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Appendix A. Search Strategy

Search Strategy for Innovator versus Generic Antiepileptic Drug Evaluation for MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (each in OVID starting in 1950), Web of Science (limited to meeting abstracts only)

1. generic.mp.
2. innovator.mp.
3. nonproprietary.mp.
4. drugs, generic/
5. therapeutic equivalency/
6. (brand adj name).mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Epilepsy/ or epilepsy.mp.
9. epilep$.mp.
10. seiz$.mp.
11. convuls$.mp.
12. 8 or 9 or 10 or 11
13. 7 and 12

Search Strategy for Older versus Newer Antiepileptic Drug Evaluation for MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (each in OVID starting in 1950), Web of Science (limited to meeting abstracts only)

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

43. 30 and 43
44. 44 and (11 or 24)

Appendix B. Data Extraction Forms

Study Identification for Innovator versus Generic Antiepileptic Drug Evaluation

First Author:	Year:	RefID #:
Funding Source ❑ Industry ❑ Government/Foundation ❑ Academia ❑ Other/Unknown	Specify:	Countries:

Design Characteristics for Innovator versus Generic Antiepileptic Drug Evaluation

Study Design	Randomization Adequate?	Double Blinded?	Blinding Adequate?	Allocation Concealment?	Concealment Adequate?	Description of Withdrawals?	Intent-to-Treat?
❑ RCT – Parallel ❑ Case Report ❑ RCT – Crossover ❑ Other ❑ Obs – Cohort ❑ Obs – Case Control ❑ Obs – Cross-Sectional ❑ Obs – Registry	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ Single	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A

Study Protocol for Innovator versus Generic Antiepileptic Drug Evaluation

Innovator AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Generic #1 AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Generic #2 AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Generic #3 AED name:	Dosage Form and Manufacturer:	Dose/Frequency:	Total Daily Dose:
Run-in period? ❑ Yes	Describe Run-in:	Patients removed from run-in, why:	

❑ No		
Overall #enrolled:	Overall #analyzed:	
Duration of Treatment:	Duration of follow-up:	

Study Population for Innovator versus Generic Antiepileptic Drug Evaluation

Inclusion Criteria	**Exclusion Criteria**
Age (range):	Age (range):
Gender (if applicable):	Gender (if applicable):
Seizure Etiology: ❑ Any ❑ Partial: specify ❑ Generalized: specify ❑ Other: specify	Seizure Etiology: ❑ Partial: specify ❑ Generalized: specify ❑ Other: specify
Seizure Onset: ❑ New Onset ❑ Chronic ❑ Other: specify	Seizure Onset: ❑ New Onset ❑ Chronic ❑ Other: specify
Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)	Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)
Prior AED use: ❑ None ❑ Other: specify	❑ Prior AED use/Timing: (e.g. No AEDs within 2 months) ❑ Pregnancy Risk ❑ Pregnancy ❑ Lactation

Other relevant criteria:	❑ History of Status Epilepticus ❑ Mental Retardation ❑ Psychiatric Disorder: specify ❑ Neurologic Disorder: specify ❑ Alcoholism / Drug Abuse: frequency?

Baseline Characteristics for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED	Generic AED #1	Generic AED #2	Generic AED #3
Sample size (n)				
Age (years) [Mean ± SD]				
Percent Males (%)				
Body Weight (kg) [Mean ± SD]				
Race, (n) %				
Caucasian				
Black				
Asian				
Hispanic				
Other-specify:				
Epilepsy History				
New Onset, n (%)				
Chronic Epilepsy, n (%)				
Age at Onset of Epilepsy, years				
Epilepsy duration, years				
No. Seizures in Past [Time-specify] [Mean ± SD]				
Seizure type				

	Innovator AED	Generic AED #1	Generic AED #2	Generic AED #3
Partial Seizures (no further definition), n (%)				
Simple Partial, n (%)				
Complex Partial, n (%)				
With Secondary Generalization, n (%)				
Generalized (no further definition), n (%)				
Tonic-Clonic, n (%)				
Myoclonic, n (%)				
Absence, n (%)				
Atonic, n (%)				
Unclassified, n (%)				
Prior/Concurrent AED Use				
Untreated, n (%)				
Carbamazepine, n (%) / mea dose±SD				
Phenytoin, n (%) / mean dose±SD				
Valproic Acid, n (%) / mean dose±SD				
Other, n (%) / mean dose±SD – specify:				

Pharmacokinetic Outcomes (Continuous) – Means (Standard Deviations or Standard Errors; please specify) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3		Specify comparison:	
Sample size (n)										
	End of study Mean (SD)*	**P-value**	**End of study Mean (SD)**	**P-value**	**End of study Mean (SD)**	**P-value**	**End of study Mean (SD)**	**P-value**	**Mean Difference between groups (SD)**	**P-value for Difference Between Groups**
C_{max}										
C_{min}										
C_{ss}										
AUC										
T_{max}										
Range										
Total Serum AED conc (mg/l)										
Free Serum AED conc (mg/l)										

*If not reported as mean and SD, please specify

Withdrawals and Discontinuations (Categorical) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Overall withdrawals								
Withdrawal due to ineffective treatment								
Withdrawal due to ADRs								
ADRs causing study withdrawal								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								

Seizure Outcomes – Means (Standard Deviations or Standard Errors; please specify) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		**Generic AED #1**		**Generic AED #2**		**Generic AED #3**	
Sample size (n)								
Continuous Outcomes below:								
	Mean Change from Baseline (SD)	**P- value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**
Seizure Frequency (per month)								
	End of Study Mean (SD)		**End of Study Mean (SD)**		**End of Study Mean (SD)**		**End of Study Mean (SD)**	
Dose needed for seizure control (mg/day)								
Breakthrough Seizures (mean, SD)								
Categorical Outcomes below:								
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Breakthrough Seizures (number of events total)								
Status Epilepticus								
Switchback rate Specify starting/final drugs:								

*If not reported as mean and SD, please specify

Comparative Tolerance and Harm (Categorical) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Mortality								
Medical service utilization:								
Office/ER visits (number of events)								
Hospitalilzations (number of events)								
Hospital stay duration (mean±SD)								
Composite of Ambulance/ ER/ Hospitalizations								
Other:								
Loss of Driver's License								
Loss of employment								

Comparative Tolerance and Harm (Categorical) for Innovator versus Generic Antiepileptic Drug Evaluation

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N	Number of patients (%)	N
Overall ADRs with/without withdrawal from study								
Overall ADRs reported								
ADRs **without** withdrawal from study								
Skin Rash								
Suicidal Ideation								
Hypotension								
Neurological Adverse Events								
Asthenia								
Ataxia								
Diplopia								
Dizziness								
Headache								
Nystagmus								
Somnolence								
Tremor								
Mood or Cognition-related Adverse Events								
Aggression								
Anxiety								

	Innovator AED		Generic AED #1		Generic AED #2		Generic AED #3	
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Depression								
Impaired Cognition								
Emotional Lability								
Nervousness								
Harms specific to AED								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								
Secondary seizure injury; specify type:								
Secondary Seizure Injury Rate								

Tolerance and Harms (Continuous) – Means (Standard Deviations or Standard Errors; please specify)

	Innovator AED		**Generic AED #1**		**Generic AED #2**		**Generic AED #3**	
Sample size (n)								
	Mean Change from Baseline (SD)	**P- value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**
HRQOL – Scale used:								
HRQOL Overall score								
HRQOL Sub-score 1 Please specify								
HRQOL Sub-score 2 Please specify								
HRQOL Sub-score 3 Please specify								

Quality Rating for Innovator versus Generic Antiepileptic Drug Evaluation

❑	Good (low risk of bias) • Good studies have the least bias and are considered valid. • A study is considered good if it is randomized and controlled and provides a clear description of the population, setting, interventions, and comparison groups. • A good study performs the appropriate measurement of outcomes, statistical and analytical methods and reporting. • A good study does not have reporting errors. • Good studies have less than 20% dropout and clearly report dropouts.
❑	Fair • Fair studies may be susceptible to some bias, but the bias is not sufficient to invalidate the results. • Fair studies do not meet all of the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to caus major bias. • A fair study may be missing information, making it difficult to assess limitations and potential problems.
❑	Poor (high risk of bias) • Poor studies have significant flaws of various types that may invalidate the results. • Poor studies have serious errors in design, analysis or reporting. • Poor studies may be missing large amounts of information or have discrepancies in reporting.

Study Identification for Older versus Newer Antiepileptic Drug Evaluation

First Author:	Year:	RefID #:
Funding Source Specify: ❑ Industry ❑ Government/Foundation ❑ Academia ❑ Other/Unknown		Countries:

Study Design for Older versus Newer Antiepileptic Drug Evaluation

Study Design	Randomization Adequate?	Double Blinded?	Blinding Adequate?	Allocation Concealment?	Concealment Adequate?	Description of Withdrawals?	Intent-to-Treat?
❑ RCT – Parallel Report ❑ Case ❑ RCT – Crossover ❑ Other ❑ Obs – Cohort ❑ Obs – Case Control ❑ Obs – Cross-Sectional ❑ Obs – Registry	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ Single	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A	❑ Yes ❑ No ❑ N/A

Stratification of Randomization
❑ None ❑ Seizure Etiology – Specify Etiology : ❑ Seizure Onset – New Onset / Chronic Epilepsy ❑ Patient Age – Specify age: ❑ Study Center – Specify: ❑ Gender ❑ Other – Specify:

Patient Characteristics for Older versus Newer Antiepileptic Drug Evaluation

Inclusion Criteria	**Exclusion Criteria**
Age (range):	Age (range):
Gender (if applicable):	Gender (if applicable):
Seizure Etiology: ❑ Any ❑ Partial: specify ❑ Generalized: specify ❑ Other: specify	Seizure Etiology: ❑ Partial: specify ❑ Generalized: specify ❑ Other: specify
Seizure Onset: ❑ New Onset ❑ Chronic ❑ Other: specify	Seizure Onset: ❑ New Onset ❑ Chronic ❑ Other: specify
Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)	Seizure Frequency/Timing: (e.g. >2 seizures in past 6 mos)
Prior AED use: ❑ None ❑ Other: specify	❑ Prior AED use/Timing: (e.g. No AEDs within 2 months)
Other relevant criteria:	❑ Pregnancy Risk ❑ Pregnancy ❑ Lactation ❑ History of Status Epilepticus ❑ Mental Retardation ❑ Psychiatric Disorder: specify ❑ Neurologic Disorder: specify ❑ Alcoholism / Drug Abuse: frequency?

Study Protocol for Older versus Newer Antiepileptic Drug Evaluation

Retrospective Phase ❑Yes ❑No Time (weeks):	Describe Retrospective Phase:	
Intervention 1 Drug:		
Titration ❑Yes ❑No Duration: Dose N:	Maintenance ❑Yes ❑No Duration: Dose N:	Additional Follow-up Phase ❑Yes ❑No Specify: Duration: Dose N:
Intervention 2 Drug:		
Titration ❑Yes ❑No Duration: Dose N:	Maintenance ❑Yes ❑No Duration: Dose N:	Additional Follow-up Phase ❑Yes ❑No Specify: Duration: Dose N:
Intervention 3 Drug:		
Titration ❑Yes ❑No Duration: Dose N:	Maintenance ❑Yes ❑No Duration: Dose N:	Additional Follow-up Phase ❑Yes ❑No Specify: Duration: Dose N:
Intervention 4 Drug:		
Titration ❑Yes ❑No Duration:	Maintenance ❑Yes ❑No Duration:	Additional Follow-up Phase ❑Yes ❑No Specify:

Dose N:	Dose N:	Duration: Dose N:

Baseline Characteristics for Older versus Newer Antiepileptic Drug Evaluation

	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Sample size (n)				
Age (years) [Mean ± SD]				
Percent Males (%)				
Body Weight (kg) [Mean ± SD]				
Race, (n) %				
Caucasian				
Black				
Asian				
Hispanic				
Other-specify:				
Epilepsy History				
New Onset, n (%)				
Chronic Epilepsy, n (%)				
Age at Onset of Epilepsy, years				
Epilepsy duration, years				
No. Seizures in Past [Time-specify] [Mean ± SD]				
Seizure type				
Partial Seizures (no further definition), n (%)				
Simple Partial, n (%)				

	Intervention 1	Intervention 2	Intervention 3	Intervention 4
Complex Partial, n (%)				
With Secondary Generalization, n (%)				
Generalized (no further definition), n (%)				
Tonic-Clonic, n (%)				
Myoclonic, n (%)				
Absence, n (%)				
Atonic, n (%)				
Unclassified, n (%)				
Prior/Concurrent AED Use				
Untreated, n (%)				
Carbamazepine, n (%) / mea dose±SD				
Phenytoin, n (%) / mean dose±SD				
Valproic Acid, n (%) / mean dose±SD				
Other, n (%) / mean dose±SD – specify:				

Withdrawals and Discontinuations for Older versus Newer Antiepileptic Drug Evaluation (Categorical)

	Intervention 1		**Intervention 2**		**Intervention 3**		**Intervention 4**	
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Overall withdrawals								
Completed Study								
Withdrawal due to ineffective treatment								
Time to withdrawa due to ineffective treatment **[Mean±SD]**								
Withdrawal due to ADRs								
ADRs causing study withdrawal								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								

Seizure Outcomes for Older versus Newer Antiepileptic Drug Evaluation

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
Sample size (n)								
Continuous Outcomes below:								
	Mean Change from Baseline (SD)	**P- value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**
Seizure Frequency Specify unit of time:								
	End of Study Mean (SD)		**End of Study Mean (SD)**		**End of Study Mean (SD)**		**End of Study Mean (SD)**	
Time to first seizure Specify units:								
Categorical Outcomes below:								
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Seizure free for duration of study								
Seizure remission for 12-month period								
Seizure remission for 24-month period								
Seizure frequency reduction by 25%								
Seizure frequency reduction by 50%								
Seizure frequency reduction by 75%								

Final Health Outcomes for Older versus Newer Antiepileptic Drug Evaluation (Categorical)

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Mortality								
Medical service utilization:								
Office/ER visits (number of events)								
Hospitalilzations (number of events)								
Hospital stay duration (mean±SD)								
Composite of Ambulance/ ER/ Hospitalizations								
Other:								
Loss of Driver's License								
Loss of employment								

Adverse Events for Older versus Newer Antiepileptic Drug Evaluation (Categorical)

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Overall ADRs with/without withdrawal from study								
Overall ADRs reported								
ADRs **without** withdrawal from study								
Skin Rash								
Suicidal Ideation								
Hypotension								
Neurological Adverse Events								
Asthenia								
Ataxia								
Diplopia								
Dizziness								
Headache								
Nystagmus								
Somnolence								
Tremor								
Mood or Cognition-related Adverse Events								
Aggression								
Anxiety								

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
	Number of patients (%)	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**	**Number of patients (%)**	**N**
Depression								
Impaired Cognition								
Emotional Lability								
Nervousness								
Cosmetic Adverse Effects								
Acne								
Alopecia								
Hirsutism								
Gum Hyperplasia								
Harms specific to AED								
Specify 1:								
Specify 2:								
Specify 3:								
Specify 4:								
Specify 5:								

Other Outcomes for Older versus Newer Antiepileptic Drug Evaluation (Continuous)

	Intervention 1		Intervention 2		Intervention 3		Intervention 4	
Sample size (n)								
	Mean Change from Baseline (SD)	**P- value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**	**Mean Change from Baseline (SD)**	**P-value**
Bone density								
HRQOL – Scale used:								
HRQOL Overall score								
HRQOL Sub-score 1 Please specify								
HRQOL Sub-score 2 Please specify								
HRQOL Sub-score 3 Please specify								

Quality Rating for Older versus Newer Antiepileptic Drug Evaluation

❑	Good (low risk of bias) • Good studies have the least bias and are considered valid. • A study is considered good if it is randomized and controlled and provides a clear description of the population, setting, interventions, and comparison groups. • A good study performs the appropriate measurement of outcomes, statistical and analytical methods and reporting. • A good study does not have reporting errors. • Good studies have less than 20% dropout and clearly report dropouts.
❑	Fair • Fair studies may be susceptible to some bias, but the bias is not sufficient to invalidate the results. • Fair studies do not meet all of the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. • A fair study may be missing information, making it difficult to assess limitations and potential problems.
❑	Poor (high risk of bias) • Poor studies have significant flaws of various types that may invalidate the results. • Poor studies have serious errors in design, analysis or reporting. • Poor studies may be missing large amounts of information or have discrepancies in reporting.

Appendix C. Excluded Studies from Full-Text Review

Excluded Studies from Full-Text Review for Innovator versus Generic Antiepileptic Drug Evaluation

Reference	Reason for Exclusion
Aita JF. Generic vs. branded carbamazepine. Nebraska Medical Journal 1998;73(11): 322-3.	Not a report of new discovery in humans
Argumosa A, Herranz JL. The clinical and economic impact of generic drugs in the treatment of epilepsy. Revista de neurologia 2005;41(1):45-9.	Not a report of new discovery in humans
Jefferys R. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Klingler D, Nitsche V, Schmidbauer H. Diphenylhydantoin intoxication following the exchange of seemingly equal DPH-preparations. Wiener Medizinische Wochenschrift 1981;131(11):295-300.	Not in patients with epilepsy
Oles KS, Gal P. Bioequivalency revisited: epitol versus tegretol. Neurology 1993;43(12):2435-6.	Not a report of new discovery in humans
Perron,R. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;64(8):1485-6.	Not a report of new discovery in humans
Rackley,R. J. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Sherry JH, Bechtel T. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Simpson GM, Varga E, Reiss M, Cooper TB, Bergner PE, Lee JH. Bioequivalency of generic and brand-named chlorpromazine. Clinical Pharmacology & Therapeutics 1974;15(6):631-41.	Not in patients with epilepsy
Stetz SA. Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;65(4):657-8.	Not a report of new discovery in humans
Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2005;64(8):1485-6.	Not a report of new discovery in humans

Excluded Studies from Full-Text Review for Older versus Newer Antiepileptic Drug Evaluation

Reference	Reason for Exclusion
Aberg,L. E.;Backman,M.;Kirveskari,E.;Santavuori,P. Epilepsy and antiepileptic drug therapy in juvenile neuronal ceroid lipofuscinosis. Epilepsia 2000; 41(10):1296-1302	Not conducted in an epilepsy population
Andermann,F.;Duh,M. S.;Gosselin,A.;Paradis,P. E. Compulsory generic switching of antiepileptic drugs: high switchback rates to branded compounds compared with other drug classes. Epilepsia 2007;48(3):464-469	Not reporting outcomes of interest
Antoniuk A, Bruck I, Spessatto A, et al. West syndrome: clinical and electroencephalographic follow up of 70 patients and response to its treatment with adrenocorticotropic hormone, prednisone, vigabatrin, nitrazepam and valproate. Arq Neuropsiquiatr 2000;58(3-A):683-690	Not conducted in an epilepsy population
Bauer,J.;Buchmuller,L.;Reuber,M.;Burr,W. Which patients become seizure free with antiepileptic drugs? An observational study in 821 patients with epilepsy. Acta Neurol Scand 2008:117:55–59	Not a comparison of older versus newer antiepileptic drugs
Ben-Menachem E, Brodie M, Perucca E. Efficacy of levetiracetam monotherapy; Randomized double-blind head-to-head comparison with carbamazepine-CR in newly diagnosed epilepsy patients with partial onset or generalized tonic-clonic seizures[abstract]. European Journal of Neurology 2006;13(Suppl. 2):12	No response from author
Ben-Menachem E, Privitera M, Neto W, et al. Response to topiramate (TPM), carbamazepine (CBZ) or valproate (VPA) by seizure type in newly, diagnosed epilepsy[abstract]. Epilepsia 2005;46(Suppl.6):274	No response from author
Ben-Menachem E, Privitera M, Wang S, et al. Topiramate, carbamazepine or valproate in newly diagnosed epilepsy: Response by seizure type[abstract]. European Journal of Neurology 2005;12(Suppl. 2):119	No response from author
Berlowitz,D. R.;Pugh,M. J. Pharmacoepidemiology in community-dwelling elderly taking antiepileptic drugs. International Review of Neurology 2007;81:153-63	Not a comparison of older versus newer antiepileptic drugs
Brodie M, Ben-Menachem E, Perucca E. Efficacy of levetiracetam monotherapy; Randomised double-blind head-to-head comparison with carbamazepine-CR in newly diagnosed epilepsy patients with partial onset or generalised tonic-clonic seizures[abstract]. European Journal of Neurology 2006;13(Suppl. 2):112	No response from author
Brodie,M. J.;Yuen,A. W. Lamotrigine substitution study: evidence for synergism with sodium valproate? 105 Study Group. Epilepsy Res 1997;26(3):423-32.	Not a comparison of older versus newer antiepileptic drugs
Bryant-Comstock,L.;Moorat,A. Improvement in quality of life and severity of side effects in patients with epilepsy receiving lamotrigine or valproate [abstract]. Epilepsia 1999;40(Suppl. 7):1999	No response from the author
Buchanan,N. The use of lamotrigine in juvenile myoclonic epilepsy. Seizure 1996;5:149-151.	Not reporting outcomes of interest
Calloway,M. O.;Blum,D.;Hammer,A. E.;Kustra,R. P. Quality of life in treatment of epilepsy: Lamotrigine versus conventional anti-epileptic drug therapy [abstract]. Epilepsia 2003;44(Suppl. 8):173.	Not a report of a new discovery
Cansu A, Serdaroglu A, Camurdan O, et al. The evaluation of thyroid functions, thyroid antibodies, and thyroid volumes in children with epilepsy during short-term administration of oxcarbazepine and valproate. Epilepsia 2006;47(11):1855–9.	Not reporting outcomes of interest

Reference	Reason for Exclusion
Cansu A, Serdaroolu A, Yesilkaya E et al. The Effect of Oxcarbazepine and Valproate Therapy on Growth in Children with Epilepsy[abstract]. Epilepsia 2009;50(Suppl. 4):223.	Does not report outcomes of interest
Carius A, Schreiner A, Schauble B. Effectiveness of topiramate in patients with epilepsy transitioning from valproic acid - Results of an open-label, non-interventional trial [abstract]. European Journal of Neurology 2007;14(Suppl. 1):91.	No response from the author
Chung S, Cho E. Age- and dose-related hyponatremia during carbamazepine and oxcarbazepine therapy in children with epilepsy [abstract]. Epilepsia 2006;47(Suppl. 3);172.	Not reporting outcomes of interest
Clemens B, Menes A, Piros P, et al. Quantitative EEG effects of carbamazepine, oxcarbazepine, valproate, lamotrigine, and possible clinical relevance of the findings. Epilepsy Research 2006;70:190-9.	Not reporting outcomes of interest
Contin M, Riva R, Albani F, et al. Effect of felbamate on clobazam and its metabolite kinetics in patients with epilepsy. Therapeutic Drug Monitoring 1999;21:604-8	Not reporting outcomes of interest
De Romanis F, Sopranzi N. Lamotrigine: monotherapy in refractory epilepsy. Clinica Terapeutica 1997;148:153-8	Not a comparison of older versus newer antiepileptic drugs
De Romanis F, Sopranzi N. Felbamate: a long-term study in subjects with refractory epilepsy. Clinica Terapeutica 1997;148:83-7	Not a comparison of older versus newer antiepileptic drugs
DeToledo J, Ramsay R, Lowe M, et al. Increased seizures after discontinuing carbamazepine: results from the gabapentin monotherapy trial. Therapeutic Drug Monitoring 2000;22:753-6	Not reporting outcomes of interest
Dong X, Leppik I, White J, et al. Hyponatremia from oxcarbazepine and carbamazepine. Neurology 2005;65:1976-8	Not reporting outcomes of interest
Ehtisham A, Taylor S, Klein M, et al. Cognitive outcomes following seizure prophylaxis for intracranial hemorrhages of different subtypes with levetiracetam versus phenytoin [abstract]. Annals of Neurology 2008;64(Suppl. 12):S30	Not conducted in an epilepsy population
Ermakov A, Boldyreva S, Litvinovich, The comparative study of effectiveness of lamotrigine and other antiepileptic drugs in cryptogenic and symptomatic focal epilepsy. Zh Neurol Psikhiatr Im SS Korsahova 2007;107(12):94-7	Not in English language
Eun So-Hee, Eun B, Lee J, et al. The Effects on Cognition and Behavior of Lamotrigine Compared to Carbamazepine as Monotherapy for Children with Partial Epilepsy [abstract]. Epilepsia 2008;49(suppl. 7):88	No response from the author
Feucht M, Brantner-Inthaler S. Gamma-vinyl-GABA (vigabatrin) in the therapy of Lennox-Gastaut syndrome: an open study. Epilepsia 1994;35(5):993-8	Not a comparison of older versus newer antiepileptic drugs
Fife D, Blum D, Fisher S. Measuring the effects of antiepileptic medications on balance in older people. Epilepsy Research 2006;70:103-9	Not reporting outcomes of interest
Filho,G. M. A.;Sousa,P. S.;Garzon,E.;Sakamoto,A. C.;Yacubian,E. M. T. Psychiatric disorders in juvenile myoclonic epilepsy: A study comparing patients treated with valproate and topiramate [abstract]. Epilepsia 2005;46(Suppl. 6);180	No response from the author

Reference	Reason for Exclusion
Freidel M, Krause E, Kuhn K, et al. Oxcarbazepine in the treatment of epilepsy. Fortschr Neurol Pshchiat 2007;75:100-6	Not a comparison of older versus newer antiepileptic drugs
Garg K, Kar M, Singh K. Carbamazepine versus topiramate monotherapy: A prospective comparative study on Indian patients with single small enhancing CT lesions (SSECTLS) and seizures [abstract]. Epilepsia 2003;44 (Suppl. 8):81	No response from the author
Gates J, McCague K, D'Souza J. Oxcarbazepine is efficacious in patients with partial seizures when switching from carbamazepine phenytoin or valproate [abstract]. Epilepsia 2004;45(Suppl. 7):133	No response from the author
Gaus V, Coban I, Kretz R, et al. EURAP Germany: Seizure control and dose modifications during pregnancy under treatment with valproate, carbamazepine, and lamotrigine in monotherapy [abstract]. Epilepsia 2006;47(Suppl. S3):125	Not reporting outcomes of interest
Gaus V, Coban I, Kretz R, et al. Seizure control in the course of pregnancy under treatment with lamotrigine, carbamazepine and valproic acid in monotherapy: Observations from the German EURAP project [abstract]. Epilepsia 2005;46(Suppl. 6):261	Not reporting outcomes of interest
Gaus V, Cohan I, Dennig D, et al. EURAP Germany: Seizure control and dose modifications during pregnancy under treatment with valproate, carbamazepine and lamotrigine in monotherapy - Update 2007 [abstract]. Epilepsia 2007;48(Suppl. 6):340	Not reporting outcomes of interest
Gidal E, Tamura T, Hammer A, et al. Blood homocysteine, folate and vitamin B-12 concentrations in patients with epilepsy receiving lamotrigine or sodium valproate for initial monotherapy. Epilepsy Research 2005;64:161-6	Not reporting outcomes of interest
Gilad R, Sadeh M, Rapoport A, et al. Monotherapy of lamotrigine versus carbamazepine in patients with poststroke seizure. Clin Neuropharmacol 2007;30:189-95	Not conducted in an epilepsy population
Giorgi L, Gomez G, O'Neill F, et al. The tolerability of lamotrigine in elderly patients with epilepsy. Drugs & Aging 2001;18(8):621-30	Not a report of a new discovery
Glauser A, Privitera M, Neto W et al. Response of partial-onset or generalized seizures to topiramate, carbamazepine or valproate in newly diagnosed epilepsy [abstract]. Neurology 2005;64(Suppl. 1);A116	No response from the author
Guido M, de Tommaso M, La Neve A, et al. Event-related potentials in the evaluation of the effect of levetiracetam and carbamazepine on cognitive functions in newly diagnosed epilepsy patients: Preliminary results of a randomised trial [abstract]. Epilepsia 2007;48(Suppl. 8):107	No response from the author
Guido Mt, Goffredo R, Castriota O, et al. Event-related potentials (ERPs) in the evaluation of the effect of levetiracetam and carbamazepine on cognitive functions in adult patients with newly diagnosed epilepsy [abstract]. European Journal of Neurology 2008;15(Suppl. 3):305	No response from the author
Guo C, Ronen G, Atkinson A. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. Epilepsia 2001;42(9):1141-7.	Not reporting outcomes of interest
Hallioglu O, Okuyaz C, Mert E, et al. Effects of antiepileptic drug therapy on heart rate variability in children with epilepsy. Epilepsy Research 2008;79:49-54	Not reporting outcomes of interest
Hamed A, Fida N, Hamed E. States of serum leptin and insulin in children with epilepsy: risk predictors of weight gain. European Journal of Paediatric Neurology 2009;13:261-8	Not reporting outcomes of interest

Reference	Reason for Exclusion
Hayes F, Caldwell P, Sluss P, et al. Body weight and serum lipid levels in young women with epilepsy treated with valproate versus lamotrigine[abstract]. Epilepsia 2005;46(Suppl. 8):207	Not reporting outcomes of interest
Heller A, Wright W, LaRoche S, et al. A comparison of levetiracetam and phenytoin as seizure prophylaxis for aneurysmal subarachnoid hemorrhage [abstract]. Epilepsia 2007;48(Suppl. 6):331	Not conducted in an epilepsy population
Herranz J, Argumosa A, Rejas J, et al. Model-based evaluation of the cost-effectiveness of pregabalin, levetiracetam and generic gabapentin versus standard therapy as an add-on anti-epileptic therapy in patients with refractory epilepsy: A Spanish perspective [abstract]. Epilepsia 2005;46(Suppl. 6):115	Not a comparison of older versus newer antiepileptic drugs
Hirfanoglu T, Serdaroglu A, Camurdan O, et al. Evaluation of thyroid functions and thyroid volumes in children with epilepsy in long term administration of carbamazepine, oxcarbazepine and valproic acid [abstract]. Epilepsia 2005;46(Suppl. 6):241	Not reporting outcomes of interest
Hirfanoglu T, Serdaroglu A, Camurdan O, et al. Thyroid function and volume in epileptic children using carbamazepine, oxcarbazepine and valproate. Pediatrics International 2007;49:822-6	Not reporting outcomes of interest
Hirsch L, Arif H, Nahm E, et al. Cross-sensitivity of skin rashes with antiepileptic drug use. Neurology 2008;71:1527-34	Not a comparison of older versus newer antiepileptic drugs
Hogan R, Bertrand M, Deaton R, et al. Total percentage body weight changes during add-on therapy with tiagabine, carbamazepine and phenytoin. Epilepsy Research 2000;41:23-8	Not reporting outcomes of interest
Houtkooper M, Lammertsma A, Meyer J, et al. Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine?. Epilepsia 1987;28(6):693-8	Not a comparison of older versus newer antiepileptic drugs
Hufnagel A, Limburg S, Evers S, et al. Safety and efficacy of rapidly i.v. titrated levetiracetam versus valproate in patients with partial epilepsy [abstract]. European Journal of Neurology 2009;16(Suppl. 6):473	No response from the author
Hyson C, Sadler M. Cross sensitivity of skin rashes with antiepileptic drugs. Canadian Journal of Neurological Sciences 1997;24:245-9	Not reporting outcomes of interest
Isojarvi J, Lofgren E, Juntunen K, et al. Effect of epilepsy and antiepileptic drugs on male reproductive health. Neurology 2004;64:247-53	Not reporting outcomes of interest
Isojarvi J, Turkka J, Pakarinen A, et al. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. Epilepsia 2001;42(7):930-4.	Not reporting outcomes of interest
Isojarvi J, Tapanainen J, Rattya J, et al. Changes in Body-Weight, Fasting Serum-Insulin and Testosterone Levels and Ovarian Structure in Women with Epilepsy After Substituting Lamotrigine for Valproate [abstract]. Epilepsia 1995;36:290	Not reporting outcomes of interest
Isojarvi J, Tapanainen J, Rattya J, et al.Body-Weight, Serum Testosterone Levels, and Ovarian Structure in Women with Epilepsy After Replacement of Valproate with Lamotrigine [abstract]. Epilepsia 1995;36(Suppl. 3):S117	Not reporting outcomes of interest
Kalviainen R, Aikia M, Mervaala E, et al. Prognosis of Newly-Diagnosed Epilepsy and Effects of Initial Vigabatrin Monotherapy Compared with Carbamazepine Monotherapy [abstract]. Neurology 1994;44(Suppl. 2):A204	No response from the author

Reference	Reason for Exclusion
Kalviainen R, Aikia M, Partanen J, et al. Randomized controlled pilot study of vigabatrin versus carbamazepine monotherapy in newly diagnosed patients with epilepsy: an interim report. Journal of Child Neurology 1991;6(Suppl. 2):2S60-9	Interim report of final analysis Final analysis included in review
Kalviainen R, Halonen T, Pitkanen A, et al.Amino acid levels in the cerebrospinal fluid of newly diagnosed epileptic patients: effect of vigabatrin and carbamazepine monotherapies. Journal of Neurochemistry 1993;60(4):1244-50	Not reporting outcomes of interest
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Kim J, Lee W. Metabolic and hormonal disturbances in women with epilepsy on antiepileptic drug monotherapy. Epilepsia 2007;48(7):1366-70	Not reporting outcomes of interest
Korabathina K, Benbadis S. Levetiracetam is as effective as carbamazepine in newly diagnosed epilepsy. Expert Review of Neurotherapeutics 2007;7(6):599-601	Not a report of a new discovery in humans
Kurul S, Dirik E, Iscan A. Serum carnitine levels during oxcarbazepine and carbamazepine monotherapies in children with epilepsy. Journal of Child Neurology 2003;18:552-4	Not reporting outcomes of interest
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Labar R. Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy: a registry study. Neurology 2002;59(6)	Not a comparison of older versus newer antiepileptic drugs
Leach J, Brodie M, Sills G, et al. Randomised comparison of lamotrigine and valproate in newly diagnosed epilepsy - Efficacy, tolerability, and endocrine effects[abstract]. Epilepsia 2006;47(Suppl. 4):164	No response from the author
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Levisohn P, Holland K, Hulihan J, et al. Topiramate or valproate in juvenile myoclonic epilepsy[abstract]. Child Neurology Society 2004;56:S117	No response from the author Duplicate of full text article included in evaluation
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Lim D, Tarapore P, Chang E, et al. Safety and feasibility of switching from phenytoin to levetiracetam monotherapy for glioma-related seizure control following craniotomy: a randomized phase II pilot study. Journal of Neurooncology 2009;93:349–354	Not conducted in an epilepsy population
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Loring D, Kamin M, Karim R. Topiramate and valproate added to carbamazepine: Effect on cognitive function in adults with epilepsy [abstract]. Neurology 2001;56(Suppl 3):A334.	No response from the author
Luef G, Rauchenzauner M, Waldmann M, et al. Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug treatment. Epilepsy Research 2009:86:42-7	Not reporting outcomes of interest
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Morrell M, Hayes F, Sluss P, et al. Reproductive endocrine function in women with epilepsy treated with lamotrigine versus valproate [abstract]. Neurology 2006;66(5):A72	Not reporting outcomes of interest

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Morrell M, Hayes F, Sluss P et al. Higher incidence of components of polycystic ovary syndrome in young women with epilepsy treated with valproate versus lamotrigine[abstract]. Epilepsia, 2005;46(Suppl. 8):88	Not reporting outcomes of interest
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Pace A, Bove L, Innocenti P, et al. Epilepsy and gliomas: incidence and treatment in 119 patients. Journal of Experimental Clinical Cancer Research 1998;17(4):479-82	Not reporting outcomes of interest
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Pack A, Morrell M, Marcus R, et al. Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. Annals of Neurology 2005;57:252-7	Interim report for trial included in evaluation
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Perry M, Holt P, Olson L, et al. Comparison of levetiracetam and carbamazepine monotherapy for partial seizures in children less than 16 years of age: A retrospective review [abstract]. Annals of Neurology 2007;62(Suppl 11):S138	No response from author

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Perry M, Holt P, Olson L, et al. Comparison of levetiracetam and carbamazepine as initial monotherapy for newly diagnosed epilepsy in children < 16 years old: A retrospective review[abstract]. Epilepsia 2007;48:351	No response from author
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Pohlmann-Eden B, Van Paesschen W, Hallstrom Y, et al. The Komet Study: an Open-Label, Randomized, Parallel-Group Trial Comparing the Efficacy and Safety of Levetiracetam with Sodium Valproate and Carbamazepine as Monotherapy in Subjects with Newly Diagnosed Epilepsy [abstract]. Epilepsia, 2008;49(suppl. 7):448-9	No response from author
Prasad A, Kuzniecky R, Knowlton R, et al. Evolving antiepileptic drug treatment in juvenile myoclonic epilepsy. Archives of Neurology 2003;60:1100-5	No evaluating endpoints of interest
Privitera M, Brodie M, Neto W, et al. Topiramate, carbamazepine, and valproate in the spectrum of newly diagnosed epilepsy [abstract]. Neurology 2001;56(8):332	Duplicate of full text included in the analysis
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Rattya J, Vainionpaa L, Knip M, et al. The effects of valproate, carbamazepine, and oxcarbazepine on growth and sexual maturation in girls with epilepsy. Pediatrics 1999;130(3):588-93	No evaluating endpoints of interest
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Rudakova G, Morozova O, Kotov A. Impact of the current antiepileptic drugs on quality of life of epileptic patients. Zhurnal Nevrologii i Psikhiatrii Imeni S.S.Korsakova 2008;3:36-40	Not in English language
Rufo Campos M, Carreno,M. Utilization of carbamazepine and oxcarbazepine in pediatric patients with partial epilepsy in Spain. An observational study. Neurologia 2009;24(1):30-9	Not a comparison of older versus newer antiepileptic drugs
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Serdaroglu A, Cansu A, Camurdan O, et al. Short-term evaluation of thyroid functions and volumes in children with epilepsy treated with oxcarbazepine and valproic acid [abstract]. Epilepsia 2005;46(Suppl.6):282	No evaluating endpoints of interest
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Sillanpaa M, Pihlaja T. Oxcarbazepine (GP 47 680) in the treatment of intractable seizures. Acta Paediatrica Hungarica 1989-99;29(3-4):359-64	No evaluating endpoints of interest
Sills G, Stephen L, Butler E, et al. A randomised open-label comparison of the efficacy, tolerability, and hormonal effects of sodium valproate and lamotrigine monotherapy in newly-diagnosed epilepsy [abstract]. Epilepsia 2006:47(S3):1	No response from author
Smith D, Marson A, Smith C, et al. Valproate versus lamotrigine and topiramate for epilepsy: Results from arm B of the sanad trial [abstract]. Epilepsia 2006;47(Suppl. 4):247	Duplicate of full text included in the evaluation
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Sorokina N, Selitsky G. Cognitive effects of topiramate and depakine for frontal lobe epilepsy[abstract]. Epilepsia 2005;6(Suppl.6):311	No response from author
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Svalheim S, Tauboll E, Luef G, et al. Differential effects of levetiracetam, carbamazepine, and lamotrigine on reproductive endocrine function in adults. Epilepsy & Behavior 2009;16:281-7	No evaluating endpoints of interest
Svalheim S, Tauboll E, Rauchenzauner M, et al. Levetiracetam, Lamotrigine and Carbamazepine Differentially Influence Sex Steroid Hormones in Patients with Epilepsy [abstract]. Epilepsia 2008;49(suppl. 7):458	No evaluating endpoints of interest
Tanabe T, Awaya Y, Matsuishi T, et al. Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome)--a nationwide questionnaire survey in Japan. Brain & Development 2008;30:629-35	No evaluating endpoints of interest
Tanganelli P, Regesta G. Vigabatrin Versus Carbamazepine in Newly-Diagnosed Epileptic Patients - a Randomized-Response Conditional Cross-Over Study[abstract]. Epilepsia 1999;36(Suppl. 3):S104	No response from author
Trinka E, VanPaesschen W, Hallstrom Y, et al. The Komet Study: an Open-Label, Randomized, Parallel-Group Trial Comparing the Efficacy and Safety of Levetiracetam with Sodium Valproate and Carbamazepine as Monotherapy in Subjects with Newly Diagnosed Epilepsy[abstract]. Epilepsia 2009;50(Suppl. 4):45	No response from author
Trudeau V, Dimond K, Smith F et al. Gabapentin (Gbp Neurontin(r)) Monotherapy Compared with Carbamazepine (Cbz) Monotherapy and Combination Gbp Plus Cbz (Gbp/cbz) Therapy in Patients with Medically Refractory Partial Seizures - a 3-Way Cross-Over Trial (94536)[abstract]. Epilepsia 1995;36(Suppl. 4):68	No response from author
Tutor-Crespo M, Hermida J, Tutor J. Relation of blood platelet count during carbamazepine and oxcarbazepine treatment with daily dose, and serum concentrations of carbamazepine, carbamazepine-10, 11-epoxide, and 10-hydroxycarbazepine. Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic 2007;151(1):91-4	No evaluating endpoints of interest
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Vajda F, Hitchcock A, Graham J, et al. Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. European Journal of Neurology 2006;13:645-54	No evaluating endpoints of interest
Vajda F, O'Brien T, Hitchcock A, et al. The Australian registry of anti-epileptic drugs in pregnancy: experience after 30 months. Journal of Clinical Neuroscience 2003;10(5):543-9	No evaluating endpoints of interest
Van Paesschen W, Duncan J, Connelly A. A comparison of the neuropathological effects of vigabatrin and carbamazepine in patients with newly diagnosed localization-related epilepsy using MR-based cerebral T2 relaxation time measurements. Epilepsy Research 1998;29:155-60	No evaluating endpoints of interest
Vasquez B, Sachdeo R, Chang G, et al. Tiagabine or phenytoin as first add-on therapy for complex partial seizures[abstract]. Neurology 1998;50:A199	No response from author
Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia 2004;45(11):1330-7	No evaluating endpoints of interest

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Viteri C, Codina M, Cobaleda S, et al. Validacion de la version espanola del cuestionario de calidad de vida en epilepsia QOLIE-10. Neurologia 2008;23(3):157-67	Not in English language
Wheless J, Neto W, Twyman R. Topiramate, carbamazepine, and valproate as first-line monotherapy in children/adolescents with newly diagnosed epilepsy[abstract]. Annals of Neurology 2003;54:S135-6	No response from author
Wheless J, Neto W, Wang S. Topiramate, carbamazepine, and valproate in children with newly diagnosed epilepsy: A unique trial design[abstract]. Neurology 2001;56(8):A234-5	No response from author
Wilensky A, Friel P, Ojemann L, et al. Zonisamide in epilepsy: a pilot study. Epilepsia 1985;26(3):212-20	No evaluating endpoints of interest
Williamson P, Kolamunnage-Dona R, Philipson P, et al. Joint modelling of longitudinal and competing risks data. Statististics in Medicine 2008; 27:6426-38	No evaluating endpoints of interest
Yu L, Huang Y, Sun H, et al. Effects of topiramate and carbamazepine on thyroid hormone level in adults with epilepsy. Neural Regeneration Research 2006;1(8):706-9	No evaluating endpoints of interest
Yu P, Zhu G, Xu Y, et al. Cognitive Function and Quality of Life Effect of Valproate, Carbamazepine, and Lamotrigine in Patients with Newly Diagnosed Epilepsy After 2-Year Follow-Up [abstract]. Epilepsia 2009;50(Suppl. 10):139	No response from author
Zamponi N, Cardinali C. Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children. Archives of Neurology 1999;56:605-7	No evaluating endpoints of interest
Zarubova J, Hill M. The Effect of Lamotrigine, Carbamazepine and Valproate on the Levels of Free and Conjugated Steroids in the Serum of Premenopausal Women with Epilepsy[abstract]. Epilepsia 2009;50(Suppl. 4):84	No response from author
Zelnik,N.;Isler,N.;Goez,H, et al. Vigabatrin, lamotrigine, topiramate and serum carnitine levels. Pediatric Neurology 2008;39:18-21	No evaluating endpoints of interest

Appendix D. Glossary

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

Benign Rolandic Epilepsy: An epilepsy syndrome that occurs in childhood and usually resolves by adolescence or early adulthood. It is characterized by simple partial seizures involving the mouth and face or generalized tonic clonic seizures.

Biopharmaceutics Classification System (BCS): Classification of antiepileptic medications based on properties and relegated into 4 classes; high solubility/high permeability (Class I, optimal class with lowest risk of absorption variability), low solubility/high permeability (Class II), high solubility/low permeability (Class III) and low solubility/low permeability (Class IV).

Bone Mineral Density (BMD): A measurement of the amount of bone matter per square centimeter, expresses as grams/centimeter^2 or Z-score.
Cmax: The maximal concentration of antiepileptic medication obtained after dosing.
Confidence Intervals (CIs): A range that is likely to include the given value. Usually presented as a percent (%). For example, a value with 95% confidence interval implies that when a measurement is made 100 times, it will fall within the given range 95% of the time.
Correlation Coefficient: A value (which usually ranges from zero to one) that indicates the degree of relationship between two variables. For example, a correlation coefficient of one would indicate a strong relationship.
Css: The concentration of antiepileptic medication obtained at steady state.
DerSimonian and Laird Random-Effects Model: A statistical method based on the assumption that the effects observed in different studies (in a meta-analysis) are truly different.
Health Related Quality of Life (HRQoL): Assessment of the overall well-being of a patient. Usually in the form of questionnaires that can be tailored to specific disease states such as cystic fibrosis.
Egger's Weighted Regression Statistics: A method of identifying and measuring publication bias.
Epilepsy: A clinical phenomenon in which a person has recurrent seizures due to a chronic underlying process. The main types of seizures include partial (simple partial, complex partial, partial with secondary generalization) and generalized (absence, tonic-clonic, tonic, atonic, myoclonic).
Generalized Epilepsy: A type of epilepsy characterized by seizure activity that occurs in diffuse regions of the brain simultaneously.
I^2: Measure of degree of variation due to statistical heterogeneity. Usually reported as a percent ranging from 0 to100.
Juvenile Myoclonic Epilepsy: An epilepsy syndrome associated with central nervous system delays or dysfunction from a variety of causes, including developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions.

Lennox-Gastaut Epilepsy Syndrome: An epilepsy syndrome that occurs in children and is defined by the following triad: multiple seizure types (generalized tonic-clonic, atonic, and atypical absence), specific electroencephalographic findings (<3 Hz spike-and-wave discharges), and impaired cognitive function.
Mesial Temporal Lobe Epilepsy Syndrome: An epilepsy syndrome associated with complex partial epilepsy and hippocampal sclerosis.
Meta-Analysis: The process of extracting and pooling data from several studies investigating a similar topic to synthesize a final outcome.
Partial Epilepsy: A type of epilepsy characterized by seizure activity in discrete areas of the cerebral cortex.
Publication Bias: The possibility that published studies may not represent all the studies that have been conducted, and therefore, create bias by being left out of a meta-analysis.
Q Statistic: A test to assess the presence of statistical heterogeneity among several studies.
Relative Risks (RRs): The ratio of an event occurring in an exposed group to an event occurring in a non-exposed group in a given population. A ratio of one indicates no difference in the risk between the two groups.
Risk difference: The absolute difference in the event rate between two comparison groups. A risk difference of zero indicates no difference between comparison groups.
Sensitivity 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
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.
Z-Score: The number of standard deviations above or below the mean for the patient's age, sex and ethnicity.

Appendix E. Abbreviations

Abbreviation	Definition
"A" Rated generic	Generic drug that is equivalent to the brand name product in safety and effectiveness as determined by FDA
AED	Antiepileptic drug(s)
AOE	Applicability of Evidence
AUC	Area Under the Curve
AV defect	Atrioventricular defect
BCS	Biopharmaceutics Classification System
BMI	Body Mass Index
Ca^{2+}	Calcium ion
CI	Confidence Interval
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
C_{ss}	Average Steady-state Concentration
CNS	Central Nervous System
CP	Complex Partial Seizures
CR	Controlled Release
CT	X-ray Computed Tomography
CYP	Cytochrome P enzyme
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EQ-5D	Descriptive Health Related Quality of Life States
ER	Emergency Room
FDA	Food and Drug Administration
GABA	Gamma Amino Butyric Acid
GTCS	Generalized Tonic Clonic Seizures
H	High
HR	Hazard Ratio
I	Insufficient
IBW	Ideal Body Weight
ICS	International Classification of Epileptic Seizures
ILAE	International League Against Epilepsy
IQ	Intelligence Quotient
JME	Juvenile Myoclonic Epilepsy
L	Low
M	Moderate
MRI	Magnetic Resonance Imaging
Na^{+}	Sodium ion
NEWQOL	Newly Diagnosed Epilepsy Quality of Life
NMDA	N-methyl D-aspartic acid
NNT	Number Needed to Treat
NRCT	Non Randomized Controlled Trial
OBS	Observational Study
PCOS	Polycystic Ovary Disease
PE	Partial Epilepsy
QOLIE-89	Quality of Life in Epilepsy-89
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation

Abbreviation	Definition
SMD	Standardized Mean Difference
SOE	Strength of Evidence
SR	Sustained Release
SANAD	Standard And New Antiepileptic Drugs
SEALS Inventory	Side Effect and Life Satisfaction Inventory
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
T_{max}	Time to Maximum Concentration
WMD	Weighted Mean Difference

Appendix F. Baseline Characteristics for Included Studies and Trials

Table 1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Antiepileptic Drug Class									
Zachry,2009 (N=1664)	Retrospective Observational (Case-control)	United States	Abbott Laboratories sponsored the study and three authors were employees	Fair – Retrospective, uses case-control methodology which has more inherent limitations, did not control for factors other than epilepsy diagnosis code and age. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported	Innovator antiepileptic	"A" rated generic antiepileptic	Six months before the index date	Cases : Received ambulance transport, emergency department visitation, or inpatient hospitalization for epilepsy occurred between July 1 and December 31, 2006 (the index date). Controls: Ambulatory office visit for with a primary diagnosis of epilepsy between July 1 and December 31, 2006 (the index date)	ICD-9 code for infantile spasms, aged below 12 or over 64 years of age, or did not have continuous insurance coverage for 6 months before the index date Cases were matched 3:1 for age and ICD-9 codes to controls, other controls were excluded
Rascati, 2009 (N=3964)	Retrospective Observational (Case-control)	United States	Unrestricted educational grant from Abbott Laboratories	Fair – Retrospective, uses case-control methodology which has more inherent limitations, did not control for factors other than epilepsy diagnosis code	Various	Various Only "A" rated generics were evaluated	-	Patients with and ICD-9 code for epilepsy (excluding infantile spasm) in the PharMetrics database (a database accounting for 55 million	Patients with an ICD-9 code for infantile spasms Cases were matched 3:1 for age (within 5 years), gender, and ICD-9 codes to controls, other

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
				and age. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported				patients from across the United States) between 12 and 64 years of age, continuous insurance coverage and a prescription for antiepileptic drugs for 145 days. Cases were identified if they had an epilepsy related acute event (ambulance service, emergency department visit, or hospitalization) between Oct. 1, 2005 and Dec. 31, 2006 and no acute event 6 months prior. Controls were identified if they had epilepsy and visited a doctor's office during the same time period but did not have an acute event.	controls were excluded

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Devine, 2010 (N=11796) ESI Study	Retrospective Observational Cohort study	United States	Express Scripts, Inc.	Fair – Retrospective, uses case-control methodology which has more inherent limitations, controlled for factors such as epilepsy diagnosis code, age, gender, geographical location, co-morbidities, disease severity, interacting medication, non-adherence, patient diagnosis, baseline disease state, and time. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported	Various	Various Only "A" rated generics were evaluated	90 days before the index date	The study population was made up of individuals with stable epilepsy and AED use during the last 6 months of 2005. Patients were included in the study if they: (1) had a primary or secondary diagnosis of epilepsy, (2) had a prescription claim for an AED with a days' supply carrying over through January 1, 2006, (3) had eligibility for medical and prescription benefit coverage as of July 1, 2005 through June 30, 2006, and (4) were between the ages of 18 and 64 (inclusive) as of January 1, 2006	Patients younger than 18 years old were not included in the study due to unstable hormone levels increasing their risk for epilepsy exacerbations. Patients 65 years and older were not included because they are not represented in the MarketScan commercial database. Patients were excluded when there was one or more inpatient or emergency room claim with a primary diagnosis of epilepsy between July 1 and December 31, 2005, as patients with a recent history of exacerbation of epilepsy may be at high risk for repeat seizures

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Labiner, 2010a (N=18125)	Retrospective Observational Cohort study	United States	GlaxoSmithKline One author is an employee of GlaxoSmithKline	Poor – Not limited to "A" rated generics, dosing may or may not have been similar, administrative claims data does not have several potentially relevant confounders (including disease severity), there may be inaccuracies in coding of diagnoses and procedures, whether drugs dispensed were consumed and how were consumed is not known, if limited to innovator or branded generics is not known, exact brand names and forms included not reported	Branded carbamazepine, phenytoin, primidone, zonisamide (if limited to innovator or branded generics is not known, exact brand names and forms included not reported)	Carbamazepine gabapentin, phenytoin, primidone, zonisamide (Manufacturers not reported)	From target medication dispensing until 30 days after the last drug supply was obtained, health coverage ended, or the end of data availability, whichever occurred first. Mean observation period ~ 4 years	Patients 18 years or older with 2 or more years of continuous health plan e-ollment, an ICD-9 code for nonfebrile convulsions (ICD-9: 780.3 or 780.39), dispensing of target drugs (carbamazepine , gabapentin, phenytoin, primidone, zonisamide) at least twice, and at least 60 days worth of drugs dispensed during the first 90 days of treatment. Stable patients only	For gabapentin, only monotherapy use was permitted to reduce the risk of use in nonepilepsy indications

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Labiner, 2010b (N=15500)	Retrospective Observational Cohort study	United States	GlaxoSmithKline One author is an employee of GlaxoSmithKline	Poor – Not limited to "A" rated generics, dosing may or may not have been similar, administrative claims data does not have several potentially relevant confounders (including disease severity), there may be inaccuracies in coding of diagnoses and procedures, whether drugs dispensed were consumed and how were consumed is not known, if limited to innovator or branded generics is not known, exact brand names and forms included not reported	Branded carbamazepine, phenytoin, primidone, zonisamide (if limited to innovator or branded generics is not known, exact brand names and forms included not reported)	Carbamazepine gabapentin, phenytoin, primidone, zonisamide	From target medication dispensing until 30 days after the last drug supply was obtained, health coverage ended, or the end of data availability, whichever occurred first. Mean observation period ~ 4 years	Patients 18 years or older with 2 or more years of continuous health plan e-ollment, an ICD-9 code for nonfebrile convulsions (ICD-9: 780.3 or 780.39), dispensing of target drugs (carbamazepine , gabapentin, phenytoin, primidone, zonisamide) at least twice, and at least 60 days worth of drugs dispensed during the first 90 days of treatment. Unstable patients only	For gabapentin, only monotherapy use was permitted to reduce the risk of use in nonepilepsy indications
Carbamazepine									

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Kauko, 1974 (N=20)	Two Concurrently run unblinded "before and after" trials	Finland	Drug provided by Ciba-Geigy	Poor – Before and after evaluations, exclusion criteria and demographics not well described, only pharmacokinetic endpoints evaluated, no measure of AUC, not an "A" rated generic in the United States	Tegretol (Ciba-Geigy) tablets 15.6 mg/kg/day	Carbamazepine (Laake Oy) 15.6 mg/kg/day Not an "A" rated generic in the United States	20 weeks	In the first trial, patients had to be taking generic carbamazepine at baseline. In the second trial, patients had to be taking Tegretol at baseline	-
Glende, 1983 (N=5)	Ramdomized crossover design	Germany	Unknown		Tegretol (Ciba-Geigy) tablets	Carbamazepine (AWD Dresden) Not an "A" rated generic in the United States	4 weeks (2 weeks per phase)	The patients had been receiving carbamazepine for several years	-
Jumao-as, 1989 (N=10)	Randomized Double-blind Crossover	United States	Veterans Administration and University of Pittsburgh	Fair – Demographics not well described, dose of carbamazepine not reported, not an "A" rated generic in the United States	Tegretol (Ciba-Geigy) tablets	Carbamazepine (Parke-Davis) tablets Not currently an "A" rated generic in the United States	10 weeks (5 weeks per phase)	The patients had to be receiving carbamazepine prior to entry and had at least 1 seizure in the past year.	-
Hartley, 1990 (N=23)	Randomized Crossover Blinding not reported	United Kingdon	Ciba-Geigy funded the study and provided carbamazepine tablets. UK Generics provided the generic tablets	Fair – Short duration of followup, not an "A" rated generic in the United States	Tegretol (Ciba-Geigy) Tablets 16.2 mg/kg/day	Carbamazepine (United Kingdom Generics) 16.2 mg/kg/day Not an "A" rated generic in the United States	12 weeks (6 weeks per phase)	Patients needed to experience at least 3 seizures in the past to be included	-

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Hartley, 1991 (N=12)	Randomized Crossover Blinding not reported	United Kingdom	-	Fair – Blinding not reported, exact dose of carbamazepine not reported, not an "A" rated generic in the United States	Tegretol (Ciba-Geigy) Tablets ~20mg/kg/day	Carbamazepine (Ethical Generics) Tablets ~20mg/kg/day Not an "A" rated generic in the United States	12 weeks (6 weeks per phase)	-	-
Oles, 1992a (N=20)	Randomized Double-blind Crossover	United States	Financial support: Lemmon Co; Drug: Ciba-Geigy	Good –	Tegretol (Ciba-Geigy) Tablets 12.4 (3.5) mg/kg daily	Carbamazepine (Lemmon Co) Tablets 12.4 (3.5) mg/kg daily An "A" rated generic in the United States	6 months (3 months in each phase with pharmacokinetics determined 2 weeks into each phase)	Patients had to be seizure-free for over 5 months	Taking carbamazepine for less than 6 months, and hepatic or renal disease
Oles, 1992b (N=20)	Randomized Double-blind Crossover	United States	Financial support: Lemmon Co; Drug: Ciba-Geigy	Good - Followup was brief	Tegretol (Ciba-Geigy) Tablets 21.9 (6.2) mg/kg daily	Carbamazepine (Lemmon Co) Tablets 21.9 (6.2) mg/kg daily An "A" rated generic in the United States	6 months (3 months in each phase with pharmaco-kinetics determined 2 weeks into each phase)	Patients had to have refractory seizures.	Taking carbamazepine for less than 6 months, and hepatic or renal disease
Reunanen, 1992 (N=21)	Randomized Single-blind Crossover	Finland	-	Poor – Single-blinded, not an "A" rated generic in the United States, short duration of followup	Tegretol Retard (Ciba-Geigy) Tablets 685 (268) mg/day	Carbamazepine (Laakefarmos) Tablets 685 (268) mg/day Not an "A" rated generic in the United States	4 weeks (2 weeks per phase)	Patients age 18-65 years with epilepsy	Seizure within the past 4 months; severe psychiatric, renal, hepatic, gastrointestinal, other disease that impact absorption; drug or alcohol abuse

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Silpakit, 1997 (N=18)	Randomized Double-blind Three phase Crossover	Thailand	Srithanya Hospital Fund	Fair – Not an "A" rated generic in the United States, short duration of followup	Tegretol (Ciba-Geigy) Tablets 677.8 (155.5) mg/day	Carbamazepine (Central Poly) 677.8 (155.5) mg/day Carbamazepine (Condrugs) 677.8 (155.5) mg/day Carbamazepine (Pharmaland) 677.8 (155.5) mg/day Not an "A" rated generic in the United States	12 weeks (3 weeks each phase)	Patients had to have epilepsy, epilepsy with psychosis, or temporal lobe psychosis	Seizure free for <5 months, abnormal renal or liver function, electrolyte of blood count abnormalities
Aldenkamp, 1998 (N=12)	Randomized Open-Label Crossover	Netherlands	Unknown	Fair – Not an "A" Rated Generic in the United States, Open Label	Tegretol (Ciba-Geigy) Tablets Average dose for all products: 717 (180)mg	Carbamazepine (Pharmachemie) Tablets Carbamazepine (Pharbita) Tablets Average dose for all products 717 (180)mg Not an "A" rated generic in the United States	9 days total, 3 days per therapy	Outpatients with average intelligence with ages between 18 and 60 years. Epilepsy treated with carbamazepine monotherapy for >2 months	Psychiatric, heart, liver, kidney, thyroid, pulmonary, or hematologic disorders; neurological deficits other than epilepsy; or use of non-antiepileptic neurological agents except modest alcohol intake

