
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
Mood And Cognition					
Newer vs. Carbamazepine	4 RCT	No	Different scales and subscales, data inconclusive	SOE: I	AOE: I
Newer vs. Phenytoin	1 RCT	No	No effect	SOE: I	AOE: I
Newer vs. Valproic Acid	5 RCT	No	Different scales and subscales, data inconclusive	SOE: I	AOE: 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	AOE: I
Bone Density					
Newer vs. Older	No data	No	No data	SOE: I	AOE: I
Innovator vs. Generic	No data	No	No data	SOE: I	AOE: I
Alopecia					
Newer vs. Carbamazepine	6 RCT	Yes	No effect, [RR 0.60 (0.23, 1.58)]	SOE: L	AOE: M
Newer vs. Valproic Acid	8 RCT	Yes	Risk of alopecia was reduced with newer antiepileptic medications vs. valproic acid [RR 0.18 (0.10, 0.31), NNT 10]	SOE: M	AOE: M
Acne					
Newer vs. Phenytoin	1 RCT	No	No effect, [RR 2.78 (0.82, 9.53)]	SOE: I	AOE: L
Gum Hyperplasia					
Newer vs. Phenytoin	2 RCT	Yes	Risk of gum hyperplasia was reduced with newer antiepileptic medications vs. phenytoin [RR 0.10 (0.04, 0.27), NNT 6]	SOE: H	AOE: L

Legend: AOE=Applicability of Evidence; CR=Controlled Release; H=High; I=Insufficient; L=Low; M=Moderate; MD=Mean Difference; SMD=Standardized Mean Difference; NRCT=Non-Randomized 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

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Future Research

Limitations of Current Research

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, out patient medical care or hospitalization.

Our evaluation of newer versus older antiepileptic medications provide population wide 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.

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 of 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 which 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 do 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.

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Future Avenues for Research

For the newer versus older comparison, future direct comparative clinical trials future 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 studies would also be beneficial. More extensive evaluations of medical service utilization in controlled clinical trials and observational studies are also warranted.

Future research should not be directed at evaluating whether "A" rated versions of innovator and generic medications provide similar seizure control, pharmacokinetics, and tolerability in a large population. Instead, randomized, controlled trials should be directed at determining whether patients switched from one "A" rated version of a medication to another "A" rated version have alterations in intermediate and final health outcomes versus continuing on their original antiepileptic medication. 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 randomizing 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, healthcare 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 included 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.

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