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Garnett, 2005 (N=980)	Retrospective Observational (Cohort)	United States	Shire US, Inc	Poor – Retrospective design, data on outcomes not adjusted for confounders, dose not controlled, some changes in CBZ exposure after study entry, not limited to "A" rated generics	Tegretol (Novartis) Tablets	Carbamazepine Tablets Not limited to "A" rated products	-	Patients 18 years or older with ICD-9-CM codes for epilepsy and started on immediate release carbamazepine between 1999 and 2001 in the PharMetrics database	Incomplete data records or a history of pre-existing conditions (aplastic anemia, agranulocytosis , Lyell's or Stevens-Johnson syndrome, psychosis, brain cancer, visual disturbances, ataxia, confusion, diplopia, or vertigo

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
LeLorier, 2008d (N=851)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript		Tegretol CR	Carbamazepine Whether they were "A" rated products in the United States is not known. Whether only sustained release generics were allowed in the study is not known	Mean duration of observation 1,117 (307.6) days	Patients with medical and pharmacy claims in Quebec's provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Tegretol CR for at least sixty days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy	-
Clobazam									
Andermann, 2007b (N=1600)	Retrospective Observational Before-and-after	Canada	GlaxoSmithKline	Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only "A" rated generics were used is not known	Frisium	Clobazam (manufacturers not reported) Whether only "A' rated generics were used is not known	The study period ranged from 1 year before generic entry to March 2006	Patients who continuously used Frisium for 3 or more months in the 6 months preceding generic entry.	Patients who were not switched to the generic counterpart

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
LeLorier, 2008b (N=1060)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript	Poor – Retrospective, whether generics were "A" rated was unknown, no attempts made to correct for baseline differences	Frisium	Clobazam Whether they were "A" rated products in the United States is not known	Mean duration of observation 1,090 (329.4) days	Patients with medical and pharmacy claims in Quebec's provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Frisium for at least 60 days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy	-
Gabapentin									

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
LeLorier, 2008c (N=202)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript	Poor – Retrospective, whether generics were "A" rated was unknown, no attempts made to correct for baseline differences	Neurontin	Gabapentin Whether they were "A" rated products in the United States is not known	Mean duration of observation 1,019 (351.5) days	Patients with medical and pharmacy claims in Quebec's provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Neurontin for at least 60 days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy	-
Lamotrigine									

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Andermann, 2007a (N=1142)	Retrospective Observational Before-and-after	Canada	GlaxoSmithKline	Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only "A" rated generics were used is not known	Lamictal Group who switched to generic and then switched back: 252.2 mg and 250.7 mg. Group who switched to generic but did not switch back: 255.3 mg	Lamotrigine (manufacturers not reported) Group who switched to generic and then switched back: 254.6 mg. Group who switched to generic but did not switch back: 271.1 mg Whether only "A' rated generics were used is not known	The study period ranged from 1 year before generic entry to March 2006	Patients who continuously used Lamictal for 3 or more months in the 6 months preceding generic entry.	Patients who were not switched to the generic counterpart
LeLorier, 2008a (N=671)	Retrospective Observational (Cohort study)	Canada	GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript	Poor – Retrospective, whether generics were "A" rated was unknown, no attempts made to correct for baseline differences	Lamictal (GlaxoSmithKline) 239.1 mg/day	Lamotrigine (manufacturer(s) not reported) 251.4 mg/day Whether they were "A" rated products in the United States is not known	Mean duration of observation 1,098 (327.9) days	Patients with medical and pharmacy claims in Quebec's provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Lamictal for at least sixty days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy	-

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Nielsen, 2008a (N=9)	Before-and-after Unblinded	Denmark	Funding for the study was not reported but one author was on the UCB advisory board and another author has received speaker fees and sponsorship from several pharmaceutical companies	Poor – Before and after design, multiple generics being compared to a single innovator product, small sample size, population all had concerns or problems on generic medication in the past, not "A" rated generics in the United States, short duration of followup	Lamictal 755.6 (202) mg	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada) 755.6 (202) mg Generics stated to be bioequivalent with innovator lamotrigine. Not "A" rated generics in the United States	17 days, patients were on Lamictal for 2 weeks and then on a generic for 7-15 days	Patients had to have reported a problem after switching from innovator to generic to be eligible for entry into the trial	-
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin									
Lund, 1974 (N=9)	Prospective Before-and-after	Sweden	Swedish Medical Research Council	Poor Sequential, not randomized	Epanutin (Parke-Davis) capsules, 100 mg Patients continued on same dose from baseline	Phenytoin sodium (Leo) capsules, 100 mg Patients continued on same dose from baseline	Epanutin days 1 to 8, phenytoin sodium days 9-19	Epileptic outpatients	-

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Chen, 1982 (N=18)	Prospective Crossover	United Kingdom	-	Poor Sequential, not randomized. Different dosage forms compared (tab vs cap)	Epanutin (Parke-Davis) capsules, 100 mg, 50 mg Patients continued on same dose from baseline\	Phenytoin sodium (Boots) tablets, 100 mg, 50 mg Phenytoin sodium (Cox) tablets, 100 mg, 50 mg Phenytoin sodium (Kerfoot) tablets, 100 mg, 50 mg Phenytoin sodium (McCarthy UK) tablets, 100 mg, 50 mg Patients continued on same dose from baseline	3 weeks per product	Aged 26 to 68 years on long-term treatment with phenytoin	-
Hodges, 1986 (N=30)	Randomized Crossover	United Kingdom	Parke-Davis	Fair Not the same dosage form compared	Phenytoin (Parke-Davis) capsules, 50 mg Dose ranged from 5 to 7.5 mg/kg/day	Phenytoin (Boots) tablets, 50 mg Phenytoin (Evans) tablets, 50 mg Dose ranged from 5 to 7.5 mg/kd/day	4 weeks per product	New patients between 3 and 15 years	-
Kishore, 1986 (N=60)	Randomized Parallel	India	-	Fair Blinding uncertain	Dilantin (Parke-Davis, India) capsules, 100 mg In patients weighing <55kg, 200 mg/day In patients ≥55 kg, 300 mg/day	Phenytoin (Epsolin, Cadila) tablets, 100 mg Phenytoin (Eptoin, Boots India) tablets, 100 mg Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules, 100 mg Salt forms not reported In patients weighing <55kg, 200 mg/day In patients ≥55 kg, 300 mg/day	3 months	Newly diagnosed epilepsy patients	-

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Mikati, 1992 (N=10)	Randomized Crossover Double-blinded	United States	-	Fair Not all patients with epilepsy. Sample size small	Dilantin (Parke-Davis) capsule, 100 mg	Phenytoin (Phenytex, manufacturer not reported) capsules, 100 mg	3 months per product	Adults aged 18 to 60 years receiving phenytoin monotherapy for seizure prophylaxis. All but one had partial or generalized seizures. One patient was receiving phenytoin prophylaxis after intracranial surgery	Patients judged to have poor compliance or judged to be u-eliable in reporting the necessary information, side effects, or seizures
Soryal, 1992 (N=14)	Randomized Crossover Observer-blinded	United Kingdom	-	Fair Different dosage forms	Epanutin (Parke-Davis) capsules, 100 mg, 50 mg Patients continued on same dose from baseline	Phenytoin sodium (Evans) tablets, 100 mg, 50 mg Phenytoin sodium (APS) tablets, 100 mg, 50 mg Phenytoin sodium (Cox) tablets, 100 mg, 50 mg Phenytoin sodium (Kerfoot) tablets, 100 mg, 50 mg Phenytoin sodium (Regent) tablets, 100 mg, 50 mg Patients continued on same dose from baseline	4 weeks per product	Patients with epilepsy from the Epilepsy Unit on maintenance treatment with phenytoin	-
Topiramate									

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Duh, 2009 (N=948)	Retrospective Observational Registry database	Canada	Ortho-McNeil Janssen Scientific Affairs	Poor	Topamax (Ortho-McNeil)	Topiramate (Various manufacturers) Also provided switchback rates for: Lamotrigine Gabapentin Divalproex Clobazam Clonazepam Valproate Carbamazepine	Starting 180 days before generic entry or January 2000, through the end of patient eligibility, treatment discontinua-tion or October 2007	Patients from the RAMQ database with epilepsy with continuous health plan coverage, treated for at least 60 days with the branded version of one of the AED or non-AED study drugs before the generic entry date, and at least one dispensing of the studied drug (brand or generic) following generic entry, and continuous use of the studied drug throughout the study period	-

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Paradis, 2009[a] (N=1164)	Retrospective Observational Registry database	Canada	Janssen-Cilag EMEA	Poor	Topamax (Ortho-McNeil)	Topiramate (Various manufacturers)	From January 2006 to September 2008	Patients from the RAMQ database with epilepsy with continuous health plan coverage, treated for at least 60 days with the branded version of one of the AED or non-AED study drugs before the generic entry date, and at least one dispensing of the studied drug (brand or generic) following generic entry, and continuous use of the studied drug throughout the study period	-
Valproic Acid									
Vadney, 1997 (N=64)	Randomized Crossover Open-label	United States	Texas Department of Mental Health and Mental Retardation	Fair Not blinded	Depakene (Abbott)	Valproic acid (Solvay)	4 weeks per product	Patients at an Intermediate Care Facility for the Mentally Retarded who were already receiving either valproic acid or Depakene for primary diagnosis of seizure disorder	Individuals who could not be at the facility for consistent observation, those who required any change in an antieptileptic drug or psychotropic medication, or residents who experienced toxicity

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Innovator Product (Manufacturer), Dose	Generic Product (Alternate Name, Manufacturer), Dose	Followup	Inclusion Criteria	Exclusion Criteria
Andermann, 2007c (N=2017)	Retrospective Observational Before-and-after	Canada	GlaxoSmithKline	Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only "A" rated generics were used is not known	Depakene	Valproic Acid (manufacturers not reported) Whether only "A" rated generics were used is not known	The study period ranged from 1 year before generic entry to March 2006	Patients who continuously used Depakene for 3 or more months in the 6 months preceding generic entry	Patients who were not switched to the generic counterpart

[a]Reports on same database as Duh 2009
Legend: -=not reported; N=sample size

Table 2. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drug

Study, year	Group	N	Mean Age (SD)	Male (%)	Body weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Antiepileptic Drug Class										
Rascati, 2009	Cases	991	35.6 (15.1)	49.0	-	-	-	-	-	-
	Controls	2973	35.6 (15.1)	48.6	-	-	-	-	-	-
Zachry, 2009	Cases	416	37.4 (14.8)	45.0	-	-	-	-	-	-
	Controls	1248	37.5 (14.7)	44.2	-	-	-	-	-	-
Devine, 2010	Cases	2949	42	43.9	-	-	-	-	-	-
	Controls	8847	44	44.7	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported) Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	52.5 (16.0)	47.6	-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported) Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	49.1 (16.1)	49.2	-	-	-	-	-	-
Carbamazepine										
Kauko, 1974	Tegretol (Ciba-Geigy) Tablets Generic Carbamazepine (Laake Oy) Tablets	20	20 years (Range: 7 to 34)	70.0	-	-	-	-	-	-

						Race				
Study, year	**Group**	**N**	**Mean Age (SD)**	**Male (%)**	**Body weight (kg)**	**Caucasian (%)**	**Black (%)**	**Asian (%)**	**Hispanic (%)**	**Other (%)**
Glende, 1983	Tegretol (Ciba-Geigy) Tablets Carbamazepine (AWD Dresden) Tablets	5	Range: 19-42 years	80	Range: 50-83	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets Generic Carbamazepine (Parke Davis) Tablets	10	Range: 34 – 70 Years	100.0	-	-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy) Carbamazepine (Ethical Generics)	23	10.7 (2.9)	60.9	35.8 (11.8)	-	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets Generic Carbamazepine (Ethical Generics) Tablets	12	10.6 (2.8)	75.0	-	-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Lemmon Co) Tablets	20	33.4 (15.4)	-	-	-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Lemmon Co) Tablets	20	36.8 (16.2)	-	-	-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Central Poly) Tablets Carbamazepine (Condrugs) Tablets Carbamazepine (Pharmaland) Tablets	18	32.9 (9.1)	50	53.9 (11.9)	-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	42.7 (12.7)	40	-	-	-	-	-	-

Study, year	Group	N	Mean Age (SD)	Male (%)	Body weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
	Carbamazepine Slow Release (Laakefarmos) Tablets									
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	45.1 (10.6)	58.3	-	-	-	-	-	-
	Carbamazepine (Pharmachemie) Tablets									
	Carbamazepine (Pharbita) Tablets									
Garnett, 2005	Tegretol (Novartis) Tablets	275	40.6 (SE 0.8)	41.1	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	43.5 (SE 0.6)	40.0	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	40 (17.3)	50.6	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)									
Clobazam										
Andermann, 2007b	Frisium (manufacturer not reported)	1600	38.5 (20.5)	50.8	-	-	-	-	-	-
	Clobazam (manufacturers not reported)									
LeLorier, 2008b (N=1060)	Frisium (manufacturer not reported)	1060	38 (18.5)	47.4	-	-	-	-	-	-
	Clobazam (manufacturer not reported)									
Gabapentin										
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	49 (18.5)	39.6	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)									
Lamotrigine										

Study, year	Group	N	Mean Age (SD)	Male (%)	Body weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Andermann, 2007a	Lamictal (GlaxoSmithKline) Lamotrigine (manufacturers not reported)	1445	38.9 (20.8)	46.5	-	-	-	-	-	-
LeLorier, 2008	Lamictal (GlaxoSmithKline) Lamotrigine (manufacturer(s) not reported)	671	39 (18.7)	43.8	-	-	-	-	-	-
Nielsen, 2008	Lamictal (manufacturer not reported) Lamotrigine (Copyform Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)	9	43.8 (10.4)	66.7	-	-	-	-	-	-
Levetiracetam; Oxcarbazepine, Phenobarbital or Primidone, Phenytoin										
Lund, 1974	Epanutin (Parke-Davis) capsules Phenytoin sodium (Leo) capsules	9	-	-	-	-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules Phenytoin sodium (Boots) tablets Phenytoin sodium (Cox) tablets Phenytoin sodium (Kerfoot) tablets Phenytoin sodium (McCarthy UK) tablets	18	-	-	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules Phenytoin (Boots) tablets Phenytoin (Evans) tablets	30	9.5 years of 30 initially enrolled	60% of 30 initially enrrolled	-	-	-	-	-	-

Study, year	Group	N	Mean Age (SD)	Male (%)	Body weight (kg)	Race				
						Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Kishore, 1986	Dilantin (Parke-Davis, India) capsules Phenytoin (Epsolin, Cadila) tablets Phenytoin (Eptoin, Boots India) tablets Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	60	30.3 (11.3)	-	55.4 (5.1)[m] 49 (7.5)[f]	-	-	-	-	-
Mikati, 1992[a]	Dilantin (Parke-Davis) capsules Phenytoin (Phenytex, manufacturer not reported) capsules	10	-	54% of 13 enrolled	-	-	-	-	-	-
Soryal, 1992[a]	Epanutin (Parke-Davis) capsules Phenytoin sodium (Evans) tablets Phenytoin sodium (APS) tablets Phenytoin sodium (Cox) tablets Phenytoin sodium (Kerfoot) tablets Phenytoin sodium (Regent) tablets	14	Range 18 to 67 years	35%	All within 20% of IBW	-	-	-	-	-
Topiramate										
Duh, 2009 (N=948)	Topamax (Ortho-McNeil)	875	34.5 (17.0)	39.3%	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	37.5 (16.1)	41.4%	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	33.7 (14.7)	32.3%	-	-	-	-	-	-
Paradis, 2009[b] (N=1164)	Topamax (Ortho-McNeil) Topiramate (Various manufacturers)	1164	39.8 (17.2)	38.3%	-	-	-	-	-	-
Valproic Acid										

						Race				
Study, year	**Group**	**N**	**Mean Age (SD)**	**Male (%)**	**Body weight (kg)**	**Caucasian (%)**	**Black (%)**	**Asian (%)**	**Hispanic (%)**	**Other (%)**
Vadney, 1997	Depakene (Abbott) Valproic acid (Solvay)	64	39.6 (Range 17 to 72)	-	59.6 kg (Range 35 to 94)	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported) Valproic Acid (manufacturers not reported)	2017	44.4 (18.2)	48.0	-	-	-	-	-	-

[a]Crossover Study
[b]Reports on same database as Duh 2009
Legend: -=not reported; IBW=ideal body weight; [f]=value for females; kg=kilograms, N=sample size, [m]=value for males; SD=standard deviation

Table 3. Baseline characteristics of controlled studies comparing innovator versus generic antiepileptic drugs

			Epilepsy History				Seizure Type					
Study, year	**Group**	**N**	**New-Onset (%)**	**Chronic (%)**	**Age at Onset (SD)**	**Epilepsy Duration (SD)**	**Partial (otherwise not reported) (%)**	**Simple Partial (%)**	**Complex Partial (%)**	**Generalized (otherwise not reported) (%)**	**Tonic-Clonic (%)**	**Absence (%)**
Antiepileptic Drug Class												
Rascati, 2009	Cases	991	-	-	-	-	21.7	-	-	31.7	-	-
	Controls	2973	-	-	-	-	21.7	-	-	31.7	-	-
Zachry, 2009	Cases	416	-	-	-	-	45.6	-	-	39.6	-	-
	Controls	1248	-	-	-	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	20.4	-	-	16.9	-	-
	Controls	8847	-	-	-	-	20.4	-	-	16.9	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-	-
Carbamazepine												
Kauko, 1974	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-	-

			Epilepsy History				Seizure Type					
Study, year	**Group**	**N**	**New-Onset (%)**	**Chronic (%)**	**Age at Onset (SD)**	**Epilepsy Duration (SD)**	**Partial (otherwise not reported) (%)**	**Simple Partial (%)**	**Complex Partial (%)**	**Generalized (otherwise not reported) (%)**	**Tonic-Clonic (%)**	**Absence (%)**
	Generic Carbamazepine (Laake Oy) Tablets											
Glende, 1983	Tegretol (Ciba-Geigy) Tablets Carbamazepine (AWD Dresden) Tablets	5	-	-	-	-	-	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets Generic Carbamazepine (Parke Davis) Tablets	10	-	-	-	-	-	-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy) Carbamazepine (Ethical Generics)	23	56.5%	43.5%	-	-	-	8.7	8.7	-	82.6	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Ethical Generics) Tablets	12	-	-	-	-	-	-	Patients had experienced 3 complex partial or tonic-clonic seizures in the past	-	Patients had experienced 3 complex partial or tonic-clonic seizures in the past	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Lemmon Co) Tablets	20	-	-	-	-	-	-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Lemmon Co) Tablets	20	-	-	-	-	-	-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	-	-	16.0 (9.6)	-	5.0	15.0	80.0	-	-

			Epilepsy History				Seizure Type					
Study, year	**Group**	**N**	**New-Onset (%)**	**Chronic (%)**	**Age at Onset (SD)**	**Epilepsy Duration (SD)**	**Partial (otherwise not reported) (%)**	**Simple Partial (%)**	**Complex Partial (%)**	**Generalized (otherwise not reported) (%)**	**Tonic-Clonic (%)**	**Absence (%)**
	Carbamazepine Slow Release (Laakefarmos) Tablets											
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Central Poly) Tablets Carbamazepine (Condrugs) Tablets Carbamazepine (Pharmaland) Tablets	18	-	-	-	7.0 (5.7)	-	-	22.2	-	44.4	-
Aldenkamp, 1998 (N=12)	Tegretol (Ciba-Geigy) Tablets Generic (Pharmachemie) Tablets Generic (Pharbita) Tablets	12	0	100	-	178.4 (193) mo	75.0	-	16.7	8.3	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported) Carbamazepine CR (manufacturer not reported)	851	-	-	-	-	-	-	-	-	-	-
Clobazam												
Andermann, 2007b	Frisium (manufacturer not reported) Clobazam (manufacturers not reported)	1600	-	-	-	-	-	-	-	-	-	-

			Epilepsy History				Seizure Type					
Study, year	**Group**	**N**	**New-Onset (%)**	**Chronic (%)**	**Age at Onset (SD)**	**Epilepsy Duration (SD)**	**Partial (otherwise not reported) (%)**	**Simple Partial (%)**	**Complex Partial (%)**	**Generalized (otherwise not reported) (%)**	**Tonic-Clonic (%)**	**Absence (%)**
LeLorier, 2008b	Frisium (manufacturer not reported) Clobazam (manufacturer not reported)	1060	-	-	-	-	-	-	-	-	-	-
Gabapentin												
LeLorier, 2008c	Neurontin (manufacturer not reported) Gabapentin (manufacturer not reported)	202	-	-	-	-	-	-	-	-	-	-
Lamotrigine												
Andermann, 2007	Lamictal (GlaxoSmithKline) Lamotrigine (manufacturers not reported)	1142	-	-	-	-	-	-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline) Lamotrigine (manufacturer(s) not reported)	671	-	-	-	-	-	-	-	-	-	-
Nielsen, 2008a	Lamictal (manufacturer not reported) Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)	9	-	-	-	-	-	-	55.6	11.1	-	22.2
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin												

			Epilepsy History				Seizure Type					
Study, year	Group	N	New-Onset (%)	Chronic (%)	Age at Onset (SD)	Epilepsy Duration (SD)	Partial (otherwise not reported) (%)	Simple Partial (%)	Complex Partial (%)	Generalized (otherwise not reported) (%)	Tonic-Clonic (%)	Absence (%)
Lund, 1974	Epanutin (Parke-Davis) capsules Phenytoin sodium (Leo) capsules	9	-	-	-	-	-	-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules Phenytoin sodium (Boots) tablets Phenytoin sodium (Cox) tablets Phenytoin sodium (Kerfoot) tablets Phenytoin sodium (McCarthy UK) tablets	18	-	-	-	-	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules Phenytoin (Boots) tablets Phenytoin (Evans) tablets	30	-	-	-	-	-	-	13%	-	87%	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules Phenytoin (Epsolin, Cadila) tablets Phenytoin (Eptoin, Boots India) tablets Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	60	60	-	-	-	-	-	-	-	-	-
Mikati, 1992[a]	Dilantin (Parke-Davis) capsules Phenytoin (Phenytex, manufacturer not reported) capsules	10	-	-	-	-	-	-	-	-	-	-

			Epilepsy History				Seizure Type					
Study, year	**Group**	**N**	**New-Onset (%)**	**Chronic (%)**	**Age at Onset (SD)**	**Epilepsy Duration (SD)**	**Partial (otherwise not reported) (%)**	**Simple Partial (%)**	**Complex Partial (%)**	**Generalized (otherwise not reported) (%)**	**Tonic-Clonic (%)**	**Absence (%)**
Soryal, 1992[a]	Epanutin (Parke-Davis) capsules Phenytoin sodium (Evans) tablets Phenytoin sodium (APS) tablets Phenytoin sodium (Cox) tablets Phenytoin sodium (Kerfoot) tablets Phenytoin sodium (Regent) tablets	14	-	-	-	-	-	-	-	-	-	-
Topiramate												
Duh, 2009 (N=948)	Topamax (Ortho-McNeil)	875	-	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-	-	-	-	-
Paradis, 2009[a] (N=1164)	Topamax (Ortho-McNeil) Topiramate (Various manufacturers)	1164	-	-	-	-	-	-	-	-	-	-
Valproic Acid												
Vadney, 1997	Depakene (Abbott) Valproic acid (Solvay)	64	-	-	-	-	-	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-	-	-	-

			Epilepsy History				Seizure Type					
Study, year	**Group**	**N**	**New-Onset (%)**	**Chronic (%)**	**Age at Onset (SD)**	**Epilepsy Duration (SD)**	**Partial (otherwise not reported) (%)**	**Simple Partial (%)**	**Complex Partial (%)**	**Generalized (otherwise not reported) (%)**	**Tonic-Clonic (%)**	**Absence (%)**
	Valproic Acid (manufacturers not reported)											

[a]Crossover Study
Legend: -=not reported; N=sample size; SD=standard deviation

Table 4. Prior or concurrent AED use in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproid Acid (%)	Combination Therapy (%)
Antiepileptic Drug Class							
Rascati, 2009	Cases	991	0	-	-	-	-
	Controls	2973	0	-	-	-	-
Zachry, 2009	Cases	416	0	-	-	-	-
	Controls	1248	0	-	-	-	-
Devine, 2010	Cases	2949	0	-	-	-	-
	Controls	8847	0	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	0	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		0	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	0	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		0	-	-	-	-
Carbamazepine							
Kauko, 1974	Tegretol (Ciba-Geigy) Tablets Generic Carbamazepine (Laake Oy) Tablets	20	0	100	-	-	80
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	0	100	-	-	Some were reported as receiving combination therapy
	Carbamazepine (AWD Dresden) Tablets						
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets Generic Carbamazepine (Parke Davis) Tablets	10	-	100	10	-	40
Hartley, 1990	Tegretol (Ciba-Geigy) Carbamazepine (Ethical Generics)	23	56.5	43.5	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Ethical Generics) Tablets	12	-	-	-	-	-

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproid Acid (%)	Combination Therapy (%)
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Lemmon Co) Tablets	20	0	100	0	0	0
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Lemmon Co) Tablets	20	0	100	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets Carbamazepine Slow Release (Laakefarmos) Tablets	20	0	100	15	25	-
Silpakit, 1997 (N=18)	Tegretol (Ciba-Geigy) Tablets Carbamazepine (Central Poly) Tablets Carbamazepine (Condrugs) Tablets Carbamazepine (Pharmaland) Tablets	18	0	100	0	5.6	38.9
Aldenkamp, 1998 (N=12)	Tegretol (Ciba-Geigy) Tablets Generic (Pharmachemie) Tablets Generic (Pharbita) Tablets	12	0	100	0	0	0
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	0	12.7	4.4	-
	Generic (Various/Unspecified) Tablets	705	-	0	17.0	8.9	-
LeLorier 2008d	Tegretol CR (manufacturer not reported) Carbamazepine CR (manufacturer not reported)	851	0	100	-	-	51.8
Clobazam							
Andermann, 2007b	Frisium (manufacturer not reported) Clobazam (manufacturers not reported)	1600	0	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported) Clobazam (manufacturer not reported)	1060	0	-	-	-	93.9
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported) Gabapentin (manufacturer not reported)	202	0	-	-	-	83.2
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	0	0	0	0	71.1

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproid Acid (%)	Combination Therapy (%)
	Lamotrigine (manufacturers not reported)						
LeLorier, 2008a	Lamictal (GlaxoSmithKline) Lamotrigine (manufacturer(s) not reported)	671	0	19.2	-	15.2	82.7
Nielsen, 2008a	Lamictal (manufacturer not reported) Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)	9	0	-	-	11.1	55.6
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin							
Lund, 1974	Epanutin (Parke-Davis) capsules Phenytoin sodium (Leo) capsules	9	-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules Phenytoin sodium (Boots) tablets Phenytoin sodium (Cox) tablets Phenytoin sodium (Kerfoot) tablets Phenytoin sodium (McCarthy UK) tablets	18	-	Concurrent treatment was usually phenobarbital, primidone, or carbamazepine.	100%	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules Phenytoin (Boots) tablets Phenytoin (Evans) tablets	19	-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules Phenytoin (Epsolin, Cadila) tablets Phenytoin (Eptoin, Boots India) tablets	15 15 15	-	-	-	-	-

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproid Acid (%)	Combination Therapy (%)
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15					
Mikati, 1992[a]	Dilantin (Parke-Davis) capsules Phenytoin (Phenytex, manufacturer not reported) capsules	10	0	0	100%	0	0
Soryal, 1992a	Epanutin (Parke-Davis) capsules Phenytoin sodium (Evans) tablets Phenytoin sodium (APS) tablets Phenytoin sodium (Cox) tablets Phenytoin sodium (Kerfoot) tablets Phenytoin sodium (Regent) tablets	14	-	-	-	-	-
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	70%, products not reported
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	71%, products not reported
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	72%, products not reported
Paradis, 2009[b]	Topamax (Ortho-McNeil)	-	-	-	-	-	78.9%, products not reported
	Topiramate (Various manufacturers)	-					
Valproic Acid							
Vadney, 1997	Depakene (Abbott) Valproic acid (Solvay)	64	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported) Valproic Acid (manufacturers not reported)	2017	0	-	-	100	-

aCrossover Study
bReports on same database as Duh 2009
Legend: -=not reported; N=sample size

Table 5. Study design and populations of studies comparing older versus newer antiepileptic drugs

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Reinikainen, 1987 (N= 40)	Randomized Double Blind Parallel Group	Finland	Study medication provided by: Ciba-Geicy	Fair	**Carbamazepine** Increased gradually up to 600-1200 mg/day during the first 2 or 3 weeks according to the clinical condition	**Oxcarbazepine** Increased gradually up to 400-800 mg/day during the first 2 or 3 weeks according to the clinical condition	48-50 weeks
Danner, 1988 (N=25)	Randomized Double Blind Cross Over	Unknown	Unknown	Fair	**Carbamazepine** 200 mg twice a day Dosages were increased to 4 tablets daily, if necessary	**Oxcarbazepine** 300 mg twice a day Dosages were increased to 4 tablets daily, if necessary	24 weeks
Dam, 1989 (N=194)	Randomized Double Blind Parallel Group	Denmark Finland Norway Sweden	Ciba-Geigy Ltd.	Fair	**Carbamazepine** Starting Dose: 200 mg/day Mean final dose: 684 mg/day Daily dose adjusted from starting dose at weekly intervals to obtain the best possible therapeutic effect associated with satisfactory tolerability The titration phase was was between 4 and 8 weeks. Once the optimal dose had been determined, treatment was continued using that dose for 12 weeks (maintenance period I) and for a further 36 weeks (maintenance period II) in patients who were well controlled and willing to continue the study	**Oxcarbazepine** Starting Dose: 300 mg/day Mean final dose: 1040 mg/day Daily dose adjusted from starting dose at weekly intervals to obtain the best possible therapeutic effect associated with satisfactory tolerability The titration phase was between 4 and 8 weeks. Once the optimal dose had been determined, treatment was continued using that dose for 12 weeks (maintenance period I) and for a further 36 weeks (maintenance period II) in patients who were well controlled and willing to continue the study	56 weeks
Sachdeo, 1992 (N=44)	Randomized Double Blind Parallel Group Active Control	United States	Not specified	Poor	**Valproic Acid** Initial dose: 15 mg/kg/day to the closest 250 mg	**Felbamate** Titrated to 3,600 mg/dayor the maximum tolerated dose on study day 6	56-day basline period Study day1 – one-third reduction in dosage of previous AED. Seizure calenders, vitals and clinical lab exams were obtained on days 14, 28, 42, 70, 112. Patients completed study after 112 days of double blind treatment.

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Faught, 1993 (N=111)	Randomized Double Blind Active Control Parallel Group	United States	Wallace Laboratories	Fair	**Valproic Acid** Constant dosage of 15 mg/kg/day or their maximum tolerated dosage throughout the treatment period Mean dose 3600 mg/d	**Felbamate** Days 1-2: 1200 mg/day Days 3-5: 2400 mg/day Remainder of the treatment period: 3600 mg/day or maximum tolerated dose Mean dose 1081.8 mg/d	16 weeks
Brodie, 1995 (N=260)	Randomized Double Blind Parallel Group	8 Countries in the United Kingdom	Wellcome Foundation	Fair	**Carbamazepine** Week 1: 200 mg/day Week 2: 200 mg twice a day Week 3-4: 200 mg in the morning and 40 0mg in the evening (600 mg/day) Week 6-24: The daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant adverse events had been reported provided that the drug was in the lower half of the target range or lower. Median daily dose of patients who completed the study: 600 mg	**Lamotrigine** Week 1: 50 mg/day Week 2: 50 mg twice a day Week 3-4: 50 mg in the morning and 100 mg in the evening (150mg/day) Week 6-24: The daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant adverse events had been reported provided that the drug was in the lower half of the target range or lower. Median daily dose of patients who completed the study: 150 mg	52 weeks
Kalviainen, 1995 (N=100)	Randomized Open-Label Parallel Group	Finland	Unknown	Poor	**Carbamazepine** Titration: Daily dose Increased to a plasma level of 35 μ mol/L (therapeutic range 20 to 50 μ mol/L) or lower in cases of complete seizure control or dose related side effects If clinically necessary, the doses of were regularly increased until seizures were controlled or toxic effects developed	**Vigabatrin** Titration: Daily dose increased to a mean level of 50 mg/kg or lower in cases of complete seizure control or dose related side effects Dosages were not increased beyond 50 mg/kg, even in the cases of inadequate control because doses in excess of 50 mg/kg do not provide additional benefit	12 months
Sabers, 1995 (N= 52)	Prospective Observational Observer Blinded	Denmark	Ciba Geigy A/S Denmark The Danish Medical Research Council The Jacob and Olga Madsen Foundation Sygekassernes Helsefond	Fair	**Carbamazepine** Mean dose: 8.4 mg/kg/day Phenobarbital Mean dose: 1.4 mg/kg/day **Phenytoin** Mean dose: 4.7 mg/kg/day **Valproic Acid** Mean dose: 18.6 mg/kg/day	**Oxcarbazepine** Mean dose: 13.3 mg/kg/day	16 weeks

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Reunanen, 1996 (N= 343)	Randomized Open Label Parallel Group	Australia Czech Republic Denmark Eire Finland Germany Italy Netherlands Norway	Unknown	Good	**Carbamazepine** Week 1-2: 200 mg/day in 2 divided doses Week 3-4: 400 mg/day in 2 divided doses Week5-30: 600 mg/day in 2 divided doses	**Lamotrigine 100 mg** Week 1-2: 25 mg/day Week 3-4: 50 mg/day Week 5-30: 100 mg/day **Lamotrigine 200 mg** Week 1-2: 25 mg/day Week 3-4: 50 mg/day Week 5-30: 200 mg/day	30 weeks
Tanganelli, 1996 (N= 51)	Randomized Response Conditional Cross-over	Italy	Unknown	Poor	**Carbamazepine** Starting dose: 0.2 g/day Titration: the dose was progressively increased at weekly intervals by 0.2 g Maximum recommended dose: 1.4 g/day	**Vigabatrin** Starting dose: 1.0 g/day Titration: the dose was progressively increased at weekly intervals 0.5 g at a time Maximum recommended dose: 3.5 g/day	Run-in: 8 weeks Phase 1: Randomization to vigabatrin or Carbamazepine treatment - 16 weeks Phase 2: cross-over – 16 weeks Only patients with intolerable seizures or adverse events switched to the cross-over phase Phase 3: combined therapy - 16 weeks
Bill, 1997 (N=287)	Randomized Double Blind Paralell Group	Argentina Brazil Mexico South Africa	Unknown	Good	**Phenytoin** 8-week Titration Phase: 100 mg and increased bi-weekly based on clinical response to reach 150-800 mg/day at the end of the 8 weeks Mean daily dose at the start of Maintenance treatment: 313.4 mg/day	**Oxcarbazepine** 8-week Titration Phase: 300 mg and increased bi-weekly based on clinical response to reach 450-2400 mg/day at the end of the 8 weeks Mean daily dose at the start of maintenance treatment: 1028.4 mg/day	56 weeks
Christie, 1997 (N=249)	Randomized Double Blind Parallel Group	Belgium Brazil France Germany The Netherlands South Africa Spain United Kingdom	Unknown	Fair	**Valproate** Flexible Titration Phase: 300 mg/day increased biweekly based on clinical response during the 8 week period Maintenance Phase: 900-2400 mg three times a day during the 48 week period Mean dose during maintenance phase: 1146.2 mg/day	**Oxcarbazepine** Flexible Titration Phase: 300 mg/day increased biweekly based on clinical response during the 8 week period Maintenance Phase: 900-2400 mg/day three times a day during the 48 week period Mean dose during maintenance phase: 1052.8 mg/day	56 weeks

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Guerreiro, 1997 (N=193)	Randomized Double Blind Parallel Group	Argentina Brazil	Novartis	Fair	**Phenytoin** Titration: 50 mg/day increased gradually based on clinical response No fixed titration schedule except that patients were to be on a 3 times a daily regimen with daily doses from 150-800 mg/day Maintenance: Daily dose range and 3 times daily regimen were to be continued during the maintenance period	**Oxcarbazepine** Titration: 150 mg/day increased gradually based on clinical response No fixed titration schedule except that patients were to be on a 3 times daily regimen with daily doses from 450-2400 mg/day Maintenance: Daily dose range and 3 times daily regimen were to be continued during the maintenance period	56 weeks
Chadwick, 1998 (N=292)	Randomized Carbamazepin Arm:Open-Label Gabapentin Arm: Double Blind	Europe Australia South Africa Canada	Parke Davis	Poor	**Carbamazepine** 600 mg/day	**Gabapentin** Gabapentin Arm A: 300 mg/day Gabapentin Arm B: 900 mg/day Gabapentin Arm C: 1800 mg/day	24 weeks
Brodie, 1999a (N=150)	Randomized Double Blind Double Dummie Parallel Group	United Kingdom	Unknown	Good	**Carbamazepine** Weeks 1-2: 100 mg daily Weeks 3-4: 100 mg twice a day Weeks 5-6: 200 mg twice a day Weeks 7-24: 200-2000 mg daily Dosage could be adjusted from week 6 onwards while maintaining the blind After titrating to 400 mg daily, upward adjustments by 200 mg increments were made in response to further seizures. Reductions in dosage by 100 mg decrements were allowed on the emergence of side effects	**Lamotrigine** Weeks 1-2: 25 mg daily Weeks 3-4: 25 mg twice a day Weeks 5-6: 50 mg twice a day Weeks 7-24: 75-500 mg daily Dosage could be adjusted from week 6 onwards while maintaining the blind After titrating to 100 mg daily, upward adjustments by 50 mg increments were made in response to further seizures. Reductions in dosage 25 mg were allowed on the emergence of side effects	24 weeks
Brodie, 1999b (N=215)	Randomized Controlled Trial Parallel Group	Austria Belgium Czech Republic France Hungary Italy Netherlands Portugal Slovenia South Africa Spain United Kingdom	Unknown	Fair	**Valproic Acid** Titrated from 0.5 gram/day to a maintenance of 1.5 grams/day by 0.5 gram increments at 2 week intervals	**Vigabatrin** Titrated from an initial 1 gram/day to a standard 3 grams/day by 1 gram increments at 2 week intervals	12 weeks
Chadwick, 1999 (N=457)	Randomized Double Blind Parallel Group	44 European Centres	Hoechst Marion Roussell	Fair	**Carbamazepine** Week 1-6: 200 mg/day Maintenance: 600 mg/day Maximum: 1600 mg/day	**Vigabatrin** Week 1-6: 1000 mg/day Maintenance: 2000 mg/day Maximum: 4000 mg/day	52 weeks

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Gobbi, 1999 (N=80)	Prospective Observational open-label, comparative trial	Italy	Unknown	Poor	**Carbamazepine** Initial dose: 9-20 mg/kg/day Mean initial dose: 17.1 mg/kg/day Maintenance dose: 9-38 mg/kg/day Mean maintenance dose: 18.9 mg/kg/day	**Vigabatrin** Initial dose: 20-80mg/kg/day Mean intial dose: 46.8mg/kg/day Maintenance dose: 20-90mg/kg/day Mean maintenance dose: 50.5 mg/kg/day	12 months
Steiner, 1999 (N=181)	Randomized Double Blind Parallel Group	United Kingdom Germany Belgium	Wellcome Foundation LTD	Fair	**Phenytoin** Week 1-2: 200 mg/day at night Week 3-4: 300 mg/day at night From then on, the dose of either drug could be increased by one capsule if seizure control wasinadequate and no clinically significant adverse events had occurred Modal and maximal daily doses were 300 and 600 mg respectively	**Lamotrigine** Week 1-2: 100 mg/day at night Week 3-4: 150 mg/day at night From then on, the dose of either drug could be increased by one capsule if seizure control was inadequate and no clinically significant adverse events had occurred. Modal and maximal daily doses were 150 and 400 mg respectively	48 weeks
Aldenkamp, 2000 (N=53)	Randomized Observer Blinded Parallel Group	Netherlands	Unknown	Good	**Valproic Acid** A 12-week titration interval with dosage increments of 150 mg/wk until a maximum daily dosage of 1800 mg/day or maximum tolerated dose Mean Dose: 1384 (377.0) mg/day	**Topiramate** Starting Dose: 25 mg/week Titration: Increased weekly to at least 200mg/day during the first 8 weeks Target Dosage Range: 200 to 400 mg/day Mean Dose: 251.1 (101.8) mg/day	20 weeks
Gillham, 2000 (N=260)	Randomized Double Blind Parallel Group	15 European Countries	Galxo Wellcome	Fair	**Carbamazepine** Dosing not reported	**Lamotrigine** Dosing not reported	48 weeks
Biton, 2001 (N=133)	Controlled Randomized Trial Parallel Group	United States	Glaxo Wellcome Incorporated	Fair	**Valproic Acid** Dose Escalation Phase: starting 10-15 mg/kg/day Maintenance Phase: target dose 20 mg/kg/day Adjustment for clinical efficacy during maintenance phase: 10-60 mg/kg/day	**Lamotrigine** Dose Escalation Phase: 25 mg/day Maintenance Phase: target dose 200 mg/day Adjustment in dosing for clinical efficacy during maintenance phase: 100-500 mg/day	34 weeks
Cramer, 2001 (N=349)	Randomized Double Blind Parallel Group	United States	Abbott Laboratories	Good	**Carbamazepine** Dosing not reported **Phenytoin** Dosing not reported	**Tiagabine** Dosing not reported	16 weeks
Kwan, 2001 (N=381)	Prospective Observational	Scotland	Unknown	Poor	**Carbamazepine** Median:600 mg/day Interquartile Range: 400-600 mg/day **Valproic Acid** Median: 1000 mg/day Interquartile Range: 825-1500 mg/day	**Lamotrigine** Median: 200 mg/day Interquartile Range: 150-300 mg/day	5.6 ± 3.4 years

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Nieto-Barrera, 2001 (N=618)	Randomized Open label Parallel Group	Italy Slovakia Germany Denmark United Kingdom Spain	Not specified	Good	**Carbamazepine** Patients aged 2–12 years: 5-40 mg/kg/day Patients aged 13 years or older: 100–1500 mg/day Doses were increased until the best response was obtained according to data sheet recommendations	**Lamotrigine** During the maintenance phase patients aged 2–12 years: increased by a max of 0.5-1 mg/kg every 1–2 weeks up to 2-15 mg/kg/day Patients aged 13 years or older: Increased by a maximum of 25–50 mg every 1–2 weeks until an optimal response was achieved up to a max of 700 mg/day	24 weeks
Sackellares, 2002 (N= 133)	Randomized Parallel Group	United States	Glaxo Wellcome	Fair	**Valproic Acid** Dose escalation phase: starting 10-15 mg/kg/day Maintenance phase: target dose 20 mg/kg/day Adjustment for clinical efficacy during maintenance phase: 10-60 mg/kg/day	**Lamotrigine** Dose escalation phase: 25 mg/day Maintenance phase: target dose 200 mg/day Adjustment in dosing for clinical efficacy during maintenance phase: 100-500 mg/day	34 weeks Health related quality of life evaluated at baseline, week 10 and week 32
Biton, 2003 (N=38)	Randomized Parallel Group	United States	GlaxoSmithKline	Fair	**Valproic Acid** Dose Escalation Phase: starting 10-15 mg/kg/day Maintenance Phase: target dose 20 mg/kg/day Adjustment for clinical efficacy during maintenance phase: 10-60 mg/kg/day Mean dose during the maintenance phase: 1520 (379) mg/day	**Lamotrigine** Dose Escalation Phase: 25 mg/day Maintenance Phase: target dose 200 mg/day Adjustment in dosing for clinical efficacy during maintenance phase: 100-500 mg/day Mean dose during the maintenance phase: 261 (76) mg/day	34 weeks
Meador, 2003 (N= 76)	Randomized Double blind Placebo Controlled Parallel Group	Unknown	Ortho McNeal Pharmaceutical	Fair	**Valproic Acid** 250 mg/day up to 2,250 mg/day	**Topiramate** 50 mg/day up to 400 mg/day	24 weeks

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Privitera, 2003 (N=613)	Randomized Double Blind Parallel Group	Australia Brazil Belgium Canada Columbia Costa Rica Denmark Finland France Germany Israel Italy Netherlands New Zeland Norway United States United Kingdom South Africa Spain Sweden	Johnson & Johnson	Good	**Carbamazepine** Starting dose: 200 mg/day increased 200 mg every 2 weeks Final dose: 600 mg/day **Valproic Acid** Starting dose: 250 mg/day increased weekly in 250 mg increments Final dose: 1250 mg/day	**Topiramate 100 mg** Starting dose: 25 mg/day increased weekly in 25 mg increments Final dose: 100 mg/day **Topiramate 200 mg** Starting dose: 25 mg/day increased weekly to 50, 100, 150, and 200 mg/day Final dose: 200 mg/day	6 months after the last patient was randomized
Clemens, 2004 (N=20)	Prospective Observational Cross-over	Hungary	Unknown	Fair	**Carbamazepine** Average daily dose during baseline period: 1100 mg/day	**Oxcarbazepine** At the first evaluation after the baseline period, the patients took carbamazepine as in the baseline period. In the next week, 150 mg oxcarbazepine was substituted for every 100 mg carbamazepine, as proposed for patients with refractory seizures.	Unknown
Coppola, 2004 (N=38)	Randomized Open Label Parallel Group	Italy	Not Sponsored by any commercial organization	Fair	**Valproic Acid** Started at 10 mg/kg/day and increased by 5 mg/kg/day every 3 days until seizures were controlled or intolerable side effects occurred up to a maximum of 30 mg/kg/day given in three divided doses. Mean daily dose at 3 months: 22.6 mg/kg/day Mean daily dose at 12 months: 25.4 mg/kg/day	**Lamotrigine** Initial dosing: 0.5 mg/kg twice a day for 2 weeks followed by 1.0 mg/kg/day for an additional 2 days Thereafter doses were increased in 1 mg/kg/day increments every 5 days until seizures were controlled, intolerable adverse effects occurred or a maximum of 12 mg/kg/day had been reached Mean daily dose at 3 months: 6.5 mg/kg/day Mean daily dose at 12 months: 8.3 mg/kg/day	12 months

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Fakhoury, 2004 (N=302)	Randomized Open-Label Parallel Group	United States	GlaxsoSmithKline	Poor	**Carbamazepine** Determined by the clinician and intended to be consistent with dosing recommendations in the product label **Valproic Acid** Determined by the clinician and intended to be consistent with dosing recommendations in the product label	**Lamotrigine** Added to prestudy AED (carbamazepine or valproic acid) according to the dosing recommendations in the product label	28 weeks
Wheless, 2004 (N=613)	Randomized Double Blind	Unknown	Johnson and Johnson Pharmaceutical Research & Development	Fair	**Carbamazepine** Starting dose 200 mg/day, increased 200 mg every 2 weeks to a total dose of 600 mg/day **Valproic Acid** Starting dose: 250 mg/day Dose increased weekly in 250mg increments to a total dose of 1250 mg/day	**Topiramate 100 mg** Starting dose: 25 mg/day Dose increased weekly in 25 mg increments **Topiramate 200 mg** Starting dose: 25 mg/day Dose increased weekly to 50, 100, 150 and 200 mg/day	Screening visit Titration phase- 35 days Stabilization – until patient exited or until 6 months after the last patient was enrolled. Study duration was up to 685 days. Mean duration of treatment was 307 days
Rowan, 2005 (N= 593)	Randomized Double Blind Double Dummy Parallel Group	United States	Study funding: Veteran Affairs cooperative study program Study medication provided by: GlaxoSmithKline Pfizer	Fair	**Carbamazepine** Target dose: 600 mg/day Titration: started at 200 mg/day and increased by 200 mg/day every every 2 weeks to 600 mg/day to the target of 600 mg/day	**Gabapentin** Target dose: 1500 mg/day Titration: started at 300 mg/day and increased by 300 mg/day every 3 days to the target of 1500 mg/day **Lamotrigine** Target dose: 150 mg/day Titration: started at 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg/day for 1 week, followed by 150 mg/day	52 weeks
Sobaniec, 2005 (N= 54)	Prospective Observational	Poland	None specified	Fair	**Carbamazepine** 18 mg/kg every 12 hours	**Vigabatrin** 50 mg/kg every 12 hours	24 weeks

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Steinhoff, 2005 (N=269)	Randomized Open Label Parallel Group	Germany	GlaxoSmithKline	Good	**Carbamazepine** Daily dose in adults: 200-400 mg/day Recommended maintenance dose in adults: 600-1200 mg/day Daily dose in patients between 11 and 15 years of age: 200-300 mg/day Recommended maintenance dose in children between 11 and 15 years of age: 600-1000 mg/day **Valproic Acid** Initial dose: 5-10 mg/kg/day Titration: increased every 4-7th day by approximately 5 mg/kg Recommended daily maintenance dose for children between 6 and 14 years of age or persons with a body weight between 20-40 kg: 600-1200 mg/day Recommended daily maintenance dose for adolescents from 14 years of age or older or persons with a body weight between 40-60 kg: 600-1500 mg Recommended daily maintenance dose for adults weighing at least 60 kg: 1200-2100 mg/day	**Lamotrigine** Week 1-2: 25 mg/day Week 3-4: 50 mg/day Week 5 and on: 100 mg/day or 50 mg twice a day Recommended maintenance dose: 100-200 mg/day The investigators were allowed to escalate the dose further for clinical reasons up to a maximum of 500 mg/day	24 weeks
Babayigit, 2006 (N=68)	Retrospective Observational (Case Control)	Turkey	Unknown	Fair	**Carbamazepine** 15-25 mg/kg/day **Valproic Acid** 15-40 mg/kg/day	**Oxcarbazepine** 15-30 mg/kg/day	4 months
Brodie, 2007 (N=576)	Randomized Double Blind Parallel Group	12 European Countries and South Africa	UCB Pharma	Good	**Carbamazepine-Controlled Release** Titration Period: 200 mg/day Dosing Level 1: 200 mg twice a day Patients experiencing a seizure during the first evaluation period had their dose increased over 2 weeks with intermediate daily doses of 600 mg Dosing Level 2: 400 mg twice a day Patients experiencing a seizure at dose level 2 progressed to dose level 2 with intermediate dosing of 600 mg twice a day Dosing Level 3: 1000 mg/day	**Levetiracetam** Titration Period: 500 mg/day Dosing Level 1: 500 mg twice a day Patients experiencing a seizure during the first eval period had their dose increased over 2 weeks with intermediate daily doses of 1500mg Dosing Level 2: 1000 mg twice a day Patietns experiencing a seizure at dose level 2 progressed to dose level 3 with intermediate dosing of 1500 mg twice a day Dose Level 3: 2500 mg/day	Up to 1 year Patients achieving the primary endpoint (6-month seizure freedom) continued on treatment for a further 6-month maintenance period
Donati, 2007 (N=112)	Randomized Open-label Active-Control Three-Arm Parallel Group	7 European countries	Novartis	Poor	**Carbamazepine** Mean daily dose: 14.4 (3.6) mg/kg/day **Valproic Acid** Mean daily dose 20.7 (7.5) mg/kg/day	**Oxcarbazepine** Mean daily dose: 19.6 (6.4) mg/kg/day	6 months

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Kang, 2007 (N=112)	Randomized Observer Blinded Open-label Parallel Group	Korea	Johnson & Johnson	Fair	**Carbamazepine** Initial dose: 10 mg/kg.day Titration dose: 20 mg/kg/day over 4 weeks Maximum dose: 30 mg/kg/day Average daily dose during maintenance phase: 3.4 (1.6) mg/kg/day	**Topiramate** Initial dose: 12.5 mg/day Titration dose: to at least 50 mg/day in patients < 30 kg and 75 mg/day in patients > 30 kg over 4 weeks Maximum dose: 4 mg/kg/day Average daily dose during maintenance phase: 21.6 (3.2) mg/kg/day	28 weeks
Kim, 2007 (N=33)	Prospective Observational	Korea	Unknown	Poor	**Carbamazepine** Dose not reported **Valproic Acid** Dose not reported	**Lamotrigine** Dose not reported	6 months
Levisohn, 2007 (N= 28)	Randmoized, Open Label Parallel Group	United States	Unknown	Poor	**Valproic Acid** Median daily dose: 750 mg/day	**Topiramate** Median daily dose: 250 mg/day	26 weeks
Marson, 2007 SANAD Arm A (N= 1721)	Randomized Open Label Parallel Group	United Kingdom	Health Technology Assessment Program GlaxoSmithKline Janssen-Cilag Novartis Pfizer Sanofi-Synthelabo Wellcome Trust	Fair	**Carbamazepine** Maintenance dose (above 16 years of age): 600 mg/day Maintenance dose (children under 16 years of age): 15-20 mg/kg/day	**Lamotrigine** Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mk/gk/day **Gabapentin** Maintenance dose (above 16 years of age): 1200 mg/day Maintenance dose (children under 16 years of age): 30-45 mg/kg/day **Topiramate** Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mg/kg/day **Oxcarbazepine** Maintenance dose (above 16 years of age): 900 mg/day Maintenance dose (children under 16 years of age): 15-30mg/kg/day	Primary outcome measures: 1.) time from randomization to treatment failure (stopping randomized drug because of inadequate seizure control, intolerable side-effects, or both; or the addition of other antiepileptic drugs, whichever was earliest) 2.) the time from randomization to a 1-year period of remission of seizures Secondary outcome measures: 1.) time from randomization to a first seizure 2.) time to achieve a 2-year period of remission of seizures

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Marson, 2007 SANAD Arm B (N= 716)	Randomized Open Label Parallel Group	United Kingdom	Health Technology Assessment Program GlaxoSmithKline Janssen-Cilag Novartis Pfizer Sanofi-Synthelabo Wellcome Trust	Fair	**Valporic Acid** Maintenance dose (above 16 years of age): 1000 mg/day Maintenance dose (children under 16 years of age): 20-30 mg/kg/day	**Lamotrigine** Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mk/gk/day **Topiramate** Maintenance dose (above 16 years of age): 150 mg/day Maintenance dose (children under 16 years of age): 3-6 mk/gk/day	Primary outcome measures: 1.) time from randomization to treatment failure (stopping randomized drug because of inadequate seizure control, intolerable side-effects, or both; or the addition of other antiepileptic drugs, whichever was earliest) 2.) the time from randomization to a 1-year period of remission of seizures Secondary outcome measures: 1.) time from randomization to a first seizure 2.) time to achieve a 2-year period of remission of seizures
Saetre, 2007 (N= 186)	Randomized Double Blind Double Dummy Parallel Group	Croatia Finland France Italy Norway	GlaxoSmithKline	Good	**Carbamazepine** Initial dose: 100 mg/day Maintenance dose: 400 mg/day Maximum dose: 2000 mg/day Titration: 100 mg/day for 2 weeks increased to 100 mg twice a day for 2 weeks, then increased to 200 mg twice a day up to a max of 1000 mg twice a day	**Lamotrigine** Initia dose: 25 mg/day Maintenance dose: 100 mg/day Maximum dose: 500 mg/day Titration: 25mg/day for 2 weeks increased to 25 mg twice a day for 2 weeks, then increased to 50 mg twice a day up to a max of 250 mg twice a day	40 weeks

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Stephen, 2007 (N=225)	Randomized Open-label Parallel Group	United Kingdom	Unknown	Good	**Valproic Acid** Titration: Weeks 1-2: 500 mg/day Weeks 3-4: 500 mg twice daily Weeks 5-6: - Weeks 7-8: - Weeks 9-10: - Target dose: 1000 mg/day Dosage adjustments: 200-500 mg/day	**Lamotrigine** Titration: Weeks 1-2: 25 mg/day Weeks 3-4: 25 mg twice daily Weeks 5-6: 50mg twice daily Weeks 7-8: 50 mg/100 mg Weeks 9-10: 100 mg twice daily Target dose: 200 mg/day Dosage adjustments 25-50 mg/day	1 year
Morrell, 2008 (N=447)	Randomized Open label Parallel Group	Asia Europe North America South America	GlaxoSmithKline	Good	**Valproic Acid** Target maintenance dose: 1000 mg/day.	**Lamotrigine** The target maintenance dose was 100 to 200 mg/day with the dose not to exceed 500 mg/day. The target doses for lamotrigine added to enzyme-inducing AED and nonenzyme inducing AED were 200 to 400mg/day and 100 to 200mg/day, respectively	1 year
Pack, 2008 (N=93)	Prospective Observational Cross Sectional	United States	National Institute of Health GlaxoSmithKline	Poor	**Carbamazepine** Dose not specified **Phenytoin** Dose not specified **Valproate** Dose not specified	**Lamotrigine** Dose not specified	1 year
Perry, 2008 (N=86)	Retrospective Observational Cohort study	United States	UCB, Inc	Fair	**Carbamazepine** Dose not specified	**Levetiracetam** Dose not specified	Mean duration of followup for the carbamazepine group in months: 33.5 (17.8) Meanduration of followup for the levetiracetam group in months: 23.1 (12.7)
Kim, 2009 (N=146)	Prospective Observational	Korea	Unknown	Poor	**Carbamazepine** Mean dose: 12.8 (3.2) mg/kg/day	**Topiramate** Mean dose: 4.9 (2.5) mg/kg/day	48 months
Kwan, 2009 (N= 81)	Randmoized Open Label Parallel Group	China	Unknown	Poor	**Valproic Acid** Initial dose: 400 mg/day Maintenance dose: 800 mg/day Mean daily dose: 796 mg/day	**Lamotrigine** Starting dose: 25 mg/day Maintenance dose: 100 mg/day Mean daily dose: 108 mg/day	12 months

Study, year (N)	Study Design	Country	Study Funding	Quality Rating	Older AED and Dose	Newer AED and Dose	Follow-up
Ma, 2009 (N= 497)	Prospective Observational	China	Foundation	Fair	**Carbamazepine** Daily dose required required by the majority of patients: 12.59 (4.76) mg/kg/day **Valproic Acid** Daily dose required by the majority of patients: 21.12 (6.74) mg/kg/day	**Topiramate** Daily dose required by the majority of patients: 4.68 (0.85) mg/kg/day	1 year
Glauser, 2010 (N= 451)	Randomized Double Blind Active Comparator	United States	Study Funding: National Institute of Health Medications provided by: Pfizer Abbott Laboratories GlaxoSmithKline	Good	**Ethosuximide** Mean dose 33.5 (15.3)mg/kg/day **Valproic Acid** Mean dose 34.9 (15.8)mg/kg/day	**Lamotrigine** Mean dose 9.7 (6.3) mg/kg/day	16 weeks
Ramsay, 2010 (N=261)	Randomized Double Blind Double Dummie Active Comparator	United States	Ortho-McNeil Janssen	Good	**Phenytoin** Initial target dose: 1000 mg, given as 3 divided doses on Day 1 (400, 300 and 300 mg, respectively, at 2-hour intervals) Maintenance Period: 300 mg/day	**Topiramate** Intial target dose: 100 mg/day, given as 3 divided doses on Day 1 (50, 25 and 25 mg, respectively, at 2-hour intervals) Maintenance Period: 50 mg twice a day	4 weeks

Legend: AED=antiepileptic drug; N=sample size

Table 6. Inclusion and exclusion criteria of studies comparing older versus newer antiepileptic drugs

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Reinikainen, 1987 (N= 40)	Adult patients with chronic epilepsy on phenytoin monotherapy with unsatisfactory seizure control or unwanted effects entered the study	Pregnancy or a desire to become pregnant Organic heart disease, especially atrioventricular block, liver, kidney or thyroid dis, abnormally low leukocyte or platelet counts, inoperable tumours Known hypersensitivity to tricyclic antidepressants or carbamazepine, and uncooperative patients Also patients treated concomitantly with oral anticoagulants, propoxyphene and dextropropoxyphene, tetracycline, clofibrate, monoamine oxidase inhibitors and tricyclic antidepressants were excluded
Danner, 1988 (N=25)	Previously untreated newly diagnosed patients	Patients with other neurological disorders, neoplasms, diabetes, alcoholism, hepatic or renal diseases, or any other condition or medication which could interfere with neuronal function
Dam, 1989 (N=194)	Men or women aged 15-65 years, suffering from newly diagnosed and previously untreated epilepsy Only patients with primary generalized seizures (tonic-clonic seizures), and with partial seizures with or without secondary generalization, according to the International Classification of Epileptic Seizures	Women who were pregnant or trying to become pregnant Patients with known heart, liver, kidney and thyroid disorders Patients with abnormally low leukocyte and/or platelet counts, inoperable tumors or known hypersensitivity to CBZ or tricyclic antidepressants Patients who were being treated with drugs known to interact with CBZ were also excluded
Sachdeo, 1992 (N=44)	Men and women, aged 18yrs and older >90 lbs Patients with uncontrolled partial onset seizures classified according to the ICS EEG or video/telemetry consistent with partial onset seizures Current AED regimen consisting of one AED at therapeutic plasma levels, with a second permitted if the plasma level was sub-therapeutic 8 or more partial onset seizures during a 56-day baseline No evidence of progressive CNS lesions on CNS MRI or CT Awareness seizures Adequate birth control measures	Status epilepticus Poor compliance history Current benzodiazepine use Recent drug or alcohol abuse Significant medical illness Previous suicide attempts Included only if failed only 1 AED at clinically toxic doses
Faught, 1993 (N=111)	Patients with partial onset seizure with or without secondary generalization Seizures were classified according to the International Classification of Seizures During the 56-day baseline period, patients were required to have eight or more partial onset seizures, have no more than 20 consecutive seizure-free days, and take only one standard AED at a therapeutic level Second AED could be taken if the serum/plasma level was less than 50% of the accepted low for therapeutic range Abnormal EEG consistent with a seizure disorder, CT or MRI confirming the absence of a progressive lesion, weight more than 41 kg, an ECG without significant findings, and, if a female of childbearing potential, the use of an accepted method of birth control	Patients were excluded who had a history of status epilepticus in the previous 3 months while receiving an adequate dose of an AED, a treatable or progressive seizure etiology, a seizure pattern characterized by clusters, a history of benzodiazepine use on a regular basis, significant psychiatric disorders, serious medical conditions, poor compliance, drug or alcohol abuse within the previous year, or suicide attempts Patients who, by history, had taken more than one AED at clinically toxic dose without adequate seizure control were excluded
Brodie, 1995 (N=260)	Patients 13 years and older Newly diagnosed epilepsy Stratified according to type of seizures – partial seizures without secondary generalization, and primary or secondary generalized tonic-clonic seizures No patient had received previous treatment with antiepileptic drug	-
Kalviainen,1995 (N=100)	A total of 100 patients aged 15 to 64 years who had had at least two unprovoked epileptic seizures during the previous 2 years or one seizure and distinct electroencephalographic changes indicative of epilepsy were included in the study	Patients with alcohol-related seizures, current alcohol or other drug abuse, progressive neurologic disorders, mental retardation, severe psychiatric problems, or other severe medical disorders were excluded from the study

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Sabers, 1995 (N= 52)	Patients with newly diagnosed epilepsy and patients with epilepsy admitted as in- or out-patients to the University Clinic of Neurology, Hvidovre Hospital 1984-1988 who had been without any antiepileptic drug treatment for a period of at least 4 months	Patients were excluded if they had severe brain damage, any medical disease which may cause encephalopathy, progressive brain disorder, or were drug or alcohol abusers
Reunanen, 1996 (N= 343)	Patients (either sex) >12 years of age Confident diagnosis of newly diagnosed or recurrent epilepsy, with partial and/or generalised tonic-clonic seizures classifiable by the International Classification of Seizures Patients with current epilepsy were defined as those who had previous chronic treatment for epilepsy but no more than two doses of antiepileptic drug in the 6 months before inclusion At least two seizures in the previous 6 months, with at least one in the previous 3 months, but no more than 30 in any one of the preceding 6 months or a history of status epilepticus No antiepileptic medication in the 6 months prior to the trial other than 1 or 2 doses of acute treatment	Presence of other significant organic or psychiatric disease or abnormal laboratory values Abuse of any medication or substances, which might have interfered with the study objectives Pregnancy, lactation or exposure to risk of pregnancy
Tanganelli, 1996 (N= 51)	Age between 18 and 65 years At least two untreated and unprovoked seizures, complex partial (CP) type, with or without secondary generalization, in the previous 8 weeks (run-in)	History of alcohol or drug abuse Presence of a brain tumor or progressive neurological disease An IQ score < 90 Presence or history of psychiatric, cardiac, renal, hepatic or metabolic disease, pregnancy or the risk of pregnancy
Bill, 1997 (N=287)	Age: 16-65 years New onset epilepsy Partial seizures with or without secondary generalization Generalized tonic colnic seizures without partial onset A minimum of 2 seizures separated by 48 hours within the 6 months preceding entry No prior AED except for emergency treatment of seizures for a maximum of 3 weeks prior to entry	Pregnancy risk History of status epilepticus Sever psych illness or mental retardation Progressive neurologic disorder Alcoholism Drug abuse Any significant organic disease
Christie, 1997 (N=249)	Age: 15-65 years Newly diagnosed epilepsy with partial seizures with or without secondary generalization or generalized tonic-clonic seizures without partial onset Patients had to have a minimum of two seizures separated by at least 48 hours within the 6 months preceding trial entry No previous AED treatment was allowed except for emergency treatment of seizures for a maximum of 3 weeks prior to trial entry	Pregnancy or risk of becoming pregnant History of status epileptius Severe psychiatric illness Sever mental retardation Progressive neurologic disorder Alcoholism or drug abuse Significant organic disease
Guerreiro, 1997 (N=193)	Patients had to have a minimum of 2 seizures, separted by at least 48 hours, in the 6 months before entering the study No previous AED treatment was allowed except for emergency treatment of seizures for a mazimum of 3 weeks prior to trial enrolment	Pregnancy or risk of becoming pregnant, history of status epilepticus, severe psychiatric illness or sever mental retardation, progressive neurologic disorder, alcoholism or drug abuse, and any significant organic disease

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Chadwick, 1998 (N=292)	Patients with newly diagnosed partial epilepsy who were AED therapy naïve or who had received fewer than 2 weeks of AED therapy, which was discontinued before study entry Patients were also accepted if they had a history of epilepsy in remission for at least 2 years without AED treatment but were experiencing a recurrence of seizures Within the 6 months before the start of study medication, eligible patients had to have had at least two unprovoked, reliably evaluated and classified partial seizures or generalized tonic-clonic seizures At least 12 years of age and weighed between 40 and 110 kg Women of childbearing potential were not lactating, had a reliable method of contraception during the study	Idiopathic generalized epilepsy defined as a family history of epilepsy, morning myoclonus, generalized tonic clonic seizures on awakening, or generalized spike or wave on EEG Patients were also excluded from the study if they had ever experienced status epilepticus, had pregressive encephalopathy or findings suggesting a progressive structural lesion in the CNS, had taken an investigational drug within the past 3 months, had a medical or psychiatric condition or disease that could affect the study outcome
Brodie, 1999a (N=150)	Patietns age 65 years and above with newly diagnosed epilepsy Each patient reported 2 or more seizures of any type during the previous year with at least once event during the past 6 months Standard ILAE definitions of idiopathic, symptomatic and cryptogenic epilepsies	-
Brodie, 1999b (N=215)	Patients between the ages of 12-75 years with simple or complex partial seizures with or without secondary generalization who were inadequately controlled on carbamazepine monotherapy Experienced a minimum of 1 seizure a month for the previous 6 months At least 6 seizures in the last 3 months Pre-study carbamazepine must have been at the highest tolerated dose within an effective concentration range (1-4 mg/l) measured at least twice during the preceding 6 months	Patients who failed to respond to carbamazepine due to poor tolerability
Chadwick,1999 (N=457)	Newly diagnosed epilepsy Age:16-25 years Experienced at least 2 seizures in the previous 12 months	Occurrence of generalized seizure types
Gobbi, 1999 (N=80)	All types of partial epilepsy (including idiopathic cases) with onset in infancy, childhood or adolescence; a history of at least three seizures after the onset of epilepsy; and no previous treatment with any other AED	Patients with known brain tumor; progressive disease; hepatic, renal, cardiac or gastrointestinal disease; psychiatric or behavioral disturbances Patients with infantile spasms were also excluded
Steiner, 1999 (N=181)	Patients aged 14-75 years were eligible after 2 or more such seizures in the previous 6 months and at least 1 in the previous 3 months	Patients with absence seizures Previous treatment for epilepsy with any AED Chronic medical disorders Severe mental subnormality Abuse of alcohol or other substances Pregnancy or risk of becoming pregnant Clinically significant abnormal labs Severe mental abnormalities

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Aldenkamp, 2000 (N=53)	Patient with localization-related epilepsy with partial-onset seizures Aged 18-60 years Patients with minimum weight of 45 kg Steady state treatment with carbamazepine monotherapy for at least 28 days Epilepsy uncontrolled on carbamazepine or requiring another AED for other reasons	Evidence of progressive cerebral lesion, degenerative disorder, malignancy, or history of malignancy in the past 5 years Cognitive impairment that could either interfere with the cognitive testing procedure Females who do not practice reliable contraception Non-epileptic seizures Documented history with generalized status epilepticus in the past 3 months Unstable medical disease in the past 2 years including cardiovascular, hepatic, renal, gynecological, musculoskeltal, gastrointestinal, metabolic or endocrine disease History of alcohol or drug abuse, psychiatrics disorder requiring electroconvulsive therapy or of major tranquilizers (neroleptics, antidepressants, or monoamine oxidase inhibitors) in the past 6 months Patients who are schizophrenic or who have exhibited any psychotic symptoms, regular treatment with antihistamines, metoclopramide, central nervous system active compunds, or an experimental drug during the past 30 days Patient who have taken topiramate previously History of poor compliance with antiepileptic treatment or inability to maintain a seizure calendar History of nephrolithiasis and patiants who have taken any medication associated with nephrolithiasis; and use of acetazolamide, zonisimide, triamterene, or vitamin C within the past month
Gillham, 2000 (N=260)	Patients 13 years and older Newly diagnosed epilepsy Stratified according to type of seizures – partial seizures without secondary generalization, and primary or secondary generalized tonic-clonic seizures No patient had received previous treatment with antiepileptic drug	-
Biton, 2001 (N=133)	Patients age >12 years with newly or previously diagnosed epilepsy and who were experiencing any seizure type classifiable by the International Classification of Seizures	Previous use for more than 90 days of lamotrigine, divalproex sodium, valproic acid, or gabapentin Current use of an AED unless the AED could be withdrawan safely before randomization of the patient Chronic use of any medication that could influence seizure control Any medical condition requiring corticosteroid therapy growth hormone or testosterone; any acute or progressive neurologic or severe psychiatric disease Adherence to the ketogenic diet Participation in a weight-change program or any medical condition associated with significant changes in body weight Pregnancy
Cramer, 2001 (N=349)	Patients taking carbamazepine monotherapy Patients were included if their seizures were poorly controlled with baseline AED as defined as four or more complex seizures per month	-

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Kwan, 2001 (N=381)	The study included unselected patients in whom epilepsy was diagnosed and treatment was initiated at the Epilepsy Unit in the Western Infirmary in Glasgow, Scotland between 1 January 1984 and 31 December 1997 Only those who had never received AED therapy before were included in the analysis	-
Nieto-Barrera, 2001 (N=618)	Age of 2 yrs and greater Patients with newly diagnosed or with currently untreated partial epilepsy Seizures had to be easily recognised by the patients (or carer) and able to be classified by the International Classification of Seizures (1981) Patients had experienced at least 2 partial seizures in the 6 months preceding the study, with at least 1 partial seizure or at least one secondarily generalised tonic–clonic seizure in the preceding 3 months, and evidence of focal radiological or EEG abnormalities	-
Sackellares, 2002 (N= 133)	At least12 years of age Diagnosed with epilepsy Experienced any seizure type classifiable by the International Classification of Seizures If female, had a negative urine or serum pregnancy test at screening and agreed to use acceptable contraceptive methods during the study or were incapable of bearing children	Previous use for more than 90 days of lamotrigine, divalproex sodium, valproic acid, or gabapentin Current use of an antiepileptic drug unless the drug could be withdrawn safely prior to randomization Use of any investigational drug within the previous 12 weeks Chronic use of any medication that could influence seizure control Any acute or progressive neurological or severe psychiatric disease Any medical condition associated with significant changes in body weight; adherence to the ketogenic diet; participation in a weight-change program Current or planned use of vagal stimulation to control seizures
Biton, 2003 (N=38)	Age ≥ 12years Any type easily classifiable by the Intnational Classification of Seizures Patients with new onset epilepsy or previously diagnosed epilepsy or who could safely be withdrawn from any concurrent antiepilepsy drug prior to randomization	Previous use of lamotrigine or valproate for more than a total of 90 days Any contraindication or history of significant side effects with their use; treatment with vagal nerve stimulation or chronic use of a med that could influence seizure control Current use of an AED unless the AED could be withdrawn safely before randomization Severe psychiatric disorder Acute or progressive neurologic disorder or severe mental abnormality rendering the patient unable to comply with study objectives Substance abuse Diseases requiring corticosteroid growth hormone or testosterone use Adherence to a ketogenic diet Participation in wt change program Medical conditions assocociated with weight change Use of an investigational drug 12 weeks prior to or during enrolment Any significant chronic renal hepatic or cardiac disease Substance abuse Pregnancy

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Meador, 2003 (N= 76)	Age: 16-55 years with an IQ ≥ 70 Have at least three partial-onset seizures during a 28-day baseline phase despite stable dosages of carbamazepine monotherapy (trough blood level, 7 to 13 g/mL) AED other than carbamazepine had to be discontinued 28 days before the baseline visit Women had to be incapable of bearing children or be practicing adequate birth control and have a negative pregnancy test within 2 weeks of entering the study Patients needed to have CT or MRI confirmed absence of progressive cerebral lesion	Nonepileptic seizures, treatable cause of seizures Progressive neurologic disorders; status epilepticus within past 3 months. History of major medical disease within past 2 years or malignancy within past 5 years History of alcohol or drug abuse during previous year History of psychiatric or mood disorder requiring electroconvulsive therapy, tranquilizers, antidepressants, or monoamine oxidase inhibitors; schizophrenia, other psychotic symptomatology, or suicide attempt; use of benzodiazepines, barbiturates, metoclopramide hydrochloride, or routine antihistamine History of nephrolithiasis. Patients using acetazolamide, zonisamide, or triamterene; vitamin C (1 g/d); chronic antacids or calcium supplements; or any medication associated with nephrolithiasis within the past month were excluded Schizophrenia, other psychotic symptoms, experimental drug or device within 1 month History of poor compliance with past AED therapy or inability to take medication or maintain seizure calendar independently or with assistance Patients previously treated with topiramate were also excluded
Privitera, 2003 (N=613)	Patients at least 6 years of age and weigh >30 kg Epilepsy diagnosed within the 3 months before study entry Never been treated for epilepsy or treated <6 weeks with no more than one AED if temporary or urgent AED use was necessary Females had to be incapable of bearing children or be practicing adequate birth control and have a negative pregnancy test within 1 week of entering the study The absence of a progressive cerebral lesion was confirmed by computed tomography or magnetic resonance imaging prior to study entry	Non-epileptic seizures or a treatable cause of seizures Progressive or degenerative disorder; significant history of unstable medical disease within previous 2 years or malignancy within previous 5 years; psychiatric or mood disorder requiring electroconvulsive or drug therapy within previous 6 months, suicide attempt, mental retardation or impairment; alcohol or drug abuse History of nephrolithiasis; clinically significant laboratory or electrocardiographic abnormalities; inability to take medication either independently or with assistance Treatment with an experimental drug or device within previous 30 days Treatment with benzodiazepines or barbiturates on more than an occasional basis Patients using acetazolamide, zonisamide, or triamterene within 1 month of study entry were excluded because of an increased possibility of renal stone formation
Clemens, 2004 (N=20)	Adult (>18 years) patients with partial epilepsy and presumably insufficient efficacy of carbamazepine monotherapy	Alcohol and drug abuse, pregnancy or breast feeding, non-compliance, any significant medical condition except epilepsy, which could interfere with the measurements or interpretation of the results.

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Coppola, 2004 (N=38)	Age: 3-13 years Newly diagnosed typical absence seizures associated with generalized synchronous 3-Hz spike-and-wave activity lasting >3 seconds occurring spontaneously during one of two trials of 3-min hyperventilation with a 1- to 2-min rest between trials clearly observable signs of typical absence seizures (e.g. staring or impairment of consciousness) on the video record normal clinical neurologic and CT/MRI examination and informed consent by parents or caregivers.	Absences with marked eyelid or perioral myoclonus (eyelid or perioral myoclonia with absences) absences with marked limb and trunk rhythmic myoclonic jerks (myoclonic absence epilepsy) absences with single ictal myoclonic jerks of the limbs trunk or head absences with mild or not clinically detectable impairment of consciousness (e.g. juvenile myoclonic epilepsy) other types of epileptic seizures stimulus-sensitive absences: photosensitive pattern-sensitive self-induced pattern-sensitive irregular arrhythmic spike/multiple spike and slow-wave EEG discharges with marked variations of discharge frequency; central-temporal or occipital focal EEG discharges or abnormal background EEG activity; known or suspected brain lesion; progressive neurologic illness; psychiatric disorder requiring medication Chronic cardiovascular renal or hepatic disease and any disease that could interfere with drug absorption distribution metabolism or excretion; Long-term comedication with other drugs Suspected poor compliance.
Fakhoury, 2004 (N=302)	Patients ≥ 16 years of age diagnosed with epilepsy and experiencing any seizure type classifiable by the International League of Seizures were eligible for the study if they had been treated with one AED for a minimum of 4 weeks prior to screening and had experienced at least two seizures during the 8 weeks before screening Patients were determined by a clinician to be appropriate candidates for add-on therapy with lamotrigine, carbamazepine, or valproate and possible candidates for conversion to monotherapy with lamotrigine, carbamazepine, or valproate Females were eligible only if they had a negative urine or serum pregnancy test at screening and agreed to use acceptable contraceptive methods during the study or were incapable of bearing children	Patients were excluded if they were treated with more than one AED at screening or if they were being treated with phenobarbital or primidone that could not be withdrawn over an 8 week period.
Wheless, 2004 (N=119)	Children and adolescent (age 6 and up, ≥ 30 kg) Diagnosed epilepsy within 3 months before study enrollment Never treated for epilepsy, although temporary or emergency AED use for <6 wks was allowed, as was history of AED treatment for a self limiting condition such as febrile seizures Absence of progressive cerebral lesion confirmed by CT or MRI prior to study entry	Nonepileptic seizures or a treatable cause for seizures Progressive or degenerative disorder Significant history of unstable medical disease within the previous 2 years or malignancy within the previous 5 years Psychiatric or mood disorder requiring ECT or drug therapy within the previous 6 months Suicide attempt, mental retardation or impairment, alcohol or drug abuse Chronic treatment with benzodiazepines, treatment with experimental drug or device within the previous 30 days History of nephrolithiasis, clinically significant lab or ECG abnormalities, treatment with expiremental medication/device within 30 days, patients using acetazolamide, zonisamide, triamterene within 1 month of study

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Sobaniec, 2005 (N= 54)	Patients aged 2-17 years, with history of partial seizures with or without secondary generalization with at least two seizures in 6 months prior to entry into the study Patients on vigabtrin or carbamazepine therapy Patients had to be physically healthy for their age, with no history of major chronic illness	Patients with chronic epilepsy Patients with a history of sensitivity or adverse reactions to vigabatrin or carbamazepine Children with a significant history of heart disease, history of other neurological or psychiatric disorders Patients requiring concomitant medications which could interfere with patients' compliance or study conduct, i.e. sedatives, hypnotics, antidepressants, and neuroleptics Participation in a study with another experimental drug within 4 weeks prior to entering the study Patients with any disease of the gastrointestinal system, liver or kidneys, or abnormal condition which compromises a function of the systems and could result in a possibility of altered absorption, excessive Accumulation or impaired metabolism or excretion of the study drug. Clinically changed values of lab tests
Steinhoff, 2005 (N=239)	Patients 12 years of age and greater with newly diagnosed epilepsy Unequivocal diagnosis of ≥ 1 seizure and electroclinical or imaging features indicating the onset of an epilepsy syndrome requiring AED treatment	None specified
Rowan, 2005 (N= 593)	Untreated newly diagnosed patients with epileptic seizures and were untreated, treated only acutely (<4 weeks), or treated but with subtherapeutic levels A minimum of 1 seizure during the 3 months preceding enrollment was required	No restriction regarding concomitant diseases was imposed excepting those conditions likely to lead to a life expectancy of less than 12 months, progressive neurologic disease, or conditions that would significantly affect the response to treatment Patients on chronic AEDs Severe psychiatric conditions, current alcoholism, illicit drug use, or a history of noncompliance
Babayigit, 2006 (N=68)	Patients were chosen from normally active outpatients who had no other diseases	Excluded from the study were children who had used a different antiepileptic drug in the past, those with abnormal neurologic examination findings, with detected pathology in brain imaging techniques, as well as children who had motor-mental retardation and progressive brain disease, malnutrition, family history of osteoporosis, any disorder affecting growth and development, and additive medication usage that may affect bone metabolism
Brodie, 2007 (N=576)	Age: ≥ 16 years Newly Diagnosed Partial or Generalized seizures with clear focal origin Generalized Tonic-Clonic seizures without clear focal origin Experienced ≥ 2 unprovoked seizures separated by at least 48 hours during the past year with at least 1 seizure during the previous 3 months	Pseudoseizures Seizures occurring only in clusters Clinical ECG findings suggestive of idiopatic generalized-epilepsy
Donati, 2007 (N=112)	Previously untreated male or female patients aged 6 to <17 years with a history of at least two unprovoked partial seizures (including all seizure subtypes of simple and complex partial seizures and partial seizures evloving to secondarily generalized seizures) were included in the study	Patients with more than two secondarily generalized tonic-clonic seizures within the 3 months prior to randomisation were excluded In addition, patients were excluded if they had a history of clinically relevant psychiatric disorders, attention deficit disorder (minimal brain dysfunction in children), comorbid neurologic disease (other than epilepsy), or other diseases adversely affecting cognitive abilities

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Kang, 2007 (N=112)	Patients 5-15 years old with normal intelligence that had at least two partial seizures during 6 months at baseline. Clinical and electroencephalography findings compatible with benign rolandic epilepsy in addition to at least one of the following: parent and/or patient wanted to take antiepileptic drugs; daytime seizures; at least 1 episode of a convulsive seizure during 6 months. Study entry required magnetic resonance imaging to confirm the absence of a progressive cerebral lesion.	Evidence of a progressive cerebral lesion or neurodegenerative metabolic disorder. Cognitive impairment that could interfere with the cognitive testing procedure History of psychiatric disorder requiring major tranqulizers in the past 6 months Regular treatment with antihistamines, central nervous system active compounds during the past 30 days History of poor compliance with antiepileptic treatment or inability to maintain a seizure calendar independently or with assistance History of nephrolothiasis and patients who had taken any medication associated with nephrolithasis Patients previously treated with topiramate or carbamazepine
Kim, 2007 (N=33)	Patients aged 18-50 years with newly diagnosed, drug-naïve, epilepsy	Patients with epilepsy were excluded if they had: (1) a history of taking antiepileptic or other medications that affect bone metabolism (e.g., steroids, diuretics, vitamin D, calcium supplements, bisphosphonates, calcitonin) (2) had any endocrine or medical disorders (e.g., hypothyroidism, renal diseases) (3) had a history of nutritional deficiency or excessive alcohol intake (more than five drinks per day for > 1 year) (4) had limitations in ambulation or daily physical activity (5) were pregnant or breastfeeding within the previous 6 months (6) were menopausal or on hormonal treatments (7) had any progressive neurological disorders other than epilepsy
Levisohn, 2007 (N= 28)	Adolescents/adults (12–65 years old, P25 kg) with a confirmed diagnosis of JME. Diagnostic criteria included myoclonic jerks, seizure onset at 8–26 years of age, and coexistent generalized tonic-clonic seizures with generalized epileptiform abnormalities on EEG consistent with JME Patients had to have active epilepsy in the form of myoclonus or P1 PGTCS in the 3 months before study entry Topiramate or valproate could be initiated as monotherapy or as an adjunct to another AED (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy Females of childbearing potential had to be premenarchal, physically incapable of bearing children, or practicing an acceptable method of contraception	Exclusion criteria included: Previous discontinuation of topiramate or valproate due to an adverse event, abnormal cranial CT or MRI scan Dementia or mental retardation Progressive myoclonic epilepsy Cclinically unstable medical conditions History of nephrolithiasis SGOT and/or SGPT levels greater than two times the upper limit of the normal range Co-therapy with a carbonic anhydrase inhibitor or barbiturate AED Use of an experimental medication or device within 30 days of study entry.
Marson, 2007 SANAD Arm A (N= 1721)	Patients were included in arm A of SANAD if they had a history of two or more clinically definite unprovoked epileptic seizures in the previous year and if carbamazepine was deemed the better standard treatment option, compared with valproate, by the recruiting clinician This allocation allowed inclusion of patients with newly diagnosed epilepsy, patients who had failed treatment with previous monotherapy (as long as the drug failure did not include one of the drugs present in the randomisation), and patients who had entered a period of remission from seizures but had relapsed after withdrawal of treatment	Patients were excluded if: The clinician or patient felt that treatment was contraindicated All their seizures had been acute symptomatic seizures (including febrile seizures) They were aged 4 years or younger There was a history of progressive neurological disease

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Marson, 2007 SANAD Arm B (N= 716)	Patients were included in arm B of SANAD if they had a history of two or more clinically definite unprovoked epileptic seizures in the previous year and if the recruiting seizures, and a history of epilepsy in a first-degree family member Clinicians were asked to identify seizures and epilepsy syndromes by International League Against Epilepsy classifications as far as was possible, at least to differentiate between partial onset (focal) or generalized onset seizures However, where there was uncertainty, patients were recorded as having unclassified convulsive or other unclassified seizures. Results of any electroencephalogram or brain imaging around the time of randomisation were recorded	Patients were excluded if: The clinician or patient felt that treatment was contraindicated All their seizures had been acute symptomatic seizures (including febrile seizures) They were aged 4 years or younger There was a history of progressive neurological disease
Saetre, 2007 (N= 186)	Age ≥65 years Newly diagnosed epilepsy, with a history of two or more recurrent unprovoked seizures either partial (with or without secondary generalization) or primarily generalized tonic– clonic, and at least one of the seizures during the previous 6 months Clinical indication to initiate AED treatment Life expectancy >1year	A history of absence, tonic, atonic or myoclonic seizures Greater than >2-week intake of any AED in the previous 6 months, or any previous intake of carbamazepine or lamotrigine Treatment with any AED for five elimination half-lives in the period immediately preceding study entry Severe psychiatric disease or severe intellectual impairment Acute or chronic hepatic failure; Significant unpaced AV defect; Alcohol or substance abuse Abnormal blood or chemistry tests
Stephen, 2007 (N=225)	Age 13 yrs and over Newly diagnosed epilepsy A minimum of two unprovoked seizures (irrespective of seizure type), with at least one witnessed event, were required for inclusion, although individuals presenting with a single seizure and relevant underlying neuropathology could also be recruited	Pregnancy or planning to be pregnant Previous exposure to valproic acid or lamotrigine or who were taking warfarin, were specifically excluded
Morrell, 2008 (N=447)	Females 13-40 years of age Seizure Classification: Confident diagnosis of epilepsy and seizures that could be recognized by the subject or a caregiver All subjects had either newly diagnosed/untreated epilepsy (ie, fewer than 2 weeks of prior antiepileptic drug treatment) or inadequately controlled epilepsy despite treatment with a single antiepileptic drug for at least 3 months Subjects treated for uncomplicated febrile seizures before age 7 were eligible to participate	Pregnant, less than 6 months postpartum, breast-feeding, or planning a pregnancy during the course of the study or within 3 weeks after the last dose of study drug BMI more than 35 kg/m^2 Previous treatment with lamotrigine, valproate, or felbamate Women chronically treated with any other medication (other than one chronic antiepileptic drug) known to influence seizure control For newly diagnosed/untreated subjects, treatment for up to 2 weeks with an antiepileptic drug other than lamotrigine, valproate, or felbamate was allowed before enrolment in the study; however, the antiepileptic drug was to be discontinued within 2 weeks after the initiation of study medication Medical conditions or past surgeries that could affect hormone levels or menstrual function (eg, oophorectomy, adrenal dysfunction, Cushing's syndrome, diabetes, thyroid dysfunction) Serious or unstable medical or psychological condition, a current history of alcohol or drug abuse, clinically significant impairment of renal or hepatic function, or use of any investigational drug within the 30 days before study enrolment Women taking hormone mediactions, abnormal labs (increased androgen levels or signs of decreased ovarian reserve

Study, year (N)	Inclusion Criteria	Exclusion Criteria
Pack, 2008 (N=93)	Premenopausal women aged between 18 and 40 years with epilepsy and with normal menstrual cycles participated in the study All were receiving a single AED (carbamazepine, lamotrigine, phenytoin, or valproate) for at least 6 months before enrollment	Pregnant and postmenopausal women Impaired motor function, diseases that affect the skeleton (primary hyperparathyroidism, Paget disease, multiple myeloma) Patients on glucocorticoids and excessive doses of vitamin D or A
Perry, 2008 (N=86)	Patients were required to be less than 16 years of age at the time carbamazepine or levetiracetam was initiated as initial monotherapy for newly diagnosed partial epilepsy and to be followed clinically for at least 6 months	Patients were excluded if the diagnosis of nonepileptic events was confirmed by video-electroencephalography (EEG), or if the chart had been lost or destroyed
Kim, 2009 (N=146	Children with epilepsy under the age of 2 treated at the pediatric neurology clinic in Kyungpook National University Hopsital, Daegu, Korea	-
Kwan, 2009 (N= 81)	Chinese patients with epilepsy aged between 18 and 55 years and not receiving AED therapy were recruited Patients had either newly diagnosed, untreated epilepsy or a recurrence of seizures after a period of remission with AED therapy completely withdrawn for at least a year Seizures and epilepsy syndromes were classified according to international guidelines Both male and premenopausal female patients were eligible for inclusion	Women were excluded if pregnant, breastfeeding, planning a pregnancy during the course of the study, diagnosed as having PCOS, oophorectomized, taking oral contraceptive pills or hormone replacement therapy, or postmenopausal Patients were also excluded if they had medical conditions or existing treatment that could affect hormone or insulin concentrations (e.g., diabetes mellitus, adrenal dysfunction, thyroid dysfunction, glucocorticoid therapy)
Ma, 2009 (N= 497	Patients whose epilepsy was diagnosed and treated at the Neurology Department of the Beijing Children's Hospital between 1 January 2000 and 31 December 2004, with follow-up lasting through December 2007 In all, 520 children who followed a treatment regimen for more than 1 year and who had not previously received antiepileptic drugs therapy were retrospectively studied	-
Glauser, 2010 (N= 451)	Children between 2.5 and 13 years of age were eligible to participate if they met the following criteria: Had childhood absence epilepsy of new onset that was clinically diagnosed according to the International League Against Epilepsy classification of epilepsy syndromes (including frequent clinical absence seizures and reported normal development) Had bilateral synchronous, symmetric spike waves (2.7 to 5 Hz) on a normal background with at least 1 electrographically recorded seizure lasting 3 seconds or more on a 1-hour, awake video EEG Weighed 10 kg or more Had a body-mass index below the 99th percentile Had a normal complete blood count and normal levels of serum alanine aminotransferase, serum aspartate aminotransferase, and bilirubin The girls had to be premenarchal	Children were ineligible if they met any of the following criteria: Had received antiseizure medication for more than 7 days before randomization Had a history of nonfebrile seizures other than absence seizures (e.g. afebrile generalized tonic–clonic or myoclonic seizures) Had a history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy (e.g., generalized tonic– clonic or myoclonic seizures) Had a history of a severe dermatologic reaction to any medication, or had a history of major psychiatric disease, autistic- spectrum disorder, or any clinically significant medical condition
Ramsay, 2010 (N=261)	12 to 65 years of age Weight ≥110 lbs 1 to 20 unprovoked complex partial or Primary/secondarily generalized tonic clonic seizures within the past 3 months seizures indicative of new-onset epilepsy or epilepsy relapse candidates for rapid initiation of AED therapy	AED use ≤30 days prior to randomization

Legend: -=not reported, AED=antiepileptic drugs; AV defect=Atrioventricular defect; BMI=body mass index; CNS=central nervous system; CP=Complex partial seizures; CT=x-ray computed tomography, ECG=Electrocardiogram; ECT= Electroconvulsive therapy; EEG=Electroencephalography, ICS=International classificatin of epileptic seizures; ILAE=International Leage Againse Epilepsy; IQ=Intelligence quotient; JME=Juvenile myoclonic epilepsy; MRI=magnetic

resonance imaging; N=sample size; PCOS=Polycystic ovary disease; PE=partial epilepsy; SGTCS=Partial generalized tonic clonic seizures; SANAD Arm A=Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B=Standard and New Antiepileptic Drugs Trial Arm B; SGOT=Serum glutamic oxaloacetic transaminase; SGPT=Serum glutamic pyruvic transaminase

Table 7. Baseline characteristics of studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Mean age (SD)	Male (%)	Mean Body weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Danner 1988*	Carbamazepine	13	-	-	-	-	-	-	-	-
	Oxcarbazepine	12	-	-	-	-	-	-	-	-
Dam, 1989	Carbamazepine	100	-	51	68 (13)	-	-	-	-	-
	Oxcarbazepine	94	-	48	67 (13)	-	-	-	-	-
Faught, 1993	Valproate	55	34.5	36	72.2	85	9.09	-	-	5.45
	Felbamate	56	33.4	57	73.8	80	12.5	-	-	7.14
Brodie, 1995	Carbamazepine	129	-	45	-	-	-	-	-	-
	Lamotrigine	131	-	41	-	-	-	-	-	-
Kalviainen, 1995	Carbamazepine	50	37 (16)	48	-	-	-	-	-	-
	Vigabatrin	50	33 (16)	42	-	-	-	-	-	-
Sabers, 1995	Carbamazepine	11	32.5	72.7	-	-	-	-	-	-
	Valproic Acid	11	22.8	54.5	-	-	-	-	-	-
	Phenobarbital	9	31.1	66.7	-	-	-	-	-	-
	Phenytoin	11	36.8	72.7	-	-	-	-	-	-
	Oxcarbazepine	10	38.8	50	-	-	-	-	-	-
Tanganelli, 1996	Carbamazepine	25	34.8	60	-	-	-	-	-	-
	Vigabratin	26	37.9	62	-	-	-	-	-	-
Reunanen, 1996	Carbamazepine	117		50	69	-	-	-	-	-
	Lamotrigine 100 mg	115	30	54	71	-	-	-	-	-
	Lamotrigine 200 mg	111	33	58	69	-	-	-	-	-
Bill, 1997	Phenytoin	144	26.6	64	64.9	47	16	-	-	37
	Oxcarbazepine	143	27.1	57	63.6	50	15	-	-	34
Christie, 1997	Valproic Acid	121	32.47 (-)	55.4	70.2 (-)	-	-	-	-	-
	Oxcarbazepine	128	32.45 (-)	46.9	69.9 (-)	-	-	-	-	-
Guerreiro, 1997	Pheyntion	96	10.85	52	40.7	83	6.25	-	-	10.4
	Oxcarbazepine	97	10.22	47	36.4	82	11	-	-	6.19
Chadwick, 1998	Carbamazepine	74	34 (16.4)	44	-	-	-	-	-	-
	Gabapentin 300 mg	72	37 (17.3)	56	-	-	-	-	-	-
	Gabapentin 900 mg	72	34 (16.0)	49	-	-	-	-	-	-
	Gabapentin 1800 mg	74	37 (16.9)	55	-	-	-	-	-	-
Brodie, 1999a	Carbamazepine	48	76 (-)	58	68	-	-	-	-	-
	Lamotrigine	102	77 (-)	54	68	-	-	-	-	-

Study, year	Group	N	Mean age (SD)	Male (%)	Mean Body weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Brodie, 1999b	Valproic Acid	107	-	50.5		-	-	-	-	-
	Vigabatrin	108	-	48.1		-	-	-	-	-
Chadwick, 1999	Carbamazepine	226	36 (16)	54	-	-	-	-	-	-
	Vigabatrin	220	35 (15)	53	-	-	-	-	-	-
Gobbi, 1999	Carbamazepine	40	7.8	55	-	-	-	-	-	-
	Vigabatrin	40	7.5	45	-	-	-	-	-	-
Steiner, 1999	Phenytoin	95	-	57	-	-	-	-	-	-
	Lamotrigine	86	-	55	-	-	-	-	-	-
Aldenkamp, 2000	Valproic Acid	29	39.4 (11.4)	52	76.2 (18.0)	-	-	-	-	-
	Topiramate	24	34.7 (10.2)	63	75.9 (17.5)	-	-	-	-	-
Gillham, 2000	Carbamazepine	129	-	-	-	-	-	-	-	-
	Lamotrigine	131	-	-	-	-	-	-	-	-
Biton, 2001	Valproate	68	30.1 (14)	46	-	88	9	0	3	-
	Lamotrigine	65	34.5 (16)	42	-	86	8	3	3	-
Cramer, 2001	Carbamazepine	76	41 (-)	55	-	-	-	-	-	-
	Tiagabine	67	41 (-)	46	-	-	-	-	-	-
	Phenytoin	101	33 (-)	35	-	-	-	-	-	-
	Tiagabine	105	37 (-)	45	-	-	-	-	-	-
Kwan, 2001[†]	Carbamazepine	212	35.2 (19.4)	51	-	-	-	-	-	-
	Sodium Valproate	101			-	-	-	-	-	-
	Lamotrigine	78			-	-	-	-	-	-
Nieto-Barrera, 2001	Carbamazepine	201	-	47	20	-	-	-	-	-
	Lamotrigine	417	-	47	19	-	-	-	-	-
Sackellares, 2002	Valproate	55	33.8 (12.4)	45	-	-	-	-	-	-
	Lamotrigine	53	39 (13.8)	42	-	-	-	-	-	-
Biton, 2003	Valproate	20	16.0 (3)	45	64 (16.8)	90	5	0	5	-
	Lamotrigine	18	16.2 (3)	33	64 (15.5)	89	0	11	0	-
Meador, 2003	Valproate	29	37	52	-	-	-	-	-	-
	Topiramate	34	41	35	-	-	-	-	-	-
Privitera, 2003	Carbamazepine	126	-	52	-	-	-	-	-	-
	Valproic Acid	78	-	44	-	-	-	-	-	-
	Topiramate 100 mg	210	-	55	-	-	-	-	-	-
	Topiramate 200 mg	199	-	55	-	-	-	-	-	--
Clemens, 2004	Carbamazepine	20	24	38	-	-	-	-	-	-

Study, year	Group	N	Mean age (SD)	Male (%)	Mean Body weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
	Oxcarbazepine	20	24	38	-	-	-	-	-	-
Coppola, 2004	Valproic Acid	19	-	52.6	-	-	-	-	-	-
	Lamotrigine	19	-	36.8	-	-	-	-	-	-
Fakhoury, 2004	Carbamazepine	46	40.3 (12.9)	46	-	-	-	-	-	-
	Lamotrigine	98	41.0 (14.8)	41	-	-	-	-	-	-
	Valproic Acid	53	39.0 (12.7)	38	-	-	-	-	-	-
	Lamotrigine	105	38.3 (13.3)	44	-	-	-	-	-	-
Wheless, 2004	Carbamazepine	23	12	35	-	-	-	-	-	-
	Valproic Acid	19	13	42	-	-	-	-	-	-
	Topiramate 100 mg	38	13	59	-	-	-	-	-	-
	Topirate 200 mg	39	13	68	-	-	-	-	-	-
Rowan, 2005	Carbamazepine	198	71.9 (7.7)	93.8	-	67.2	26.3		2.5	Other: 4
	Gabapentin	195	72.9 (7.5)	96.7	-	70.3	22.6		5.1	Other: 2.1
	Lamotrigine	200	71.9 (7.4)	97.5	-	69.5	23.5		5.5	Other: 1.5
Steinhoff, 2005	Carbamazepine	88	43.1 (17.3)	61.4	-	-	-	-	-	-
	Lamotrigine	88	46.6 (18.8)	59.1	-	-	-	-	-	-
	Valproate	30	23.3 (10.7)	46.7	-	-	-	-	-	-
	Lamotrigine	33	22.3 (13.0)	39.4	-	-	-	-	-	-
Sobaniec, 2005	Carbamazepine	28	9.01 (3.20)	61	-	-	-	-	-	-
	Vigabratin	26	9.90 (2.30)	50	-	-	-	-	-	-
Babayigit, 2006	Carbamazepine	23	12.4 (3.93)	61	43.9 (15.51)	-	-	-	-	-
	Valproic Acid	31	11.18 (4.07)	4	38.15 (16.89)	-	-	-	-	-
	Oxcarbazepine	14	13.13 (3.17)	36	46.56 (13.65)	-	-	-	-	-
Brodie, 2007	Carbamazepine-Controlled Release	291	15.8	58.8	73.6 (15.2)	92.1	3.4	1.4	-	6.0
	Levetiracetam	285	16.6	51.2	73.7 (16.8)	91.9	1.8	0.4	-	3.1
Donati 2007	Carbamazepine	28	-	57.1	-	-	-	-	-	-
	Valproic Acid	29	-	48.3	-	-	-	-	-	-
	Oxcarbazepine	55	-	38.2	-	-	-	-	-	-
Kang, 2007	Carbamazepine	54	8.7 (2.0)	59	31.0 (33.7)	-	-	-	-	-

Study, year	Group	N	Mean age (SD)	Male (%)	Mean Body weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
	Topiramate	58	8.7 (1.9)	55	30.6 (31.2)	-	-	-	-	-
Kim, 2007	Carbamazepine	10	25.9 (11.3)	80	-	-	-	-	-	-
	Valproic Acid	15	26.0 (11.0)	66	-	-	-	-	-	-
	Lamotrigine	8	24.1 (9.9)	25	-	-	-	-	-	-
Levisohn, 2007	Valproic Acid	9	-	46	-	-	-	-	-	-
	Topiramate	19	-	32	-	-	-	-	-	-
Marson 2007 SANAD Arm	Carbamazepine	378	39.2 (18.3)	55.0	-	-	-	-	-	-
	Gabapentin	377	37.8 (17.9)	54.9	-	-	-	-	-	-
	Lamotrigine	378	36.8 (18.3)	55.0	-	-	-	-	-	-
	Oxcarbazepine	210	40.1 (18.0)	52.9	-	-	-	-	-	-
	Topiramate	378	38.4 (18.6)	55.0	-	-	-	-	-	-
Marson 2007 SANAD Arm B	Valproic Acid	238	22.5 (14.5)	60.1	-	-	-	-	-	-
	Lamotrigine	239	22.8 (14.3)	59.4	-	-	-	-	-	-
	Topiramate	239	22.3 (13.3)	59.4	-	-	-	-	-	-
Saetre, 2007	Carbamazepine – Sustained Release	91	73.1 (5.5)	49	73.9 (12.7)	-	-	-	-	-
	Lamotrigine	93	74.3 (6.2)	62	71.3 (11.8)	-	-	-	-	-
Stephen, 2007	Valproic Acid	111	-	56	Male: 76.4 (14.6) Female: 63.6 (13.6)	-	-	-	-	-
	Lamotrigine	114	-	47	Male: 76.3 (18.7) Female: 66.7(12.6)	-	-	-	-	-
Morrell, 2008	Valproate	222	22.9 (7.3)	0	56.0 (11.6)	51	4	-	8	
	Lamotrigine	219	21.8 (6.3)	0	55.4 (11.0)	55	3	-	5	
Pack, 2008	Carbamazepine	41	34 (5)	0	66 (18)	76	-	-	-	-
	Valproate	14	30 (7)	0	66 (17)	67	-	-	-	-
	Phenytoin	15	33 (5)	0	70 (23)	47	-	-	-	-
	Lamotrigine	23	30 (6)	0	73 (17)	61	-	-	-	-

Study, year	Group	N	Mean age (SD)	Male (%)	Mean Body weight in kg (SD)	Caucasian (%)	Black (%)	Asian (%)	Hispanic (%)	Other (%)
Perry, 2008	Carbamazepine	20	-	13	-	-	-	-	-	-
	Levetiracetam	66	-	48	-	-	-	-	-	-
Kim, 2009	Carbamazepine	105	8.4 (5.6) months	42.9	-	-	-	-	-	-
	Topiramate	41	(6.4) months	53.7	-	-	-	-	-	-
Kwan, 2009	Valproic Acid	44	Male: 30.9 Female: 36.9	50	-	-	-	-	-	-
	Lamotrigine	37	Male: 35.4 Female: 32.5	49	-	-	-	-	-	-
Ma, 2009‡	Carbamazepine	120	6.8 (3.6)	-	-	-	-	-	-	-
	Valproic Acid	234		-	-	-	-	-	-	-
	Topiramate	143		-	-	-	-	-	-	-
Glauser, 2010	Valproic Acid	147	-	48	-	73	20	-	-	7
	Ethosuximide	155	-	42	-	71	21	-	-	8
	Lamotrigine	149	-	38	-	79	17	-	-	4
Ramsay, 2010	Phenytoin	127	35.3 (15.5)	56.7	82.2 (19.0)	58.3	27.6	0.8	-	13.4
	Topiramate	132	33.2 (14.1)	40.2	83.5 (25.9)	68.2	22.7	0	-	9.1

* Age and % male are reported but can not be determined for each treatment group
† Mean age and % male is not reported for the individual drugs, but is reported for the total population
‡ For the whole population and not for individual treatment groups
Legend: -=not reported; N=Sample size; SANAD Arm A=Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B=Standard and New Antiepileptic Drugs Trial Arm B; SD=standard deviation

Table 8. Epilepsy history and seizure type for studies comparing older versus newer antiepileptic drugs

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Reinikainen, 1987	Carbamazepine	18	-	-	-	-	-	39	-	-	-	22	-	Mixed: 22 Unclassifiable: 5 Simple/complex partial: 17
	Oxcarbazepine	16	-	-	-	-	-	25	-	-	-	38	-	Mixed: 31 Unclassifiable: 6 Simple/complex partial: 6
Danner, 1988	Carbamazepine	13	-	-	-	-	-	-	-	-	-	-	-	
	Oxcarbazepine	12	-	-	-	-	-	-	-	-	-	-	-	
Dam, 1989	Carbamazepine	100	-	-	-	-	-	-	-	-	-	-	-	
	Oxcarbazepine	94	-	-	-	-	-	-	-	-	-	-	-	
Sachdeo, 1992	Valproate	22	-	100	-	-	-	100	-	-	-	-	-	-
	Felbamate	22	-	100	-	-	-	100	-	-	-	-	-	-
Faught, 1993	Valproic Acid	55	-	-	-	-	Mean Baseline Seizure Frequency per 28 days: 21.3	86	-	-	-	25	-	
	Felbamate	56	-	-	-	-	Mean Baseline Seizure Frequency oper 28 days: 12.4	68	-	-	-	32	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Brodie, 1995	Carbamazepine	129	100	-	-	-		57	-	-	-	48	-	
	Lamotrigine	131	100	-	-	-		56	-	-	-	46	-	
Kalviainen, 1995	Carbamazepine	50	-	-	-	-	-	22	-	8	2	-	-	
	Vigabatrin	50	-	-	-	-	-	20	-	8	8	-	-	
Reunanen, 1996	Carbamazepine	117	-	-	Mean age at first seizure: 28	-	-	-	-	-	-	-	-	-
	Lamotrigine100 mg	115	-	-	Mean age at first seizure: 29	-	-	-	-	-	-	-	-	-
	Lamotrigine 200 mg	111	-	-	Mean age at first seizure: 26	-	-	-	-	-	-	-	-	-
Tanganelli, 1996	Carbamazepine	25	-	-	-	-	-	-	-	100	-	-	-	-
	Vigabratin	26	-	-	-	-	-	-	-	100	-	-	-	-
Bill, 1997	Phenytoin	144	-	-	-	Mean duration since onset of seizures in weeks: 89.4	Mean number of seizures at baseline: 20.0 Mean seizure frequency per week at baseline: 0.84	68.1	-	-	31.9	-	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
	Oxcarbazepine	143	-	-	-	Mean duration since onset of seizures in weeks: 94.6	Mean number of seizures at baseline: 17.5 Mean seizure frequency per week at baseline: 0.98	58.7	-	-	40.6	-	-	No seizure type defined: 0.7
Christie, 1997	Valproic Acid	121	100	-	-	Mean duration in weeks since onset: 181	Mean seizure frequency per week at baseline: 1.09	64.5	-	-	35.5	-	-	
	Oxcarbazepine	128	122	-	-	Mean duration in weeks since onset: 178	Mean seizure frequency per week at baseline: 0.58	59.4	-	-	40.6	-	-	
Guerreiro, 1997	Pheyntion	96	100	0	-	Mean number ofweeks since onset of seizures: 37.7	-	81.3	-	-	17.7	-	-	No type indicated: 1
	Oxcarbazepine	97	100	0	-	Mean number ofweeks since onset of seizures: 30.2	-	75.2	-	-	22.7	-	-	No type indicated: 2.1

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Chadwick, 1998	Carbamazepine	74	100	-	-	Mean duration of epilepsy in months: 1.3 (2.3)	-	-	43	43	50	23	-	
	Gabapentin 300 mg	72	100	-	-	Mean duration of epilepsy in months: 1.0 (2.2)	-	-	24	39	44	31	-	
	Gabapentin 900 mg	72	100	-	-	Mean duration of epilepsy in months: 0.6 (1.0)	-	-	29	44	53	19	-	
	Gabapentin 1800 mg	74	100	-	-	Mean duration of epilepsy in months: 1.5 (4.5)	-	-	36	46	55	15	-	
Brodie, 1999a	Carbamazepine	48	100	-	-	-	-	-	-	-	-	-	-	
	Lamotrigine	102	100	-	-	-	-	-	-	-	-	-	-	
Brodie, 1999b	Valproic Acid	107	-	100	-	-	Mean number of seizures at baseline per month: 6.9	-	-	-	-	-	-	
	Vigabatrin	108	-	100	-	-	Mean number of seizures at baseline per month: 6.8	-	-	-	-	-	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Chadwick, 1999	Carbamazepine	226	100	-	-	-	-	-	28	40	66	-	-	
	Vigabatrin	220	100	-	-	-	-	-	34	42	63	-	-	
Gobbi, 1999	Carbamazepine	40	-	-	-	-	-	33	50	43	-	18	-	
	Vigabatrin	37	-	-	-	-	-	46	62	62	-	0	-	
Steiner, 1999	Phenytoin	95	-	-	25	-	-	27	21	-	-	52	-	-
	Lamotrigine	86	-	-	25	-	-	28	23	-	-	49	-	-
Aldenkamp, 2000	Vaproic Acid	29	-	-	-	-	Median baseline seizure rate per month: 5.8	-	-	-	-	-	-	-
	Topiramate	24	-	-	-	-	Median baseline seizure rate per month: 5.9	-	-	-	-	-	-	-
Gillham, 2000	Carbamazepine	129	-	-	-	-	-	-	-	-	-	-	-	
	Lamotrigine	131	-	-	-	-	-	-	-	-	-	-	-	
Biton, 2001	Valproate	68	35	-	26 (13) N=31	-	-	26		24		81		

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
	Lamotrigine	65	34	-	28 (16) N=34	-	-	28		26		77		
Cramer, 2001	Carbamazepine	76	0	100	-	Mean duration of epilepsy in years: 21	Mean number of complex partial seizures per month: 15 (30) n=76	-	-	100	-	-	-	
	Tiagabine	67	0	100	-	Mean duration of epilepsy in years: 23	Mean number of complex partial seizures per month: 29 (82) n=66	-	-	99	-	-	-	
	Phenytoin	101	0	100	-	Mean duration of epilepsy in years: 20	Mean number of complex partial seizures per month: 22 (66) N=100	-	-	100	-	-	-	
	Tiagabine	105	0	100	-	Mean duration of epilepsy in years: 25	Mean number of complex partial seizures per month: 13 (28) N=104	-	-	100	-	-	-	
Kwan, 2001	Carbamazepine	212	100	-	-	-	-	-	-	-	-	-	-	
	Valproic Acid	101	100	0	-	-	-	-	-	-	-	-	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
	Lamotrigine	78	100	0	-	-	-	-	-	-	-	-	-	
Nieto-Barrera, 2001	Carbamazepine	201	100	-	-	-	Mean number of seizures at baseline per month: 6.84	63	16	39	1	-	-	-
	Lamotrigine	417	100	-	-	-	Mean number of seizures at baseline per month: 10.07	55	21	44	1	-	-	-
Sackellares, 2002	Valproate	55	-	-	-	-	-	-	--	-	-	-	-	-
	Lamotrigine	53	-	-	-	-	-	-	-	-	-	-	-	-
Biton, 2003	Valproate	20	-	-	15.5 N=12	-	-	0	-	-	100	-	-	
	Lamotrigine	18	-	-	14.9 N=14	-	-	11	-	-	89	-	-	
Meador, 2003	Valproate	29	-	-	-	-	-		-	-	-	-	-	
	Topiramate	34	-	-	-	-	-		-	-	-	-	-	
Privitera, 2003	Carbamazepine	126	-	-	-	-	-	73	-	-	28	-	-	Unclassified: 1
	Valproic Acid	78	-	-	-	-	-	42	-	-	63	-	-	Unclassified: 1
	Topiramate 100 mg	210	-	-	-	-	-	64[§]	-	-	38[§]	-	-	Unclassified: 3
	Topiramate 200 mg	199	-	-	-	-	-	64[§]	-	-	38[§]	-	-	Unclassified: 3

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Clemens, 2004	Carbamazepine	20	-	-	-	-	-	-	-	-	-	-	-	
	Oxcarbazepine	20	-	-	-	-	-	-	-	-	-	-	-	
Coppola, 2004	Valproic Acid	19	100	0	7.5	Mean duration of epilepsy in years: 6.9 months	-	-	-	-	-	-	100	
	Lamotrigine	19	100	0	7.5	Mean duration of epilepsy in years: 4.5 months	-	-	-	-	-	-	100	
Fakhoury, 2004	Carbamazepine	46	0	100	-	-	Mean number of seizures during the 2 months prior to screening: 17.7 (50.1)	30	33	70	-	-		
	Lamotrigine	98	0	100	-	-	Mean number of seizures during the 2 months prior to screening: 14.2 (37.6)	40	26	57	-	-		
	Valproic Acid	53	-	-	-	-	Mean number of seizures during the 2 months prior to screening: 8.3 (14.3)	-	28	72	36	-	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
	Lamotrigine	105	-	-	-	-	Mean number of seizures during the 2 months prior to screening: 6.6 (11.0)	-	33	62	29	-	-	
Wheless, 2004	Carbamazepine	23	-	-	-	-	-	74	-	-	22			Unclassified: 0
	Valproate	19	-	-	-	-	-	32	-	-	74			Unclassified: 1
	Topiramate 100mg/day	38	-	-	-	-	-	57*	-	-	38*	-	-	Unclassified: 10*
	Topirate 200mg/day	39	-	-	-	-	-	57 *	-	-	38*	-	-	Unclassified: 10*
Rowan, 2005	Carbamazepine	198	-	-	-	-		4.7	13.5	42.0	-	29.0	-	Generalized tonic clonic and partial: 10.9 Mixed partial: 4.7
	Gabapentin	195	-	-	-	-		6.8	11.5	42.2	-	22.4	-	Generalized tonic clonic and partial: 2 Mixed partial: 6.8
	Lamotrigine	200	-	-	-	-		4.1	14.3	45.4	-	24.5	-	Generalized tonic clonic and partial:11.7 Mixed partial: 4.1
Sobaniec, 2005	Carbamazepine	28	-	-	-	-	-	71	4	25	-	-	-	
	Vigabratin	26	-	-	-	-	-	88	4	8	-	-	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Steinhoff, 2005	Carbamazepine	88	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 12.4 (27.3)	-	-	-	-	-	-	-
	Lamotrigine	88	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 12.9 (37.1)	-	-	-	-	-	-	-
	Valproate	30	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 23 (52.5)	-	-	-	-	-	-	-
	Lamotrigine	33	100	-	-	-	Mean total number of seizures during the last 6 months prior to recruitment: 16.4 (43.6)	-	-	-	-	-	-	-
Babayigit, 2006[†]	Carbamazepine	23	-	-	-	-	-	42	-	-	58	-	-	
	Valproic Acid	31	-	-	-	-	-	42	-	-	39	-	-	
	Oxcarbazepine	14	-	-	-	-	-	42	-	-	58	-	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Brodie, 2007	Carbamazepine-Controlled Release	291	100	-	-	-	-	79.7	-	-	-	20.3	-	
	Levetiracetam	285	100	-	-	-	-	80	-	-	-	20	-	
Donati, 2007	Carbamazepine	28	0	100	-	-	-	57.1	32.1	60.7	-	-	-	
	Valproic Acid	29	0	100	-	-	-	37.9	41.4	57.1	-	-	-	
	Oxcarbazepine	55	0	100	-	-	-	56.4	41.8	41.8	-	-	-	
Kang, 2007	Carbamazepine	54	-	-	-	Mean time since first seizure in months: 7.9 (9.2)	-	-	-	-	-	-	-	-
	Topiramate	58	-	-	-	Mean time since first seizure in months: 8.4 (11.2)	-	-	-	-	-	-	-	-
Kim, 2007	Carbamazepine	10	100	0	-	-	-	70	-	-	30	-	-	
	Valproic Acid	15	100	0	-	-	-	33	-	-	66	-	-	
	Lamotrigine	8	100	0	-	-	-	25	-	-	75	-	-	
Levisohn, 2007	Valproic Acid	9	-	-	-	-	-	-	-	-	-	44	22	
	Topiramate	19	-	-	-	-	-	-	-	-	-	63	11	
Marson, 2007 SANAD Arm A	Carbamazepine	378	-	-	-	-	-	1.1	-	-	0.8	-	-	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
	Gabapentin	377	-	-	-	-	-	1.3	-	-	0.8	-	-	
	Lamotrigine	378	-	-	-	-	-	1.6	-	-	1.1	-	-	
	Oxcarbazepine	210	-	-	-	-	-	1.4	-	-	2.4	-	-	
	Topiramate	378	-	-	-	-	-	1.6	-	-	1.9	-	-	
Marson, 2007 SANAD Arm B	Valproic Acid	238	-	-	18.3 (13.7)	-	-	0	-	-	64.7	-	-	
	Lamotrigine	239	-	-	17.5 (12.1)	-	-	0.4	-	-	60.7	-	-	
	Topiramate	239	-	-	17.6 (11.5)	-	-	0.8	-	-	63.5	-	-	
Saetre, 2007	Carbamazepine - Sustained Release	91	-	-	-	Mean time elapsed from diagnosis of epilepsy in months: 1.3 (4.2)	-	-	-	-	-	-	-	-
	Lamotrigine	93	-	-	-	Mean time elapsed from diagnosis of epilepsy in months: 1.3 (3.7)	-	-	-	-	-	-	-	-
Stephen, 2007	Valproate	111	100	-	-	-	-	52‡	-	-	-	21‡	-	Juvenile myoclonic epilepsy: 0.08
	Lamotrigine	114	100	-	-	-	-	52‡	-	-	-	21‡	-	Juvenile myoclonic epilepsy: 0.08

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
Morrell, 2008	Valproate	222	85	15	Mean age at first seizure: 19.1 (8.2)	3.8 (5.7)	-	36	-	-	59	-	-	Both partial and generalized: 2
	Lamotrigine	219	80	20	Mean age at first seizure: 18.3 (7.4)	3.4 (5.3)	-	38	-	-	59	-	-	Both partial and generalized: 3
Pack, 2008	Carbamazepine	41	-	100	-	-	-	-	-	-	-	-	-	-
	Valproate	14	-	100	-	-	-	-	-	-	-	-	-	-
	Phenytoin	15	-	100	-	-	-	-	-	-	-	-	-	-
	Lamotrigine	23	-	100	-	-	-	-	-	-	-	-	-	-
Perry, 2008	Carbamazepine	20	-	-	-	-	-	-	-	-	-	-	-	-
	Levetiracetam	66	-	-	-	-	-	-	-	-	-	-	-	-
Kim, 2009	Carbamazepine	105	-	-	-	-	-	43.8	-	-	46.7	-	-	
	Topiramate	41	-	-	-	-	-	19.5	-	-	70.7	-	-	
Kwan, 2009	Valproic Acid	44	-	-	-	-	-	36	-	-	64	-	-	
	Lamotrigine	37	-	-	-	-	-	43	-	-	58	-	-	
Glauser, 2010	Ethosuximide	155	100	-	-	-	-	-	-	-	-	-	100	
	Valproic Acid	147	100	-	-	-	-	-	-	-	-	-	100	

Study, Year	Group	N	New Onset Eiplepsy (%)	Chronic Epilepsy (%)	Mean age at onset (SD)	Mean Epilepsy Duration (SD)	Mean number of Seizures in Past (SD)	Partial Seizures (%)	Simple Partial Seizures (%)	Complex Partial Seizures (%)	Generalized Seizures (%)	Tonic-Clonic Seizures (%)	Absence Seizures (%)	Other (%)
	Lamotrigine	149	100	-	-	-	-	-	-	-	-	-	100	
Ramsay, 2010	Phenytoin	127	-	-	34.0 (16.4)	1.3 (4.9)	-	-	11.8	22.0	48.8	-	2.4	Myoclonic: 0.8
	Topiramate	132	-	-	31.3 (15.9)	1.8 (5.8)	-	-	6.8	28.8	38.6	-	3.8	Myoclonic: 2.3

* values represent percentages of combined Topirmate 100 mg and Topiramte 200 mg groups
† values represent percentages for all patients combined and not by treatment group
‡ values represent percentages for all patients combined and not by treatment group
§ values represent percentages of combined Topiramate 100 mg and Topiramate 200 mg group
Legend: -=not reported, N=sample size; SANAD Arm A= Standard and New Antiepileptic Drugs Trial Arm A; Arm B= Standard and New Antiepileptic Drugs Trial Arm B

Table 9. Prior or concurrent antiepileptic drug use in studies comparing newer versus older antiepileptic drugs

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Reinikainen, 1987	Carbamazepine	18			100						
N= 40											
	Oxcarbazepine	16			100						
Danner, 1988	Carbamazepine	13	-	-	-	-	-	-	-	-	-
	Oxcarbazepine	12	-	-	-	-	-	-	-	-	-
Dam, 1989	Carbamazepine	100	-	-	-	-	-	-	-	-	-
	Oxcarbazepine	94	-	-	-	-	-	-	-	-	-
Sachedo, 1992	Valproic Acid	22	0	45	14	0.09	0			32	Primidone: 0
	Felbamate	22	0	36	0.05	0.05	0.05			45	
Faught, 1993	Valproate	55	-	-	-	-	-	-	-	-	-
	Felbamate	56	-	-	-	-	-	-	-	-	-
Brodie, 1995	Carbamazepine	129	100								
	Lamotrigine	131	100								
Kalviannen, 1995	Carbamazepine	50	100								
	Vigabatrin	50	100								
Sabers, 1995	Carbamazepine	11	100								
	Phenobarbital	9	100								
	Phenytoin	11	100								
	Valproic Acid	11	100								
	Oxcarbazepine	10	100								
Tanganelli, 1995	Carbamazepine		100								
	Vigabatrin		100								
Bill, 1997	Phenytoin	144	100	-	-	-	-	-	-	-	-
	Oxcarbazepine	143	100	-	-	-	-	-	-	-	-
Christie,1997	Valproic Acid	121	-	-	-	-	-	-	-	-	-
	Oxcarbazepine	128	-	-	-	-	-	-	-	-	-
Chadwick, 1998	Carbamazepine	74	-	-	-	-	-	-	-	-	-
	Gabapentin 300 mg	72	-	-	-	-	-	-	-	-	-

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
	Gabapentin 900 mg	72	-	-	-	-	-	-	-	-	-
	Gabapentin 1800 mg	74	-	-	-	-	-	-	-	-	-
Brodie, 1999a	Carbamazepine	48	-	-	-	-	-	-	-	-	-
	Lamotrigine	102	-	-	-	-	-	-	-	-	-
Brodie, 1999b	Valproate	107		100							
	Vigabatrin	108		100							
Chadwick, 1999	Carbamazepine	226	100								
	Vigabatrin	220	100								
Gobbi, 1999	Carbamazepine	40	100								
	Vigabatrin	40	100								
Steiner, 1999	Phenytoin		100								
	Lamotrigine		100								
Gillham, 2000	Carbamazepine	129	-	-	-	-	-	-	-	-	-
	Lamotrigine	131	-	-	-	-	-	-	-	-	-
Biton, 2001	Valproate	68	35	26	49	-	-	-	-	-	41
	Lamotrigine	65	34	15	48	-	-	-	-	-	29
Cramer, 2001	Carbamazepine	76			100						
	Taigabine	67			100						
	Phenytoin	101		100							
	Tiagabine	105		100							
Kwan, 2001	Carbamazepine	212	100								
	Lamotrigine	78	100								
	Valproic Acid	101	100								
	Lamotrigine	78	100								
Nieto-Barrera, 2001	Carbamazepine	201	100	-	-	-	-	-	-	-	-
	Lamotrigine	417	100	-	-	-	-	-	-	-	-
Sackellares, 2002	Valproic Acid	55	-	-	-	-	-	-	-	-	-
	Lamotrigine	53	-	-	-	-	-	-	-	-	-
Biton, 2003	Valproate	20	50	5	25	10			6	-	-
	Lamotrigine	18	39	28	39	6	6	6		-	-

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Meador, 2003	Valproic Acid	29	-	-	-	-	-	-	-	-	-
	Topiramate	34	-	-	-	-	-	-	-	-	-
Privitera, 2003	Carbamazepine	126	62	-	-	-	-	-	-	-	-
	Valproic Acid	78	59	-	-	-	-	-	-	-	-
	Topiramate 100 mg	210	58*	-	-	-	-	-	-	-	-
	Topiramate 200 mg	199	58*	-	-	-	-	-	-	-	-
Clemens, 2004	Carbamazepine	21		100							
	Oxcarbazepine	20		100							
Coppola, 2004	Valproic Acid	19	-	-	-	-	-	-	-	-	-
	Lamotrigine	19	-	-	-	-	-	-	-	-	-
Fakhoury, 2004	Carbamazepine	46		2	48	37	4	7			Topiramate:2 Clonazepam: 0 Primidone: 0 Felbamate: 0 Mephytoin: 0
	Lamotrigine	98		0	39	46	3	7			Topiramate:3 Clonazepam:1 Primidone: 1 Felbamate: 0 Mephytoin: 0
	Valproic Acid	53		53	32	0	2	6			Topiramate: 2 Clonazepam: 2 Primidone: 2 Felbamate: 0 Mephytoin: 0
	Lamotrigine	105		56	29	0	4	7			Topiramate: 2 Clonazepam: 0 Primidone: 0 Felbamate: <1 Mephytoin: <1
Wheless, 2004	Carbamazepine	23	-	-	-	-	-	-	-	-	-
	Valproic Acid	19	-	-	-	-	-	-	-	-	-

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
	Topiramate 100 mg	38	-	-	-	-	-	-	-	-	-
	Topiramate 200 mg	39	-	-	-	-	-	-	-	-	-
Rowan, 2005	Carbamazepine	198	100								
	Gabapentin	195	100								
	Lamotrigine	200	100								
Sobianiec, 2005	Carbamazepine			100							
	Vigabatrin										Vigabatrin: 100
Steinhoff, 2005	Carbamazepine	88	-	-	-	-	-	-	-	-	-
	Lamotrigine	88	-	-	-	-	-	-	-	-	-
	Valproic Acid	33	-	-	-	-	-	-	-	-	-
	Lamotrigine	30	-	-	-	-	-	-	-	-	-
Babayigit, 2006	Carbamazepine	23		100							
	Valproic Acid	31				100					
	Oxcarbazepine	14									Oxcarbazepine: 100
Brodie, 2007	Carbamazepine-Controlled Release	291	-	-	-	-	-	-	-	-	-
	Levetiracetam	288	-	-	-	-	-	-	-	-	-
Donati, 2007	Carbamazepine	28	100								
	Oxcarbazepine	55	100								
	Valproic Acid	29	100								
	Oxcarbazepine	55	100								
Kim, 2007	Carbamazepine	10	100								
	Valproic Acid	15	100								
	Lamotrigine	8	100								
Levisohn, 2007	Valproic Acid	9	44	0	22	11					Oxcarbazepine: 0 Lamotrigine: 11 Ethosuximide: 11
	Topiramate	19	63	16	5	5					Oxcarbazepine: 5 Lamotrigine: 5

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
Marson, 2007 SANAD Arm A	Carbamazepine	378	81.8								Monotherapy not optimally treated: 15.9
	Gabapentin	377	81.2								Monotherapy not optimally treated: 15.9
	Lamotrigine	378	81.5								Monotherapy not optimally treated: 16.1
	Oxcarbazepine	210	86.2								Monotherapy not optimally treated: 15.9
	Topiramate	378	81.5								Monotherapy not optimally treated: 11.9
Marson, 2007 SANAD Arm B	Valproic Acid	238	87.7								Monotherapy not optimally treated: 8.8
	Lamotrigine	239	87.9								Monotherapy not optimally treated: 8.0
	Topiramate	239	87.5								Monotherapy not optimally treated: 8.4
Saetre, 2007	Carbamazepine	92	-	-	-	-	-	-	-	-	-
	Lamotrigine	94	-	-	-	-	-	-	-	-	-
Stephen, 2007	Valproic Acid	111	-	-	-	-	-	-	-	-	-
	Lamotrigine	114	-	-	-	-	-	-	-	-	-
Morrell, 2008	Valproate	222	85	5	3	-	4	-	-	-	Other: 2
	Lamotrigine	219	80	8	4	-	4	-	-	-	Other: 5
Pack, 2008	Carbamazepine	41		100							
	Valproate	14				100					
	Pheytoin	15			100						
	Lamotrigine	23		100							
Perry, 2008	Carbamazepine	20	-	-	-	-	-	-	-	-	-
	Levetiracetam	66	-	-	-	-	-	-	-	-	-
Kim, 2009	Carbamazepine	105	-	-	-	-	-	-	-	-	-

Study, year	Group	N	Untreated (%)	Carbamazepine (%)	Phenytoin (%)	Valproic Acid (%)	Phenobarbital (%)	Gabapentin (%)	Lorazepam (%)	Combination Therapy (%)	Other Therapy (%)
	Topiramate	41	-	-	-	-	-	-	-	-	-
Ma, 2009	Carbamazepine	120	-	-	-	-	-	-	-	-	-
	Valproic Acid	234	-	-	-	-	-	-	-	-	-
	Topiramate	143	-	-	-	-	-	-	-	-	-
Glauser, 2010	Ethosuximide	155	-	-	-	-	-	-	-	-	-
	Valproic Acid	174	-	-	-	-	-	-	-	-	-
	Lamotrigine	149	-	-	-	-	-	-	-	-	-
Ramsay 2010	Phenytoin	127	-	-	-	-	-	-	-	-	-
	Topiramate	132	-	-	-	-	-	-	-	-	-

* values represent percentages of combined Topirmate 100 mg and Topiramte 200 mg groups

Legend: -=not reported; N=Sample size SANAD Arm A= Standard and New Antiepileptic Drugs Trial Arm A; Arm B= Standard and New Antiepileptic Drugs Trial Arm B

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Appendix G. Additional Evidence Tables

Table 10. Seizure outcomes in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Change from baseline in seizure frequency, mean (SD)	Breakthrough seizures, patients (n) and events (n)	Status epilepticus, events (n)	Dose required for efficacy, mean (SD)	Switchback, events (n)
Antiepileptic Drug Class							
Rascati, 200	Cases	991	-	-	-	-	-
	Controls	2973	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-
	Controls	1248	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-
	Controls	8847	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	537 of 2095 switched to generic and then back to brand (26.5%)
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	635 of 1963 switched to generic and then back to brand (31.1%)
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Carbamazepine							
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-

Study, year	Group	N	Change from baseline in seizure frequency, mean (SD)	Breakthrough seizures, patients (n) and events (n)	Status epilepticus, events (n)	Dose required for efficacy, mean (SD)	Switchback, events (n)
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	Seizure frequency: 6.1 (12.9)	6 patients	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		Seizure frequency: 4.9 (9.2)	6 patients	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	8 Patients	-	-	-
	Carbamazepine (Ethical Generics)		-	8 Patients	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	4 patients	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	2 patients	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	18	Seizure frequency: 0.22 (0.20) per day	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		Seizure frequency: 0.25 (0.14) per day	-	-	-	-

Study, year	Group	N	Change from baseline in seizure frequency, mean (SD)	Breakthrough seizures, patients (n) and events (n)	Status epilepticus, events (n)	Dose required for efficacy, mean (SD)	Switchback, events (n)
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	198 events	-	-	-
	Carbamazepine Slow Release (Laakefarmos) Tablets		-	109 events	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	5 patients 10 events	-	-	-
	Carbamazepine (Central Poly) Tablets		-	2 patients 5 events	-	-	-
	Carbamazepine (Condrugs) Tablets		-	7 patients 14 events	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	3 patients 5 events	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	One patient*†			-
	Generic (Pharmachemie) Tablets	12	-				-
	Generic (Pharbita) Tablets	12	-				-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	20.8% of patients who switched to generic carbamazepine CR switched back to Tegretol CR.
	Carbamazepine CR (manufacturer not reported)						
Clobazam							

Study, year	Group	N	Change from baseline in seizure frequency, mean (SD)	Breakthrough seizures, patients (n) and events (n)	Status epilepticus, events (n)	Dose required for efficacy, mean (SD)	Switchback, events (n)
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	328
	Clobazam (manufacturers not reported)		-	-	-	-	
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	44.1% of patients who switched to generic clobazam switched back to Frisium
	Clobazam (manufacturer not reported)						
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	30.9% of patients who switch to generic gabapentin switched back to Neurontin
	Gabapentin (manufacturer not reported)						
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	149
	Lamotrigine (manufacturers not reported)						
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	Of the 187 patients on Lamictal who switched to generic, 51 (27.5%) switched back to brand.
	Lamotrigine (manufacturer(s) not reported)						
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-	-	-	-

Study, year	Group	N	Change from baseline in seizure frequency, mean (SD)	Breakthrough seizures, patients (n) and events (n)	Status epilepticus, events (n)	Dose required for efficacy, mean (SD)	Switchback, events (n)
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin							
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	There was no statistically significant difference in seizure frequencies	43 events	-	-	-
	Phenytoin (Boots) tablets			30 events	-	-	-
	Phenytoin (Evans) tablets			60 events	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	5 patients 13 events	-	-	-

Study, year	Group	N	Change from baseline in seizure frequency, mean (SD)	Breakthrough seizures, patients (n) and events (n)	Status epilepticus, events (n)	Dose required for efficacy, mean (SD)	Switchback, events (n)
	Phenytoin (Epsolin, Cadila) tablets	15	-	2 patients 22 events	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	2 patients 45 events	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	2 patients 3 events	-	-	-
Mikati 1992[a]	Dilantin (Parke-Davis) capsules	10	"The number of patients and their low seizure frequency do not allow for any meaningful comparison of efficacy"	-	-	-	-
	Phenytoin (Phenytex, manufacturer not reported) capsules			-	-	-	-
Soryal, 1992[a]	Epanutin (Parke-Davis) capsules	14	No statistically significant differences were found in seizure frequency between the formulations	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (Regent) tablets		-	-	-	-	-
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-

Study, year	Group	N	Change from baseline in seizure frequency, mean (SD)	Breakthrough seizures, patients (n) and events (n)	Status epilepticus, events (n)	Dose required for efficacy, mean (SD)	Switchback, events (n)
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	12.5%
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	12.5%
Paradis 2009[a]	Topamax (Ortho-McNeil)	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-
Valproic Acid							
Vadney, 1997	Depakene (Abbott)	64	There was no significant difference in the mean number of seizures on either Depakene (50.89, n=64) or valproic acid (49.83, n=64), p=0.89. 31 patients had no seizures throughout the study. 10 patients had an equal number of seizures on both Depakene and valproic acid. Of the 23 patients with uncontrolled epilepsy, there was no change in seizure patterns based on monthly seizure counts between one year prior and one year after the study	11 patients had more seizures on Depakene than valproic acid	-	-	-
	Valproic acid (Solvay)			12 patients had more seizures on valproic acid than Depakene	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	422
	Valproic Acid (manufacturers not reported)		-	-	-	-	

[a] Reports on same database as Duh 2009
* Whether patient was receiving innovator or genic at time was not reported
† Two events during brand CBZ phase

Legend: -=not reported; event (n)=number of events; N=sample size; patients (n)=number of patients with event

Table 11. Withdrawals and discontinuations in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Overall withdrawals or discontinuations (n)	Withdrawals due to ineffective treatment (n)	Withdrawals due to ADRs (n)	ADRs contributing to withdrawals (List, % of patients)
Antiepileptic Drug Class						
Rascati, 2009	Cases	991	-	-	-	-
	Controls	2973	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-
	Controls	1248	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-
	Controls	8847	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-
Carbamazepine						
Kauko; 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	0	0	0	0

Study, year	Group	N	Overall withdrawals or discontinuations (n)	Withdrawals due to ineffective treatment (n)	Withdrawals due to ADRs (n)	ADRs contributing to withdrawals (List, % of patients)
	Carbamazepine (AWD Dresden) Tablets		0	0	0	0
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	0	0	0	0
	Generic Carbamazepine (Parke Davis) Tablets		0	0	0	0
Hartley, 1990	Tegretol (Ciba-Geigy)	23	1	0	1	100 – macular rash
	Carbamazepine (Ethical Generics)		0	0	0	0
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	0	0	0	-
	Carbamazepine (Ethical Generics) Tablets		0	0	0	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	2	1	1	5
	Carbamazepine (Lemmon Co) Tablets		0	0	0	0
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	2	2	0	0
	Carbamazepine (Lemmon Co) Tablets		3	2	1	0
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	0	0	0	0
	Carbamazepine (Laakefarmos) Tablets		0	0	0	0
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	0	0	0	0
	Generic (Pharmachemie) Tablets	12	0	0	0	0
	Generic (Pharbita) Tablets	12	0	0	0	0
Garnett, 2005	Tegretol (Novartis) Tablets	275	157	-	-	-
	Generic (Various/Unspecified) Tablets	705	469	-	-	-

Study, year	Group	N	Overall withdrawals or discontinuations (n)	Withdrawals due to ineffective treatment (n)	Withdrawals due to ADRs (n)	ADRs contributing to withdrawals (List, % of patients)
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-
Clobazam						
Andermann 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-
Gabapentin						
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-
Lamotrigine						
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-
LeLorier, 2008	Lamictal (GlaxoSmithKline)	671	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-
Nielsen, 2008a	Lamictal	9	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin						
Lund, 1974	Epanutin (Parke-Davis) capsules	9	0	0	0	0

Study, year	Group	N	Overall withdrawals or discontinuations (n)	Withdrawals due to ineffective treatment (n)	Withdrawals due to ADRs (n)	ADRs contributing to withdrawals (List, % of patients)
	Phenytoin sodium (Leo) capsules		0	0	0	0
Chen, 1982	Epanutin (Parke-Davis) capsules	20	2*	0	0	0
	Phenytoin sodium (Boots) tablets					
	Phenytoin sodium (Cox) tablets					
	Phenytoin sodium (Kerfoot) tablets					
	Phenytoin sodium (McCarthy UK) tablets					
Hodges, 1986	Phenytoin (Parke-Davis) capsules	30	11*	-	-	-
	Phenytoin (Boots) tablets					
	Phenytoin (Evans) tablets					
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	0	0	0	0
	Phenytoin (Epsolin, Cadila) tablets	15	0	0	0	0
	Phenytoin (Eptoin, Boots India) tablets	15	0	0	0	0
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	0	0	0	0
Mikati 1992[a]	Dilantin (Parke-Davis) capsules Phenytoin (Phenytex, manufacturer not reported) capsules	10	2 Brand 2 Generic †	1 Brand 2 Generic	1 Brand 0 Generic	Allergic rash (100%) in Brand 0% in generic
Soryal, 1992[a]	Epanutin (Parke-Davis) capsules	17	3*	0	0	0
	Phenytoin sodium (Evans) tablets					
	Phenytoin sodium (APS) tablets					
	Phenytoin sodium (Cox) tablets					
	Phenytoin sodium (Kerfoot) tablets					
	Phenytoin sodium (Regent) tablets					
Topiramate						

Study, year	Group	N	Overall withdrawals or discontinuations (n)	Withdrawals due to ineffective treatment (n)	Withdrawals due to ADRs (n)	ADRs contributing to withdrawals (List, % of patients)
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-
Paradis, 2009[a]	Topamax (Ortho-McNeil)	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-
Valproic Acid						
Vadney, 1997	Depakene (Abbott)	72	8‡	-	-	-
	Valproic acid (Solvay)					
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-

[a] Reports on same database as Duh 2009
*Overall result of all the groups combined, results not fiven separately
† Overall only 3 patients did not complete 6 months of study, but 1 patient did not finish either of the two groups
‡ Overall results of 2 groups combined. Results not given separatel
Legend: -=not reported; N=sample size; n=number of patients that withdrew

Table 12. Final health outcomes in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
Antiepileptic Drug Class									
Rascati, 2009	Cases	991	-	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-			-	-	-	-
	Controls	8847	-			-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	11.86 events/person-years	0.15 events/person-years	1.02 days/event	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	14.26 events/person-years (unadjusted rate ratio with 95% CI = 1.20 (1.19-1.21); adjusted rate ratio (1.20 (1.19-1.21))	0.20 events/person-years (unadjusted rate ratio with 95% CI = 1.35 (1.27-1.43); adjusted rate ratio (1.31 (1.24-1.40))	1.38 days/events (unadjusted rate ratio with 95% CI = 1.36 (1.33-1.39); adjusted rate ratio (1.33 (1.30-1.36))	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	23.33 events/person-years	0.34 events/person-years	2.33 days/event	-	-	-

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	28.36 events/person-years (unadjusted rate ratio with 95% CI = 1.22 (1.21-1.22); adjusted rate ratio (1.16 (1.16-1.17))	0.47 events/person-years (unadjusted rate ratio with 95% CI = 1.38 (1.32-1.43); adjusted rate ratio (1.30 (1.25-1.36))	3.29 days/event (unadjusted rate ratio with 95% CI = 1.41 (1.39-1.43); adjusted rate ratio (1.34 (1.32-1.36))	-	-	-
Carbamazepine									
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	0	-	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		0	-	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	0	-	-	-	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		0	-	-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	0	-	-	-	-	-	-

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
	Carbamazepine (Ethical Generics)		0	-	-	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	0	-	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		0	-	-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	0	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		0	-	-	-	-	-	-
Oles 1992b	Tegretol (Ciba-Geigy) Tablets	20	0	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		0	-	-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	21	0	-	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		0	-	-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-	-	-

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	0	-	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	0	-	-	-	-	-	-
	Generic (Pharbita) Tablets	12	0	-	-	-	-	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-	-
Clobazam									
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-	-	-
Gabapentin									

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
LeLorier 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-	-
Lamotrigine									
Andermann. 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	449	-	8.24 visits per patient per year	0.49 visits per patient per year	3.29 days per patient per year	-	-	-
	Lamotrigine (manufacturer(s) not reported)	222	-	9.25 visits per patient per year	0.56 visits per patient per year	4.86 days per patient per year	-	-	-
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-	-	-
Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin									

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
Lund, 1974	Epanutin (Parke-Davis) capsules	9	0	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		0	-	-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	0	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablet		0	-	-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		0	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	0	-	-	-	-	-	-
	Phenytoin (Boots) tablets		0	-	-	-	-	-	-
	Phenytoin (Evans) tablets		0	-	-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	0	-	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	0	-	-	-	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	0	-	-	-	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	0	-	-	-	-	-	-

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
Mikati 1992[a]	Dilantin (Parke-Davis) capsules	10	0	-	-	-	-	-	-
	Phenytoin (Phenytex, manufacturer not reported) capsules		0	-	-	-	-	-	-
Soryal 1992[a]	Epanutin (Parke-Davis) capsules	14	0	-	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (APS) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		0	-	-	-	-	-	-
	Phenytoin sodium (Regent) tablets		0	-	-	-	-	-	-
Topiramate									
Duh, 2009	Topamax (Ortho-McNeil)	875	-	9.07 outpatient visits/person-year	0.48 events/person-year	2.55 days	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	9.48outpatient visits/person-year	0.52 events/person-year	3.22 days	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	8.74 outpatient visits/person-year	0.83 events/person-year	3.88 days	-	-	-
Paradis, 2009[b]	Topamax (Ortho-McNeil)	-	-	9.0 outpatient visits/person-year	0.5 events/person-year	2.4 days	-	-	-

Study, year	Group	N	Deaths	Office/ER visits (n)	Hospitalizations, events (n)	Hospital duration, mean (SD)	Composite of Ambulance/ ER/ Hospitalizations, events (n)	Loss of Drivers License, events (n)	Loss of Employment, events (n)
	Topiramate (Various manufacturers)	-	-	9.1 outpatient visits/person-year	0.6 events/person-year	3.1 days	-	-	-
Valproic Acid									
Vadney, 1997	Depakene (Abbott)	64	0	-	-	-	-	-	-
	Valproic acid (Solvay)		0	-	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-	-

[a] Crossover Study
[b] Reports on same database as Duh 2009
Legend: -=not reported, N=sample size; n=number of events; SD=standard deviation

Table 13. Secondary seizure injury in controlled studies comparing innovator versus generic antiepielptic drugs

Study, year	Group	N	Type of injury	Events (n)
Antiepileptic Drug Class				
Rascati, 2009	Cases	991	-	-
	Controls	2973	-	-
Zachry, 2009	Cases	416	-	-
	Controls	1248	-	-
Devine, 2010	Cases	2949	-	-
	Controls	8847	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-
Carbamazepine				
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-
	Generic Carbamazepine (Parke Davi Tablets		-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	-
	Carbamazepine (Ethical Generics)		-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-

Study, year	Group	N	Type of injury	Events (n)
	Carbamazepine (Ethical Generics) Tablets		-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-
	Carbamazepine (Lemmon Co) Tablet		-	-
Oles 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	21	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-
	Carbamazepine (Central Poly) Tablets		-	-
	Carbamazepine (Condrugs) Tablets		-	-
	Carbamazepine (Pharmaland) Tablets		-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-
	Generic (Pharmachemie) Tablets	12	-	-
	Generic (Pharbita) Tablets	12	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-
	Generic (Various/Unspecified) Tablets	705	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-
	Carbamazepine CR (manufacturer not reported)		-	-
Clobazam				
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-
	Clobazam (manufacturers not reported)		-	-
LeLorier 2008b	Frisium (manufacturer not reported)	1060	-	-
	Clobazam (manufacturer not reported)		-	-
Gabapentin				

Study, year	Group	N	Type of injury	Events (n)
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-
	Gabapentin (manufacturer not reported)		-	-
Lamotrigine				
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-
	Lamotrigine (manufacturers not reported)		-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-
Levetiracetam				
Oxcarbazepine				
Phenobarbital or Primidone				
Phenytoin				
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-
	Phenytoin sodium (Leo) capsules		-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-
	Phenytoin sodium (Boots) tablets		-	-
	Phenytoin sodium (Cox) tablets		-	-
	Phenytoin sodium (Kerfoot) tablets		-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-
	Phenytoin (Boots) tablets		-	-
	Phenytoin (Evans) tablets		-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	-

Study, year	Group	N	Type of injury	Events (n)
Mikati, 1992a	Dilantin (Parke-Davis) capsules	10	-	-
	Phenytoin (Phenytex, manufacturer not reported) capsules		-	-
Soryal, 1992[a]	Epanutin (Parke-Davis) capsules	14	-	-
	Phenytoin sodium (Evans) tablets		-	-
	Phenytoin sodium (APS) tablets		-	-
	Phenytoin sodium (Cox) tablets		-	-
	Phenytoin sodium (Kerfoot) tablets		-	-
	Phenytoin sodium (Regent) tablets		-	-
Topiramate				
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-
Paradis, 2009[b]	Topamax (Ortho-McNeil)	-	-	-
	Topiramate (Various manufacturers)	-	-	-
Valproic Acid				
Vadney, 1997	Depakene (Abbott)	64	-	-
	Valproic acid (Solvay)		-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-
	Valproic Acid (manufacturers not reported)		-	-

[a] Crossover Study
[b] Reports on same database as Duh 2009
Legend: -=not reported; N=sample size; n=number of events

Table 14. Change from baseline in health-related quality of life in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3
Antiepileptic Drug Class							
Rascati, 2009	Cases	991	-	-	-	-	-
	Controls	2973	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-
	Controls	1248	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-
	Controls	8847	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Carbamazepine							
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	-	-	-	-
	Carbamazepine (Ethical Generics)		-	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	21	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	-	-	-	-	-
	Generic (Pharbita) Tablets	12	-	-	-	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-
Clobazam							
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-
Nielsen, 2008a	Lamictal	9	-	-	-	-	-

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-
Levetiracetam Oxcarbazepine Phenobarbital or Primidone Phenytoin							
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-
	Phenytoin (Boots) tablets		-	-	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15					
	Phenytoin (Epsolin, Cadila) tablets	15					
	Phenytoin (Eptoin, Boots India) tablets	15					
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15					
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	-	-	-	-	-
	Phenytoin (Phenytex, manufacturer not reported) capsules		-	-	-	-	-
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (Regent) tablets		-	-	-	-	-
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-
Paradis 2009[b]	Topamax (Ortho-McNeil)	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-
Valproic Acid							
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-

Legend: -=not reported; N=sample size

Table 15. Pharmacokinetic outcomes in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	C_{max}	C_{min}	C_{ss}	AUC	T_{max}	Range
Antiepileptic Drug Class								
Rascati, 2009	Cases	991	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-	-
	Controls	8847	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-
Carbamazepine								
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	6.18 (2.21)	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	5.57 (1.61)	-	-	-	-

Study, year	Group	N	C_{max}	C_{min}	C_{ss}	AUC	T_{max}	Range
Antiepileptic Drug Class								
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	5.43 (2.06)	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	4.89 (1.87)	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	7.1 (1.9)	154.8 (41.9)	-	47.6 (16.5)
	Carbamazepine (AWD Dresden) Tablets		-	-	7.0 (1.1)	153.5 (24.9)	-	63.0 (12.0)
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	10.1 (4.0) mcg.mL	-	-	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-	9.6 (3.6) mcg/mL	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	22	9.46 (1.78)	5.75 (1.37)	-	-	-	-
	Carbamazepine (Ethical Generics)		9.50 (2.17)	5.83 (1.64)	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	10.2 (1.8) mcg/mL	-	8.20 (1.46) mcg/mL	98.9 (17.0) mcg/mL	3.6 (0.5) h	-
	Carbamazepine (Ethical Generics) Tablets		9.91 (2.31) mcg/mL	-	8.12 (2.12) mcg/mL	97.4 (25.4) mcg/mL	3.1 (0.7) h	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	19	9.8 (2.1)	-	-	54.9 (11.7)	3.5 (1.6)	-
	Carbamazepine (Lemmon Co) Tablets		10.0 (2.1)	-	-	55.2 (11.2)	3.2 (1.0)	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	17	12.2 (2.1)	-	-	67.2 (10.9) mcg/mL	3.5 (1.5)	-
	Carbamazepine (Lemmon Co) Tablets		12.4 (1.7)	-	-	69.7 (9.9) mcg/mL	3.3 (1.0)	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	5.7 (1.4)	4.5 (1.2)	5.2 (1.3)	62.0 (15.7)	4.5 (2.8)	-
	Carbamazepine (Laakefarmos) Tablets		6.5 (1.5)	4.9 (1.1)	5.8 (1.3)	69.0 (15.3)	4.0 (1.9)	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	10.5 (2.92)	8.13 (2.78)	-	85.59 (48)	3.17 (1.33)	-

Study, year	Group	N	C_{max}	C_{min}	C_{ss}	AUC	T_{max}	Range
Antiepileptic Drug Class								
	Carbamazepine (Central Poly) Tablets		10.95 (2.55)	8.20 (2.95)	-	84.98 (39.49)	2.67 (1.18)	-
	Carbamazepine (Condrugs) Tablets		10.54 (3.36)	8.29 (2.06)	-	92.98 (43.68)	2.94 (1.25)	-
	Carbamazepine (Pharmaland) Tablets		10.95 (2.25)	7.40 (2.55)	-	98.21 (129.17)	3.28 (1.32)	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	8.28 (1.1) mg/L	5.84 (0.97) mg/L	-	87.98 (12.51) mg/L	13.83 (0.58) h	2.44 (0.18) mg/L
	Generic (Pharmachemie) Tablets	12	8.17 (1.55) mg/L	6.06 (1.47) mg/L	-	87.52 (17.54) mg/L	14.83 (0.58) h	2.11 (0.22)
	Generic (Pharbita) Tablets	12	8.67 (1.96) mg/L	6.25 (1.37) mg/L	-	92.90 (20.84) mg/L	14.25 (0.42) h	2.42 (0.65) mg/L
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-
Clobazam								
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-	-
Gabapentin								

Study, year	Group	N	C_{max}	C_{min}	C_{ss}	AUC	T_{max}	Range
Antiepileptic Drug Class								
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-
Lamotrigine								
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-
Nielsen, 2008a	Lamictal	9	44.89 (8.46)	30.89 (6.11)	-	359.38 (72.87)	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		44.78 (10.31)	31.78 (8.73)	-	348.88 (89.86)	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-	-
Levetiracetam Oxcarbazepine Phenobarbital or Primidone Phenytoin								
Lund, 1974	Epanutin (Parke-Davis) capsules	9	*	*	*	*	*	*
	Phenytoin sodium (Leo) capsules		*	*	*	*	*	*
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	43.6 (22.5) mcg/ml	-	-	8.0 to 104.0
	Phenytoin sodium (Boots) tablets		-	-	45.9 (20.8) mcg/ml	-	-	9.0 to 79.0 mcg/ml

Study, year	Group	N	C_{max}	C_{min}	C_{ss}	AUC	T_{max}	Range
Antiepileptic Drug Class								
	Phenytoin sodium (Cox) tablets		-	-	39.2 (18.0) mcg/ml	-	-	11.0 to 69.0 mcg/ml
	Phenytoin sodium (Kerfoot) tablets		-	-	41.1 (16.5) mcg/ml	-	-	10.0 to 71.0 mcg/ml
	Phenytoin sodium (McCarthy UK) tablets		-	-	44.1 (21.3) mcg/ml	-	-	11.0 to 77.0 mcg/ml
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-	-
	Phenytoin (Boots) tablets		-	-	-	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15			5.45 (3.12) mcg/ml			2.06 to 10.2 mcg/ml
	Phenytoin (Epsolin, Cadila) tablets	15			9.27 (7.7) mcg/ml			3.1 to 27.9 mcg/ml
	Phenytoin (Eptoin, Boots India) tablets	15			8.3 (6.6) mcg/ml			1.9 to 24.8 mcg/ml
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15			8.77 (6.7) mcg/ml			1.2 to 29.4 mcg/ml
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	-	-	Total 11.9 (4.9) mcg/ml Free 0.93 (0.48) mcg/ml	-	-	also reported concentration per dose

Study, year	Group	N	C_{max}	C_{min}	C_{ss}	AUC	T_{max}	Range
Antiepileptic Drug Class								
	Phenytoin (Phenytex, manufacturer not reported) capsules		-	-	Total 14.2 (8.2) mcg/ml Free 1.14 (0.64) mcg/ml	-	-	-
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	16.4 (5.7) mcg/ml	-	-	174.6 (58.8) mcg/ml*hr	There was no significant difference in T_{max} between the formulations (p<0.066)	-
	Phenytoin sodium (Evans) tablets		15.1 (5.5) mcg/ml	-	-	155.9 (55.6) mcg/ml*hr	There was no significant difference in T_{max} between the formulations (p<0.066)	-
	Phenytoin sodium (APS) tablets		15.6 (5.5) mcg/ml	-	-	160.7 (53.7) mcg/ml*hr	There was no significant difference in T_{max} between the formulations (p<0.066)	-
	Phenytoin sodium (Cox) tablets		18.2 (7.6) mcg/ml	-	-	187.5 (82.8) mcg/ml*hr	There was no significant difference in T_{max} between the formulations (p<0.066)	-
	Phenytoin sodium (Kerfoot) tablets		15.1 (5.4) mcg/ml	-	-	148.2 (60.9) mcg/ml*hr	There was no significant difference in T_{max} between the formulations (p<0.066)	-

Study, year	Group	N	C_{max}	C_{min}	C_{ss}	AUC	T_{max}	Range
Antiepileptic Drug Class								
	Phenytoin sodium (Regent) tablets		13.1 (4.2) mcg/ml	-	-	132.8 (44.4) mcg/ml*hr	There was no significant difference in T_{max} between the formulations (p<0.066)	-
Topiramate								
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-
Paradis 2009[b]	Topamax (Ortho-McNeil)	-	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-	-
Valproic Acid								
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-

* A statistically significant increase in the plasma level of phenytoin occurred in 5 out of 9 patients after change from one brand of sodium-DPH (Epanutin, Parke-Davis) to another (Na-DPH, Leo)
Legend: -=not reported; AUC=area under the curve; C^{max}=maximum concentration; C^{min}=minimum concentration at steady state; C^{ss}=average steady-state concentration; N=sample size; T^{max}=time to maximum concentration

Table 16. Adverse events in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Overall adverse events	Adverse events without study withdrawal	Skin rash	Hypotension	Suicidal ideation
Antiepileptic Drug Class							
Rascati, 2009	Cases	991	-	-	-	-	-
	Controls	2973	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-
	Controls	1248	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-
	Controls	8847	-	-	-	-	-
Labiner,2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-
Carbamazepine							
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	43	43	2	-	-

Study, year	Group	N	Overall adverse events	Adverse events without study withdrawal	Skin rash	Hypotension	Suicidal ideation
	Generic Carbamazepine (Parke Davis) Tablets		45	45	2	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	-	-	1	-	-
	Carbamazepine (Ethical Generics)		-	-	0	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	-	-	-	-	-
	Generic (Pharbita) Tablets	12	-	-	-	-	-
Garnett 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-

Study, year	Group	N	Overall adverse events	Adverse events without study withdrawal	Skin rash	Hypotension	Suicidal ideation
Clobazam							
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-
Gabapentin							
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-
Lamotrigine							
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-
Nielsen, 2008a	Lamictal (manufacturer not reported)	9	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-
Levetiracetam Oxcarbazepine Phenobarbital or Primidone Phenytoin							
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-

Study, year	Group	N	Overall adverse events	Adverse events without study withdrawal	Skin rash	Hypotension	Suicidal ideation
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	4	*	-	-	-
	Phenytoin (Boots) tablets	19	3	*	-	-	-
	Phenytoin (Evans) tablets	19	3	*	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	-	-	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	-	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	-	-	-	-
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	†	†	†	†	†
	Phenytoin (Phenytex, manufacturer not reported) capsules		‡	‡	‡	‡	‡
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	§	§	§	§	§
	Phenytoin sodium (Evans) tablets		§	§	§	§	§
	Phenytoin sodium (APS) tablets		§	§	§	§	§
	Phenytoin sodium (Cox) tablets		§	§	§	§	§

Study, year	Group	N	Overall adverse events	Adverse events without study withdrawal	Skin rash	Hypotension	Suicidal ideation
	Phenytoin sodium (Kerfoot) tablets		§	§	§	§	§
	Phenytoin sodium (Regent) tablets		§	§	§	§	§
Topiramate							
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-
Paradis, 2009[b]	Topamax (Ortho-McNeil)	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-
Valproic Acid							
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-

* Overall, side effects appeared more frequently with increasing serum levels, but this was not statistically significant.
† Incidence of adverse events was not statistically significant between two groups. ($p>0.25$) The most common side effects included headaches, GI upset, fatigue, dizziness, and lethargy.
‡ One patient developed intolerable side effects after changing from brand to generic therapy, with gradual onset of difficulty in concentration, headaches, ataxia, diplopia, and progressive somnolence
§ No statistically significant differences were found when comparing incidence of side effects. Commonly experienced side effects included headache, drowsiness, visual disturbances, mental slowness, fatigue, and malaise.
Legend: -=not reported; N=sample size

Table 17. Neurological adverse events in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Combined neurological events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
Antiepileptic Drug Class											
Rascati, 2009	Cases	991	-	-	-	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-	-	-	-	-
	Controls	8847	-	-	-	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-	-	-
Carbamazepine											
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-	-	-

Study, year	Group	N	Combined neurological events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	4	2	7	-	7	-
	Generic Carbamazepine (Parke Davis) Tablets		-	-	-	4	1	7	-	6	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	0	-	-	0	-	0	-	0	-
	Carbamazepine (Ethical Generics)		5	-	-	2	-	1	-	1	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-	-	-

Study, year	Group	N	Combined neurological events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-	-	-	-	-
	Carbamazepine (Pharmaland)		-	-	-	-	-	-	-	-	-
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-	-	-	-	-
	Generic (Pharmachemie) Tablets	12	-	-	-	-	-	-	-	-	-
	Generic (Pharbita) Tablets	12	-	-	-	-	-	-	-	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	75.7 events per 1000 person-years	-	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	145.7 events per 1000 person-years	-	-	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-	-	-	-
Clobazam											
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-	-	-	-

Study, year	Group	N	Combined neurological events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-	-	-	-
	Clobazam (manufacturer not reported)		-	-	-	-	-	-	-	-	-
Gabapentin											
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-	-	-	-
Lamotrigine											
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-	-	-	-	-
Nielsen, 2008a	Lamictal	9	-	-	-	-	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-	-	-	-	-
Levetiracetam Oxcarbazepine Phenobarbital or Primidone Phenytoin											
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-	-	-	-	-

Study, year	Group	N	Combined neurological events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-	2	-	-	-
	Phenytoin (Boots) tablets		-	-	-	-	-	0	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-	1	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-	-	-	-	-	-	-	-	-
	Phenytoin (Epsolin, Cadila) tablets	15	-	-	-	-	-	-	-	-	-
	Phenytoin (Eptoin, Boots India) tablets	15	-	-	-	-	-	-	-	-	-
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-	-	-	-	-	-	-	-	-
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	-	-	-	-	-	-	-	-	-
	Phenytoin (Phenytex, manufacturer not reported) capsules		-	-	-	-	-	-	-	-	-
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-	-	-	-	-

Study, year	Group	N	Combined neurological events (n)	Asthenia	Ataxia	Diplopia	Dizziness	Headache	Nystagmus	Somnolence	Tremor
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin sodium (Regent) tablets		-	-	-	-	-	-	-	-	-
	Phenytoin BP, Thomas Kerfoot		-	-	-	-	-	-	-	-	-
	Phenytoin BP, Regent Laboratories		-	-	-	-	-	-	-	-	-
Topiramate											
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-	-	-	-
Paradis 2009[b]	Topamax (Ortho-McNeil)	-	-	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-	-	-	-	-
Valproic Acid											
Vadney, 1997	Depakene (Abbott)	64	-	-	-	-	-	-	-	-	-
	Valproic acid (Solvay)		-	-	-	-	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-	-	-	-

Legend: -=not reported; N=sample size; n=number of events

Table 18. Mood and cognition effects in controlled studies comparing innovator versus generic antiepileptic drugs

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
Antiepileptic Drug Class									
Rascati, 2009	Cases	991	-	-	-	-	-	-	-
	Controls	2973	-	-	-	-	-	-	-
Zachry, 2009	Cases	416	-	-	-	-	-	-	-
	Controls	1248	-	-	-	-	-	-	-
Devine, 2010	Cases	2949	-	-	-	-	-	-	-
	Controls	8847	-	-	-	-	-	-	-
Labiner, 2010a	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	18,125	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-
Labiner, 2010b	Branded carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)	15,500	-	-	-	-	-	-	-
	Carbamazepine, gabapentin, phenytoin, primidone, zonisamide (manufacturer not reported)		-	-	-	-	-	-	-
Carbamazepine									
Kauko, 1974a	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-
Kauko, 1974b	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-
	Generic Carbamazepine (Laake Oy) Tablets		-	-	-	-	-	-	-
Glende, 1983	Tegretol (Ciba-Geigy) Tablets	5	-	-	-	-	-	-	-
	Carbamazepine (AWD Dresden) Tablets		-	-	-	-	-	-	-
Jumao-as, 1989	Tegretol (Ciba-Geigy) Tablets	10	-	-	-	-	-	-	-

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
	Generic Carbamazepine (Parke Davis) Tablets		-	-	-	-	-	-	-
Hartley, 1990	Tegretol (Ciba-Geigy)	23	1	-	-	-	-	-	-
	Carbamazepine (Ethical Generics)		1	-	-	-	-	-	-
Hartley, 1991	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	-	-	-
	Carbamazepine (Ethical Generics) Tablets		-	-	-	-	-	-	-
Oles, 1992a	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-
Oles, 1992b	Tegretol (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-
	Carbamazepine (Lemmon Co) Tablets		-	-	-	-	-	-	-
Reunanen, 1992	Tegretol Retard (Ciba-Geigy) Tablets	20	-	-	-	-	-	-	-
	Carbamazepine (Laakefarmos) Tablets		-	-	-	-	-	-	-
Silpakit, 1997	Tegretol (Ciba-Geigy) Tablets	18	-	-	-	-	-	-	-
	Carbamazepine (Central Poly) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Condrugs) Tablets		-	-	-	-	-	-	-
	Carbamazepine (Pharmaland) Tablets		-	-	-	-	-	-	-

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
Aldenkamp, 1998	Tegretol (Ciba-Geigy) Tablets	12	-	-	-	-	Finger Tapping (number of taps): 67.7 (8.7) Visual Reaction Time (ms): 274.0 (36.4) Binary Choice Reaction Time (ms): 364.1 (41.5) Visual Searching Task (s): 9.3 (1.9) Recognition Task (number out of 24): 20.2 (1.5) Neurotoxicity Scale: 6.75 (5.6)	-	-

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
	Generic (Pharmachemie) Tablets	12	-	-	-	-	Finger Tapping (number of taps): 64.8 (8.2) Visual Reaction Time (ms): 312.0 (76.0) Binary Choice Reaction Time (ms): 415.5 (58.3) Visual Searching Task (s): 7.5 (2.0) Recognition Task (number out of 24): 20.4 (3.2) Neurotoxicity Scale: 13.8 (12.8)	-	-

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
	Generic (Pharbita) Tablets	12	-	-	-	-	Finger Tapping (number of taps): 62.5 (3.6) Visual Reaction Time (ms): 287.1 (47.6) Binary Choice Reaction Time (ms): 384.9 (44.3) Visual Searching Task (s): 7.8 (3.6) Recognition Task (number out of 24): 19.7 (2.1) Neurotoxicity Scale: 2.92 (2.7)	-	-
Garnett, 2005	Tegretol (Novartis) Tablets	275	-	-	-	-	-	-	-
	Generic (Various/Unspecified) Tablets	705	-	-	-	-	-	-	-
LeLorier, 2008d	Tegretol CR (manufacturer not reported)	851	-	-	-	-	-	-	-
	Carbamazepine CR (manufacturer not reported)		-	-	-	-	-	-	-
Clobaza									
Andermann, 2007b	Frisium (manufacturer not reported)	1600	-	-	-	-	-	-	-
	Clobazam (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008b	Frisium (manufacturer not reported)	1060	-	-	-	-	-	-	-

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
	Clobazam (manufacturer not reported)		-	-	-	-	-	-	-
Gabapentin									
LeLorier, 2008c	Neurontin (manufacturer not reported)	202	-	-	-	-	-	-	-
	Gabapentin (manufacturer not reported)		-	-	-	-	-	-	-
Lamotrigine									
Andermann, 2007a	Lamictal (GlaxoSmithKline)	1142	-	-	-	-	-	-	-
	Lamotrigine (manufacturers not reported)		-	-	-	-	-	-	-
LeLorier, 2008a	Lamictal (GlaxoSmithKline)	671	-	-	-	-	-	-	-
	Lamotrigine (manufacturer(s) not reported)		-	-	-	-	-	-	-
Nielsen, 2008a	Lamictal	9	-	-	-	-	-	-	-
	Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada)		-	-	-	-	-	-	-
Levetiracetam Oxcarbazepine Phenobarbital or Primidone Phenytoin									
Lund, 1974	Epanutin (Parke-Davis) capsules	9	-	-	-	-	-	-	-
	Phenytoin sodium (Leo) capsules		-	-	-	-	-	-	-
Chen, 1982	Epanutin (Parke-Davis) capsules	18	-	-	-	-	-	-	-
	Phenytoin sodium (Boots) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
	Phenytoin sodium (McCarthy UK) tablets		-	-	-	-	-	-	-
Hodges, 1986	Phenytoin (Parke-Davis) capsules	19	-	-	-	-	-	-	-
	Phenytoin (Boots) tablets		-	-	-	-	-	-	-
	Phenytoin (Evans) tablets		-	-	-	-	-	-	-
Kishore, 1986	Dilantin (Parke-Davis, India) capsules	15	-						
	Phenytoin (Epsolin, Cadila) tablets	15	-						
	Phenytoin (Eptoin, Boots India) tablets	15	-						
	Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules	15	-						
Mikati, 1992	Dilantin (Parke-Davis) capsules	10	-	-	-	-	-	-	-
	Phenytoin (Phenytex, manufacturer not reported) capsules		-	-	-	-	-	-	-
Soryal, 1992	Epanutin (Parke-Davis) capsules	14	-	-	-	-	-	-	-
	Phenytoin sodium (Evans) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (APS) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Cox) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Kerfoot) tablets		-	-	-	-	-	-	-
	Phenytoin sodium (Regent) tablets		-						
Topiramate									
Duh, 2009	Topamax (Ortho-McNeil)	875	-	-	-	-	-	-	-

Study, year	Group	N	Mood Disorders Not reported (n)	Aggression	Anxiety	Depression	Impaired cognition	Emotional lability	Nervousness
	Topiramate (Various manufacturers) – Single Product Users	331	-	-	-	-	-	-	-
	Topiramate (Various manufacturers) – Multiple Product Users	99	-	-	-	-	-	-	-
Paradis, 2009[b]	Topamax (Ortho-McNeil)	-	-	-	-	-	-	-	-
	Topiramate (Various manufacturers)	-	-	-	-	-	-	-	-
Valproic Acid									
Vadney, 1997	Depakene (Abbott)	64		-	-	-	-	-	-
	Valproic acid (Solvay)			-	-	-	-	-	-
Andermann, 2007c	Depakene (manufacturer not reported)	2017	-	-	-	-	-	-	-
	Valproic Acid (manufacturers not reported)		-	-	-	-	-	-	-

Legend: -=not reported; N=sample size; n=number of events

Table 19. Seizure outcomes in studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Change from baseline in seizure frequency Mean (SD)	Time to first seizure specify units
Dam, 1989	Carbamazepine	82	No. seizures per month before treatment: 5.8 (14.7) No of seizures during 48 week maintenance phase treatment: 0.3 (1.4)	-
	Oxcarbazepine	83	No. seizures per month before treatment : 2.9 (7.0) No of seizures during 48 week maintenance phase treatment : 0.4 (3.0)	-
Brodie, 1995	Carbamazepine	129	-	
	Lamotrigine	131	-	There was no significant difference between the drugs in time to first seizure after 6 weeks' treatment for the whole study population Hazard ratio: 0.8 95% CI: 0.6-2.1
Reunanen, 1996*	Carbamazepine	117	-	
	Lamotrigine100 mg	115	-	Time to first seizure Hazard ratio: 0.8 95% CI: 0.5-1.4
	Lamotrigine 200 mg	111	-	Time to first seizure Hazard ratio: 0.9 95% CI: 0.5-1.6

Study, year	Group	N	Change from baseline in seizure frequency Mean (SD)	Time to first seizure specify units
Bill,1997	Phenytoin		Mean Seizure Frequency per week at Baseline: 0.84 (-) N=144 Mean Seizure Frequency per week during 48 week Maintenance: 0.06 (0.15) N=119	-
	Oxcarbazepine		Mean Seizure Frequency per week at Baseline: 0.98 (-) N=143 Mean Seizure Frequency per week during 48 week Maintenance: 0.08 (0.26) N=118	-
Christie,1997	Sodium Valproate		Mean seizure frequency/week at baseline: 1.09 (3.13) N=121 Mean seizure frequency during 48 week maintenance treatment: 0.40 (1.95) N=106	-
	Oxcarbazepine		Mean seizure frequency/week at baseline: 0.58 (1.39) N=128 Mean seizure frequency per week during 48 week maintenance treatment: 0.17 (0.81) N=106	-

Study, year	Group	N	Change from baseline in seizure frequency Mean (SD)	Time to first seizure specify units
Guerreiro, 1997	Pheyntion		Mean Seizure Frequency at Baseline: 0.66/week (-) N=96 Mean Seizure Frequency During 48 week Maintenance: 0.04/ week (-) N=77	-
	Oxcarbazepine		Mean Seizure Frequency at Baseline: 0.68/week (-) N=97 Mean Seizure Frequency During 48 week Maintenance: 0.07/week (-) N=81	-
Chadwick, 1999	Carbamazepine	226	-	Time to first seizure after dose stabilization Adjusted hazard ratio:1.79 95% CI: 1.33-2.40
	Vigabatrin	220	-	Time to first seizure after dose stabilization Adjusted hazard ratio:1.79 95% CI: 1.33-2.40
Steiner, 1999[†]	Phenytoin	95	-	
	Lamotrigine	86	-	Time to first seizure after 6 weeks of treatment 1.4, 95% CI: 0.8 to 2.3
Privitera, 2003	Carbamazepine	126	-	NS
	Valproic Acid	78	-	NS
	Topiramate 100 mg	210	-	NS
	Topiramate 200 mg	199	-	NS
Wheless, 2004	Carbamazepine	23	-	NS

Study, year	Group	N	Change from baseline in seizure frequency Mean (SD)	Time to first seizure specify units
	Valproate	19	-	NS
	Topiramate 100 mg	38	-	NS
	Topiramate 200 mg	39	-	NS
Kang, 2007	Carbamazepine	43	Mean percentage change from baseline to maintenance in seizure frequency -100%	-
	Topiramate	45	Mean percentage change from baseline to maintenance in seizure frequency -100%	-
Marson, 2007* SANAD Arm A	Carbamazepine	378	-	
	Gabapentin	377	-	Pairwise comparison for time to first seizure Hazard ratio: 1.35 95% CI: 1.14-1.60
	Lamotrigine	378	-	Pairwise comparison for time to first seizure Hazard ratio: 1.23 95% CI: 1.04-1.45
	Oxcarbazepine	210	-	Pairwise comparison for time to first seizure Hazard ratio: 1.06 95% CI: 0.84-1.33
	Topiramate	378	-	Pairwise comparison for time to first seizure: Hazard ratio: 1.05 95% CI: 0.89-1.25

Study, year	Group	N	Change from baseline in seizure frequency Mean (SD)	Time to first seizure specify units
Marson, 2007‡	Valproic Acid	238		
SANAD				
Arm B				
	Lamotrigine	239		Pairwise comparison for time to first seizure
				Hazard ratio: 0.71
				95% CI: 0.57-0.88
	Topiramate	239		Pairwise comparison for time to first seizure
				Hazard ratio: 0.91
				95% CI: 0.73-1.14
Ramsay , 2010†	Pheyntoin	127	-	
	Topiramate	132	-	HR: 2.0
				95% CI: 0.98-4.12

*Carbamazepine group is referent
†Phenytoin group is referent
‡Valproic acid group is referent
Legend: -=not reported, 95% CI=95% Confidence Interval, N=Sample size; NS=not significant; SANAD Arm A= Standard and New Antiepileptic Drugs Trial Arm A; Arm B= Standard and New Antiepileptic Drugs Trial Arm B; SD=Standard deviation

Table 20. Seizure outcomes in studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Seizure free for duration of study	Seizure Remission 12-month period (%)	Seizure Remission 24-month period (%)	Seizure Frequency reduction by 50%	Seizure Frequency reduction by 75%
Danner,1988	Carbamazepine	13	9	-	-	-	-
	Oxcarbazepine	12	8	-	-	-	-
Dam, 1989	Carbamazepine	82	49	-	-	67	-
	Oxcarbazepine	83	43	-	-	67	-
Brodie, 1995	Carbamazepine	129	49	-	-	-	-
	Lamotrigine	131	51	-	-	-	-
Kalviaine, 1995	Carbamazepine	50	26	-	-	-	-
	Vigabatrin	50	16	-	-	-	-
Sabers 1995	Carbamazepine	11	8	-	-	-	-
	Phenobarbital	9	9	-	-	-	-
	Phenytoin	11	9	-	-	-	-
	Valproic Acid	11	7	-	-	-	-
	Oxcarbazepine	10	5	-	-	-	-
Reunanen, 1996	Carbamazepine	117	64	-	-	-	-
	Lamotrigine 100 mg	115	59	-	-	-	-
	Lamotrigine 200 mg	111	67	-	-	-	-
Tanganelli, 1996	Carbamazepine	25	End of phase 1 before the crossover 14 (56%)	-	-	-	-
	Vigabratin	26	End of phase 1 before the crossover 12 (46.1%)	-	-	-	-
Bill, 1997	Phenytoin	119	69				
	Oxcarbazepine	118	70				
Christie,1997	Valproic Acid	121	57	-	-	-	-
	Oxcarbazepine	128	60	-	-	-	-
Guerreiro, 1997	Pheyntion	77	46	-	-	-	-
	Oxcarbazepine	81	49	-	-	-	-
Brodie, 1999	Carbamazepine	48	10	-	-	-	-

Study, year	Group	N	Seizure free for duration of study	Seizure Remission 12-month period (%)	Seizure Remission 24-month period (%)	Seizure Frequency reduction by 50%	Seizure Frequency reduction by 75%
	Lamotrigine	102	40	-	-	-	-
Gobbi,1999	Carbamazepine	40	29	-	-	-	-
	Vigabatrin	37	22	-	-	-	-
Steiner, 1999	Phenytoin	95	22	-	-	-	-
	Lamotrigine	86	19	-	-	-	-
Biton, 2001	Valproate	68	18	-	-	-	-
	Lamotrigine	65	19	-	-	-	-
Kwan, 2001	Carbamazepine	212	88	-	-	-	-
	Valproic Acid	101	59	-	-	-	-
	Lamotrigine	78	48	-	-	-	-
Nieto-Barrera, 2001	Carbamazepine	152	111	-	-	-	-
	Lamotrigine	329	215	-	-	-	-
Biton, 2003	Valproate	20	9	-	-	-	13 of 19 (68%) patients had a 75% reduction from baseline in generalized tonic-clonic seizure frequency from baseline
	Lamotrigine	18	6	-	-	-	10 of 15 (67%) patients had a 75% reduction from baseline in generalized tonic-clonic seizure frequency from baseline
Privitera, 2003	Carbamazepine	126	55	-	-	-	-
	Valproic Acid	78	34	-	-	-	-
	Topiramate 100 mg	210	103	-	-	-	-
	Topiramate 200 mg	199	88	-	-	-	-
Coppola, 2004	Valproic Acid	19	13	-	-	-	-
	Lamotrigine	19	10	-	-	-	-
Fakhoury, 2004	Carbamazepine	25	8	-	-	18	-

Study, year	Group	N	Seizure free for duration of study	Seizure Remission 12-month period (%)	Seizure Remission 24-month period (%)	Seizure Frequency reduction by 50%	Seizure Frequency reduction by 75%
	Lamotrigine	55	23	-	-	37	-
	Valproic Acid	21	2	-	-	8	-
	Lamotrigine	51	16	-	-	27	-
Wheless, 2004	Carbamazepine	23	9	-	-	-	-
	Valproic Acid	19	10	-	-	-	-
	Topiramate 100 mg	38	24	-	-	-	-
	Topiramate 200 mg	39	23	-	-	-	-
Rowan, 2005	Carbamazepine	70	45	-	-	-	-
	Gabapentin	95	45	-	-	-	-
	Lamotrigine	111	57	-	-	-	-
Steinhoff, 2005	Carbamazepine	88	72	-	-	-	-
	Lamotrigine	88	62	-	-	-	-
	Valproate	30	25	-	-	-	-
	Lamotrigine	33	20	-	-	-	-
Brodie, 2007	Carbamazepine-Controlled Release	291	155	-	-	-	-
	Levetiracetam	285	142	-	-	-	-
Donati, 2007	Carbamazepine	28	13	-	-	-	-
	Valproic Acid	29	16	-	-	-	-
	Oxcarbazepine	55	32	-	-	-	-
Kang, 2007	Carbamzaepine	43	30	-	-	-	-
	Topiramate	45	31	-	-	-	-
Levisohn, 2007	Valproic Acid	9	4	-	-	-	-
	Topiramate	19	8	-	-	-	-
Marson, 2007 SANAD Arm A	Carbamazepine	362	-	254	168	-	-
	Gabapentin	359	-	215	132	-	-

Study, year	Group	N	Seizure free for duration of study	Seizure Remission 12-month period (%)	Seizure Remission 24-month period (%)	Seizure Frequency reduction by 50%	Seizure Frequency reduction by 75%
	Lamotirgine	365	-	245	155	-	-
	Oxcarbazepine	200	-	128	68	-	-
	Topiramate	358	-	225	140	-	-
Marson, 2007 SANAD Arm B	Valproic Acid	232	-	180	124	-	-
	Lamotrigine	231	-	168	102	-	-
	Topiramate	230	-	178	108	-	-
Saetre, 2007	Carbamazepine – Sustained Release	91	60	-	-	-	-
	Lamotrigine	93	50	-	-	-	-
Stephen, 2007	Valproate	111	52	-	-	-	-
	Lamotrigine	114	54	-	-	-	-
Morrell, 2008	Valproate	211	97	-	-	-	-
	Lamotrigine	201	74	-	-	-	-
Perry, 2008	Carbamazepine	11	3	-	-		
	Levetiracetam	25	8	-	-		
Kim, 2009	Carbamazepine	105	-	-	-	-	-
	Topiramate	41	-	-	-	-	-
Kwan, 2009	Valproic Acid	44	13		-	-	-
	Lamotrigine	37	17		-	-	-
Ma, 2009	Carbamazepine	120	70	-	-	-	-
	Valproic Acid	234	180	-	-	-	-
	Topiramate	143	88	-	-	-	-
Ramsay, 2010	Phenytoin	127	117	-	-	-	-
	Topiramate	132	108	-	-	-	-

Legend: -=not reported; N=Sample size; SANAD Arm A= Standard and New Antiepileptic Drugs Trial Arm A; Arm B= Standard and New Antiepileptic Drugs Trial Arm B; SD

Table 21. Withdrawals and discontinuations in studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
Reinikainen, 1987	Carbamazepine	18	6*	-	-	-	Increased seizures: 2 (6%) Poor compliance: 2 (6%)
	Oxcarbazepine	16		-	-	-	
Danner, 1988	Carbamazepine	13	-	-	-	3	Allergic Rash: 3 (23%)
	Oxcarbazepine	12	-	-	-	1	Allergic Rash: 1(8.33%)
Dam, 1989	Carbamazepine	98	-	2	-	25	Allergy: 16 (16%) Visual Disturbances: 1 (1%) Headache: 1 (1%) Tiredness/fatigue: 3 (3%) Nausea: 1 (1%) Diarrhoea: 2 (2%) Loss of hair: 2 (2%) Leukopenia: 1 (1%) Liver parameters increased: 1 (1%)
	Oxcarbazepine	92	-	2	-	13	Allergy: 9 (10%) Dizziness/vertigo: 2 (2%) Tiredness/fatigue: 1 (1%) Physical lability: 1 (1%)
Sachdeo, 1992	Valproic Acid	22	1	-	-	-	-
	Felbamate	22	1	-	-	-	-

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
Brodie, 1995	Carbamazepine	129	63	3	-	27	Rash: 22 (17%) Headache: 3 (2%) Asthenia: 6 (5%) Dizziness: 3 (2%) Vomiting: 1 (1%) Malaise: 5 (4%) Nausea: 3 (2%) Ataxia: 5 (4%) Sleepiness: 5 (4%)
	Lamotrigine	131	46	3	-	15	Rash: 15 (12%) Headache: 5 (4%) Asthenia: 5 (4%) Dizziness: 3 (2%) Vomiting: 3 (2%) Malaise: 1 (1%) Nausea: 1 (1%) Ataxia: 0 Sleepiness: 0
Kalviainen, 1995	Carbamazepine	50	20	3	-	12	Rash: 7 (14%) Hepatotoxicity: 3 (6%) Elevation of blood glucose: 1 (2%) Confusion and personality change: 1 (2%)

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
	Vigabatrin	50	20	13	-	0	Rash: 0 Hepatotoxicity: 0 Elevation of blood glucose: 0 Confusion and personality change: 0
Reunanen, 1996	Carbamazepine	117	29	0	-	12	-
	Lamotrigine 100 mg	115	23	1	-	5	-
	Lamotrigine 200 mg	111	10	0	-	5	-
Tanganelli, 1996	Carbamazepine	25	-	-	-	1	-
	Vigabratin	26	-	-	-	0	-
Bill, 1997	Phenytoin	144	61	1	-	16	Rash: 10 (7%) Hirsutism/Gum Hyperplasia: 5 (3.5%) Other: 1 (0.7%)
	Oxcarbazepine	143	56	1	-	5	Rash: 1 (0.7%) Hirsutimsm/Gum Hyperplasia: 0 Other: 4 (2.8%) (1 patient in the other group withdrew due to suicidal ideation)

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
Christie, 1997	Sodium Valproate	121	41	6	-	10	Allergic Reaction: 0 Hair loss: 4 (3.31%) Pregnancy: 2 (1.65%) Nausea: 2 (1.65%) Drowsiness: 0 Other: 2 (1.65%)
	Oxcarbazepine	128	52	6	-	15	Allergic Reaction with skin symptoms: 6 (4.69%) Hair Loss: 0 Pregnancy: 1 (0.8%) Drowsiness: 2 (1.56%) Other: 2 (1.56%)
Guerreiro, 1997	Pheyntion	96	34	3	-	14	Hypertrichosis and/or gingival hyperplasia: 10 (10%) (1 patient also had ataxia) Rash: 4 (4%) (1 patient also had fever, ataxia, dizziness and vomiting)
	Oxcarbazepine	97	24	4	-	2	Rash: 2 (2%)
Chadwick, 1998	Carbamazepine	74	47	-	-	18	-
	Gabapentin 300 mg	72	54	-	-	0	-

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
	Gabapentin 900 mg	72	44	-	-	3	-
	Gabapentin 1800 mg	74	46	-	-	10	-
Brodie, 1999a	Carbamazepine	48	28	0	-	20	Rash: 9 (19%) Somnolence: 3 (6%) Asthenia: 3 (6%) Nausea: 1 (2%) Incoordination: 1 (2%)
	Lamotrigine	102	30	0	-	18	Rash: 3 (3%) Somnolence: 2 (2%) Asthenia: 1 (1%) Nausea: 3 (3%) Incooridination: 3 (3%)
Brodie, 1999b	Valproate	107	32	19	-	12	-
	Vigabatrin	108	22	11	-	12	-
Chadwick, 1999†	Carbamazepine	229	97	9		61	-
	Vigabatrin	228	98	23	No significant treatment differences between vigabatrin and carbamazepine groups Hazard ratio: 0.83 95% CI: 0.57-1.20	43	-
Gobbi, 1999	Carbamazepine	40	0	0	-	0	0

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
	Vigabatrin	37	9	8	-	0	0
Steiner, 1999	Phenytoin	95	50	2	-	18	-
	Lamotrigine	86	45	1	-	13	-
Aldenkamp, 2000	Valproic Acid	30	4	1	-	-	-
	Topiramate	29	8	0	-	-	-
	Lamotirgine	146	18	-	-	35	-
Biton, 2001	Valproate	68	30	-	-	9	-
	Lamotrigine	65	19	-	-	6	-
Kwan, 2001	Carbamazepine	212	124	53	-	57	-
	Sodium Valproate	101	43	26	-	13	-
	Lamotrigine	78	30	20	-	8	-
Nieto-Barrera, 2001	Carbamazepine	201	46	-	-	27	-
	Lamotrigine	417	79	-	-	38	-
Biton, 2003	Valproate	20	6	-	-	1	Aspiration of fluids: 1(5%)
	Lamotrigine	18	3	-	-	1	Multiple side effects leading to withdrawal for 1 patient including mental confusion insomnia somnolence increased appetite dizziness ataxia nystagmus resting tremor and intention tremor 1 (5.55%)
Meador, 2003	Valproate	29	4	-	-	2	-

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
	Topiramate	34	7	-	-	6	-
Privitera, 2003	Carbamazepine	126	56	10	-	32	-
	Valproic Acid	78	43	9	-	18	-
	Topiramate 100 mg	210	91	23	-	40	-
	Topiramate 200 mg	199	95	18	-	55	-
Clemens, 2004	Carbamazepine	20	-	-	-	-	-
	Oxcarbazepine	20	-	-	-	1	Rash: 1 (5%)
Coppola, 2004	Valproic Acid	19	3	3	-	0	0
	Lamotrigine	19	6	6	-	0	0
Fakhoury, 2004	Carbamazepine	46	7	-	-	12	-
	Lamotrigine	98	19	-	-	14	-
	Valproic Acid	53	16	-	-	11	-
	Lamotrigine	105	28	-	-	14	-
Wheless, 2004	Carbamazepine	23	55[‡]	16[§]	-	1	-
	Valproic Acid	19			-	6	-
	Topiramate 100 mg	38			-	4	-
	Topiramate 200 mg	39			-	7	-
Rowan, 2005	Carbamazepine	197	127	5	-	61	-
	Gabapentin	194	99	8	-	42	-
	Lamotrigine	199	88	11	-	24	-
Sobaniec, 2005	Carbamazepine	28	0	-	-	-	-
	Vigabratin	26	4	-	-	-	-

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
Steinhoff, 2005	Carbamazepine	88	29	0	-	17	-
	Lamotrigine	88	24	1	-	7	-
	Valproate	30	4	0	-	1	-
	Lamotrigine	33	5	2	-	2	-
Brodie, 2007	Carbamazepine-Controlled Release	291	97	13	-	56	Vertigo: 2 (0.7%) Nausea: 3 (1.0%) Asthenia: 3 (1.0%) Fatigue: 4 (1.4%) Ataxia: 3 (1.0) Dizziness: 3 (1.0%) Somnolence: 2 (0.7%) Aggression: 3 (1.0%) Anxiety: 1 (0.3%) Depression: 2 (0.7%) Rash: 9 (3.1%)

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
	Levetiracetam	285	95	31	-	41	Vertigo: 6 (2.1%) Nausea: 0 Asthenia: 0 Fatigue: 5 (1.8%) Ataxia: 0 Dizziness: 2 (0.7%) Somnolence: 6 (2.1%) Aggression: 0 Anxiety: 3 (1.1%) Depression: 5 (1.8%) Rash: 4 (1.4%)
Kang, 2007	Carbamazepine	54	11	-	-	5	-
	Topiramate	58	13	-	-	6	-
Kim, 2007	Carbamazepine	10	0	0	-	0	-
	Valproic Acid	15	0	0	-	0	-
	Lamotrigine	8	0	0	-	0	-
Levisohn, 2007	Valproic Acid	9	5	0	-	1	-
	Topiramate	19	7	2	-	2	-
Marson 2007 SANAD Arm A	Carbamazepine	378	227	43	-	102	-
	Gabapentin	376	249	99	-	57	-
	Lamotrigine	378	197	60	-	60	-
	Oxcarbazepine	210	117	24	-	49	-
	Topirimate	374	241	55	-	101	-
Marson 2007 SANAD Arm B	Valproic Acid	238	141	21	-	35	-

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
	Lamotrigine	237	128	53	-	25	-
	Topirimate	238	154	28	-	57	-
Saetre, 2007	Carbamazepine-Sustained Release	91	30	-	-	23	-
	Lamotrigine	93	25	-	-	13	-
Stephen, 2007	Valproate	111	55	16	-	26	-
	Lamotrigine	114	43	11	-	15	-
Morrell, 2008	Valproate	225	55	1	-	9	-
	Lamotrigine	222	52	2	-	9	-
Perry, 2008	Carbamazepine	20	4	-	-	1	Increased irritability: 1 (5%)
	Levetiracetam	66	22	2	-	8	Behaviour changes : 5 (63%) Irritability or mood change: 1 (12%) Increased seizure frequency Rash: 1(12%) Undetermined: 1(12%)
Kim, 2009	Carbamazepine	105	89	24	-	7	-
	Topiramate	41	31	5	-	1	-
Kwan, 2009	Valproic Acid	44	16	1	-	5	-
	Lamotrigine	37	9	0	-	5	-
Ma, 2009	Carbamazepine	120	-	21	-	20	-
	Valproic Acid	234	-	40	-	10	-
	Topirimate	143	-	25	-	17	-

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
Glauser, 2010	Ethosuximide	154	20	-	-	37	Nervous system, behavioural or psychological effects: 12 (32%) Digestive disorders: 9 (24%) Rash: 6 (16%) Fatigue: 3 (8%) Headache: 3 (8%) BMI increase that met exit criterion: 0 Laboratory abnormalities: 1 (3%) Other: 4 (11%)
	Valproic Acid	146	15	-	-	25	Nervous system, behavioural or psychological effects: 20 (57%) Digestive disorders: 6 (17%) Rash: 2 (6%) Fatigue: 5 (14%) Headache: 2 (6%) BMI increase that met exit criterion: 4 (11%) Laboratory abnormalities: 2 (6%) Other: 5 (14%)

Study, year	Group	N	Withdrawal for any reason (n)	Withdrawal due to ineffective treatmei (n)	Time to withdrawal due to ineffective treatment	Withdrawal due to adverse drug events (n)	Adverse drug even contributing to withdrawals n (%)
	Lamotrigine	146	18	-	-	35	Nervous system, behavioural or psychological effects: 9 (36%) Digestive disorders: 3 (12%) Rash: 5 (20%) Fatigue: 2 (8%) Headache: 2 (8%) BMI increase that met exit criterion: 1 (4%) Laboratory abnormalities: 2 (8%) Other: 4 (16%)
Ramsay, 2010	Phenytoin		17 N=128	-	-	17 N=127	Cognitive adverse events: 2 (1.5%)
	Topiramate		27 N=133	-	-	9 N=132	Skin Rash: 8 (6.3%)

* 6 patietns withdrew for any reason from the total population
† carbamazepine group is referent
‡ 55 patients withdrew for any reason from the total population
§16 patients withdrew from the total population due to lack of efficacy
Legend: -=not reported, n=number of patients with event; N=Sample size; SANAD Arm A= Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B=Standard and New Antiepileptic Drugs Trial Arm B

Table 22. Final health outcomes in studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Deaths (n)	Office/ER visits (n)	Hospitalizations events (n)	Composite of Ambulance/ ER/ Hospitalizations events (n)
Reunanen, 1996	Carbamazepine	117	0	-	-	-
	Lamotrigine 100 mg	115	1	-	-	-
	Lamotrigine 200 mg	111	1	-	-	-
Bill, 1997	Phenytoin	144	2	-	-	-
	Oxcarbazepine	143	0	-	-	-
Brodie, 1999a	Carbamazepine	48	2	-	3	-
	Lamotrigine	102	0	-	0	-
Brodie, 1999b	Valproate	107	0	-	-	-
	Vigabatrin	108	0	-	-	-
Chadwick, 1999	Carbamazepine	229	1	-	-	-
	Vigabatrin	228	2	-	-	-
Steiner, 1999	Phenytoin	95	2	-	-	-
	Lamotrigine	86	0	-	-	-
Fakhoury, 2004	Carbamazepine	46	0	-	-	-
	Lamotrigine	98	2	-	-	-
	Valproic Acid	53	0	-	-	-
	Lamotrigine	105	1	-	-	-
Rowan, 2005	Carbamazepine	198	15	-	-	-
	Gabapentin	195	11	-	-	-
	Lamotrigine	200	8	-	-	-
Marson, 2007	Valproic Acid	238	4	-	-	-

Study, year	Group	N	Deaths (n)	Office/ER visits (n)	Hospitalizations events (n)	Composite of Ambulance/ ER/ Hospitalizations events (n)
SANAD Arm B						
	Lamotrigine	239	4	-	-	-
	Topirimate	239	3	-	-	-
Marson, 2007 SANAD Arm A	Carbamazepine	378	18	-	-	-
	Gabapentin	377	19	-	-	-
	Lamotrigine	378	12	-	-	-
	Oxcarbazepine	210	5	-	-	-
	Topirimate	378	17	-	-	-
Glauser, 2010	Ethosuximide	154	-	-	4	-
	Valproic Acid	146	-	-	2	-
	Lamotirgine	146	-	-	2	-
Ramsay, 2010	Phenytoin	127	0	-	-	-
	Topiramate	132	0	-	-	-

Legend: -=not reported; ER-emergency room; N=sample size; (n)=number of deaths or events; SANAD Arm A= Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B=Standard and New Antiepileptic Drugs Trial Arm B

Table 23. Health-related quality of life for studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Cramer, 2001					Work-driving-social relations	Attention-concentration	Memory	Language	Seizure worry
	Carbamazepine		QOLIE-89	60.2 (18)* N=55	Change from baseline in subscore: 8.0 P=0.004 N=33	Change from baseline in subscore: 3.5 P=NS N=33	Change from baseline in subscore: 1.3 P=NS N=33	Change from baseline in subscore: 3.0 P=NS N=33	Change from baseline in subscore: 11.8 P=0.016 N=33
	Tiagabine		QOLIE-89	61.0 (19)* N=47	Change from baseline in subscore: 7.1 P=NS N=14	Change from baseline in subscore:6.5 P=0.002 N=14	Change from baseline in subscore: 7.4 P=0.042 N=14	Change from baseline in subscore: 12.9 P=0.004 N=14	Change from baseline in subscore: 11.6 P=0.03 N=14
					Role limit-physical	Seizure Worry			
	Phenytoin		QOLIE-89	63.0 (17)* N=58	Change from baseline in subscore: 11.2 P=NS N=28	Change from baseline in subscore: 12.2 P=0.007 N=28	-	-	-
	Tiagabine		QOLIE-89	62.0 (16)* N=66	Change from baseline in subscore: -11.3 P=NS N=23	Change from baseline in subscore: 9.2 P=0.032 N=23	-	-	-
Gillham, 2000	Carbamazepine	60	SEALS Inventory	Change from baseline in total score: 0.32 P=0.394	-	-	-	-	-
	Lamotrigine	73	SEALS Inventory	Change from baseline in total score: -3.08 P<0.001	-	-	-	-	-

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Marson, 2007 SANAD Arm					Anxiety†	Depression†	Adverse Events Profile†	Neurotoxicity†	
	Carbamazepine	195	NEWQOL	-					
	Gabapentin	197	NEWQOL	-	-0.01 (-0.78 to 0.76)	0.28 (-0.37 to 0.94)	0.60 (-1.15 to 2.34)	-0.12 (-2.86 to 2.63)	
	Lamotrigine	177	NEWQOL	-	-0.09 (-0.88 to 0.70)	-0.35 (-1.02 to 0.33)	0.47 (-1.38 to 2.32)	-1.30 (-4.09 to 1.50)	
	Oxcarbazepine	92	NEWQOL	-	-0.13 (-1.10 to 0.83)	-0.29 (-1.11 to 0.53)	0.45 (-1.83 to 2.72)	-0.72 (-4.12 to 2.68)	
	Topiramate	172	NEWQOL	-	-0.84 (-1.63 to -0.04)	0.09 (-0.59 to 0.77)	-0.60 (-2.42 to 1.23)	-1.60 (-4.43 to 1.24)	
Marson, 2007 SANAD Arm A					Anxiety‡	Depression‡	Global Quality of Life‡		
	Carbamazepine	195	NEWQOL	-					
	Gabapentin	197	NEWQOL	-	1.02 (0.65 to 1.59)	1.34 (0.81 to 2.21)	0.88 (0.61 to 1.28)		
	Lamotrigine	177	NEWQOL	-	0.96 (0.61 to 1.52)	0.74 (0.44 to 1.27)	0.76 (0.52 to 1.12)		
	Oxcarbazepine	92	NEWQOL	-	1.02 (0.58 to 179)	1.13 (0.57 to 2.24)	1.34 (0.84 to 2.15)		
	Topiramate	172	NEWQOL	-	0.62 (0.38 to 0.99)	1.13 (0.68 to 1.89)	0.91 (0.62 to 1.34)		
Marson, 2007 SANAD Arm A									
	Carbamazepine	195	EQ-5D§						
	Gabapentin	197	EQ-5D	0.01 (-0.04 to 0.06)					
	Lamotrigine	177	EQ-5D	0.02 (-0.03 to 0.06)					
	Oxcarbazepine	92	EQ-5D	0.01 (-0.05 to 0.07)					
	Topiramate	172	EQ-5D	0.03 (-0.02 to 0.08)					
Marson, 2007 SANAD Arm B					Anxiety‖	Depression‖	Adverse Events Profile‖	Neurotoxicity‖	
	Valproic Acid	73	NEWQOL	-					

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
	Lamotrigine	68	NEWQOL	-	0.89 (-0.34 to 2.12)	-0.48 (-1.41 to 0.45)	0.73 (-2.52 to 3.89)	-1.29 (-5.34 to 2.75)	
	Topirimate	68	NEWQOL	-	-0.08 (-1.31 to 1.15)	-0.40 (-1.34 to 0.54)	-0.08 (-3.29 to 3.26)	-0.37 (-4.48 to 3.75)	
Marson, 2007 SANAD Arm B					Anxiety¶	Depression¶	Global Qualtiy of Life¶		
	Valproic Acid	73	NEWQOL	-					
	Lamotrigine	68	NEWQOL	-	1.40 (0.46 to 3.10)	0.82 (0.33 to 2.07)	1.17 (0.64 to 2.16)		
	Topirimate	68	NEWQOL	-	0.87 (0.37 to 2.00)	0.81 (0.31 to 2.09)	0.95 (0.51 to 1.77)		
Marson, 2007 SANAD Arm B									
	Valproic Acid	73	EQ-5D#						
	Lamotrigine	68	EQ-5D	0.02 (-0.04 to 0.08)					
	Topirimate	68	EQ-5D	0.04 (-0.002 to 0.10)					
Meador, 2003	Valproic Acid	25	QOLIE-89	Baseline: 61 (16)* Maintenance: 61 (17)*	-	-	-	-	-
	Topiramate	27	QOLIE-89	Baseline: 57 (15)* Maintenance: 59 (14)*	-	-	-	-	-
Sackellares, 2002					Health Perception	Energy/Fatigue	Social Isolation	Medication effects	Attention/concentration
	Valproate	55	QOLIE-89	-	Odds ratio: 4.0 95% CI: 1.6-10.6	Odds ratio: 2.3 95% CI: 1.1-5.3	Odds ratio: 2.8 95% CI:1.1-7.6	Odds ratio: 2.3 95% CI: 0.9-5.7	Odds ratio: 2.1 95% CI: 0.9- 4.8
	Lamotrigine	53	QOLIE-89	-					

Study, year	Group	N	Scale used	Overall Score	Subscore 1	Subscore 2	Subscore 3	Subscore 4	Subscore 5
Steiner, 1999	Phenytoin	95	SEALS Inventory	Estimated difference between treatments in the overall change from baseline: 4.0 95% CI: 0.7-7.3 P=0.02	-	-	-	-	-
	Lamotrigine	86	SEALS Inventory		-	-	-	-	-

* mean (standard deviation)
† continuous measures of NEWQOL, carbamazepine is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI
‡ ordinal measures of NEWQOL, carbamazepine is referent and values for ordinal measures are the exponential coefficients from a proportional odds model, with 95% CIs, such that values represent the odds of increasing severity of outcome
§ continuous measures of EQ-5D, carbamazepine is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI
|| continuous measures of NEWQOL, valproic acid is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI
¶ ordinal measures of NEWQOL, valproic acid is referent and values for ordinal measures are the exponential coefficients from a proportional odds model, with 95% CIs, such that values represent the odds of increasing severity of outcome
# continuous measures of EQ-5D, valproic acid is referent and values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CI
**lamotrigine is refernt
Legend: -=not reported; EQ-5D=Descriptive Health Realted Quality of Life States; HR=Hazard Ratio; N=Sample size; NEWQOL=Newly Diagnosed Epilepsy Quality of Life; QOLIE-89=Quality of Life in Epilepsy-89; SEALS Inventory=Side Effect and Life Satisfaction Inventory

Table 24. Adverse events in studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Overall adverse events (n)	Adverse events without study withdrawal (n)	Skin rash (n)	Hypotension (n)	Suicidal ideation (n)	Nausea (n)	Vomiting (n)
Reinikainen, 1987	Carbamazepine	18	-	11	-	-	-	1	-
	Oxcarbazepine	16	-	7	-	-	-	0	-
Dam, 1989	Carbamazepine	98	73	-	-	0	-	-	-
	Oxcarbazepine	92	63	-	-	0	-	-	-
Sachdeo, 1992	Valproic Acid	22	-	-	-	-	-	-	-
	Felbamate	22	-	-	-	-	-	1	3
Faught,1993	Valproate	39	28	-	1	-	-	1	2
	Felbamate	38	19	-	1	-	-	0	2
Brodie, 1995	Carbamazepine	129	-	-	25	-	-	2	9
	Lamotrigine	131	-	-	25	-	-	1	12
Kalviainen, 1995	Carbamazepine	45	55	55	-	-	-	-	-
	Vigabatrin	43	49	49	-	-	-	-	-
Reunanen, 1996	Carbamazepine	117	-	-	10	-	-	9	-
	Lamotrigine100 mg	115	-	-	6	-	-	7	-
	Lamotrigine 200 mg	111	-	-	9	-	-	7	-
Tanganelli, 1996	Carbamazepine	25	24	-	1	-	-	4 events	-
	Vigabratin	26	14	-	0	-	-	1 event	-
Bill, 1997	Phenytoin	142	122	-	16	-	-	16	-
	Oxcarbazepine	136	114	-	12	-	-	13	-
Christie, 1997	Sodium Valproate	121	106	-	-	-	-	14	-
	Oxcarbazepine	128	115	-	-	-	-	11	-
Guerreiro, 1997	Pheyntion	94	79	-	5	-	-	7	5
	Oxcarbazepine	96	84	-	4	-	-	5	0
Brodie, 1999a	Carbamazepine	48	-	-	12	-	-	-	3
	Lamotrigine	102	-	-	9	-	-	-	9
Chadwick, 1999	Carbamazepine	229	195	134	22	-	-	-	-
	Vigabatrin	228	191	148	7	-	-	-	-
Gobbi, 1999	Carbamazepine	40	-	-	-	-	-	-	-
	Vigabatrin	37	-	-	-	-	-	-	-

Study, year	Group	N	Overall adverse events (n)	Adverse events without study withdrawal (n)	Skin rash (n)	Hypotension (n)	Suicidal ideation (n)	Nausea (n)	Vomiting (n)
Steiner, 1999	Phenytoin	95	59	52	9	-	-	4	-
	Lamotrigine	86	36	37	12	-	-	7	-
Biton, 2001	Valproate	68	-	-	-	-	-	16	9
	Lamotrigine	65	-	-	-	-	-	8	4
Kwan, 2001	Carbamazepine	212	78	-	22	-	-	-	-
	Valproate	101	15	-	0	-	-	-	-
	Lamotrigine	78	9	-	3	-	-	0	-
Nieto-Barrera, 2001	Carbamazepine	215	300	-	20	-	-	-	-
	Lamotrigine	452	586	-	42	-	-	-	-
Biton, 2003	Valproate	20	12	-	1	-	-	3	1
	Lamotrigine	18	14	-	1	-	-	4	4
Privitera, 2003	Carbamazepine	126	-	-	10	-	-	25	-
	Valproic Acid	78	-	-	5	-	-	11	-
	Topiramate 100 mg	210	-	-	6	-	-	15	-
	Topiramate 200 mg	199	-	-	4	-		28	-
Clemens, 2004	Carbamazepine	20	0	-	-		-	-	-
	Oxcarbazepine	20	1	-	1		-	-	-
Coppola, 2004	Valproic Acid	19	2	2	0	-	-	-	-
	Lamotrigine	19	6	6	1	-	-	-	-
Fakhoury, 2004	Carbamazepine	46	33	-	-	-	-	4	-
	Lamotrigine	98	61	-	-	-	-	1	-
	Valproic Acid	53	37	-	-	-	-	7	-
	Lamotrigine	105	56	-	-	-	-	6	-
Wheless, 2004	Carbamazepine	23	-	-	-	-	-	4	2
	Valproate	19	-	-	-	-	-	2	0
	Topiramate 100 mg	38	-	-	-	-	-	2	4
	Topiramate 200 mg	39	-	-	-	-	-	2	2
Rowan, 2005	Carbamazepine	171	-	-	6	-	-	-	-
	Gabapentin	177	-	-	0	-	-	-	-
	Lamotrigine	183	-	-	1	-	-	-	-

Study, year	Group	N	Overall adverse events (n)	Adverse events without study withdrawal (n)	Skin rash (n)	Hypotension (n)	Suicidal ideation (n)	Nausea (n)	Vomiting (n)
Sobaniec, 2005	Carbamazepine	28	-	-	-	-	-	-	-
	Vigabratin	26	-	-	-	-	-	-	-
Steinhoff, 2005	Carbamazepine	88	65	-	8	-	-	-	-
	Lamotrigine	88	38	-	5	-	-	5	-
	Valproic Acid	30	16	-	-	-	-	-	-
	Lamotrigine	33	15	-	4	-	-	-	-
Brodie, 2007	Carbamazepine-Controlled Release	291	235	-	16	-	-	31	-
	Levetiracetam	285	227	-	8	-	-	20	-
Donati, 2007	Carbamazepine	28	17	-	3	-	-	-	-
	Valproic Acid	29	17	-	0	-	-	-	-
	Oxcarbazepine	55	31	-	4	-	-	-	-
Kang, 2007	Carbamazepine	54	-	19	8	-	-	-	-
	Topiramate	58	-	16	1	-	-	-	-
Levisohn, 2007	Valproic Acid	9	-	-	2	-	-	3	-
	Topiramate	19	-	-	0	-	-	1	-
Marson, 2007 SANAD Arm A	Carbamazepine	378	-	-	38	-	-	9	-
	Gabapentin	377	-	-	13	-	-	7	-
	Lamotrigine	378	-	-	17	-	-	9	-
	Oxcarbazepine	210	-	-	20	-	-	15	-
	Topiramate	378	-	-	17	-	-	4	-
Marson, 2007 SANAD Arm B	Valproic Acid	238	-	-	2	-	-	4	-
	Lamotrigine	239	-	-	13	-	-	4	-
	Topiramate	239	-	-	1	-	-	2	-
Saetre, 2007	Carbamazepine – Sustained Release	92	51	-	12	-	-	-	-
	Lamotrigine	93	51	-	5	-	-	-	-
Morrell, 2008	Valproate	222	122	123	9	-	-	16	16

Study, year	Group	N	Overall adverse events (n)	Adverse events without study withdrawal (n)	Skin rash (n)	Hypotension (n)	Suicidal ideation (n)	Nausea (n)	Vomiting (n)
	Lamotrigine	219	123	210	10	-	-	3	6
Perry, 2008	Carbamazepine	20	14	-	0	-	-	-	-
	Levetiracetam	66	30	-	1	-	-	-	-
Kim, 2009	Carbamazepine	105	21	-	4		-	-	-
	Topiramate	41	12	-	0		-	-	-
Kwan, 2009	Valproic Acid	43	-	-	0	-	-	-	-
	Lamotrigine	37	-	-	4	-	-	-	-
Ma, 2009	Carbamazepine	120	31	11	15	-	-	-	-
	Valproic Acid	234	44	34	2	-	-	-	-
	Topiramate	143	46	29	1	-	-	-	-
Ramsay, 2010	Phenytoin	127	-	-	10	-	1	12	-
	Topiramate	132	-	-	1	-	0	9	-

Legend: -=not reported; adverse events without study withdrawal (n)=number of events; hypotension (n)=number of patients with experiencing hypotension; N=Sample size; overall adverse events (n)=number of events; nausea (n)=number of patients with experiencing nausea; SANAD Arm A=Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B=Standard and New Antiepileptic Drugs Trial Arm B; skin rash (n)=number of patients with experiencing skin rash; suicidal ideation (n)=number of patients with experiencing suicidal ideation; vomiting (n)=number of patients with experiencing vomiting

Table 25. Neurological adverse events in studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Dizziness (n)	Fatigue (n)	Headache (n)	Somnolence (n)
Reinikainen, 1987	Carbamazepine	18	-	-	1	-
	Oxcarbazepine	16	-	-	0	-
Faught, 1993	Valproate	39	2	2	9	2
	Felbamate	38	1	0	3	1
Brodie, 1995	Carbamazepine	129	22	-	32	29
	Lamotrigine	131	16	-	39	16
Kalviainen, 1995	Carbamazepine	45	9	-	1	-
	Vigabatrin	43	3	-	1	-
Reunanen, 1996	Carbamazepine	117	11.7	-	11	20
	Lamotrigine100 mg	115	7	-	21	7
	Lamotrigine 200 mg	111	5	-	20	7
Tanganelli, 1996	Carbamazepine	25	9 events	-	0 events	-
	Vigabratin	26	1 event	-	4 events	-
Bill, 1997	Phenytoin	142	22	-	27	41
	Oxcarbazepine	136	18	-	20	41
Christie, 1997	Valproic Acid	121	14		21	24
	Oxcarbazepine	128	13		13	19
Guerreiro, 1997	Pheyntion	94	21	-	14	28
	Oxcarbazepine	96	9	-	13	24
Chadwick, 1998	Carbamazepine	74	10	22	10	10
	Gabapentin 300 mg	72	5	9	10	2
	Gabapentin 900 mg	72	11	9	10	5
	Gabapentin 1800 mg	74	11	6	10	5
Chadwick, 1999	Carbamazepine	229	29	50	48	-
	Vigabatrin	228	29	45	47	-
Brodie,1999	Carbamazepine	48	8	-	8	14
	Lamotrigine	102	10	-	9	12
Steiner, 1999	Phenytoin	95	11	-	18	27
	Lamotrigine	86	8	-	9	6
Biton, 2001	Valproate	68	6	-	4	16
	Lamotrigine	65	7	-	9	5
Kwan, 2001	Carbamazepine	212	10	4	12	6
	Sodium Valproate	101	1	0	4	1
	Lamotrigine	78	0	0	2	1
Nieto-Barrera, 2001	Carbamazepine	215	18	-	25	21
	Lamotrigine	452	31	-	44	17
Biton, 2003	Valproate	20	3	-	3	3

Study, year	Group	N	Dizziness (n)	Fatigue (n)	Headache (n)	Somnolence (n)
	Lamotrigine	18	4	-	5	1
Privitera, 2003	Carbamazepine	126	16	29	29	-
	Valproic Acid	78	10	18	18	-
	Topiramate 100 mg	210	13	20	25	-
	Topiramate 200 mg	199	12	23	18	-
Coppola, 2004	Valproic Acid	19	-	-	0	-
	Lamotrigine	19	-	-	2	-
Fakhoury, 2004	Carbamazepine	46	11	-	4	12
	Lamotrigine	98	17	-	5	13
	Valproic Acid	53	6	-	4	7
	Lamotrigine	105	16	-	11	11
Wheless, 2004	Carbamazepine	23	4	4	5	3
	Valproic Acid	19	0	4	3	6
	Topiramate 100 mg	38	2	6	14	5
	Topiramate 200 mg	39	2	10	6	2
Rowan, 2005	Carbamazepine	171	55	-	30	-
	Gabapentin	177	50	-	27	-
	Lamotrigine	183	50	-	35	-
Steinhoff, 2005	Carbamazepine	88	-	38	-	-
	Lamotrigine	88	4	13	5	-
	Valproic Acid	30	-	5	-	-
	Lamotrigine	33	3	3	-	-
Sobaniec, 2005	Carbamazepine	28	-	-	-	4
	Vigabratin	26	-	-	-	2
Brodie, 2007	Carbamazepine-Controlled Release	291	40	41	74	27
	Levetiracetam	285	31	47	59	32
Donati, 2007	Carbamazepine	28	0	4	2	-
	Valproic Acid	29	0	2	7	-
	Oxcarbazepine	55	4	7	6	-
Kang, 2007	Carbamazepine	54	1	-	-	5
	Topiramate	58	1	-	-	7
Levisohn, 2007	Valproic Acid	9	1	3	1	0
	Topiramate	19	2	2	5	2
Marson, 2007 SANAD Arm A	Carbamazepine	378	14	-	21	-
	Gabapentin	377	23	-	20	-
	Lamotrigine	378	15	-	21	-
	Oxcarbazepine	210	13	-	9	-
	Topiramate	378	15	-	17	-

Study, year	Group	N	Dizziness (n)	Fatigue (n)	Headache (n)	Somnolence (n)
Marson, 2007 SANAD Arm B	Valproic Acid	238	1	-	5	-
	Lamotrigine	239	3	-	6	-
	Topiramate	239	6	-	7	-
Saetre, 2007	Carbamazepine–Sustained Release	92	9	-	10	-
	Lamotrigine	93	13	-	10	-
Stephen, 2007	Valproic Acid	111	-	-	-	-
	Lamotrigine	114	-	-	-	-
Morrell, 2008	Valproate	222	10	-	39	-
	Lamotrigine	219	11	-	29	-
Pack, 2008	Carbamazepine	41	-	-	-	-
	Valproate	14	-	-	-	-
	Phenytoin	15	-	-	-	-
	Lamotrigine	23	-	-	-	-
Perry, 2008	Carbamazepine	20	2	-	-	8
	Levetiracetam	66	1	-	-	6
Kwan, 2009	Valproic Acid	43	-	-	4	-
	Lamotrigine	37	-	-	1	-
Ma, 2009	Carbamazepine	120	2	-	6	1
	Valproic Acid	234	3	-	9	3
	Topiramate	143	1	-	3	0
Glauser, 2010	Ethosuximide	55	9	15	19	14
	Valproic Acid	147	2	18	12	4
	Lamotirgine	149	4	13	12	3
Ramsay, 2010	Phenytoin	127	35	11	15	18
	Topiramate	132	26	12	11	16

Legend: -=not reported; dizziness (n)= number of patients with dizziness; fatigue (n)= number of patients with fatigue; headache (n)= number of patients with headache; N=sample size; SANAD Arm A=Standard and New Antiepileptic Drugs Trial Arm A; SANAD Arm B=Standard and New Antiepileptic Drugs Trial Arm B; somnolence (n)= number of patients with somnolence

Table 26. Cosmetic adverse effects in studies comparing older versus newer antiepileptic drugs

Study, year	Group	N	Acne (n)	Alopecia (n)	Gum Hyperplasia (n)
Dam, 1989	Carbamazepine	98	-	2	-
	Oxcarbazepine	92	-	0	-
Kalviainen, 1995	Carbamazepine	45	-	0	-
	Vigabatrin	43	-	1	-
Bill 1997	Phenytoin	142	3	-	18
	Oxcarbazepine	136	8	-	2
Christie, 1997	Sodium Valproate	121	-	21	-
	Oxcarbazepine	128	-	11	-
Guerreiro, 1997	Pheyntion	94	-	-	24
	Oxcarbazepine	96	-	-	2
Biton, 2001	Valproate	68	-	7	-
	Lamotrigine	65	-	2	-
Biton, 2003	Valproate	20	-	3	-
	Lamotrigine	18	-	0	-
Privitera, 2003	Carbamazepine	126	-	2	-
	Valproic Acid	78	-	14	-
	Topiramate 100 mg	210	-	4	-
	Topiramate 200 mg	199	-	2	-
Fakhoury, 2004	Carbamazepine	46	-	1	-
	Lamotrigine	98	-	3	-
	Valproic Acid	53	-	6	-
	Lamotrigine	105	-	1	-
Wheless, 2004	Carbamazepine	23	-	1	-
	Valproate	19	-	2	-
	Topiramate 100 mg	38	-	0	-
	Topiramate 200 mg	39	-	0	-
Steinhoff, 2005	Carbamazepine	88	-	-	-
	Lamotrigine	88	-	4	-
	Valproate	30	-	3	-
	Lamotrigine	33	-	2	-
Donati, 2007	Carbamazepine	28	-	1	-
	Valproic Acid	29	-	3	-
	Oxcarbazepine	55	-	0	-
Levisohn, 2007	Valproic Acid	9	-	3	-
	Topirimate	19	-	2	-
Stephen, 2007	Valproate	111	-	-	-

Study, year	Group	N	Acne (n)	Alopecia (n)	Gum Hyperplasia (n)
	Lamotrigine	114	-	-	-
Morrell, 2008	Valproate	222	-	25	-
	Lamotrigine	219	-	3	-
Kim, 2009	Carbamazepine	105	-	1	-
	Topiramate	41	-	0	-

Legend: -=not reported; acne (n)=number of patients with acne; alopecia (n)=number of patients with alopecia; gum hyperplasia (n)=number of patients with gum hyperplasia; N=Sample size

Table 27. Bone mineral density effects in studies comparing older versus newer antiepitleptic drugs

Study year	Group	N	Bone Mineral Density (gm/cm^2) Mean (SD)	Bone Mineral Density (gm/cm^2) Mean (SD)	Bone Mineral Density (gm/cm^2) Mean (SD)	Bone Mineral Density (gm/cm^2) Mean (SD)	Bone Mineral Density (gm/cm^2) Mean (SD)
Babayigit, 2006	Carbamazepine	23	Lumbar Vertebrae 1	Lumbar Vertebrae 2	Lumbar Vertebrae 3	Lumbar Vertebrae 4	Lumbar Vertebrae Total
			0.648 (0.162)	0.72 (0.173)	0.732 (0.164)	0.744 (0.188)	0.665 (0.199)
	Valproic Acid	31	Lumbar Vertebrae 1	Lumbar Vertebrae 2	Lumbar Vertebrae 3	Lumbar Vertebrae 4	Lumbar Vertebrae Total
			0.596 (0.191)	0.666 (0.213)	0.692 (0.206)	0.694 (0.194)	0.665 (0.199)
	Oxcarbazepine	14	Lumbar Vertebrae 1	Lumbar Vertebrae 2	Lumbar Vertebrae 3	Lumbar Vertebrae 4	Lumbar Vertebrae Total
			0.679 (0.188)	0.747 (0.188)	0.771 (0.196)	0.767 (0.195)	0.744 (0.188)
Pack, 2008	Carbamazepine	41	Lumbar Spine	Femoral Neck	Total Hip	-	-
			Baseline: 1.016 (0.12)	Baseline: 0.792 (0.10)	Baseline: 0.889 (0.12)		
			1 year: 1.021 (0.12)	1 year: 0.794 (0.10)	1 year: 0.892 (0.11)		
	Valproate	14	Lumbar Spine	Femoral Neck	Total Hip	-	-
			Baseline: 0.998 (0.15)	Baseline: 0.838 (0.18)	Baseline: 0.926 (0.18)		
			1 year: 0.999 (0.16)	1 year: 0.843 (0.18)	1 year: 0.931 (0.19)		
	Phenytoin	15	Lumbar Spine	Femoral Neck	Total Hip	-	-
			Baseline: 1.073 (0.16)	Baseline: 0.871 (0.18)	Baseline: 0.962 (0.15)		
			1 year: 1.077 (0.17)	1 year: 0.849 (0.16)	1 year: 0.0.961 (0.15)		
	Lamotrigine	23	Lumbar Spine	Femoral Neck	Total Hip	-	-
			Baseline: 1.068 (0.11)	Baseline: 0.835 (0.11)	Baseline: 0.922 (0.11)		
			1 year: 1.066 (0.09)	1 year: 0.828 (0.11)	1 year: 0.920 (0.11)		

Legend: -=not reported; N=Sample size; SD=standard deviation

Table 28. Bone mineral density effects in studies comparing older versus newer antiepileptic drugs

Study year	Group	N	Bone Mineral Density Z score Mean (SD)
Kim, 2007	Carbamazepine	10	Before: 0.42 (0.26) After: -0.34 (0.35)
	Valproic Acid	15	Before: 0.61 (0.41) After: 0.06 (0.30)
	Lamotrigine	8	Before:0.60 (0.17) After:0.48 (0.18)

Legend: N=Sample size; SD=standard deviation

Table 29. Serious adverse events for individual antiepileptic drugs

Antiepileptic Drug	Black Boxed Warning	Warnings
Carbamazepine	Serious Dermatologic Reactions Including Toxic Epidermal Necrosis and Stevens-Johnson Syndrome Aplastic Anemia Agranulocytosis	Increased Risk of Suicidal Ideation and Behavior
Clonazepam	None	None
Ethosuximide	None	Blood Discrasias Systemic Lupus Erythematosus Increased Risk of Suicidal Ideation and Behavior
Felbamate	Aplastic Anemia Hepatic Failure	Increased Risk of Suicidal Ideation and Behavior
Gabapentin	None	Increased Risk of Suicidal Ideation and Behavior
Lacosamide	None	Increased Risk of Suicidal Ideation and Behavior
Lamotrigine	Life Threatening Skin Rashes Including Stevens-Johnson Syndrome, Toxic Epidermal Necrosis and or Skin Rash Related Death	2. Life Threatening Hypersensitivity Reactions Acute Multi Organ Failure Blood Dyscrasias Increased Risk of Suicidal Ideation and Behavior
Levetiracetam	None	Decreased Red and White Blood Cells Increased Risk of Suicidal Ideation and Behavior
Oxcarbazepine	None	Clinically Significant Hyponatremia Anaphylaxis Angioedema Multi-Organ Hypersensitivity Reaction Stevens-Johnson Syndrome Agranulocytosis Aplastic Anemia Pancytopenia Increased Risk of Suicidal Ideation and Behavior
Phenobarbital	None	None
Phenytoin	None	Skin Reactions Including Exfolative Dermatitis, Setvens-Johnson Syndrome and Toxic Epidermal Necrosis Anticonvulsant Hypersensitivity Syndrome with Multi-Organ Involvement Increased Risk of Suicidal Ideation and Behavior
Primidone	None	Increased Risk of Suicidal Ideation and Behavior
Pregabalin	None	Angioedema Hypersensitivity Reactions Increased Risk of Suicidal Ideation and Behavior

Antiepileptic Drug	Black Boxed Warning	Warnings
Rufinamide	None	QT Shortening Mulit-Organ Hypersensitivity Increased Risk of Suicidal Ideation and Behavior
Tiagabine	None	Sudden Unexpected Death in Epilepsy Increased Risk of Suicidal Ideation and Behavior
Topiramate	None	Acute Myopia and Closed Angle Glaucoma Increased Risk of Suicidal Ideation and Behavior
Valproic Acid	Heptatotoxicity Pandreatitis Teratogenicity Including Neural Tube Defects	Thrombocytopenia
Vigabatrin	Reduced Visual Acuity Permanent Vision Loss Progressive and Permanent Bilateral Concentric Visual Field Constriction	Increased Risk of Suicidal Ideation and Behavior
Zonisamide	None	Serious Skin Reactions Including Toxic Epidermal Necrosis and Stevens-Johnson Syndrome Aplastic Anemia Agranulocytosis Increased Risk of Suicidal Ideation and Behavior

Appendix H. Strength of Evidence for Outcomes

Table 30. Strength of evidence for final outcome evaluations for innovator versus generic antiepileptic drugs under key question 1

						Quality	Assessment		Summary
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Mortality			0						Insufficient

Abbreviation: AEDs=antiepileptic drugs, RCT=randomized controlled trials

Table 31. Strength of evidence for medical service utilization for innovator versus generic antiepileptic drugs under key question 1

					Quality Assessment				Summary of Findings	
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Outpatient medical care utilization (Office or ER visit)	Various	Various	4	Observational	Very serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Hospitalizations	Various	Various	4	Observational	Very serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Ambulance Services			0						Insufficient	Important
Composite of medical services	Various	Various	3	Observational	Serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Insufficient	Important
Hospital stay duration	Various	Various	4	Observational	Very serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Low	Important

Abbreviation: AED=Antiepileptic drug, ER=Emergency Room, RCT=randomized controlled trials

Table 32. Strength of evidence for health related quality of life for innovator versus generic antiepileptic drugs under key question 1

						Quality Assessment			Summary of Findings	
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Health related quality of life			0						Insufficient	Important

Abbreviation: AED=Antiepileptic drug

Table 33. Strength of evidence for final health outcomes for innovator versus generic antiepileptic drugs key question 1

					Quality		Assessment		Summary	of Findings
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Seizure Occurrence/ breakthrough seizure	Carbamazepine	8 Generics	5	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	3 Generics	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Valproic Acid	1 Generic	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Phenytoin Valproic Acid	12 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Seizure Frequency	Carbamazepine	2 Generics	2	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
	Valproic Acid	1 Generic	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Valproic Acid	3 Generics	3	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Time to first seizure			0						Insufficient	Important
Incidence of status epilepticus			0						Insufficient	Important
Seizure remission			0						Insufficient	Important
Secondary seizure injury			0						Insufficinet	Important

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 34. Strength of evidence for withdrawals due to adverse events for innovator versus generic antiepileptic drugs in key question 1

						Quality	Assessment		Summary	of Findings
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Total withdrawals	Carbamazepine	(9, 1) Generics	8 (7, 1)	RCTs, Observational	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	5 Generics	3 (2, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin	(14, 1) Generics	11 (9, 1, 1)	RCTs, non-randomized and OBS trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Carbamazepine	9 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	5 Generics	3 (2, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin	14 Generics	10 (9, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Withdrawals due to adverse events	Carbamazepine	9 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	5 Generics	3 (2, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin	14 Generics	10 (9, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 35. Strength of evidence for pharmacokinetic effects for innovator versus generic antiepileptic drugs key question 2

						Quality Assessment			Summary	of Findings
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Cmax	Carbamazepine	10 Generics	6	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Lamotrigine	1 Generic	1	Non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Phenytoin	5 Generics	1	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Carbamazepine Phenytoin Lamotrigine	16 Generics	8 (7, 1)	RCTs, non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Cmin	Carbamazepine	9 Generics	5 (4, 1)	RCTs, non-blinded trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Lamotrigine	1 Generic	1	Non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Lamotrigine	10 Generics	6 (4, 1, 1)	RCTs, non-randomized trial, non-blinded trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Css	Carbamazepine	4 Generics	4	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Phenytoin	8 Generics	3	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
	Carbamazepine Phenytoin	12 Generics	7	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
AUC	Carbamzepine	10 Generics	6	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
	Lamotrigine	1 Generic	1	Non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Phenytoin	5 Generics	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

						Quality Assessment			Summary	of Findings
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
	Carbamazepine Lamotrigine Phenytoin	16 Generics	8 (7, 1)	RCTs and non-randomized trial	Serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Tmax	Carbamazepine	9 Generics	5	RCTs	Serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 36. Strength of evidence for incidence of adverse events for innovator versus generic antiepileptic drugs in key question 3

					Quality	Assessment			Summary	of Findings
Outcome	**Brand AED**	**Generic AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Incidence of ADRs	Carbamazepine	1 Generic	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Phenytoin	2 Generics	1	RCT	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
	Carbamazepine Phenytoin	3 Generics	2	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Incidence of Skin Rash	Carbamazepine	2 Generics	2	RCTs	Serious risk of bias	No serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Loss of drivers license			0						Insufficient	Important
Loss of employment			0						Insufficient	Important
Switchback rates			0						Insufficient	Important

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 37. Strength of evidence for final outcome evaluations for older versus newer antiepileptic drugs under key question 1

					Quality Assessment				Summary of Findings	
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Mortality	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	6	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Mortality	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Mortality	Valproic Acid	Lamotrigine Topiramate Vigabatrin	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 38. Strength of evidence for medical service utilization for older versus newer antiepileptic drugs under key question 1

						Quality	Assessment		Summary	of Findings
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Use of medical services			0						Insufficient	Important
Use of ambulance services			0						Insufficient	Important
Outpatient medical care utilization			0						Insufficient	Important
Hospitalizations	Carbamazepine	Lamotrigine	1	RCT	No risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Hospitalizations	Ethsuximide	Lamotrigine	1	RCT	No risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Hospitalizations	Valproic Acid	Lamotrigine	1	RCT	No risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Ambulance Services			0						Insufficient	Important
Outpatient medical care utilization			0						Insufficient	Important
Composite of medical services			0						Insufficient	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 39. Strength of evidence for health related quality of life for older versus newer antiepileptic drugs under key question 1

					Quality		Assessment			Summary of Findings	
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**		**Quality**	**Importance**
Health related quality of life	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Tiagabine Topiramate	3	RCTs	No serious risk of bias	No graded	No serious indirectness	Serious imprecision		Insufficient	Important
Health related quality of life	Phenytoin	Lamotrigine Tiagabine	2	RCTs	No serious risk of bias	No graded	No serious indirectness	Serious imprecision		Insufficient	Important
Health related quality of life	Valproic Acid	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	No graded	No serious indirectness	Serious imprecision		Insufficient	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 40. Strength of evidence for final health outcomes for olderer versus newer antiepileptic drugs key question 1

					Quality Assessment				Summary of Findings	
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Time to first seizure	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	6	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Time to first seizure	Phenytoin	Lamotrigine Topiramate	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Time to first seizure	Valproic Acid	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Change from baseline in seizure frequency	Carbamazepine	Oxcarbazepine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Serious imprecision	Insufficient	Important
Change from baseline in seizure frequency	Phenytoin	Oxcarbazepine	2	RCTs	Very serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Insufficient	Important
Change from baseline in seizure frequency	Valproic Acid	Oxcarbazepine	1	RCT	Very serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
12 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	2	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Low	Important
12 Month Seizure Remission	Valproic Acid	Lamotrigine Topiramate	1	RCT	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important

						Quality Assessment			Summary of Findings	
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
24 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate	1	RCT	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
24 Month Seizure Remission	Valproic Acid	Lamotrigine Topirmate	1	RCT	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Seizure freedom	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin Levetiracetam	20 (15, 5)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Seizure freedom	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Seizure freedom	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	5 (4, 1)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Seizure freedom	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	15 (12, 3)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 41. Strength of evidence for withdrawals due to adverse events for older versus newer antiepileptic drugs in key question 1

					Quality	Assessment			Summary	of Findings
Outcome	**Older AED**	**Newer AED**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Total withdrawals	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	21 (16, 5)	RCTs and Observational	No serious risk of bias	Very serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Total withdrawals	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Total withdrawals	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	No graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Total withdrawals	Phenytoin	Lamotrigine Oxcarbzepine	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Total withdrawals	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate Vigababtrin	19 (17, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	16 (11, 5)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Carbamazepine Controlled Release	Lamotrigine	1	RCT	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision	Insufficient	Important
Withdrawals due to lack of efficacy	Phenytoin	Lamotrigine Oxcarbazepine	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Withdrawals due to lack of efficacy	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	15 (12, 3)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

					Quality		Assessment		Summary	of Findings
Outcome	**Older AED**	**Newer AED**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Withdrawals due to adverse events	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	24 (18, 6)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Withdrawals due to adverse events	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk or bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Withdrawals due to adverse events	Ethosuximide	Lamotrigine	1	RCT	No serious risk or bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Withdrawals due to adverse events	Phenytoin	Lamotrigine Oxcarbazepine	3	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Withdrawals due to adverse events	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	18 (16, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 42. Strength of evidence for neurologic adverse events for older versus newer antiepileptic drugs in key question 3

					Quality		Assessment		Summary	of Findings
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Headache	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	17 (15, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	17 (15, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Headache	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Fatigue	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	7	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	Low	Important
Fatigue	Carbamazepine Controlled Release	Levetiracetam	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Fatigue	Phenytoin	Topiramate	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Fatigue	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	8	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Fatigue	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important

					Quality		Assessment		Summary	of Findings
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Somnolence	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Topiramate Vigabatrin	12 (8, 4)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Somnolence	Carbamazepine Controlled Release	Levetiracetam	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Somnolence	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important
Somnolence	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	11 (9, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Somnolence	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	No serious imprecision	Insufficient	Important
Dizziness	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	19 (16, 3)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Dizziness	Carbamzepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Dizziness	Phenytoin	Lamotrigine Oxcarbazepine	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Dizziness	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	14 (12, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Dizziness	Ethosuximide	Lamotrigine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Impotant

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 43. Strength of evidence for incidence of adverse events for older versus newer antiepileptic drugs in key question 3

					Quality Assessment				Summary of Findings	
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Nausea	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	8	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Nausea	Carbamazepine Controlled Release	Levetiracetam	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Nausea	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Nausea	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	11	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Vomiting	Carbamazepine	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Vomiting	Phenytoin	Oxcarbazepine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	No serious imprecision	Insufficient	Important
Vomiting	Valproic Acid	Felbamate Lamotrigine Topiramate	5	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Skin Rash	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	18 (13, 5)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Skin Rash	Carbamzepine Controlled or Sustained Release	Lamotrigine Levetiracetam	2	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Serious imprecision	Low	Important
Skin Rash	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	4	RCTs	No serious risk of bias	Very serious inconsistency	No serious indirectness	Very serious imprecision	Insufficient	Important

						Quality	Assessment		Summary	of Findings
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Skin Rash	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	12 (10, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 44. Strength of evidence for cognition and mood for older versus newer antiepileptic drugs in key question 3

					Quality Assessment				Summary of Findings	
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Cognition	Carbamazepine	Oxcarbazepine Tiagabine Topiramate Vigabatrin	4	RCTs	No serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Insufficient	Important
Cognition	Phenytoin	Tiagabine	1	RCT	No serious risk of bias	Not graded	Serious indirectness	Serious imprecision	Insufficient	Important
Cognition	Valproic Acid	Oxcarbazepine Topiramate	5 (3, 2)	RCTs and Observational	No serious risk of bias	Serious inconsistency	Serious indirectness	Very serious imprecision	Insufficient	Important
Mood	Carbamazepine	Tiagabine	1	RCT	No serious risk of bias	Not graded	Serious indirectness	No serious imprecision	Insufficient	Important
Mood	Phenytoin	Tagabine	1	RCT	No serious risk of bias	Not graded	Serious indirectness	Serious imprecision	Insufficient	Important
Mood	Valproic Acid	Lamotrigine Topiramate	3	RCTs	No serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Insufficient	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 45. Strength of evidence for bone mineral density for older versus newer antiepileptic drugs in key question 3

						Quality	Assessment		Summary	of Findings
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Bone Mineral Density	Carbamazepine	Lamotrigine Oxcarbazepine	3	Observational	Serious risk of bias	Serious inconsistency	Serious inconsistency	Serious imprecision	Insufficient	Important
Bone Mineral Density	Phenytoin	Lamotrigine	1	Observational	Serious risk of bias	Serious inconsistency	Serious inconsistency	Serious imprecision	Insufficient	Important
Bone Mineral Density	Valproic Acid	Lamotrigine Oxcarbazepine	3	Observational	Serious risk of bias	Serious inconsistency	Serious inconsistency	Serious imprecision	Insufficient	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Table 46. Strength of evidence for cosmetic adverse effects for older versus newer antiepileptic drugs key question 3

					Quality Assessment				Summary of Findings	
Outcome	**Older AED**	**Newer AEDs**	**Number of Studies (RCTs, Obs)**	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**	**Importance**
Alopecia	Carbamazepine	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	6	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	Very serious imprecision	Low	Important
Alopecia	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	8	RCTs	No serious risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Moderate	Important
Acne	Phenytoin	Oxcarbazepine	1	RCT	No serious risk of bias	Not graded	No serious indirectness	Very serious imprecision	Insufficient	Important
Gum Hyperplasia	Phenytoin	Oxcarbazepine	2	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	High	Important

Legend: AED=antiepileptic drug; Obs=observational study; RCT=randomized controlled trial

Appendix I. Applicability of Indivual Studies and the Body of Evidence

Table 47. Evaluation of Applicability for Individual Studies for Innovator versus Generic Antiepileptic Drug Evaluation

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Zachry, 2009 N=1664	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Population, Outcomes	In this study, patients were switched from one version of the medication to another "A" rated version. This could be from innovator to generic, generic to generic, or generic to innovator. As such it is not a true comparison of innovator to generic switching. ADRs not reported
Rascati, 2009 N=3964	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Population, Outcomes	In this study, patients were switched from one version of the medication to another "A" rated version. This could be from innovator to generic, generic to generic, or generic to innovator. As such it is not a true comparison of innovator to generic switching. ADRs not reported
Devine, 2010 N=11796	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Population, Outcomes	In this study, patients were switched from one version of the medication to another "A" rated version. This could be from innovator to generic, generic to generic, or generic to innovator. As such it is not a true comparison of innovator to generic switching. ADRs not reported
Labiner, 2010a N=18125	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Outcomes	ADRs not reported

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Labiner 2010b N=15500	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Adequate sample size	Outcomes	ADRs not reported
Kauko, 1974 N=20	Study Designation: Efficacy study Composite Score: 1 of 7	Intention to treat analysis	Population, Intervention, Comparator, Outcomes, Setting	Only in mentally retarded patients No final health outcomes reported Short duration of followup (30 days) Small sample size (only 20 patients enrolled) ADRs not reported Institutionalized facility for mentally retarded Conducted in Europe Study conducted before 1990
Glende, 1983 N=5	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Outcomes, Setting	Short duration of followup (4 weeks total, 2 weeks per group) Small sample size (only 5 patients enrolled) Conducted in Europe Study conducted before 1990
Jumao-as, 1989 N=10	Study Designation: Effectiveness study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Setting	Short duration of followup (10 weeks total, 5 weeks per group) Small sample size (only 10 patients enrolled) Study conducted before 1990
Hartley, 1990 N=23	Study Designation: Efficacy study Composite Score: 3 of 7	Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Population, Intervention, Comparator, Outcomes, Setting	Patients all young (6-15 years) No final health outcomes reported Short study duration (12 weeks total, 6 weeks per group) Small sample size (only 23 patients enrolled) Patients withdrawn were taken out of the final analysis Conducted in Europe

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Hartley, 1991 N=12	Study Designation: Efficacy study Composite Score: 2 of 7	Intention to treat analysis Enrolled primary care population	Population, Intervention, Comparator, Outcomes, Setting	Patients all young (6.5-15 years) No final health outcomes reported No ADRs reported Small sample size (only 12 patients enrolled) Short duration of followup (12 weeks total, 6 weeks per group) Conducted in Europe
Oles, 1992a N=20	Study Designation: Efficacy study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Population, Intervention, Comparator	Patients had to be 13 years or older Patients had to be seizure free for extended time (5 months to 2 years) Had to have been receiving carbamazepine for at least 6 months Small sample size (only 20 patients enrolled) Short duration of followup (3 months in each group)
Oles 1992b N=20	Study Designation: Efficacy study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Population, Intervention, Comparator	Patients had to be 13 years or older Patients had to have refractory seizures (at least 2 per month in previous 3 months) Had to have been receiving CBZ for at least 6 months Small sample size (only 20 patients enrolled) Short duration of followup (3 months in each group)
Reunanen, 1992 N=21	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Setting	Small sample size (only 21 patients enrolled) Short duration of followup (3 months in each group) Conducted in Europe
Silpakit, 1997 N=18	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Setting	Small sample size (only 18 patients enrolled) Short duration of followup (12 weeks total, 3 weeks on each phase) Conducted in Asia

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Aldenkamp, 1998 N=12	Study Designation: Efficacy study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Setting	Small sample size (only 12 patients enrolled) Short duration of followup (9 days total, 3 days per therapy) Conducted in Europe
LeLorier, 2008a N=671	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes, Setting	No ADRs reported Conducted in Canada
LeLorier, 2008b N=1060	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Outcomes, Setting	No final health outcomes reported No ADRs reported Conducted in Canada
LeLorier, 2008c N=202	Study Designation: Efficacy study Composite Score: 2 of 7	Less stringent eligibility criteria Adequate study duration	Outcomes, Setting	No final health outcomes reported No ADRs reported Conducted in Canada
LeLorier 2008d N=851	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate study sample	Outcomes, Setting	No final health outcomes reported No ADRs reported Conducted in Canada
Andermann, 2007a N=1142	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Population, Outcomes, Setting	Population not well specified No final health outcomes reported No ADRs reported Conducted in Canada

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Andermann, 2007b N=1600	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Population, Outcomes, Setting	Population not well specified No final health outcomes reported No ADRs reported Conducted in Canada
Andermann, 2007c N=2017	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Adequate study duration Adequate sample size	Population, Outcomes, Setting	Population not well specified No final health outcomes reported No ADRs reported Conducted in Canada
Nielsen, 2008a N=9	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Outcomes, Setting	No final health outcomes reported No ADRs reported Short duration of followup (2 weeks on innovator and 7-15 days on generic) Small sample size (only 9 patients enrolled) Conducted in Europe
Lund, 1974 N=9	Study Designation: Efficacy study Composite Score: 3 of 7	Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Population, Setting	Patients treated with drug for at least one year admitted to hospital to exclude irregular drug intake No final health outcomes reported Short duration of followup (8 days on innovator and 11 days on generic) Small sample size (only 9 patients enrolled) Conducted in Europe Conducted before 1990
Chen, 1982 N=18	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Outcomes, Setting	No final health outcomes reported Short duration of followup (9 weeks total, 3 weeks per therapy) Small sample size (only 20 patients enrolled) Conducted in Europe Conducted before 1990

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Hodges, 1986 N=30	Study Designation: Efficacy study Composite Score: 3 of 7	Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Population, Intervention, Comparator, Setting	Only pediatric patients (3-15 years) Short duration of followup (12 weeks total, 4 weeks on each therapy) Small sample size (only 30 patients enrolled) Conducted in Europe Conducted before 1990
Kishore, 1986 N=60	Study Designation: Effectiveness study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Intention to treat analysis Enrolled primary care population	Intervention, Comparator, Setting	Short duration of followup (3 months) Small sample size (only 60 patients enrolled) Conducted in Asia Conducted before 1990
Mikati, 1992 N=10	Study Designation: Effectiveness study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Adequate study duration Intention to treat analysis Enrolled primary care population	Intervention, Comparator	Small sample size (only 10 pts enrolled)
Soryal, 1992 N=14	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes Enrolled primary care population	Intervention, Comparator, Setting	Short duration of followup (4 weeks per therapy) Small sample size (only 14 patients enrolled) Conducted in Europe
Duh, 2009 N=948	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes, Setting	No ADRs reported Conducted in Canada
Paradis, 2009[a] N=1164	Study Designation: Efficacy study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes, Setting	No ADRs reported Conducted in Canada

Study, Year	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Vadney, 1997 N=64	Study Designation: Efficacy study Composite Score: 2 of 7	Assessed final health outcomes Assessed adverse outcomes	Population, Intervention, Comparator	Limited to patients with mental retardation Short duration of followup (8 weeks total, 4 weeks on each therapy) Small sample size (only 64 patients enrolled)

Table 48. Strength of applicability for individual studies comparing older versus newer antiepileptic drugs

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Reinikainen, 1987 N=40	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed adverse outcomes Assessed final health outcomes Less stringent eligibility criteria Adequate study duration with clinically relevant treatments	Population	Small sample size (40 patients)
Danner, 1988 N= 25	Study Designation: Efficacy study Composite Score: 3 of 7	Adequate follow up period Adequate study duration with clinically relevant treatments Less stringent eligibility criteria	Population Outcomes	Small sample size (25 patients) Assessed only neurological outcomes
Dam, 1989 N= 194	Study Designation: Efficacy Study Composite Score: 6 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Assessed final health Outcomes Assessed adverse outcomes Adequate sample size	Population	Conducted in Denmark, Finland, Norway and Sweden
Sachdeo, 1992 N= 44	Study Designation: Efficacy and Safety study Composite Score: 3 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes	Population	Short follow up period Only partial-onset seizures Small sample size (44 patients)
Brodie, 1995 N=260	Study Designation: Efficacy Study Composite Score: 5 of 7	Adequate sample size Adequate study duration with clinically relevant treatments Enrolled primary care population Less stringent eligibility criteria Assessed final health outcomes	Outcomes	Adverse events not reported

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Kalviainen,1995 N= 100	Study Designation: Efficacy and Safety study Composite Score: 5 of 7	Enrolled a primary care population Adequate sample size Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome	Population	Only patients aged 15- 64 years
Reunanen, 1995 N=343	Study Designation: Efficacy Study Composite Score: 5 of 7	Adequate sample size Assessed final health outcomes Assessed adverse outcomes Less stringent eligibility criteria Enrolled primary care population	Outcomes	Short Study Duration (26 weeks)
Sabers 1995 N= 52	Study Designation: Effectiveness study Composite Score: 2 of 7	Less stringent eligibility criteria Adequate study duration with clinically relevant treatments	Population Outcomes	No final health outcomes reported Did not report adverse events Small sample size (52 patients)
Reunanen, 1996 N= 343	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Adequate sample size Enrolled primary care population	None	None
Tanganelli, 1996 N= 51	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis Enrolled primary care population	Population	Only patients with complex partial seizures Small sample size(51 patients)

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Bill, 1997 N=287	Study Designation: Efficacy Study Composite Score: 5 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate sample size Assessed final health outcomes Adequate Study duration with clinically relevant treatments	None	Adverse events not reported
Christie, 1997 N=249	Study Designation: Efficacy Study Composite Score: 5 of 7	Less stringent eligibility criteria Enrolled primary care population Adequate study duration with clinically relevant treatments Assessed final health outcomes Assessed adverse outcomes	Population	Conducted in Belgium, Brazil, France, Germany, the Netherlands and South Africa
Guerreiro, 1997 N= 193	Study Designation: Efficacy study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Enrolled primary care population	Population Setting	Only enrolled children and adolescents Only patients with partial seizures and generalized tonic-clonic seizures without partial onset (GTCS) Conducted in South America (Brazil & Argentina)
Chadwick, 1998 N=292	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	None	None
Brodie, 1999a N= 150	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed final health Outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Adequate sample size	Population	Enrolled only patients >65 yrs old

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Brodie, 1999b N=215	Study Designation: Efficacy Study Composite Score: 5 of 7	Adequate sample size Enrolled primary care population Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcomes	None	12 week Maintenance phase
Chadwick, 1999 N=457	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used intention to treat analysis Assessed adverse outcomes	Population	Conducted in 44 centers in the United Kingdom, Denmark, Finland, Israel, France, South Africa, Spain, Switzerland and Australia
Gobbi, 1999 N= 80	Study Designation: Efficacy and Safety study Composite Score: 4 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis	Population	Enrolled only children with partial epilepsy Small sample size (80 patients)
Steiner, 1999 N= 181	Study Designation: Efficacy and safety study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Less stringent eligibility criteria	Population	Patients aged 14-75years Patients with absence seizures not eligible High drop out rate in the study (50%)
Dodrill, 2000 N= 277	Study Designation: Effectiveness study Composite Score: 2 of 7	Adequate study duration with clinically relevant treatments Adequate sample size	Population Outcome	Only adults with uncontrolled partial seizures were enrolled Did not assess adverse outcomes Reports only neuropsychological outcomes

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Gillham, 2000 N= 260	Study Designation: Effectiveness study Composite Score: 3 of 7	Adequate study duration with clinically relevant treatments Adequate sample size Less stringent eligibility criteria	Outcomes	Assessed only health related quality of life Did not assess adverse outcomes
Biton, 2001 N=133	Study Designation: Efficacy Study Composite Score: 3 of 7	Less stringent eligibility criteria Enrolled primary care population Adequate study duration with clinically relevant treatments Assessed adverse outcomes	Outcomes	Reported weight, safety/tolerability data only
Cramer, 2001 N=349	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed final health outcomes Enrolled primary care population Less stringent eligibility criteria Adequate sample size	Outcomes	Short study duration (16 weeks) Adverse events not reported
Kwan, 2001 N= 391	Study Designation: Efficacy, effectiveness and safety study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcome Adequate sample size Adequate study duration with clinically relevant treatments	Population	Only patients from a single tertiary hospital in Glasgow
Nieto-Barrera, 2001 N=618	Study Designation: Efficacy Study Composite Score: 5 of 7	Enrolled primary care population Adequate sample size Assessed final health outcomes Less stringent eligibility criteria Assessed adverse events	None	Short study Duration (24 weeks long)
Sackellares, 2002 N= 133	Study Designation: Efficacy study Composite Score: 3 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration Adequate sample size	Outcomes	Did not asses adverse events

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Biton, 2003 N=38	Study Designation: Efficacy Study Composite Score: 2 of 7	Adequate study duration with clinically relevant treatments Assessed adverse outcomes	Population Outcomes	Small sample size (38 patients) Reported weight, safety/tolerability data only Enrolled only pts 12-20 yrs old
Faught, 2003 N= 111	Study Designation: Efficacy study Composite Score: 4 of 7	Assessed final health outcomes Assessed adverse outcomes Adequate sample size Used intention to treat analysis	Population	Only patients with uncontrolled partial onset seizures Short study duration (112days)
Kim, 2009 N= 146	Study Designation: Effectiveness and safety study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Enrolled a primary care population	Population	Only enrolled patients < 2yrs Conducted in Korea
Meador, 2003 N= 76	Study Designation: Efficacy Study Composite Score: 3 of 7	Use intention to treat analysis Enrolled primary care population Less stringent eligibility criteria	Population Outcomes	Only reported cognitive/Behavioral outcomes Short study duration (20 weeks) Did not report adverse outcomes Small Sample Size (63 patient)
Privitera, 2003 N=613	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Assessed adverse outcomes Adequate sample size Assessed final health outcomes Adequate study duration with clinically relevant treatments Use intention to treat analysis	None	None

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Clemens, 2004 N= 21	Study Designation: Efficacy Study Composite Score: 2 of 7	Less stringent eligibility criteria Enrolled primary care population	Population Outcomes	Small sample size (21 patients) Only reported EEG outcomes Short study duration (4 weeks) Did not report adverse events
Coppola, 2004 N= 38	Study Designation: Efficacy Study Composite Score: 4 of 7	Assessed adverse outcomes Assessed final health outcomes Used Intention to treat analysis Adequate study duration with clinically relevant treatments	Population	Only patients 3-17 yrs old Small sample size (38 patients)
Fakhoury, 2004 N= 302	Study Designation: Efficacy and Safety Composite Score: 4 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size	Population	Enrolled only patients ≥ 16 yrs
Wheless, 2004 N= 119	Study Designation: Efficacy and safety study Composite Score: 5 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis	Population	Only enrolled patients aged ≤ 16 yrs
Babayigit, 2005 N=68	Study Designation: Efficacy Study Composite Score: 0 of 7	None	Population Outcomes	Children only, one site Small sample size (68 patients) Only Bone Mineral Density and other markers Did not report adverse events

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Rowan, 2005 N= 593	Study Designation: Efficacy and Safety study Composite Score: 5 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Adequate sample size	Population	Only older patients were included Study in Veterans Administration patients in the United States
Sobaniec, 2005 N= 54	Study Designation: Efficacy and safety study Composite Score: 4 of 7	Less stringent eligibility criteria Assessed final health outcomes Assessed adverse outcome Used intention to treat analysis	Population	Only patients age 2–17 yrs with history of partial seizures Only one site in Poland Short follow-up period Small sample size (54 patients)
Steinhoff, 2005 N= 269	Study Designation: Efficacy and safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis	Population	Only enrolled patients with newly diagnosed epilepsy >12 yrs of age
Brodie, 2007 N=576	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Used Intention to treat analysis Adequate sample size Assesses final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes	None	None
Donati, 2007 N= 112	Study Designation: Efficacy study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis	Population	Only enrolled patients aged 6 to <17 yrs Assessed only cognitive function

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Kang, 2007 N=112	Study Designation: Efficacy, effectiveness and safety study Composite Score: 6 of 7	Enrolled a primary care population Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse events Use intention to treat analysis	Population	Conducted in Korea Enrolled only patients 5-15 yrs
Kim, 2007 N= 33	Study Designation: Safety study Composite Score: 4 of 7	Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis	Population Setting Outcome	Only patients aged 18 to 50 years Small sample size (33 patients) Conducted in Korea Did not assess final health outcome, only BMD was assessed
Levisohn, 2007 N=28	Study Designation: Efficacy Study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Only JME patients Small sample size (28 patients)
Marson, 2007 N=716	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Conducted in the United Kingdom

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Marson, 2007 N=1721	Study Designation: Efficacy Study Composite Score: 7 of 7	Enrolled primary care population Less stringent eligibility Criteria Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Conducted in the United Kingdom
Saetre, 2007 N=186	Study Designation: Effectiveness, efficacy, and safety study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Used intention to treat analysis Adequate sample size	Population	Older adults > 65 yrs only Only partial and primary generalized seizures
Stephen, 2007 N= 225	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcome Adequate sample size Used intention to treat analysis Less stringent eligibility criteria	None	None
Morrell, 2008 N=447	Study Designation: Efficacy Study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Assessed adverse events Adequate sample size Used intention to treat analysis	Population Outcomes	Only hormone effects studied Enrolled only women, 13-40 yrs old, with regular menstrual cycles
Pack, 2005/2008 N=93	Study Designation: Efficacy Study Composite Score: 1 of 7	Adequate study duration with clinically relevant treatments	Population Outcomes	Enrolled only women 18-40 yrs old Did not report adverse events Study reported bone outcomes only Small sample size

Study Year RefID#:	Effectiveness Study Designation and Composite Score	Effectiveness Study Criteria Met	Applicability Limitation Category	Specific Factors Limiting Applicability
Perry, 2008 N=86	Study Designation: Efficacy Study Composite Score: 3 of 7	Assessed adverse events Assessed final health outcomes Adequate study duration with clinically relevant treatments	Population	Enrolled patients <16 yrs old with newly diagnosed partial epilepsy Small Sample Size (86 patients)
Kwan, 2009 N=81	Study Designation: Efficacy study Composite Score: 6 of 7	Less stringent eligibility criteria Assessed final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes Used intention to treat analysis Enrolled a primary care population	Population	Conducted in China Small sample size (81patients)
Ma, 2009 N=497	Study Designation: Efficacy Study Composite Score: 4 of 7	Adequate study duration with clinically relevant treatments Adequate sample size Assessed final health outcomes Assessed adverse outcomes	Population	Only one center in children
Glauser, 2010 N=497	Study Designation: Efficacy and Safety study Composite Score: 5 of 7	Used Intention to treat analysis Adequate sample size Assesses final health outcomes Adequate study duration with clinically relevant treatments Assessed adverse outcomes	Population	Enrolled only children between the ages of 2.5 and 13 yrs with absence epilepsy
Ramsay, 2010 N=497	Study Designation: Efficacy and Safety study Composite Score: 6 of 7	Enrolled primary care population Less stringent eligibility criteria Adequate sample size Assessed final health outcomes Used Intention to treat analysis Assessed adverse outcomes	Population	Short study duration only 28 weeks

Table 49. Applicability rating for final outcome evaluations for innovator versus generic antiepileptic drugs under key question 1

Outcome	Brand AED	Generic AEDs	Strength of Ablity	Strength of Applicability	Overall AED Analysis	Comments
Mortality						No studies to assess strength of evidence

Abbreviation: AEDs=antiepileptic drugs, RCT=randomized controlled trials

Table 50. Applicability rating for medical service utilization for innovator versus generic antiepileptic drugs under key question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis	Comments
Outpatient medical care utilization (Office or ER visit)	Various	Various	Moderate	None of the four reports specified that they were limited to "A" rated versions of the generic AED. One report was conducted in the United States and the other three in Canada. The average age ranged between 33.7 and 52.5 years and the percentage of male participants ranged from 32.3 and 50.8%. No harms were being evaluated.	2 out of the 4 trials that evaluated this endpoint showed that outpatient visits were more frequent during the generic period compared to the brand periods and the other 2 trials showed no significant difference in outpatient visits between brand and generic periods.	
Hospitalizations	Various	Various	Moderate	None of the four reports specified that they were limited to "A" rated versions of the generic AED. One study was conducted in the United States and the other three in Canada. The average age ranged between 33.7 and 52.5 years and the percentage of male participants ranged from 32.3 and 50.8%. No harms were being evaluated.	2 out of the 4 trials that evaluated this endpoint showed hospitalizations were more frequent during the generic period compared to the brand periods. The third study showed no significant difference between generic and brand periods. The fourth study showed that multiple generic AED use was associated with higher hospitalization versus brand AED use and difference between single generic and brand AED use was not significant.	
Ambulance Services						No studies to assess strength of evidence
Composite of medical services	Various	Various	Moderate	All three studies were conducted in USA and all used "A" rated versions of the generic AED. Not a true comparison of innovator vs. generic since patients could be switched from one "A" rated generic to another "A" rated generic. The average age ranged between 35.6 and 42.0 years and the percentage of male participants ranged from 43.9 and 49%. No harms were being evaluated.	In the first and second study, cases were patients that had ambulance visit, ER visit or inpatient hospitalization and in the third study, cases were patients that had ER visit or inpatient hospitalization and controls in all three studies were patients that had office visits during the specified time period. In all three studies, cases were more likely to have undergone a switch from one "A" rated antiepileptic medication to another "A" rated version of the medication. In the third study, after adjusting for potential confounders, the odds ratio between the switch and acute epilepsy exacerbation (defined as ER visit or hospitalization) was 1.08 (95% CI: 0.91–1.29). When the time evaluated was extended to 180 days, the adjusted odds ratio of acute epilepsy exacerbations increased to 1.14 (95% CI: 0.99–1.31).	

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis	Comments
Hospital stay duration	Various	Various	Moderate	None of the four reports specified that they were limited to “A” rated versions of the generic AED. One study was conducted in the United States and the other three in Canada. The average age ranged between 33.7 and 52.5 years and the percentage of male participants ranged from 32.3 and 50.8%. No harms were being evaluated.	All 4 studies showed that average length of hospital stay was longer during the generic period compared to the brand periods.	

Abbreviation: AED=Antiepileptic drug, ER=Emergency Room, RCT=randomized controlled trials

Table 51. Applicability rating for health related quality of life for innovator versus generic antiepileptic drugs under key question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis	Comments
Health related quality of life						No studies to assess strength of evidence

Abbreviation: AED=Antiepileptic drug

Table 52. Applicability rating for final health outcomes for innovator versus generic antiepileptic drugs key question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	*Conclusion with Description of Applicability*	Overall AED Analysis	Comments
Seizure Occurrence/ breakthrough seizure	Carbamazepine Phenytoin Valproic Acid	12 Generics	Low	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.7 to 72 years and percent of male participants ranged from 50 to 100%. Body weight ranged from 35 to 94 kg in the four studies that reported it. Patients with both partial and generalized seizure types were enrolled in the two studies that reported it. All studies had fairly short duration of follow-up with maximum of 3 months per treatment group and small sample size (total n=195). All studies were conducted before 2000.	The risk of experiencing a seizure is non-significantly decreased by 11% when generic antiepileptic medications are used versus their associated innovator products [RR 0.89 (0.65 to 1.21)]	
Seizure Frequency	Carbamazepine Valproic Acid	3 Generics	Low	All 3 studies were conducted in USA. Average age ranged from 17 to 72 years and percent of male participants was 100% in the one study that reported it. Body weight ranged from 35 to 94 kg in the one study that reported it. Seizure type of patients was not reported in these 3 studies. All 3 studies had fairly short duration of follow-up with maximum of 3 months per treatment group and small sample size (total n=94). All studies were conducted before 2000	The seizure frequency is non-significantly higher in the generic antiepileptic medication group versus the innovator group [SMD 0.03 (-0.08 to 0.14) seizures over the evaluative period]	
Time to first seizure						No studies to assess strength of evidence
Incidence of status epilepticus						No studies to assess strength of evidence
Seizure remission						No studies to assess strength of evidence
Secondary seizure injury						No studies to assess strength of evidence

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 53. Applicability rating for withdrawals due to adverse events for innovator versus generic antiepileptic drugs in key question 1

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis
Total withdrawals	Carbamazepine Phenytoin	(14, 1) Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Body weight ranged from 35.5 to 83 kg in the three studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly short duration of follow-up with maximum of 3 months per group and small sample size (total n=202). All studies were conducted before 2000.	The risk of withdrawals for any reason is non-significantly decreased by 10% when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications [RR 0.90 (0.39, 2.08)]
Withdrawals due to lack of efficacy	Carbamazepine Phenytoin	14 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Body weight ranged from 35.5 to 83 kg in the three studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly short duration of follow-up with maximum of 3 months per group and small sample size (total n=202). All studies were conducted before 2000.	The risk of withdrawals due to ineffective treatment is non-significantly increased by 2% when generic antiepileptic medications were used versus their appropriate innovator antiepileptic medications [RR 1.02 (0.41 to 2.54)].
Withdrawals due to adverse events	Carbamazepine Phenytoin	14 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Body weight ranged from 35.5 to 83 kg in the three studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly short duration of follow-up with maximum of 3 months per group and small sample size (total n=202). All studies were conducted before 2000.	The risk of withdrawals due to adverse effects is non-significantly decreased by 21% when generic antiepileptic medications were used versus their appropriate innovator antiepileptic meidcations [RR 0.79 (0.28 to 2.20)]

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 54. Applicability rating for pharmacokinetic effects for innovator versus generic antiepileptic drugs key question 2

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis
Cmax	Carbamazepine Phenytoin Lamotrigine	16 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 67 years and percent of male participants ranged from 35 to 75%. Average body weight ranged from 35.8 to 53.9 kg in the two studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=149).	The standardized mean difference in the generic antiepileptic medication group was non-significantly higher than the innovator antiepileptic medication group [SMD 0.10 (-0.13 to 0.32)].
Cmin	Carbamazepine Lamotrigine	10 Generics	Low	Studies were conducted in Europe & Asia, but none were conducted in USA. Average age ranged from 7 to 45.1 years and percent of male participants ranged from 40 to 70%. Average body weight ranged from 35.8 to 53.9 kg in the two studies that reported it. Patients with various different seizure types were enrolled in the 4 studies that reported it. All studies had fairly small sample size (total n=103).	The standardized mean difference in the generic group was non-significantly higher than the generic antiepileptic medication group [SMD 0.05 (-0.21 to 0.31)].
Css	Carbamazepine Phenytoin	12 Generics	Low	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 70 years and percent of male participants ranged from 40 to 100%. Average body weight ranged from 49 to 83 kg in the two studies that reported it. Patients with both partial and generalized seizure types were enrolled in the two studies that reported it. All studies had fairly small sample size (total n=136).	The standardized mean difference in the generic group was non-significantly higher than the innovator antiepileptic medication group [SMD 0.18 (-0.09 to 0.45)].
AUC	Carbamazepine Lamotrigine Phenytoin	16 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 67 years and percent of male participants ranged from 35 to 80%. Average body weight ranged from 50 to 83 kg in the two studies that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=131).	The standardized mean difference in the generic group was non-significantly higher than the innovator antiepileptic medication group [SMD 0.05 (-0.18 to 0.28)].

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis
Tmax	Carbamazepine	9 Generics	Moderate	Studies were conducted in USA, Europe & Asia. Average age ranged from 10.6 to 45.1 years and percent of male participants ranged from 40 to 75%. Average body weight was 53.9 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=103).	The weighted mean difference for Tmax in generic carbamazepine group was same as the innovator carbamazepine group [WMD 0.00 (-0.43 to 0.43) hours].

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 55. Applicability rating for neurologic adverse events for innovator versus generic antiepileptic drugs in key question 3

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis
Headache	Carbamazepine Phenytoin	4 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 9.5 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=63).	The relative risk in the generic group was non-significantly lower than the innovator antiepileptic medication group [RR 0.95 (0.55 to 1.64)].
Diplopia	Carbamazepine	2 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 10.7 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=33).	The relative risk in the generic group was non-significantly higher than the innovator antiepileptic medication group [RR 1.28 (0.38 to 4.31)].
Somnolence	Carbamazepine	2 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 10.7 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=33).	The relative risk in the generic group was non-significantly lower than the innovator antiepileptic medication group [RR 0.90 (0.48 to 1.70)].

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 56. Applicability rating for incidence of adverse events and other outcomes for innovaotr versus generic antiepileptic drugs in key question 3

Outcome	Brand AED	Generic AEDs	Strength of Applicability	Conclusion with Description of Applicability	Overall AED Analysis	Comments
Incidence of ADRs	Carbamazepine Phenytoin	3 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 9.5 to 70 years and percent of male participants ranged from 60 to 100. Patients with various different seizure types were enrolled in the one study that specified seizure type. Both studies had fairly small sample size (total n=40).	The relative risk in the generic group was non-significantly higher than the innovator antiepileptic medication group [IRR 1.01 (0.68 to 1.51)].	**Risk of Bias:** Not "A" rated generics **Inconsistency**: I^2: 0% **Imprecision**: IRR 1.01 (0.68 to 1.51) non-significant findings
Incidence of Skin Rash	Carbamazepine	2 Generics	Low	Studies were conducted in USA & Europe. Average age ranged from 10.7 to 70 years and percent of male participants ranged from 60 to 100%. Average body weight was 35.8 kg in the one study that reported it. Patients with various different seizure types were enrolled in these studies. All studies had fairly small sample size (total n=33).	The relative risk in the generic group was non-significantly lower than the innovator antiepileptic medication group [IRR 0.74 (0.14 to 3.94)].	**Risk of Bias:** Not "A" rated generics **Inconsistency**: I^2: N/A **Imprecision**: IRR 0.74 (0.14 to 3.94) non-significant findings
Loss of drivers license						No studies to assess strength of evidence
Loss of employment						No studies to assess strength of evidence
Switchback rates						No studies to assess strength of evidence

Abbreviation: AED=Antiepileptic drug, RCT=randomized controlled trials

Table 57. Strength of applicability for the body of evidence evaluating mortality for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Mortality	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared with carbamazepine, newer antiepileptic drugs did not reduce the risk of mortality. Overall applicability is limited because the duration of follow up for the trials included in the evaluation is not adequate to evaluate mortality, the majority of the trials evaluated were conducted in the United Kingdom and multiple newer antiepileptic drugs are compared to a carbamazepine.
Mortality	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared with phenytoin, newer antiepileptic drugs did not reduce the risk of mortality. Overall applicability is limited because the duration of follow up for the trials included in the evaluation is not adequate to evaluate mortality, two of the trials were conducted outside of the United States in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin.
Mortality	Valproic Acid	Lamotrigine Topiramate Vigabatrin	Moderate	Compared with valproic acid, newer antiepileptic drugs did not reduce the risk of mortality. Overall applicability is limited because the duration of follow up for the trials included in the evaluation is not adequate to evaluate mortality, two of the trials included in the evaluation took place in the United Kingdom and multiple newer antiepileptic drugs were compared to valproic acid.

Legend: AED=antiepileptic drug

Table 58. Strength of applicability for medical service utilization for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability	Comments
Use of medical services					No studies to assess strength of evidence
Use of ambulance services					No studies to assess strength of evidence
Outpatient medical care utilization					No studies to assess strength of evidence
Hospitalizations					No studies to assess strength of evidence
Hospitalizations					No studies to assess strength of evidence
Hospitalizations					No studies to assess strength of evidence
Ambulance Services					No studies to assess strength of evidence
Outpatient medical care utilization					No studies to assess strength of evidence
Composite of medical services					No studies to assess strength of evidence

Legend: AED=antiepileptic drug

Table 59. Strength of applicability for health related quality of life for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicabi	Conclusion with Description of Applicability
Health related quality of life	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Tiagabine Topiramate	Low	Compared to carbamazepine, newer antiepileptic drugs showed an improvement in health related quality of life. Overall applicability is limited because the majority of the trials included in the evaluation were conducted in the United Kingdom and multiple newer antiepileptics are compared to a carbamazepine.
Health related quality of life	Phenytoin	Lamotrigine Tiagabine	Moderate	Compared to phenytoin, newer antiepileptic drugs did not show an improvement in health related quality of life. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin.
Health related quality of life	Valproic Acid	Lamotrigine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs did not show an improvement in health related quality of life. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.

Legend: AED=antiepileptic drug

Table 60. Strength of applicability for final health outcomes for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Time to first seizure	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not increase the time to first seizure. Overall applicability is limited because all of the trials included in the evaluation were conducted in the Europe and multiple antiepileptic drugs are compared to carbamazepine.
Time to first seizure	Phenytoin	Lamotrigine Topiramate	Moderate	Compared to phenytoin, newer antiepileptic drugs did not increase the time to first seizure. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin and because only one of the trials included in the evaluation was designed to evaluate time to first seizure as a primary efficacy endpoint.
Time to first seizure	Valproic Acid	Lamotrigine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs did not increase the time to first seizure. Overall applicability is limited because one of the trials included in the analysis was conducted in children between the ages of 6 and 16 years and multiple antiepileptic durgs were compared to valproic acid.
Change from baseline in seizure frequency	Carbamazepine	Oxcarbazepine	Moderate	Compared to carbamazepine, oxcarbazepine did not decrease the number of seizures from baseline. Overall applicability is limited because the trial was conducted in cites in Denmark, Finland, Norway and Sweden.
Change from baseline in seizure frequency	Phenytoin	Oxcarbazepine	Low	There was not enough data from the trials included to evaluate the change from baseline in seizure frequency oxcarbazepine when was compared to phenytoin. Overall applicability is limited by the lack of reported data.
Change from baseline in seizure frequency	Valproic Acid	Oxcarbazepine	Low	There was not enough data from the trials included to evaluate the change from baseline in seizure frequency when oxcarbazepine was compared to valproic acid. Overall applicability is limited by lack of reported data and because the only trial included in the evaluation was conducted at centers in Belgium, Brazil, France, Germany, the Netherlands and South Africa.
12 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not increase 12 month seizure remission. Overall applicability was limited because the trials included in the analysis were conducted in the United Kingdom, Denmark, Finland, Israel, France, South Africa, Spain, Switzerland and Australia and multiple newer antiepileptic drugs were compared to carbamazepine.

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
12 Month Seizure Remission	Valproic Acid	Lamotrigine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs did not increase 12 month seizure remission. Overall applicability is limited because the trial evaluating 12 month seizure remission was conducted in the United Kingdom and multiple newer antiepileptic drugs were compared to valproic acid.
24 Month Seizure Remission	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not increase 12 month seizure remission. Overall applicability is limited because the trial evaluating 12 month seizure remission was conducted in the United Kingdom and multiple newer antiepileptic drugs were compared to carbamazepine.
24 Month Seizure Remission	Valproic Acid	Lamotrigine Topirmate	Moderate	Compared to valproic acid, newer antiepileptic drugs did not increase 12 month seizure remission. Overall applicability is limited because the trial evaluating 12 month seizure remission was conducted in the United Kingdom and multiple newer antiepileptic drugs were compared to valproic acid.
Seizure freedom	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin Levetiracetam	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not increase seizure freedom. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine and the majority of the trials included were conducted in Europe and Scandinavia.
Seizure freedom	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared to controlled or sustained release carbamazepine, newer antiepileptic drugs did not increase seizure freedom. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Seizure freedom	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to pheyntoin, newer antiepileptic drugs do not increase seizure freedom. Overall applicability is limited because the majority of the studies included in the study were conducted in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin.

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Seizure freedom	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs do not increase seizure freedom. Overall applicability is limited because half of the studies included in the evaluation were conducted outside of the United States in China and Europe and multiple newer antiepileptic drugs were compared to valproic acid

Legend: AED=antiepileptic drug

Table 61. Strength of applicability for withdrawals due to adverse events for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AED	Strength of Applicability	Conclusion with Description of Applicability
Total withdrawals	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine and the majority of the trials included were conducted in Europe and Scandinavia.
Total withdrawals	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared to controlled or sustained release carbamazepine, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Total withdrawals	Ethosuximide	Lamotrigine	Low	Compared with ethosuximide, lamotrigine did not reduce withdrawal for any reason. Overall applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.
Total withdrawals	Phenytoin	Lamotrigine Oxcarbzepine	Moderate	Compared to phenytoin, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to the United States population is limited because the majority of the trials included in the analysis were conducted outside of the United States in Argentina, Brazil and the United Kingdom.
Total withdrawals	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate Vigababtrin	Moderate	Compared to valproic acid, newer antiepileptic drugs did not reduce withdrawal for any reason. Overall applicability is limited because half of the studies included in the evaluation were conducted outside of the United States in China and Europe and multiple newer antiepileptic drugs were compared to valproic acid.
Withdrawals due to lack of efficacy	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs increased withdrawal due to lack of efficacy. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine and the majority of the trials included were conducted in Europe and Scandinavia.

Outcome	Older AED	Newer AED	Strength of Applicability	Conclusion with Description of Applicability
Withdrawals due to lack of efficacy	Carbamazepine Controlled Release	Lamotrigine	Low	Compared to controlled release carbamazepine, lamotrigine increased withdrawal due to lack of efficacy. Overall applicability is limited to the United States because patients enrolled in Europe and South Africa.
Withdrawals due to lack of efficacy	Phenytoin	Lamotrigine Oxcarbazepine	Moderate	Compared to phenyoin, newer antiepileptics did not increase withdrawal due to lack of efficacy. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to the United States population is limited because the majority of the trials included in the analysis were conducted outside of the United States in Argentina, Brazil and the United Kingdom.
Withdrawals due to lack of efficacy	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to valproic acid, newer antiepileptic drugs did not increase withdrawal due to lack of efficacy. Overall applicability is limited because half of the studies included in the evaluation were conducted outside of the United States in China and Europe and multiple newer antiepileptic drugs were compared to valproic acid.
Withdrawals due to adverse events	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs decreased withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepiltpetics were compared to carbamazepine and the majority of the studies included in the evaluation were conducted in Europe.
Withdrawals due to adverse events	CarbamazepineControlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared to controlled or sustained release carbamazepine, newer antiepileptic drugs decreased withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Withdrawals due to adverse events	Ethosuximide	Lamotrigine	Low	Compared to ethosuximide, lamotrigine did not decrease withdrawal due to adverse events. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.

Outcome	Older AED	Newer AED	Strength of Applicability	Conclusion with Description of Applicability
Withdrawals due to adverse events	Phenytoin	Lamotrigine Oxcarbazepine	Moderate	Compared to phenyoin, newer antiepileptics did not decrease withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to the United States population is limited because the majority of the trials included in the analysis were conducted outside of the United States in Argentina, Brazil and the United Kingdom.
Withdrawals due to adverse events	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to valproic acid, newer antiepileptic drugs did not decrease withdrawal due to adverse events. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.

Legend: AED=antiepileptic drug

Table 62. Strength of applicability for neurologic adverse events for newer versus older antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Headache	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptics were compared to carbamazepine. Applicability is limited to the United States population because the majority of the trials included in the evaluation were conducted in Europe.
Headache	Carbamazepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared to controlled or sustained release carbamazepine, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Headache	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to phenytoin, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to a United States population is limited because only one of the trials included in the analysis was conducted in the United States while the rest were conducted in Europe, South America and South Africa.
Headache	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs did not decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Headache	Ethosuximide	Lamotrigine	Low	Compared to ethosuximide, lamotrigine did not decrease the incidence of headache. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.
Fatigue	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs decrease the incidence of headache. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability to a patient population in the United States is limited because the majority of the trials included in the evaluation were conducted in Europe.
Fatigue	Carbamazepine Controlled Release	Levetiracetam	Low	Compared to controlled release carbamazepine, levetiracetam did not decrease the incidence of fatigue. Overall applicability to a patient population in the United States is limited because the trial was conducted in Europe and South Africa. Applicability to a pediatric patient population is limited because the trial enrolled patients 16 years of age and older.

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Fatigue	Phenytoin	Topiramate	Low	Compared to phenytoin, topiramate did not decrease the incidence of headache. Applicability to a pediatric patient population is limited because the trial enrolled patients 12 years of age and older.
Fatigue	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs decreased the incidence of fatigue. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Fatigue	Ethosuximide	Lamotrigine	Low	Compared to ethosuximide, lamotrigine decreased the incidence of headache. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.
Somnolence	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs decreased the incidence of somnolence. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability to a United States population is limited because only three of the trials included in the analysis was conducted in the United States while the rest were conducted in Europe, China South Africa.
Somnolence	Carbamazepine Controlled Release	Levetiracetam	Low	Compared to controlled release carbamazepine, levetiracetam did not reduce the incidence of somnolence. Applicability to a patient population in the United States is limited because the trial was conducted in Europe and South Africa. Applicability to a pediatric population is limited because the trial was conducted in adolescents and adults 16 years of age and above.
Somnolence	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to phenytoin, newer antiepileptic drugs did not reduce the incidence of somnolence. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to a United States population is limited because only one of the trials included in the analysis was conducted in the United States while the rest were conducted in Europe, South America and South Africa.
Somnolence	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs reduced the incidence of somnolence. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Somnolence	Ethosuximide	Lamotrigine	Low	Compared to ethosuximide, lamotrigine decreased the incidence of somnolence. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Dizziness	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs decreased the incidence of dizziness, Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine.
Dizziness	Carbamzepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Low	Compared to controlled or sustained release carbamazepine, newer antiepileptic drugs did not decrease the incidence of dizziness. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Dizziness	Phenytoin	Lamotrigine Oxcarbazepine	Moderate	Compared to phenytoin, newer antiepileptic drugs did not decrease the incidence of dizziness. Overall applicability is limited because multiple newer antiepileptic drugs were compared to phenytoin. Applicability to a patient population in the United States is limited because the trials included in the analysis were conducted in Europe and South America.
Dizziness	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs did not decrease the incidence of dizziness. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Dizziness	Ethosuximide	Lamotrigine	Low	Compared to ethosuximide, lamotrigine did not decrease the incidence of dizziness. Applicability is limited because the trial was conducted in patients between the ages of 2.5 and 13 years.

Legend: AED=antiepileptic drug

Table 63. Strength of applicability for incidence of adverse events for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Nausea	Carbamazepine	Gabapentin Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not decrease the incidence of nausea. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine, Applicability to a United States patient populationIs limited because the majority of the studies included in the evaluation were conducted in Europe.
Nausea	Carbamazepine Controlled Release	Levetiracetam	Low	Compared to controlled release carbamazepine, levetiracetam did not decrease the incidence of nausea. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa.
Nausea	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to phenytoin, newer antiepileptic drugs did not decrease the incidence of nausea. Overall applicability is limited because the majority of the studies included in the study were conducted in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin.
Nausea	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to patients whoe received valproic acid, patients who received newer antiepileptic drugs had a decreased incidence of nausea. Overall applicability was limited because multiple newer antiepileptic drugs were compared to valproic acid.
Vomiting	Carbamazepine	Lamotrigine Topiramate	Moderate	Compared to patients treated with carbamazepine, patients treated with newer antiepileptic drugs did not have a decreased incidence of vomiting. Overall applicability was limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability is limited to the United States patient population because 2 of the 3 trials included in the evaluation were conducted in the United Kingdom.
Vomiting	Phenytoin	Oxcarbazepine	Low	Compared to patients treated with phenytoin, patients treated with oxcarbazepine had a decreased incidence of vomiting, Applicability to a patient populations in the United States because the trial was conducted in Argentina and Brazil. Applicability to an adult patient population is also limited because the trial was conducted in children and adolescents.

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Vomiting	Valproic Acid	Felbamate Lamotrigine Topiramate	Moderate	Compared to patients treated with valproic acid, patients treated with newer antiepileptic drugs did not have a decreased incidence of vomiting. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid. Applicability to an adult patient population is limited because the majority of the trials included in the evaluation were conducted in children.
Skin Rash	Carbamazepine	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to patients treated with carbamazepine, patients treated with newer antiepileptic drugs had a decreased incidence of skin rash. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine.
Skin Rash	Carbamzepine Controlled or Sustained Release	Lamotrigine Levetiracetam	Moderate	Compared to patients treated with controlled or sustained release carbamazepine, patients treated with newer antiepileptic drugs had a decreased incidence of skin rash. Overall applicability is limited because multiple newer antiepileptic drugs are compared to controlled or sustained release carbamazepine. Applicability to a United States population is limited because the trials included in the analysis were conducted in Scandinavia, Europe and South Africa. Applicability is also limited to a pediatric and adult population because one of the trials included in the analysis was conducted in patients 65 years of age or older.
Skin Rash	Phenytoin	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to patients treated with phenytoin, patients treated with newer antiepileptic drugs did not have a decrease in the incidence of skin rash. Overall applicability is limited because the majority of the studies included in the study were conducted in Europe and South Africa and multiple newer antiepileptic drugs were compared to phenytoin
Skin Rash	Valproic Acid	Felbamate Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to patients treated with valproic acid, patients treated with newer antiepileptic drugs did not have a decreased incidence of skin rash. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.

Legend: AED=antiepileptic drug

Table 64. Strength of applicability for bone mineral density for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Bone Mineral Density	Carbamazepine	Lamotrigine Oxcarbazepine	Low	Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability is limited to a patient population in the United States because only one of the three trials included in the analysis was conducted in the United States and the other trials were conducted in Turkey and Korea. Applicability is also limited to an adult male population as the largest trial included in the analysis was conducted in adult women.
Bone Mineral Density	Phenytoin	Lamotrigine	Low	Applicability is limited to an adult male population because the trial was conducted in adult women.
Bone Mineral Density	Valproic Acid	Lamotrigine Oxcarbazepine	Low	Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine. Applicability is limited to a patient population in the United States because only one of the three trials included in the analysis was conducted in the United States and the other trials were conducted in Turkey and Korea. Applicability is also limited to an adult male population as the largest trial included in the analysis was conducted in adult women.

Legend: AED=antiepileptic drug

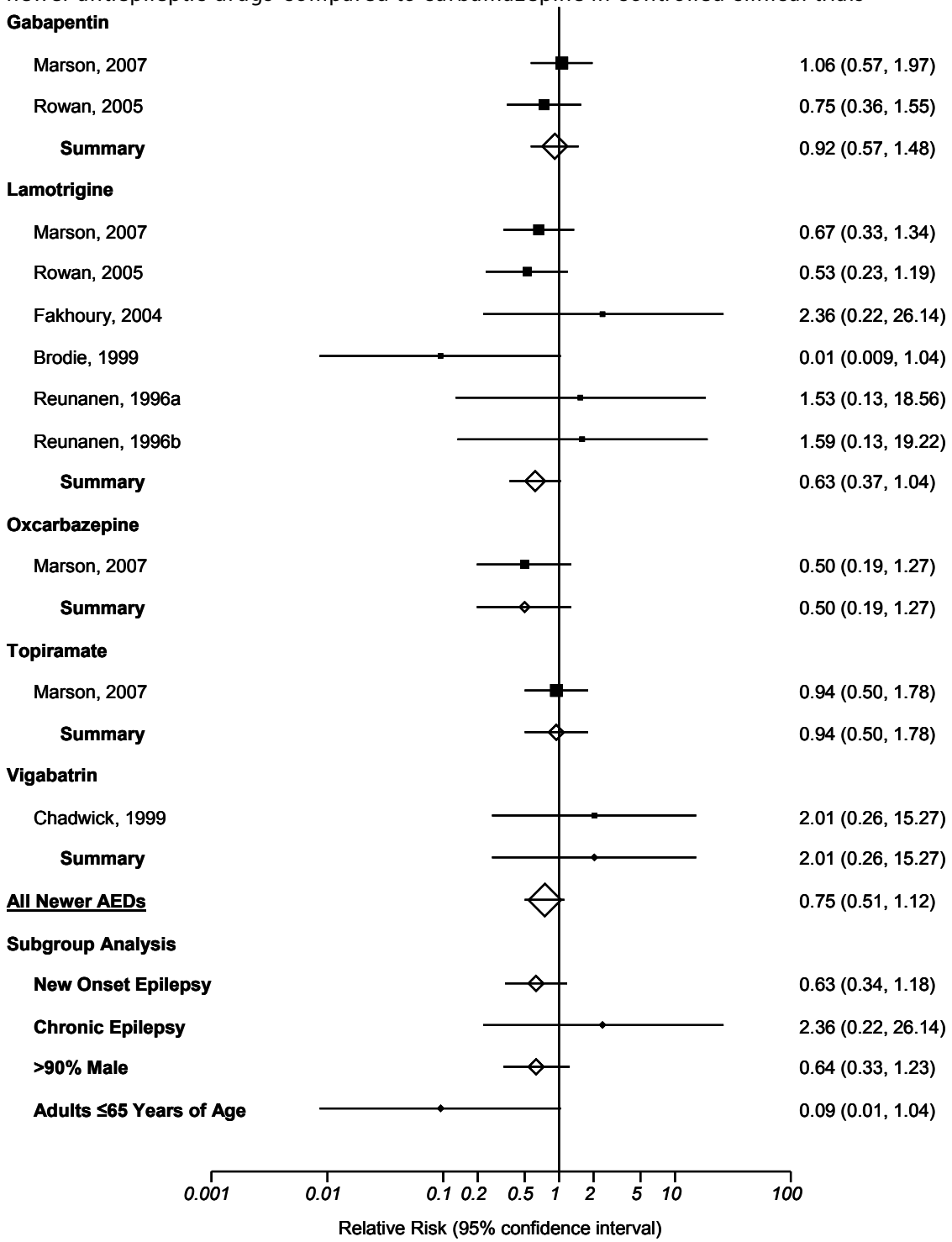
Table 65. Strength of applicability for cosmetic adverse effects for older versus newer antiepileptic drugs

Outcome	Older AED	Newer AEDs	Strength of Applicability	Conclusion with Description of Applicability
Alopecia	Carbamazepine	Lamotrigine Oxcarbazepine Topiramate Vigabatrin	Moderate	Compared to carbamazepine, newer antiepileptic drugs did not decrease the incidence of alopecia. Overall applicability is limited because multiple newer antiepileptic drugs were compared to carbamazepine.
Alopecia	Valproic Acid	Lamotrigine Oxcarbazepine Topiramate	Moderate	Compared to valproic acid, newer antiepileptic drugs decreased the incidence of alopecia. Overall applicability is limited because multiple newer antiepileptic drugs were compared to valproic acid.
Acne	Phenytoin	Oxcarbazepine	Low	Compared to phenytoin, oxcarbazepine did not decrease the incidence of acne. Applicability to a patient population in the United States is limited because the trial was conducted in Europe, South America and South Africa.
Gum Hyperplasia	Phenytoin	Oxcarbazepine	Low	Compared to phenytoin, oxcarbazepine decreased the incidence of gum hyperplasia. Applicability to a patient population in the United States is limited because the trials included in the evaluation were conducted in Europe, South America and South Africa.

Legend: AED=antiepileptic drug

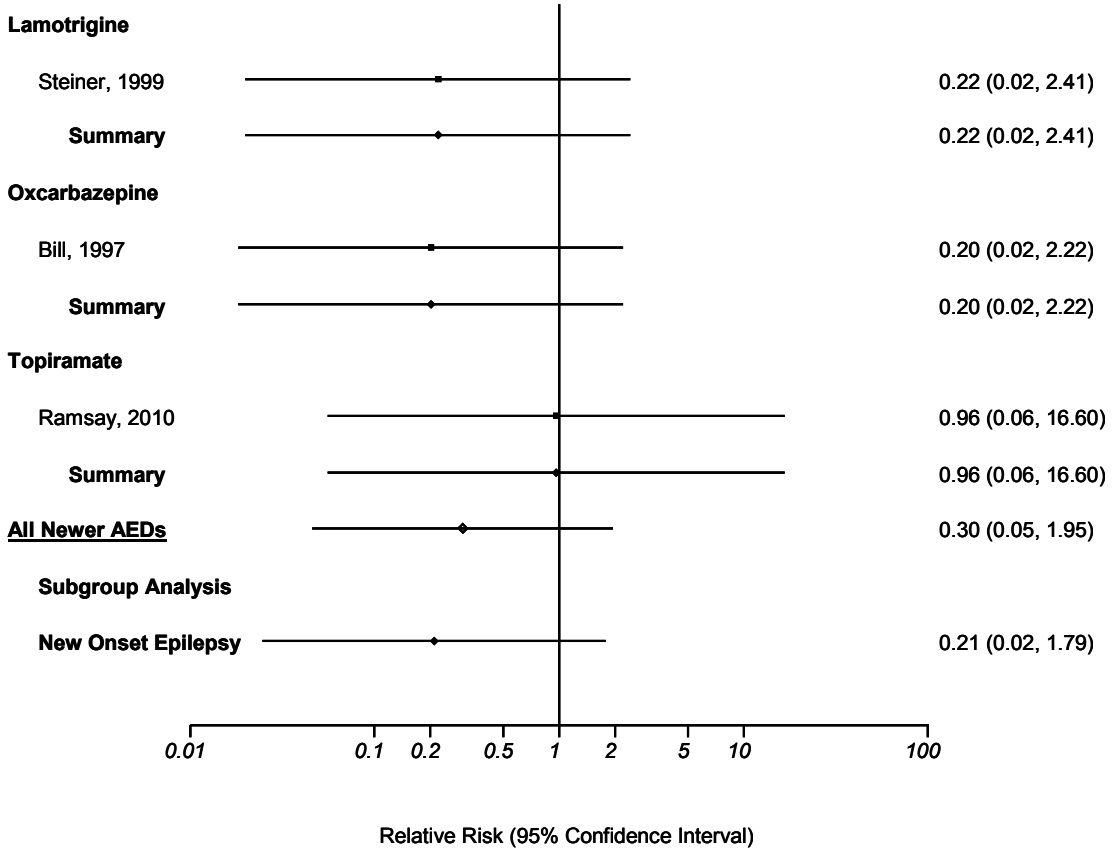
Appendix J. Forest Plots of Meta-Analysis of Efficacy and Safety Endpoints

Figure 1. Composite forest plot of meta-analysis of mortality in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



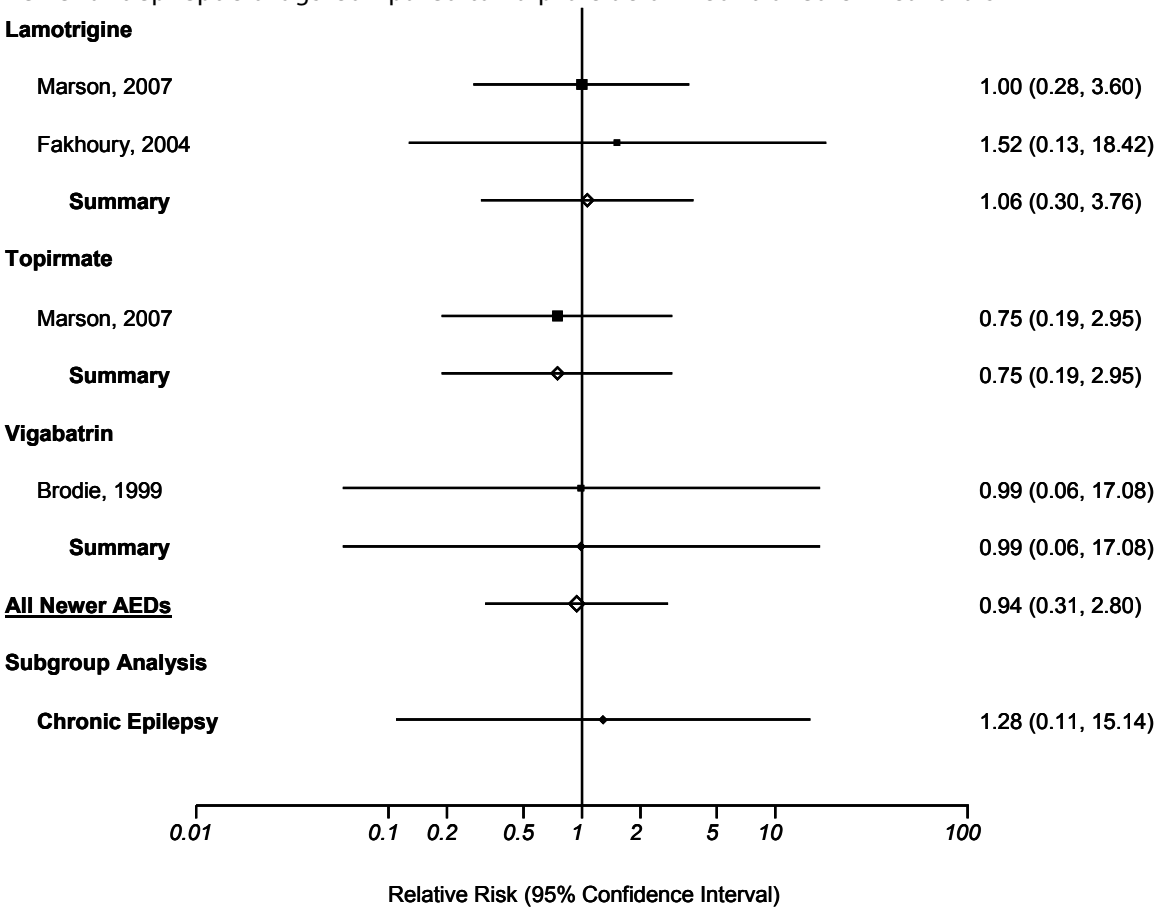
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 2. Composite forest plot of meta-analysis of mortality in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

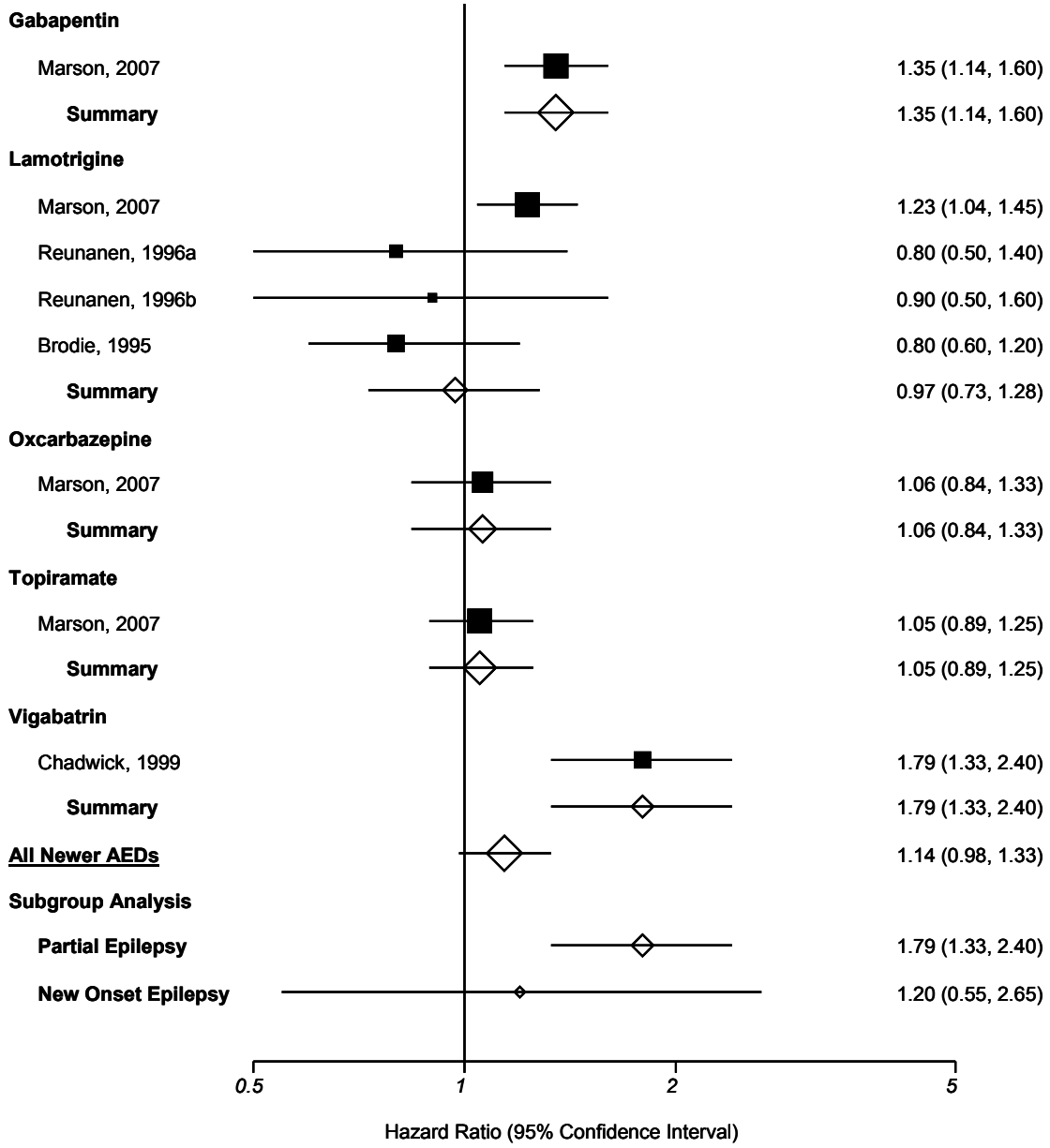
Figure 3. Composite forest plot of meta-analysis of mortality in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

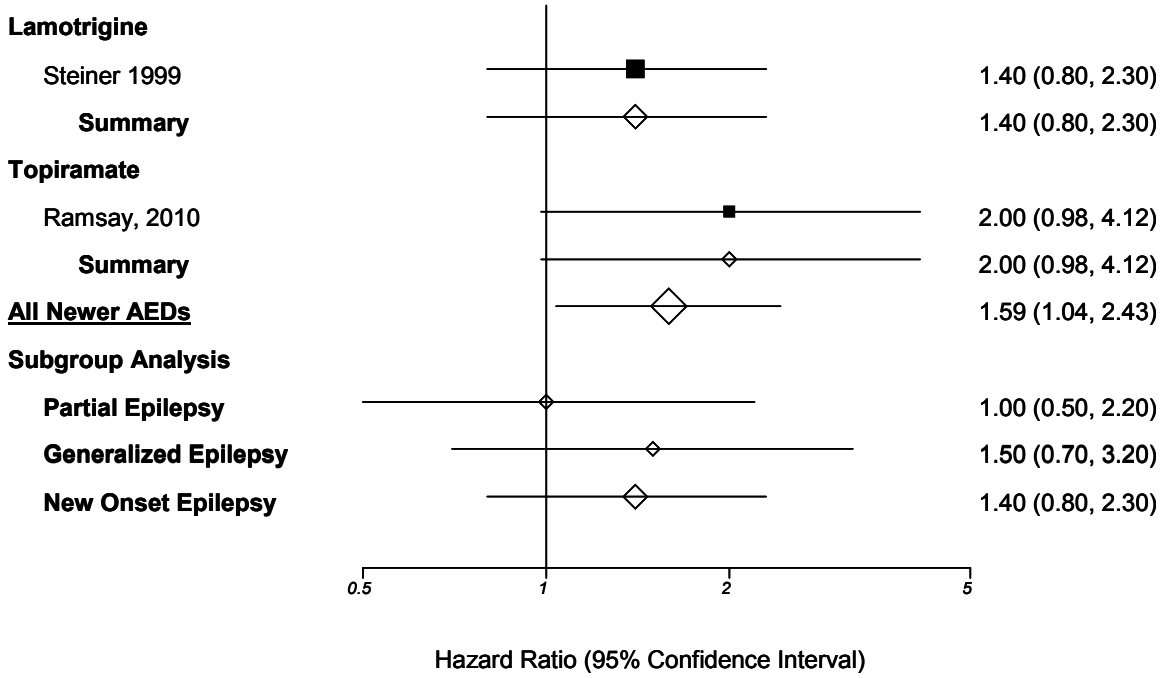
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 4. Composite forest plot of meta-analysis of time to first seizure in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



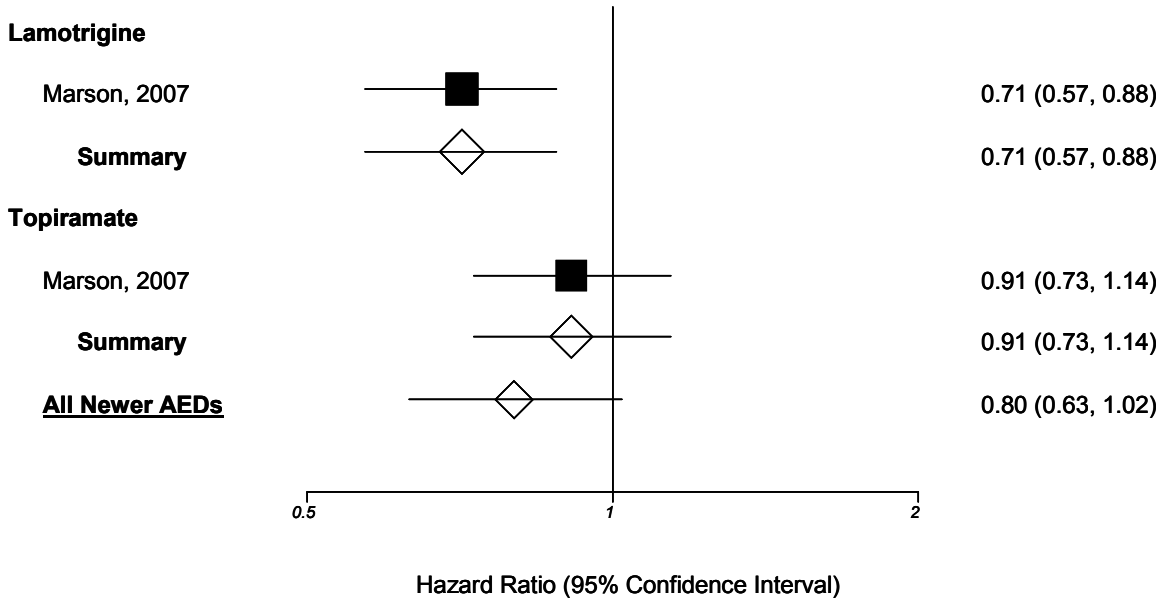
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 5. Composite forest plot of meta-analysis of time to first seizure in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



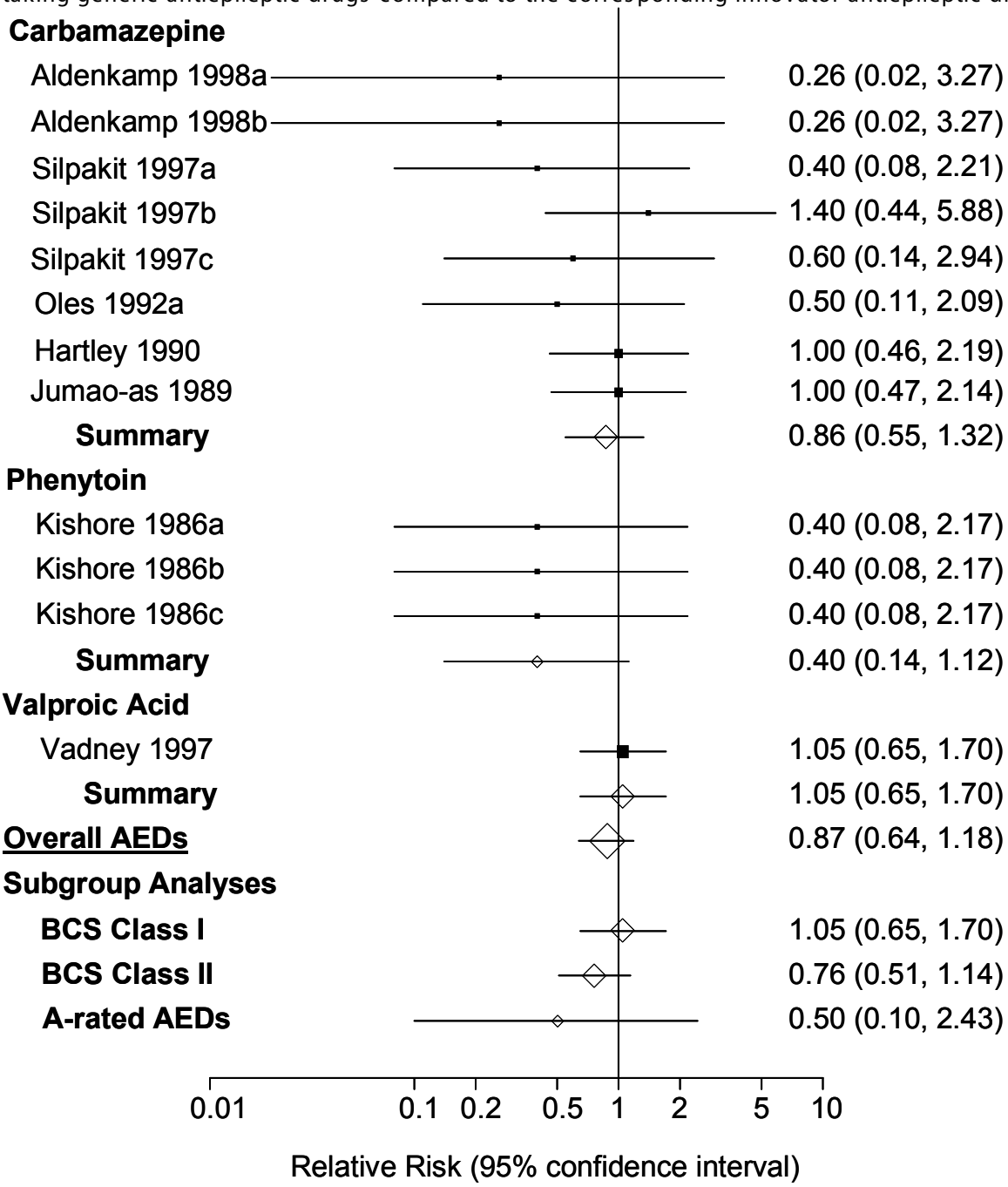
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 6. Composite forest plot of meta-analysis of time to first seizure in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

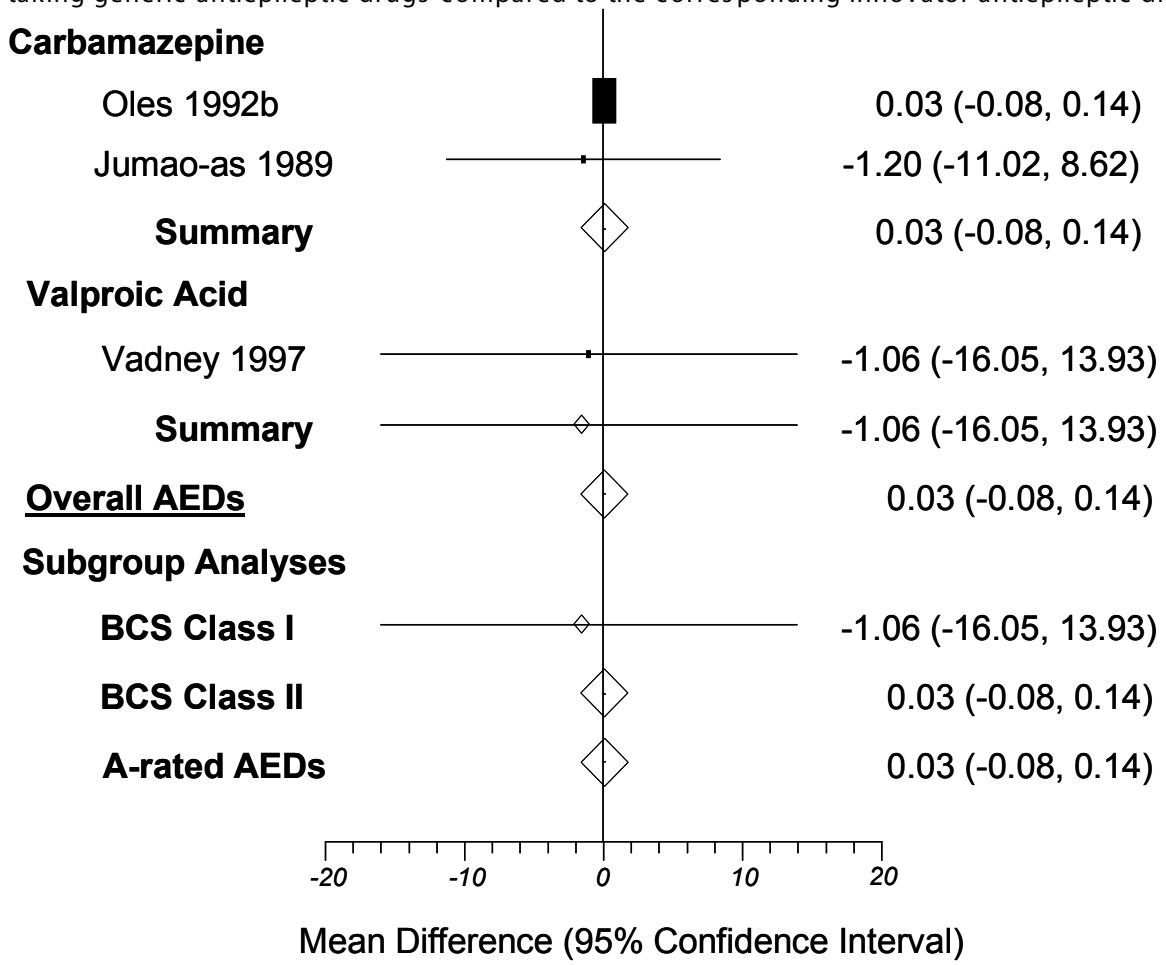
Figure 7. Composite forest plot of meta-analysis of seizure occurrence in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system

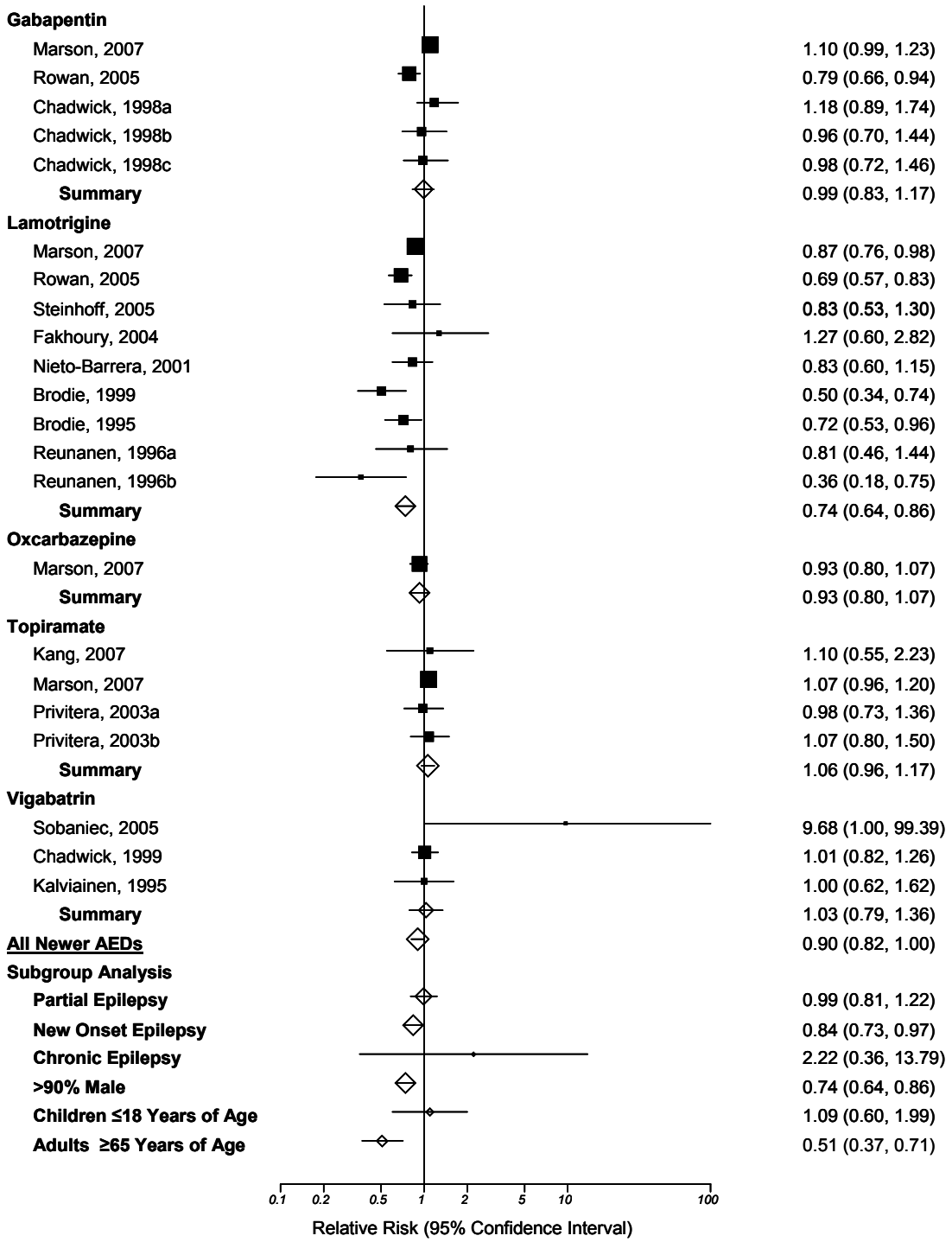
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 8. Composite forest plot of meta-analysis of seizure frequency in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



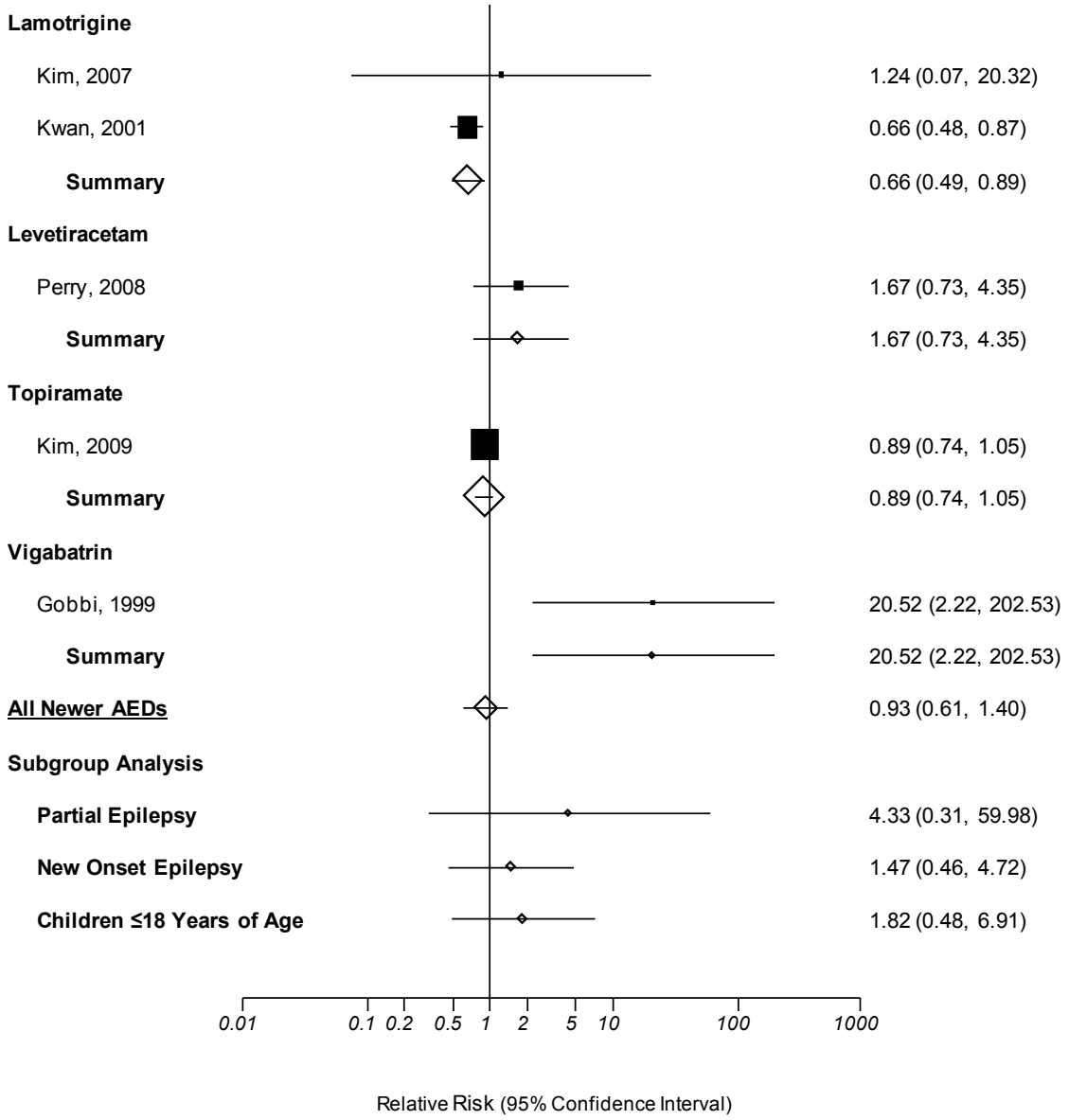
Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 9. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



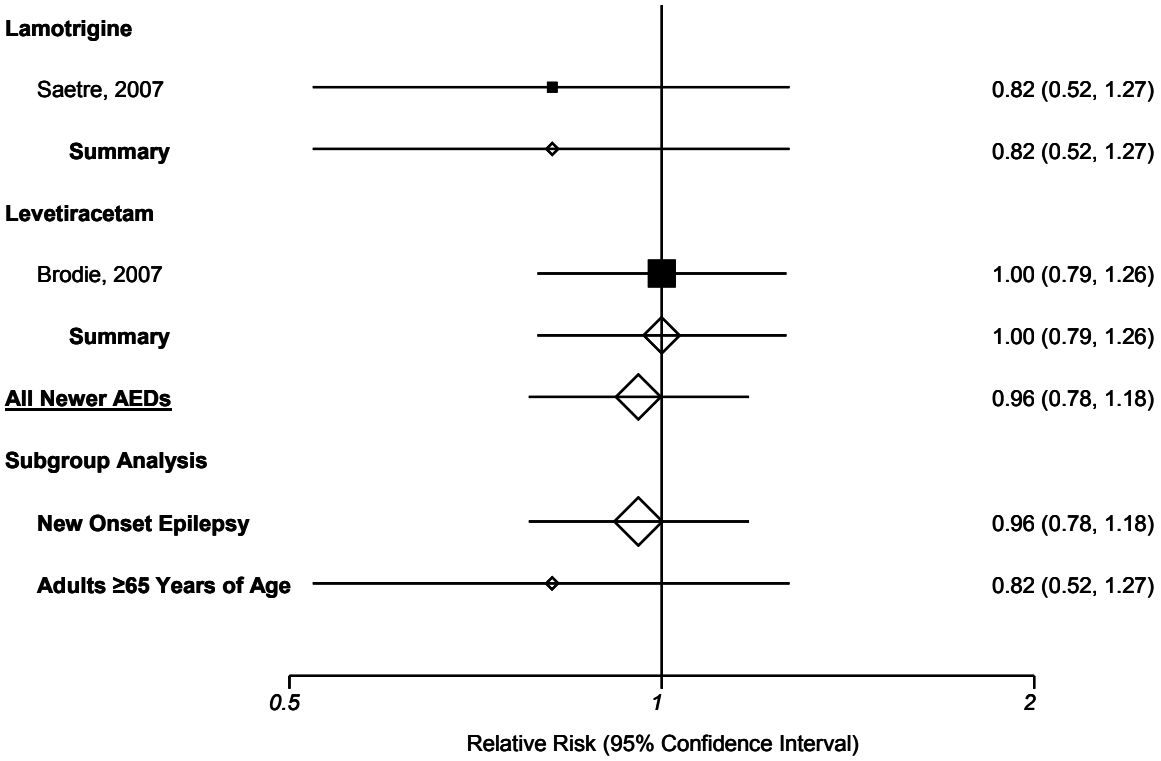
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 10. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

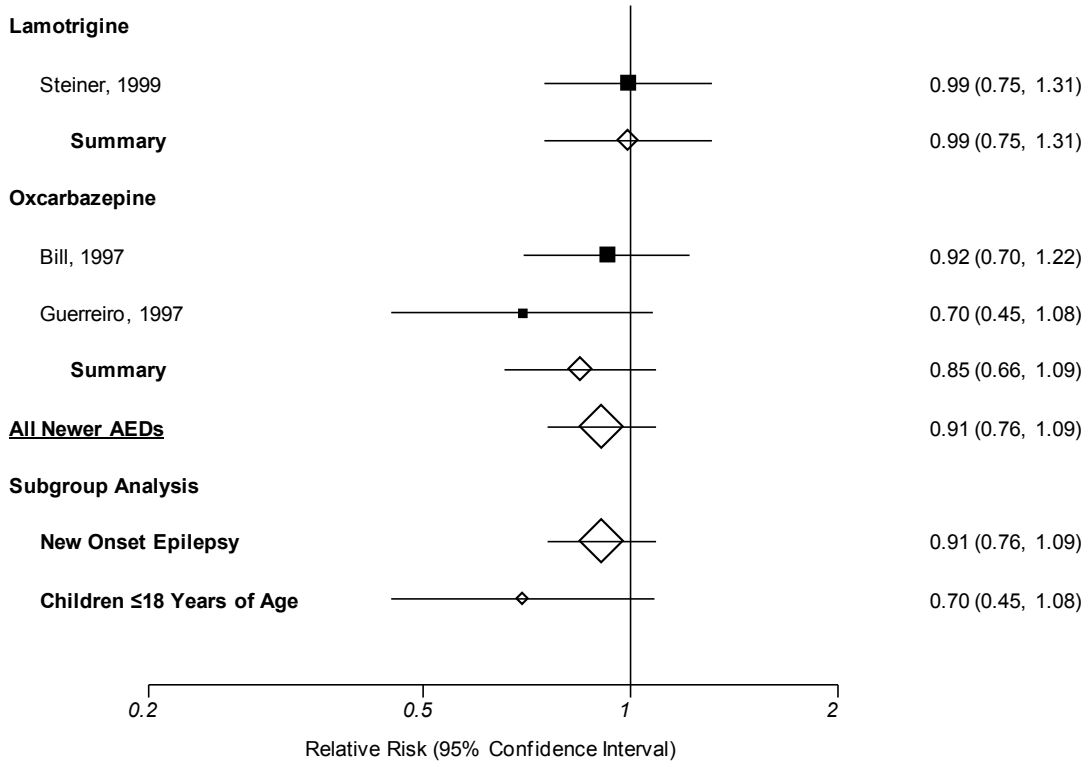
Figure 11. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared to controlled or sustained release carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

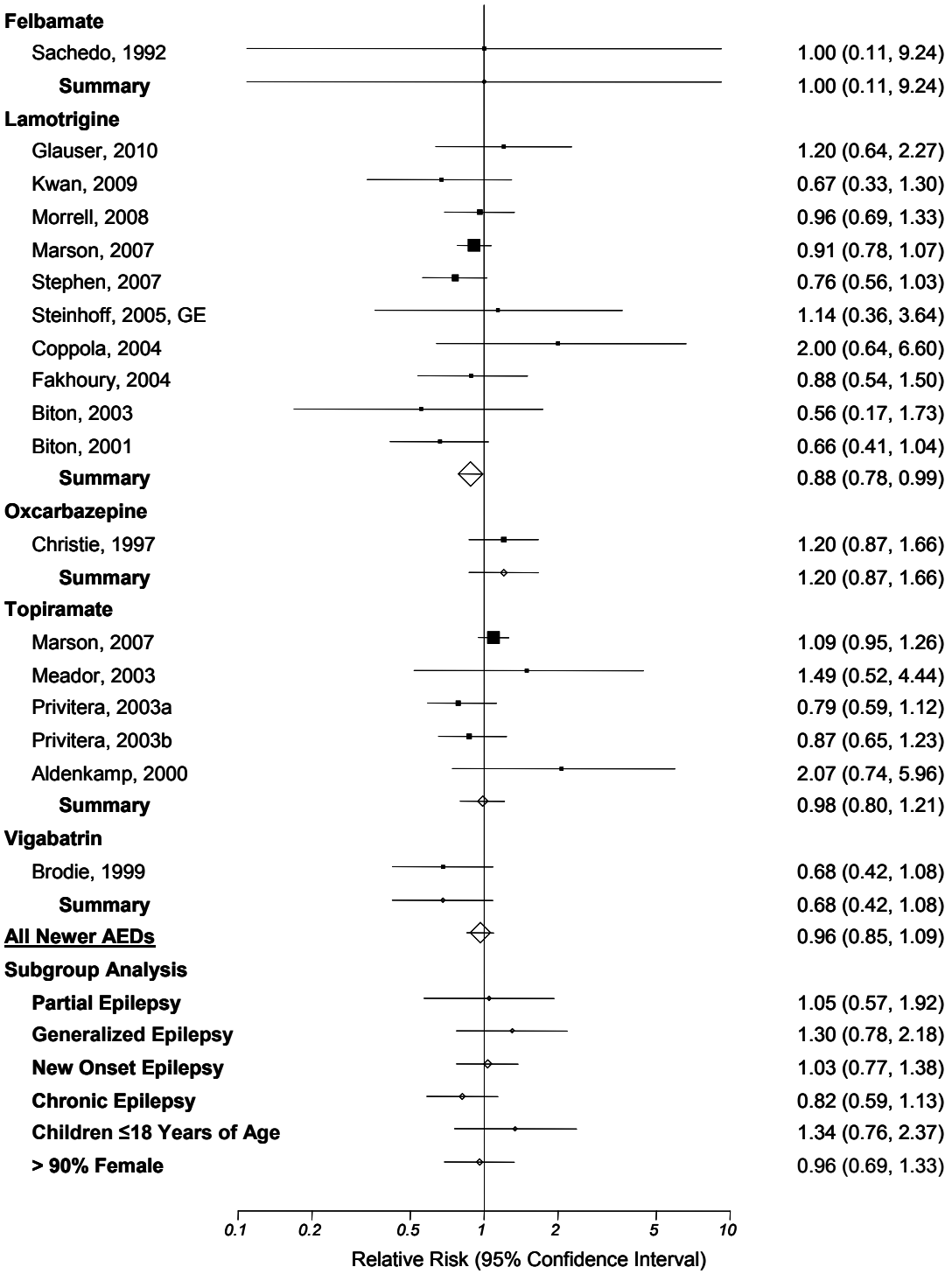
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 12. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



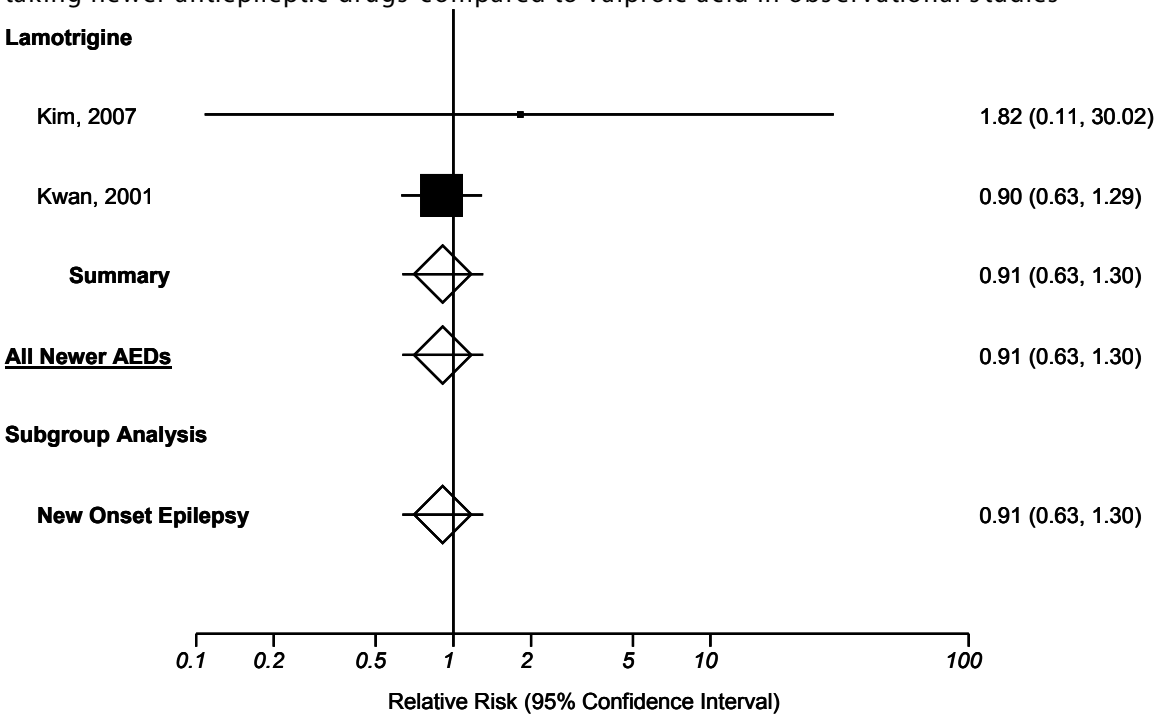
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 13. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

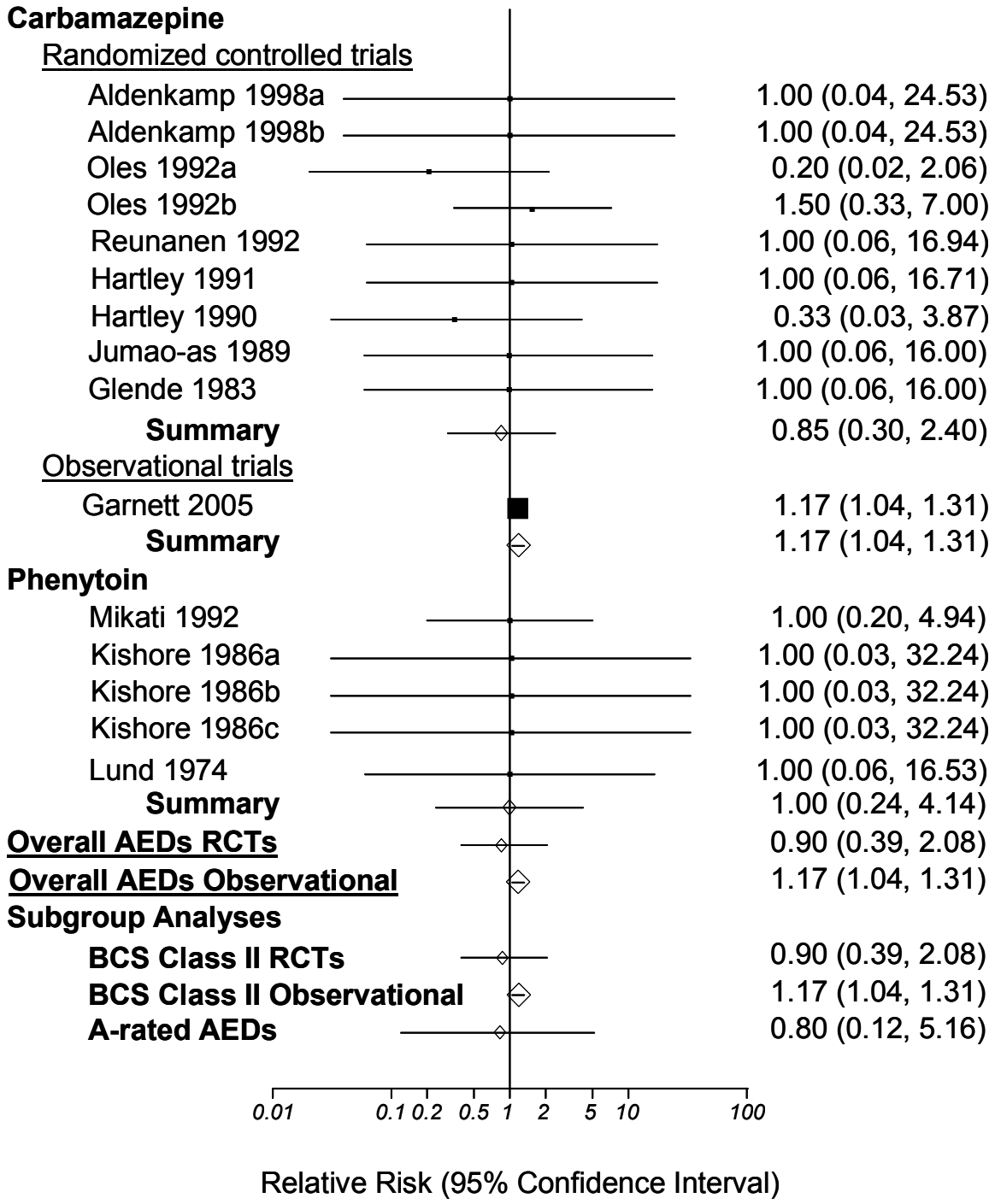
Figure 14. Composite forest plot of meta-analysis of overall withdrawal in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



Legend: AEDs=antiepileptic drugs

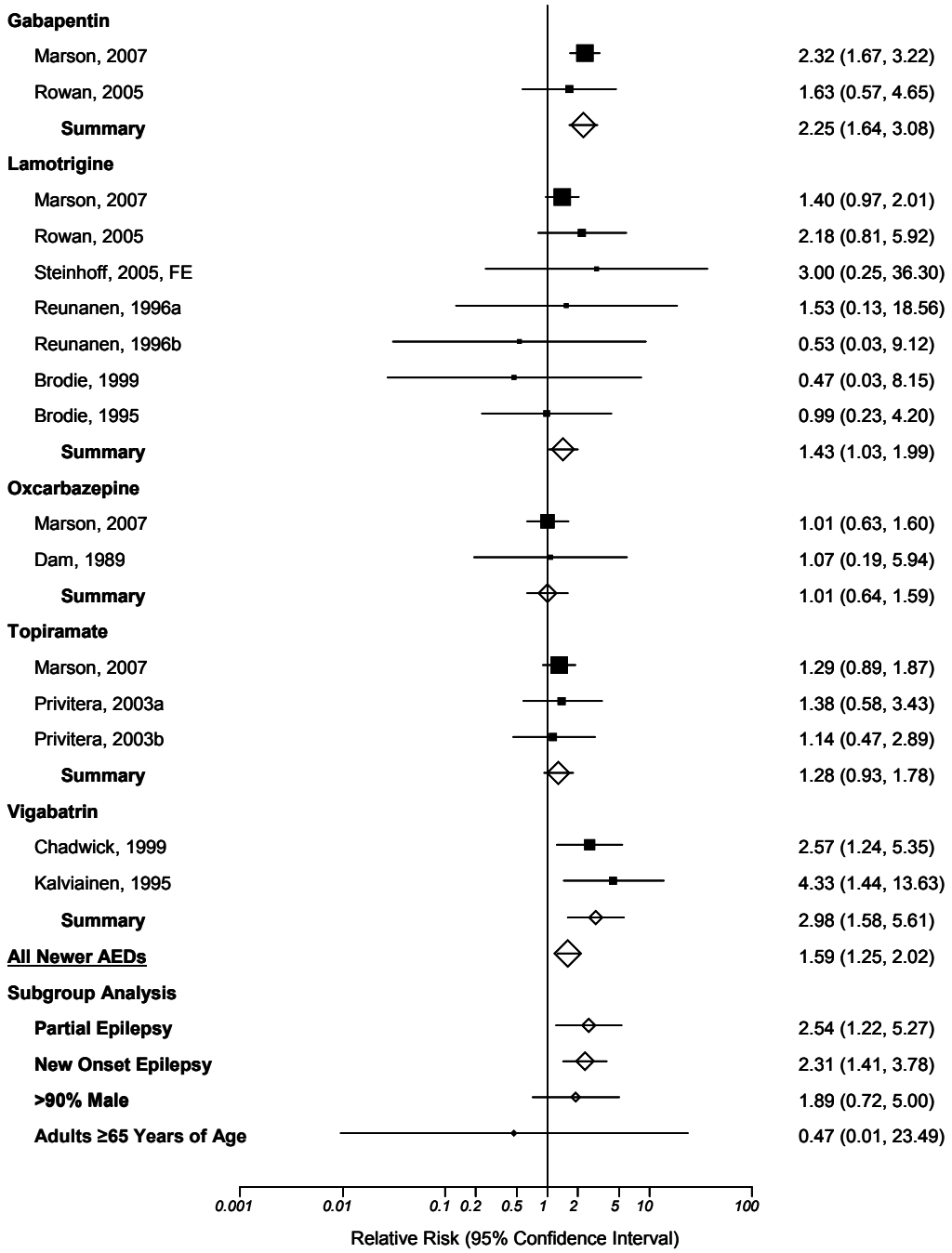
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 15. Composite forest plot of meta-analysis of withdrawals for any reason in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



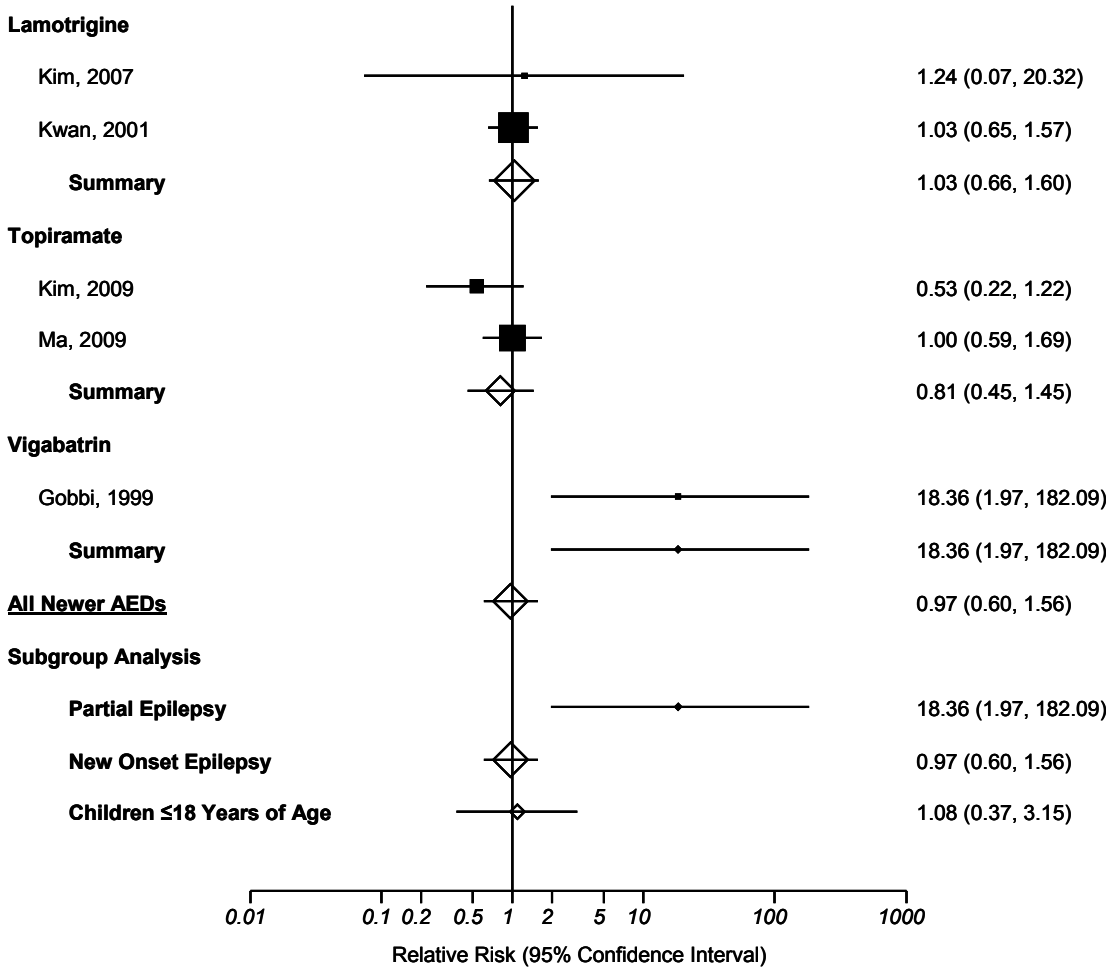
Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; RCTs=randomized controlled trials
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 16. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



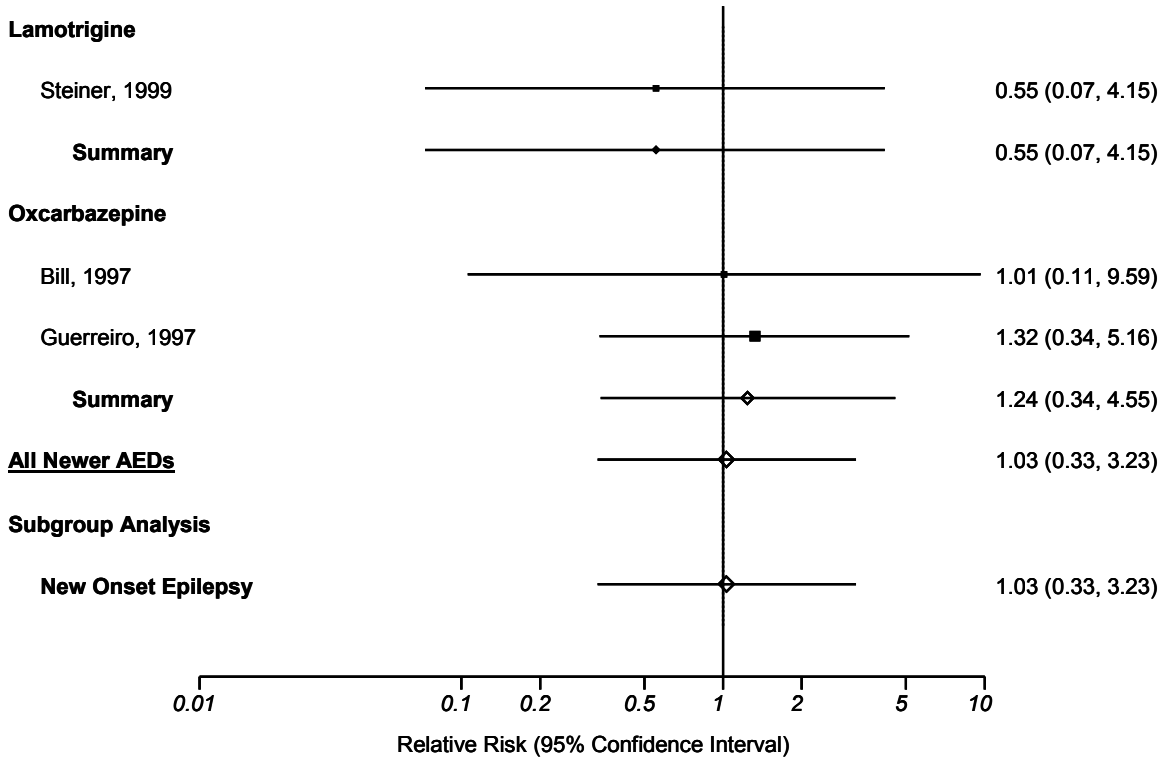
Legend: AEDs=antiepileptic drugs, FE=focalized epilepsy
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 17. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

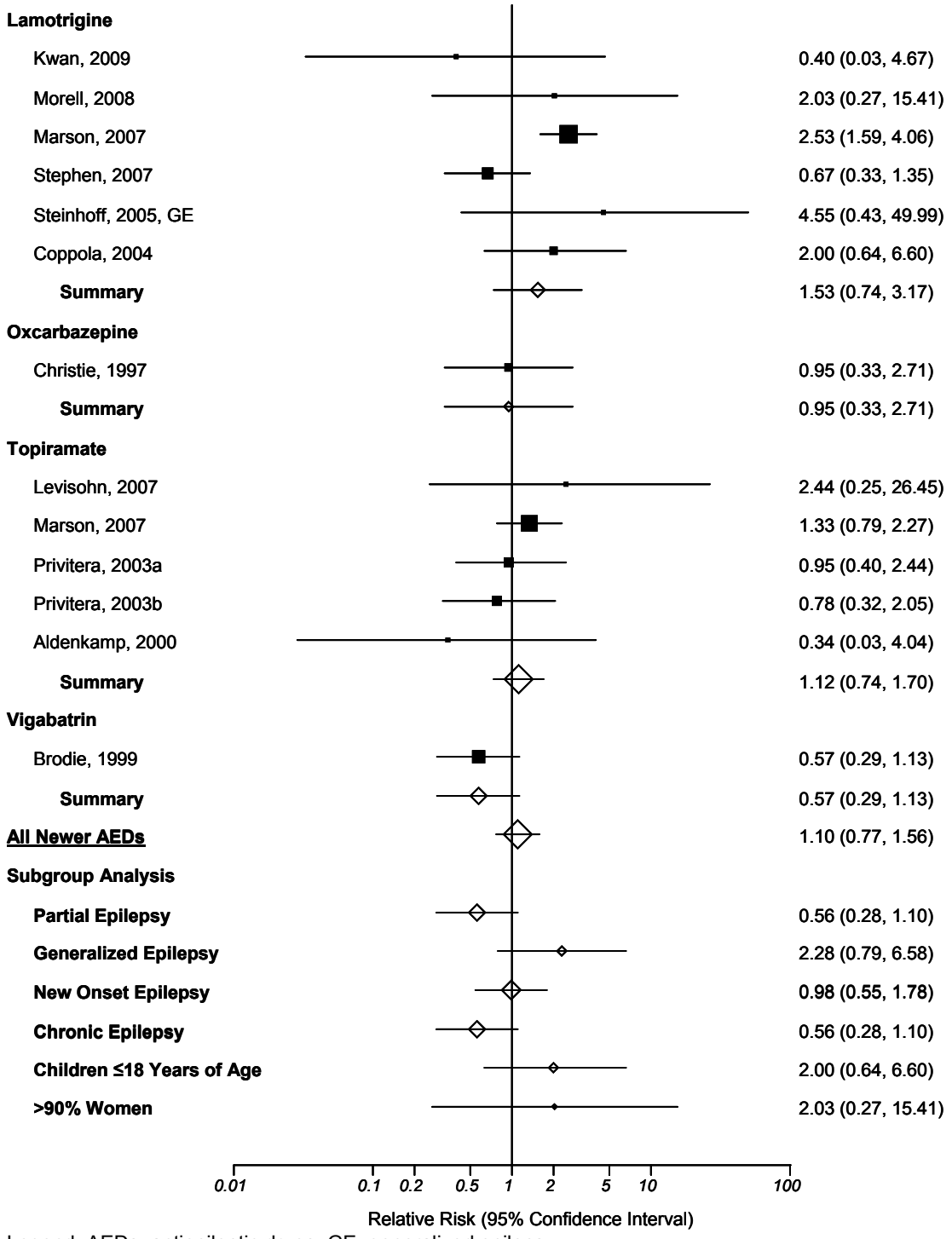
Figure 18. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

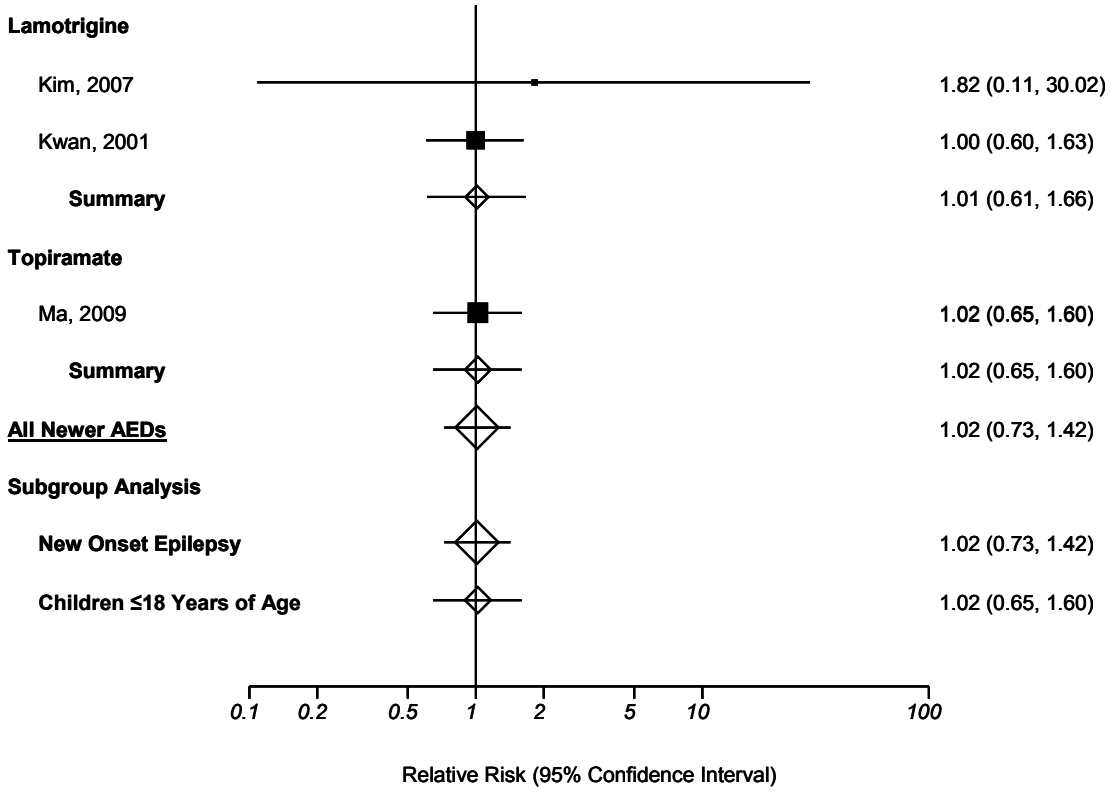
Figure 19. Composite forest plot of meta-analysis of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs, GE=generalized epilepsy

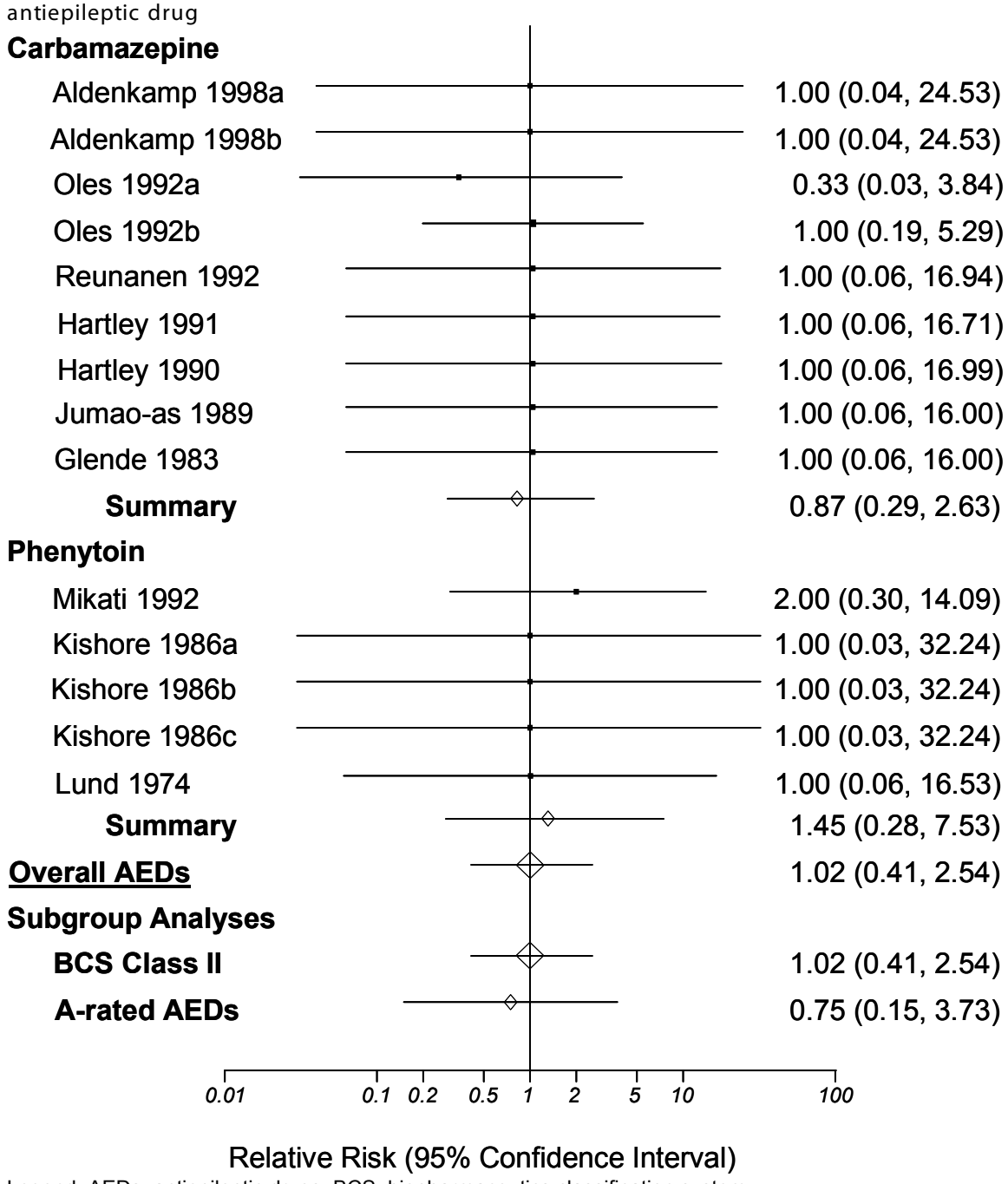
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 20. Composite forest plot of withdrawal due to lack of efficacy in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

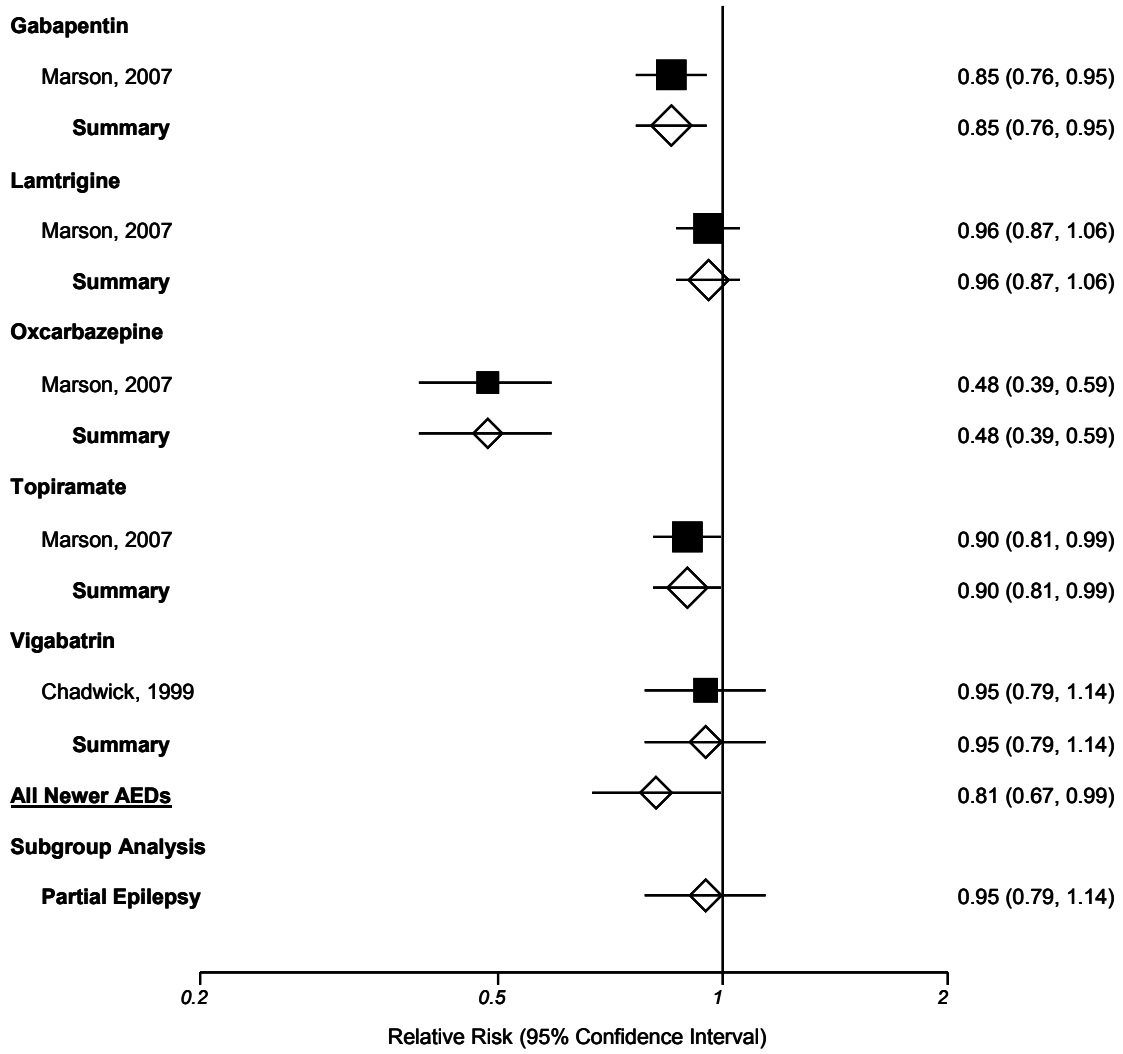
Figure 21. Composite forest plot of meta-analysis of withdrawals due to lack of efficacy in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system

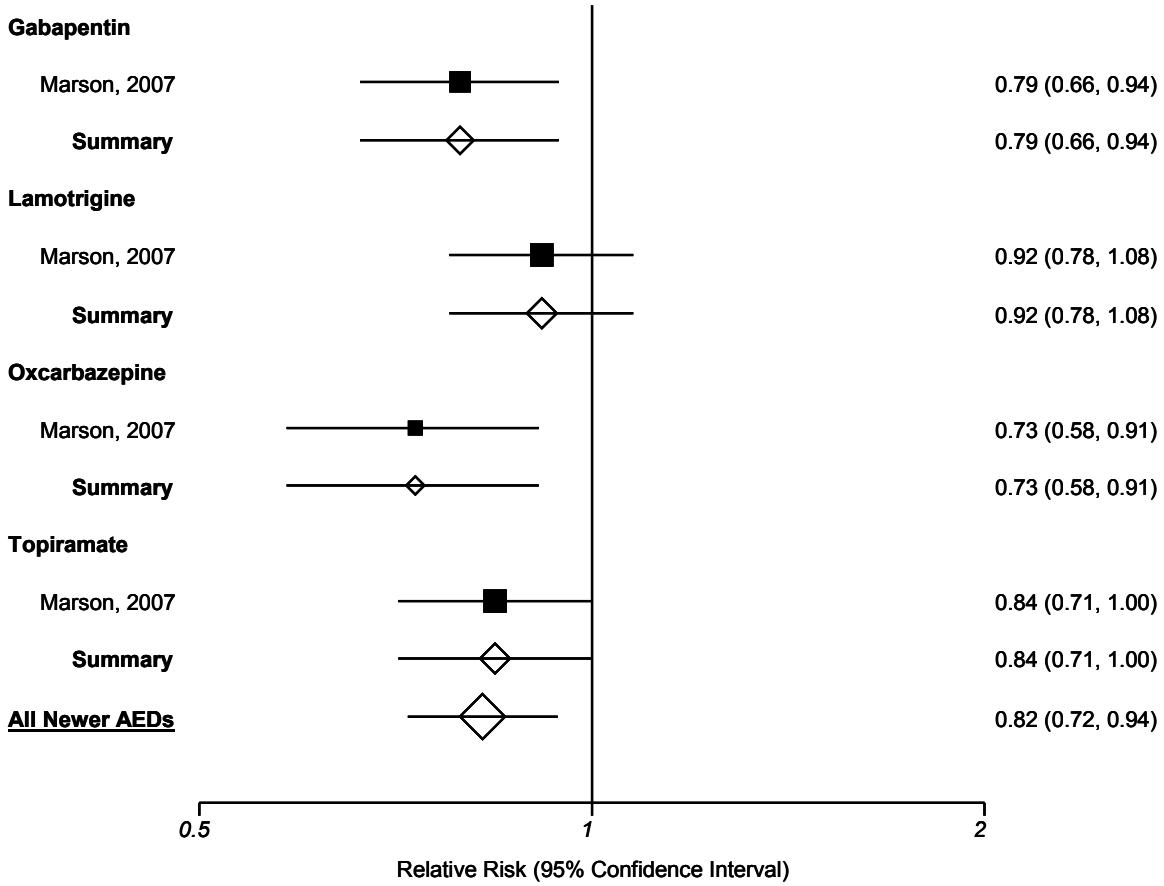
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 22. Composite forest plot of meta-analysis of twelve-month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

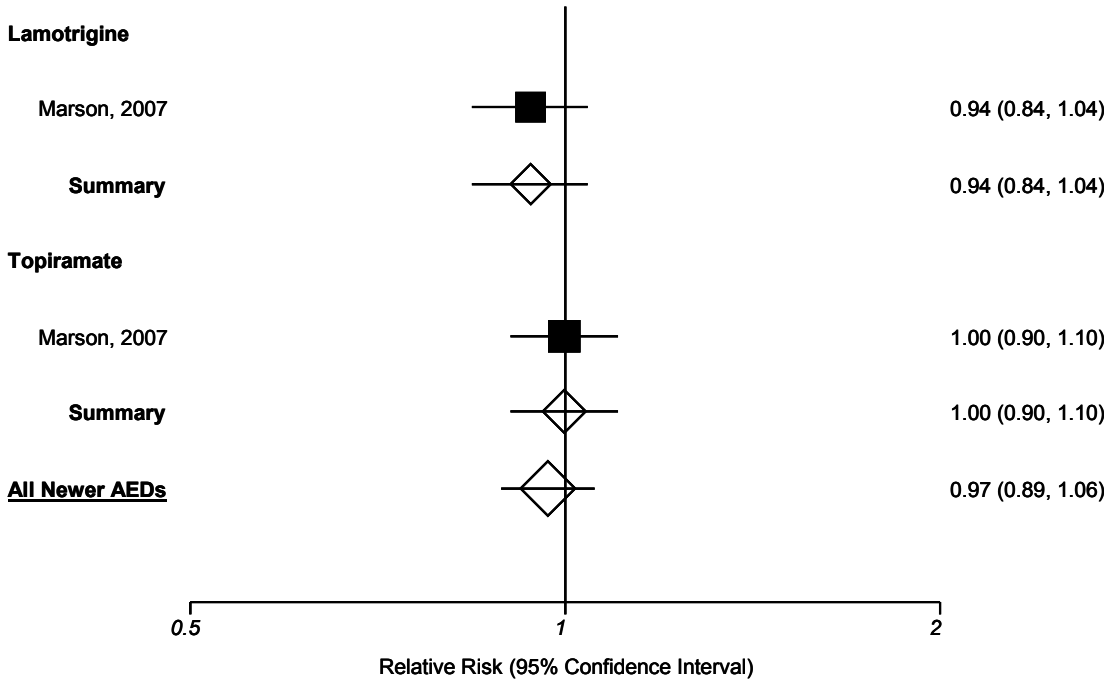
Figure 23. Composite forest plot of meta-analysis of twenty-four month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

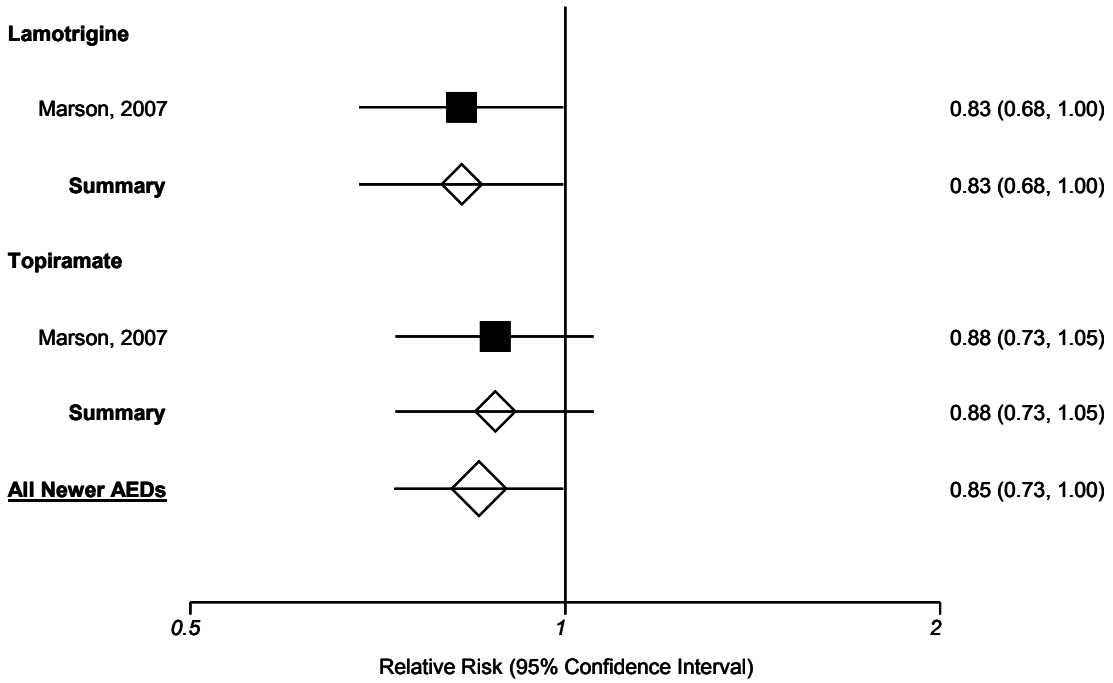
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 24. Composite forest plot of meta-analysis of twelve-month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



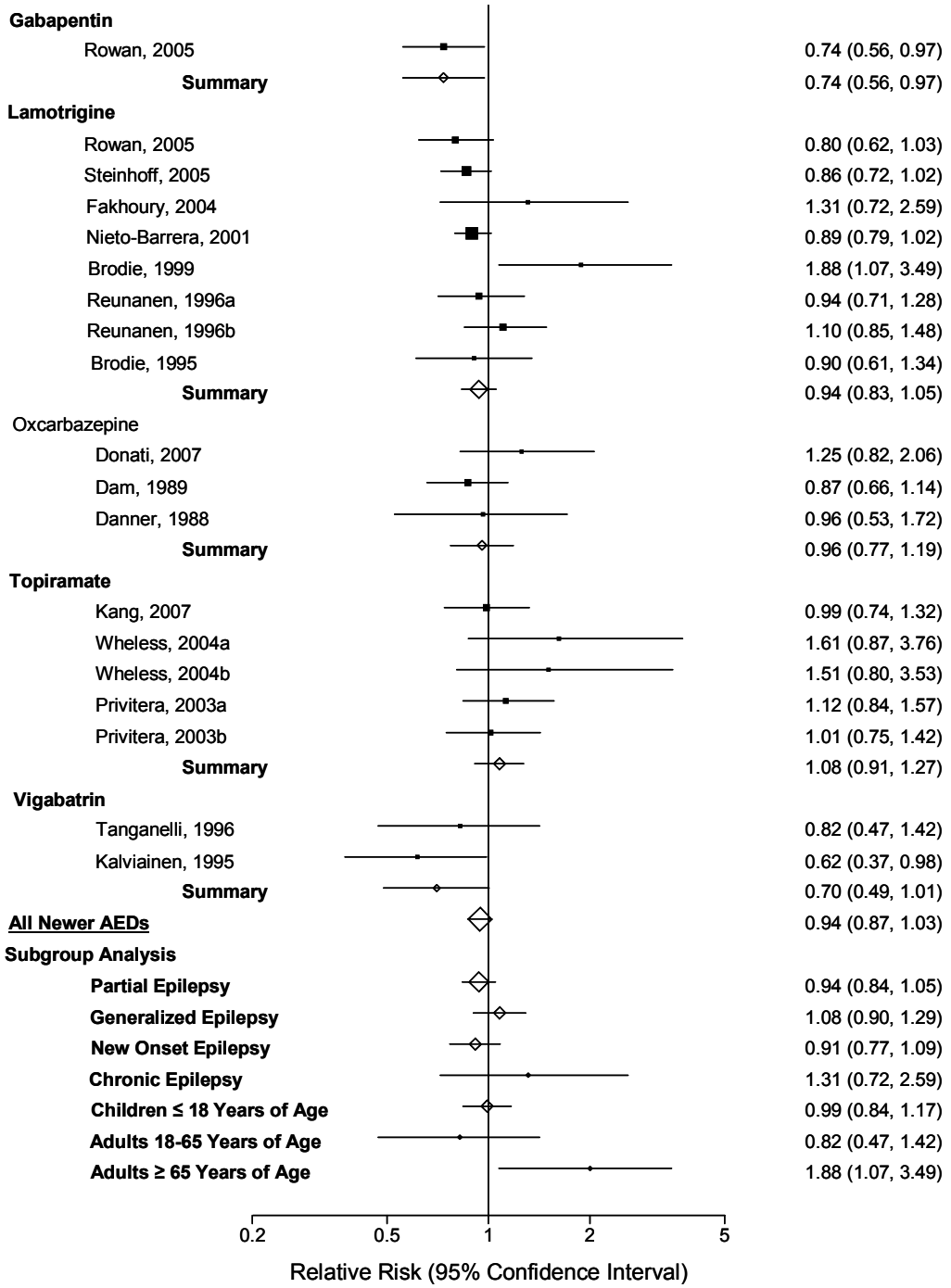
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 25. Composite forest plot of meta-analysis of twenty-four month seizure remission in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

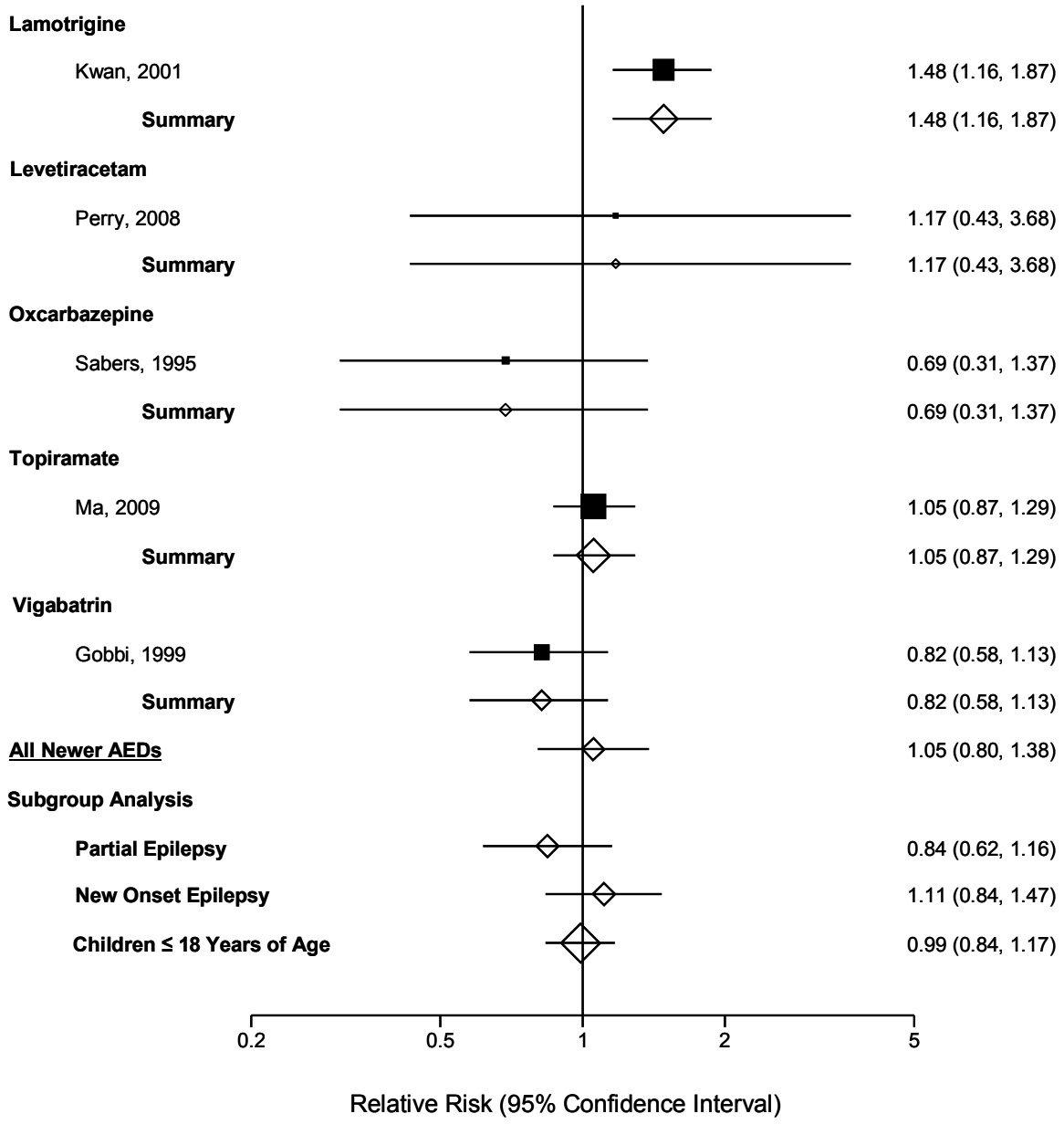
Figure 26. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

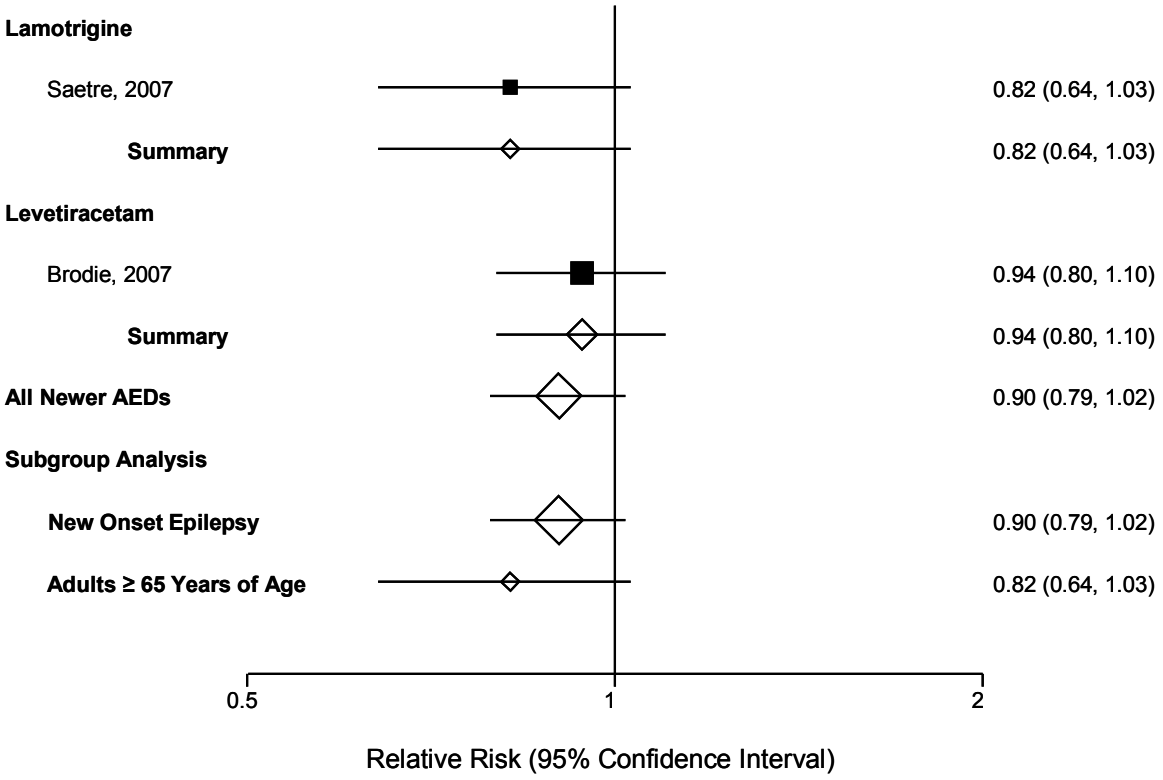
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 27. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



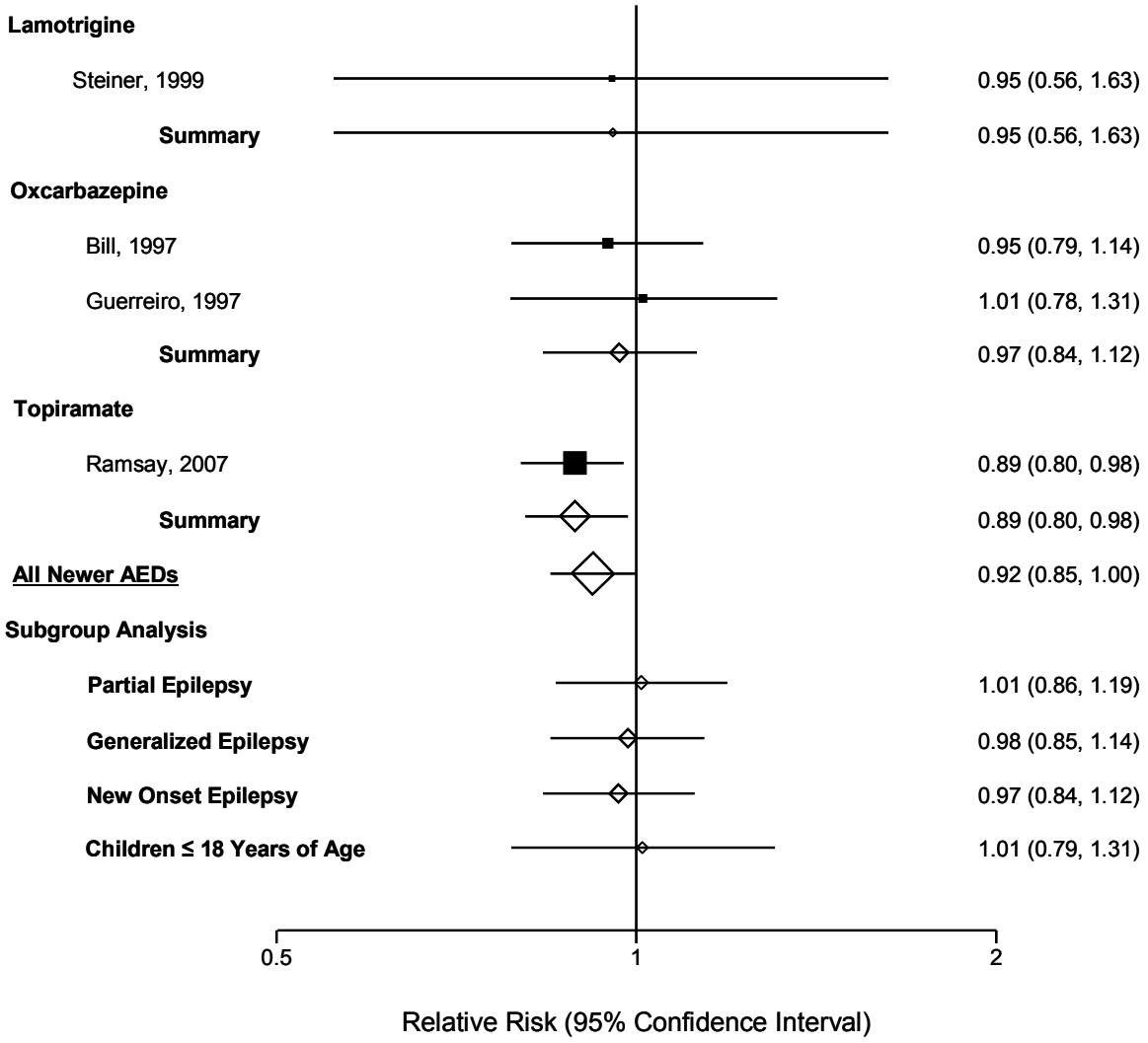
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 28. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared to controlled or sustained release carbamazepine in controlled clinical trials



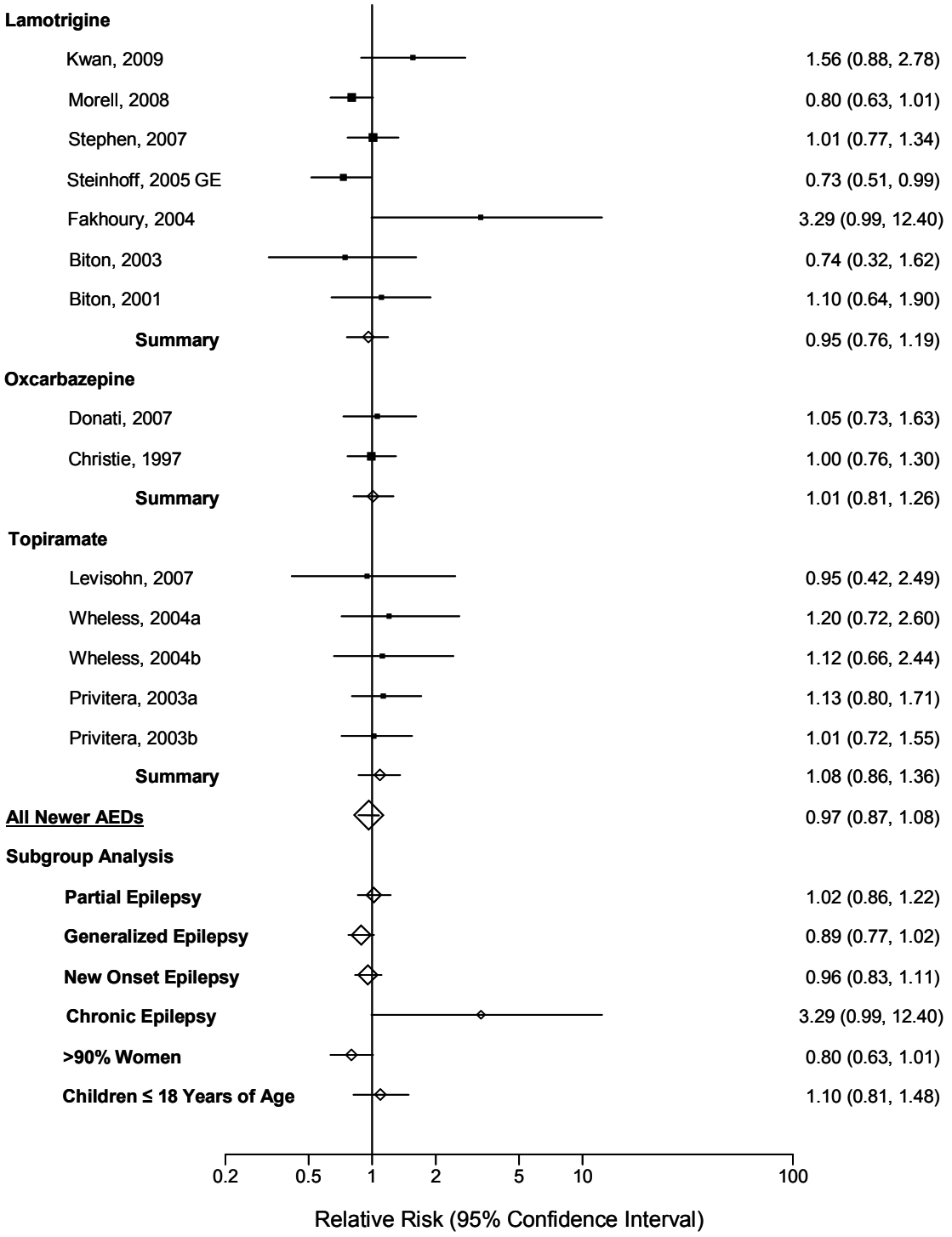
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial

Figure 29. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

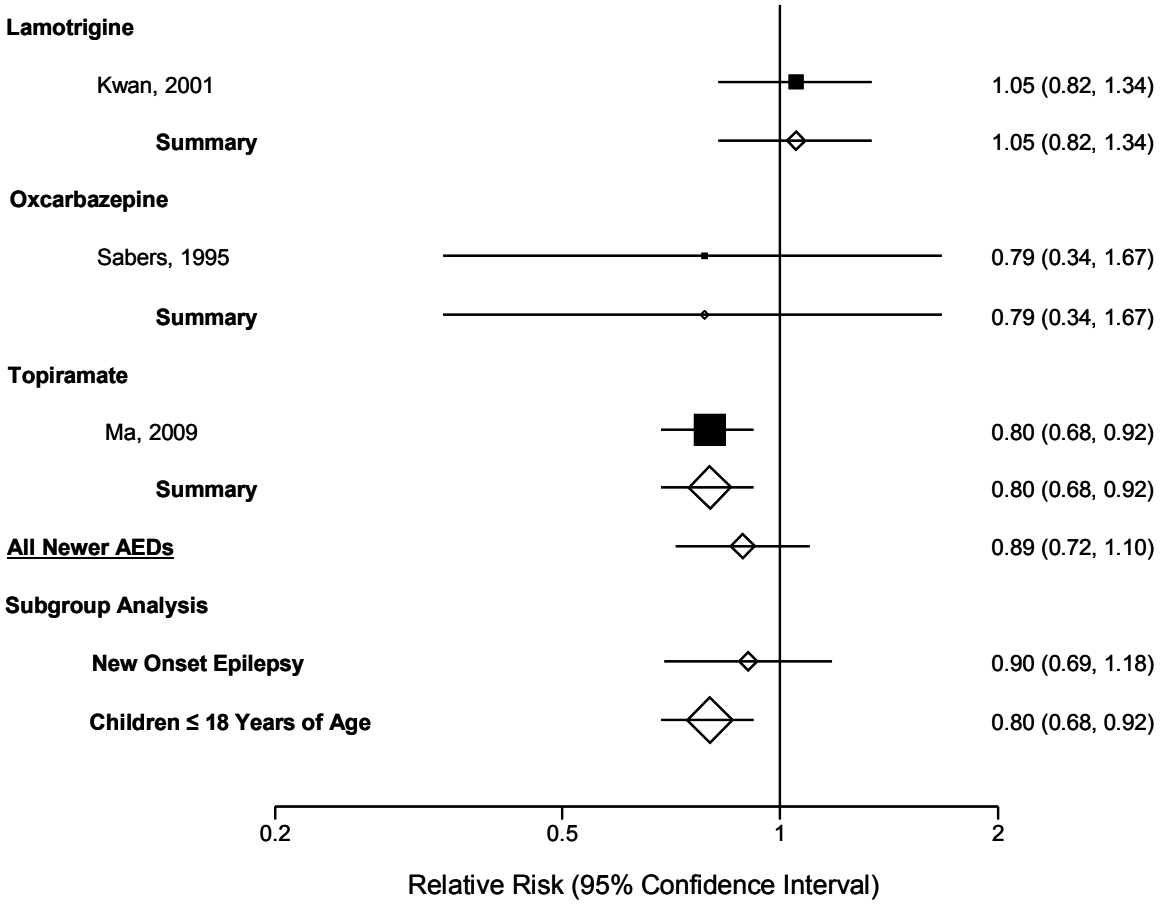
Figure 30. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

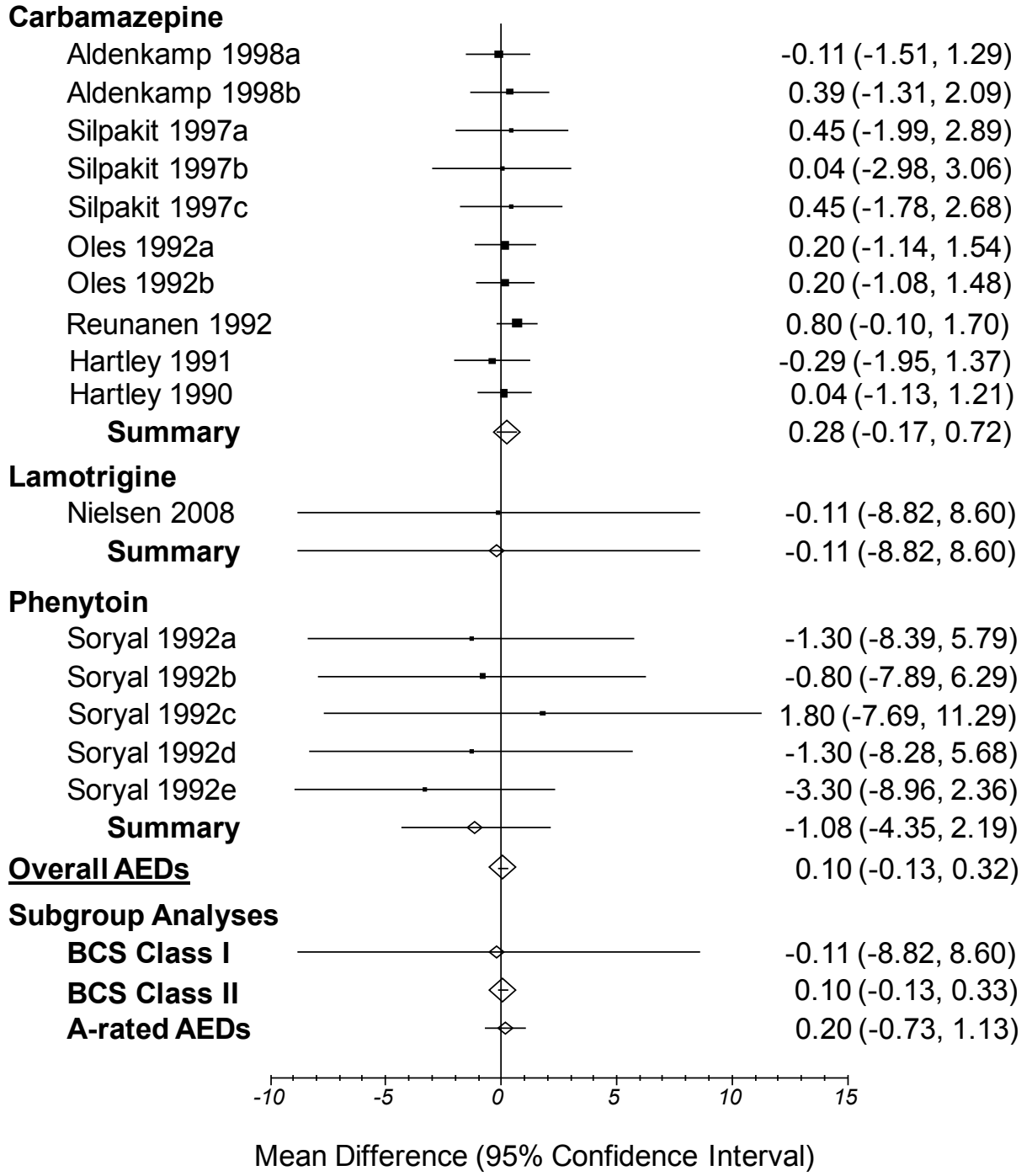
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 31. Composite forest plot of meta-analysis of seizure freedom for study duration in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



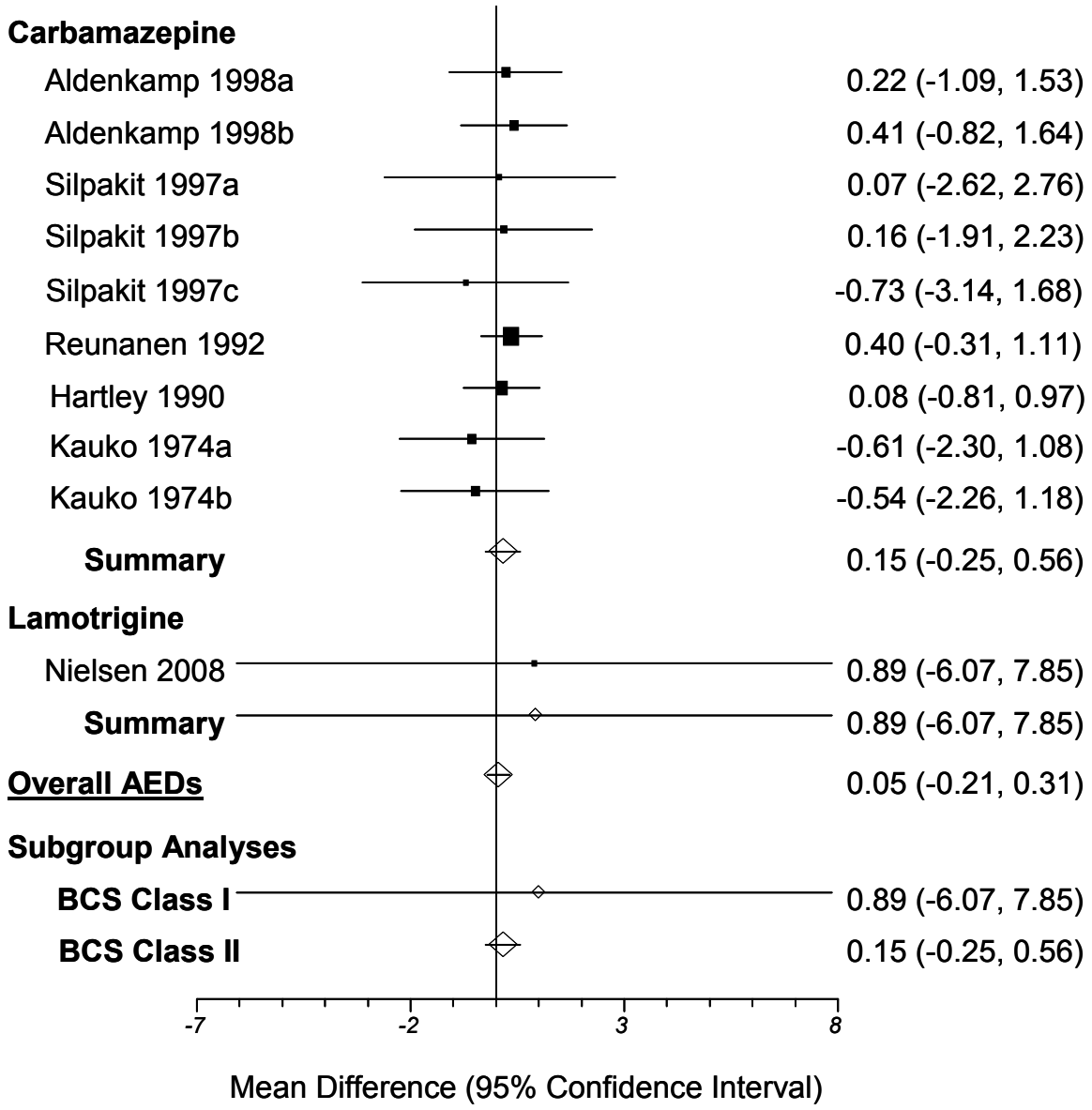
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 32. Composite forest plot of meta-analysis of maximum concentration (Cmax) in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



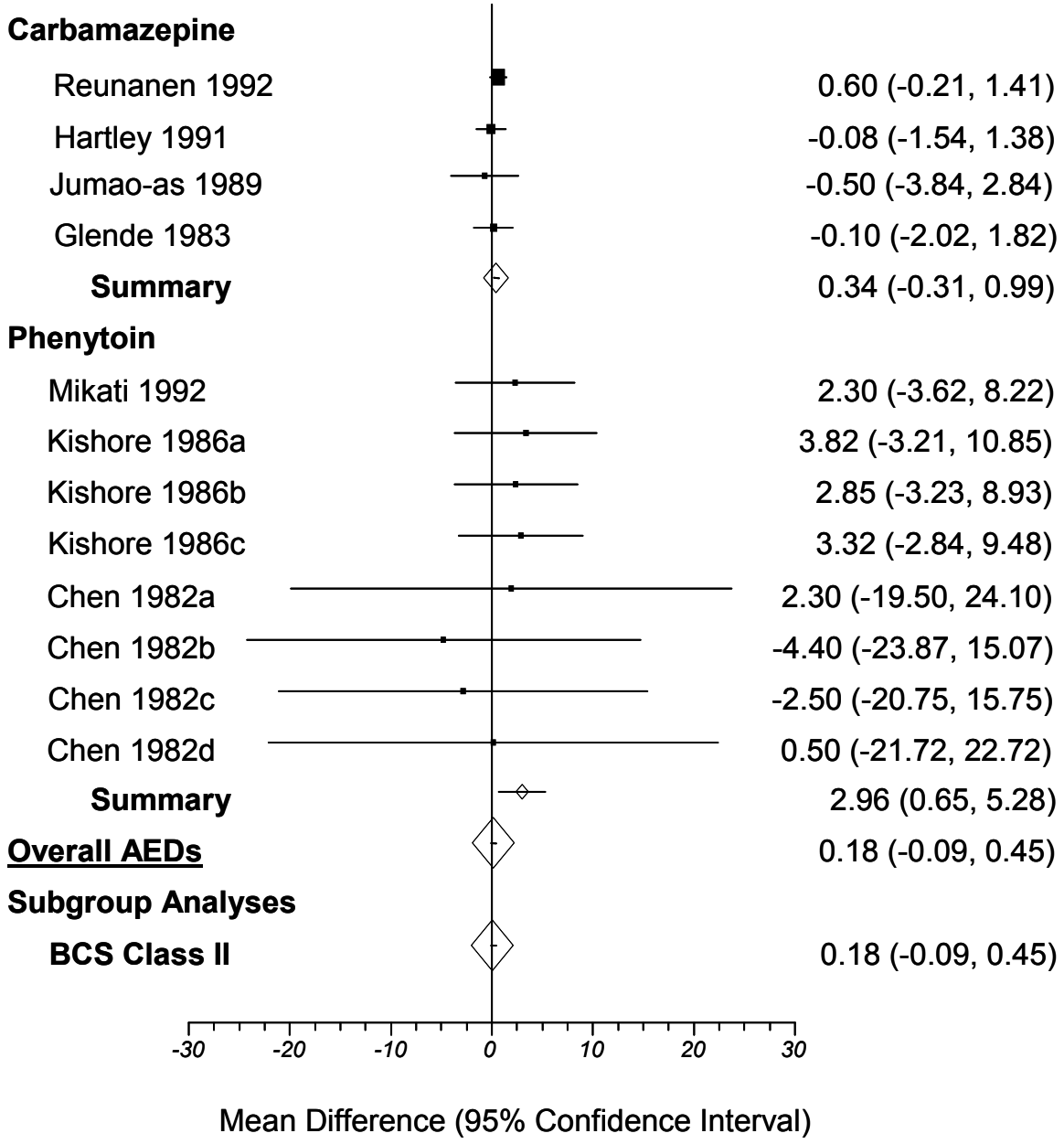
Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; Cmax=maximum concentration
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 33. Composite forest plot of meta-analysis of minimum concentration (Cmin) in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



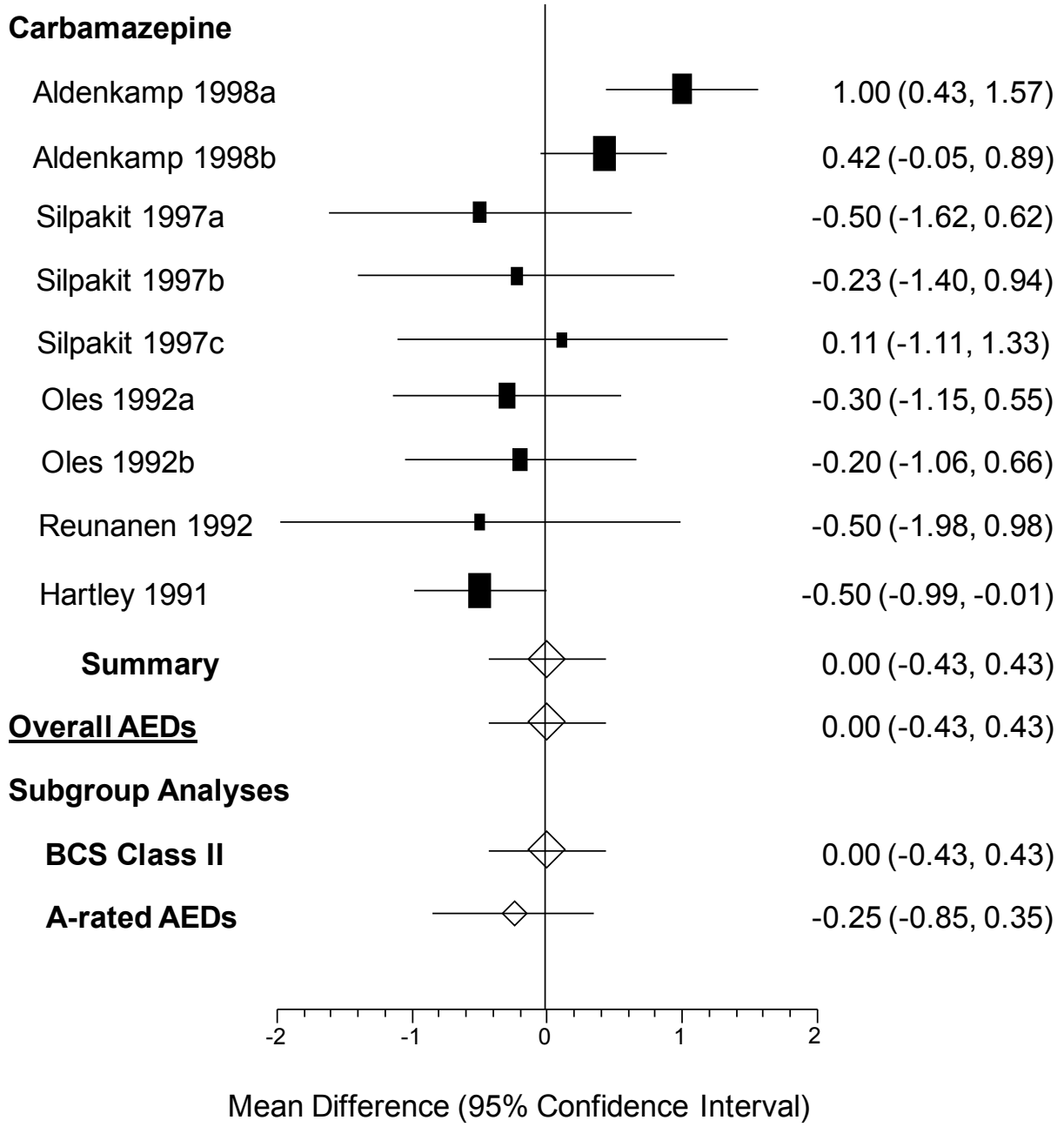
Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; Cmin=minimum concentration
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 34. Composite forest plot of meta-analysis of steady-state concentration (Css) in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; Css=concentration at steady-state
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

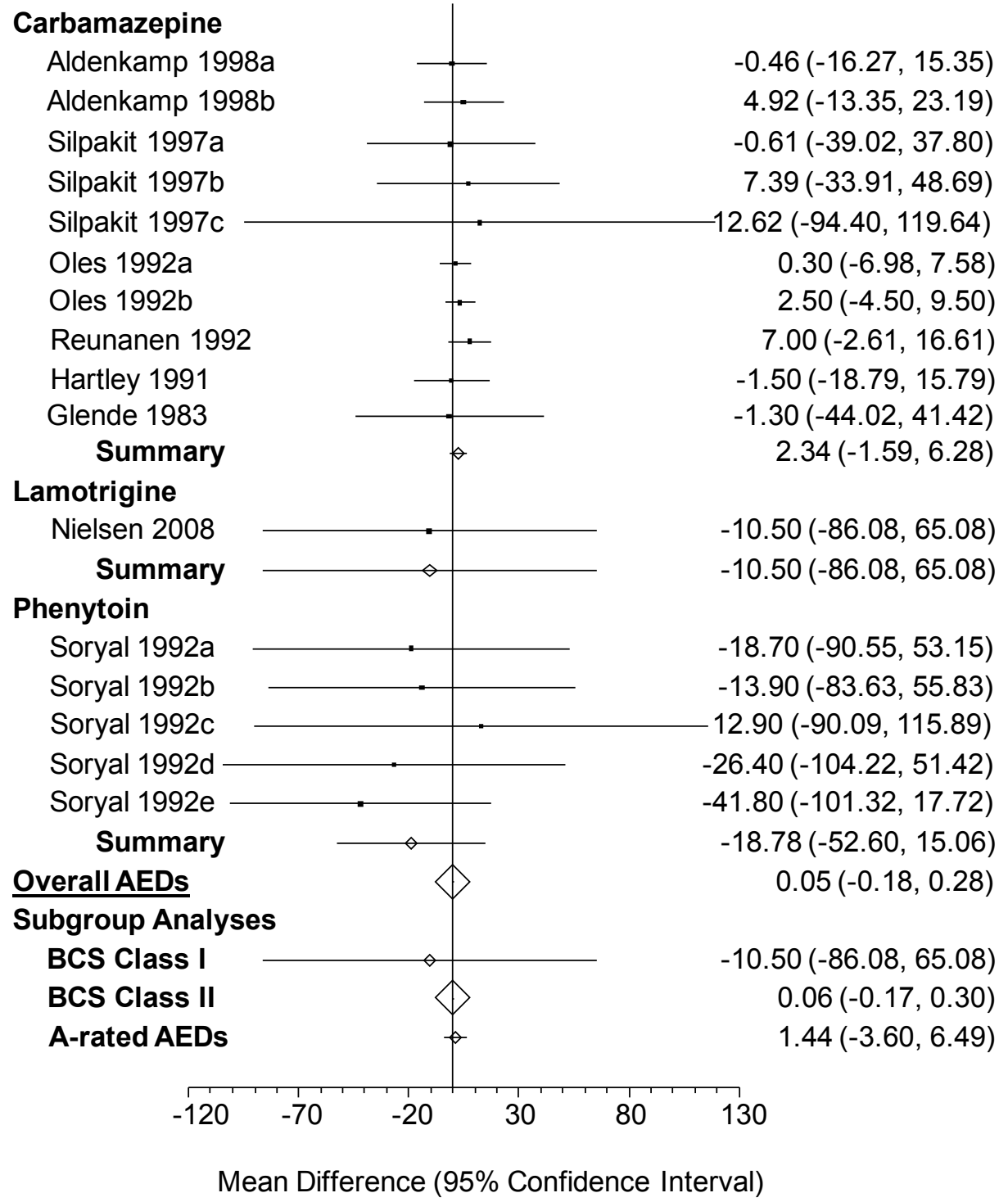
Figure 35. Composite forest plot of meta-analysis of time to maximum concentration (Tmax) in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; Tmax=time to maximum concentration.

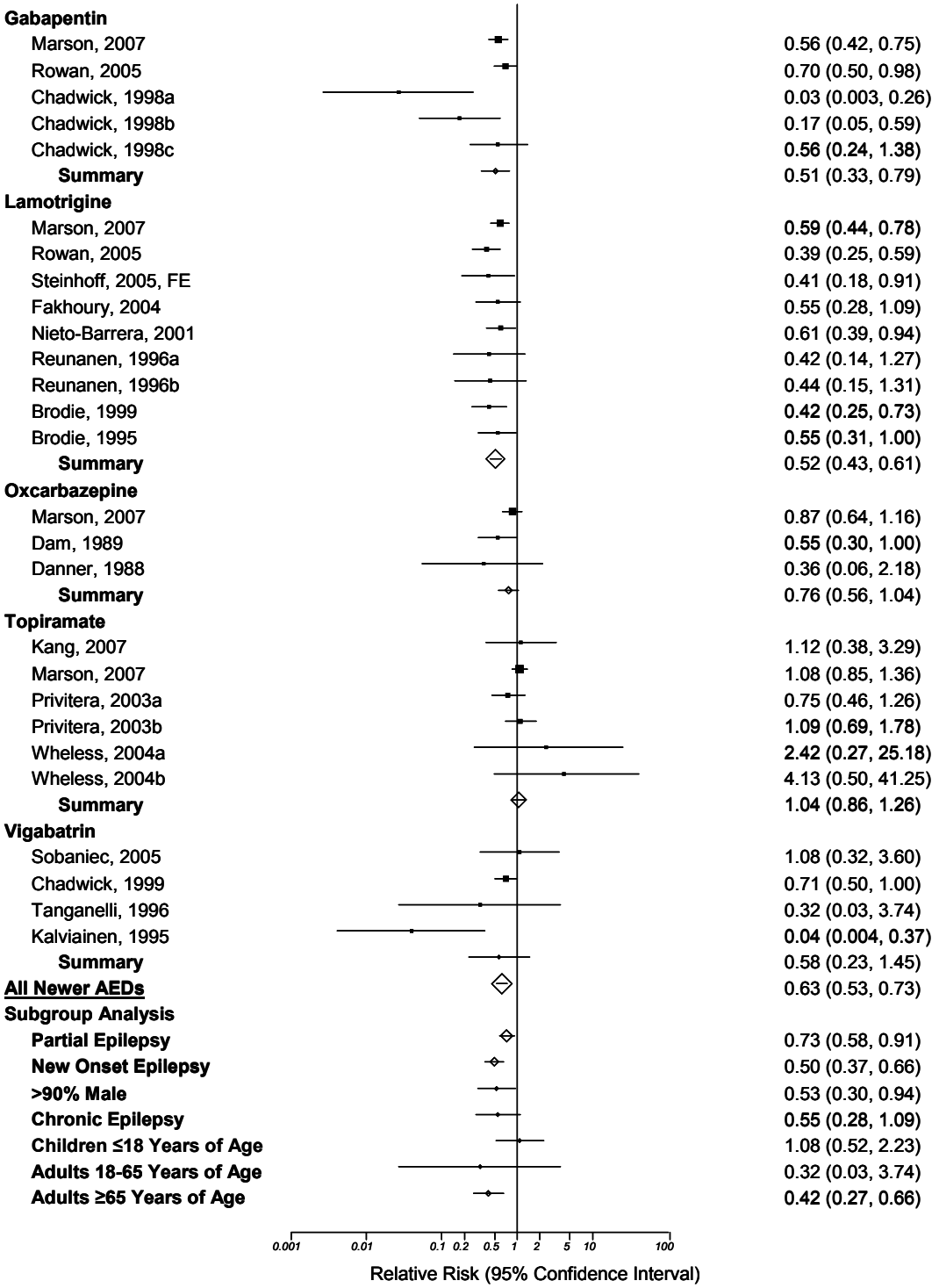
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 36. Composite forest plot of meta-analysis of area under the curve (AUC) in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system; AUC=area under the curve
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

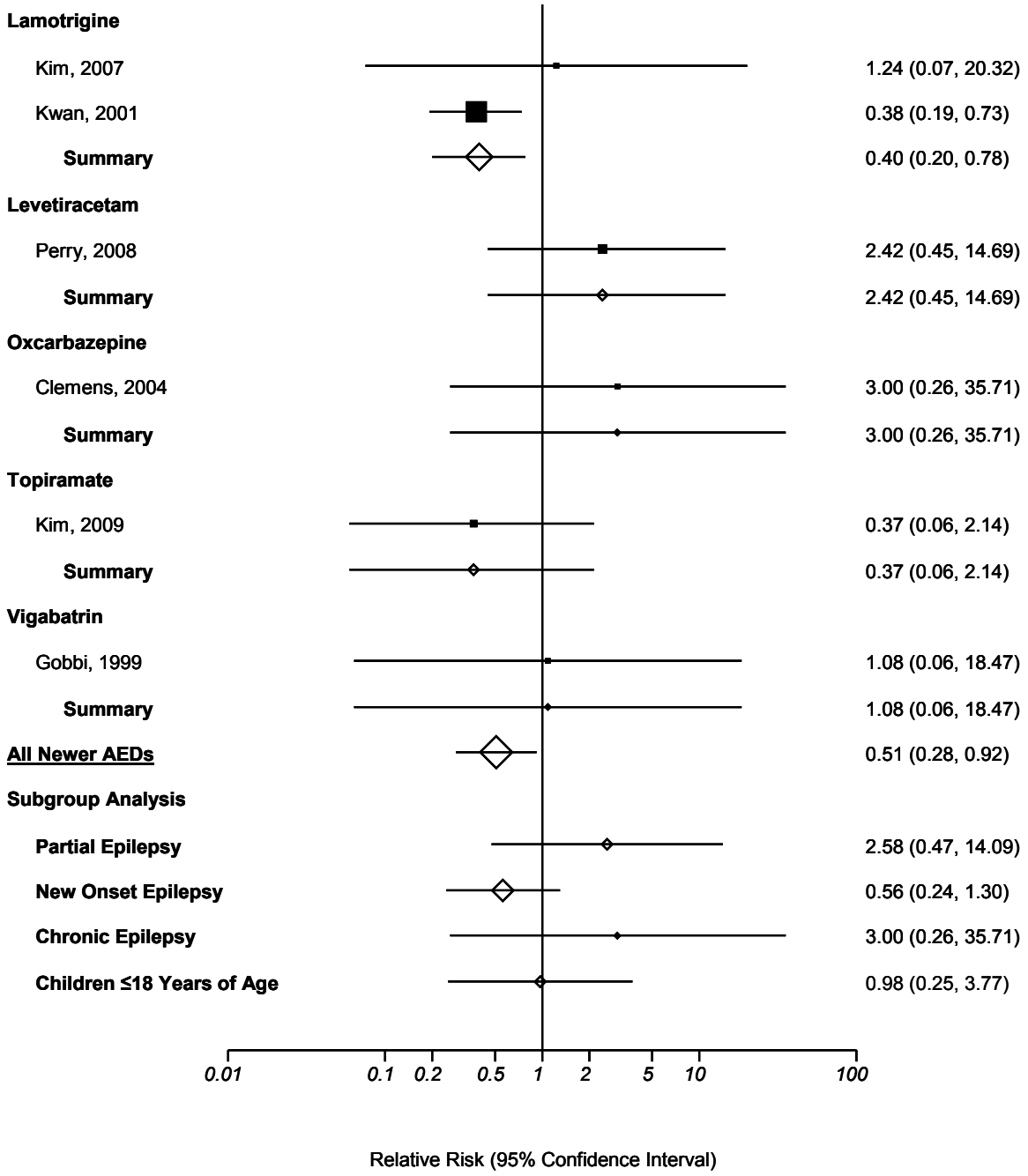
Figure 37. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs, FE=focalized epilepsy

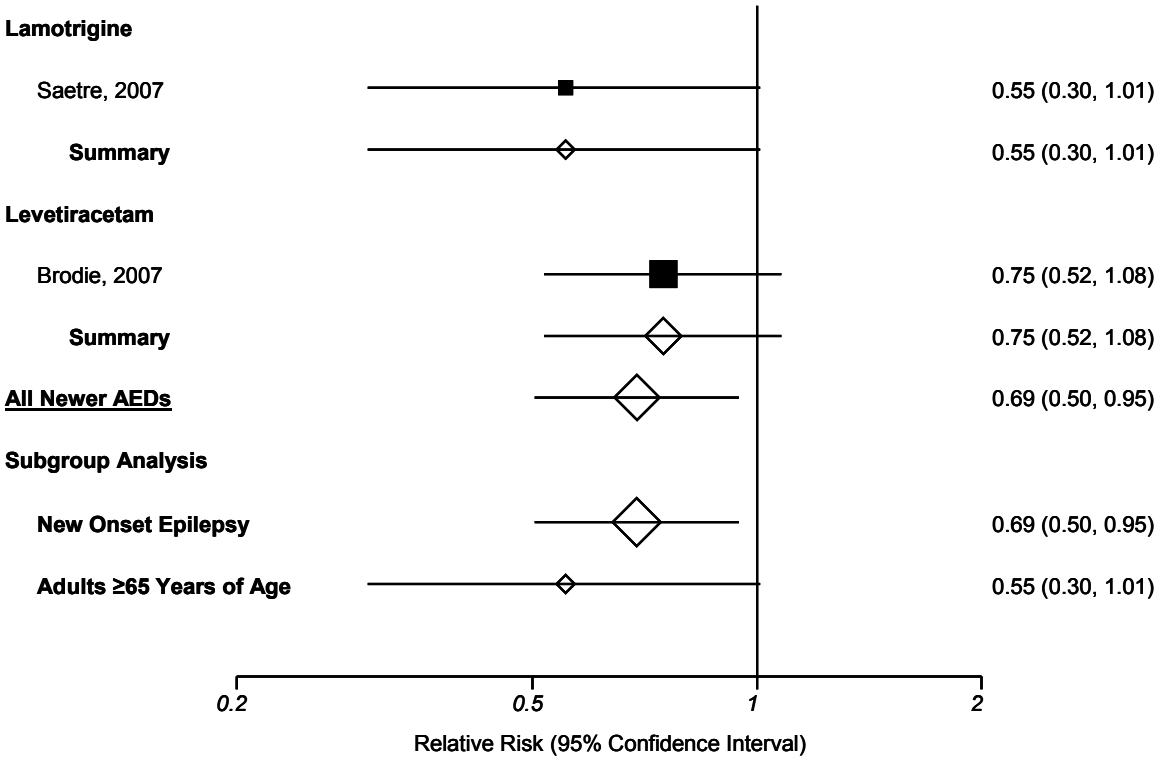
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 38. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



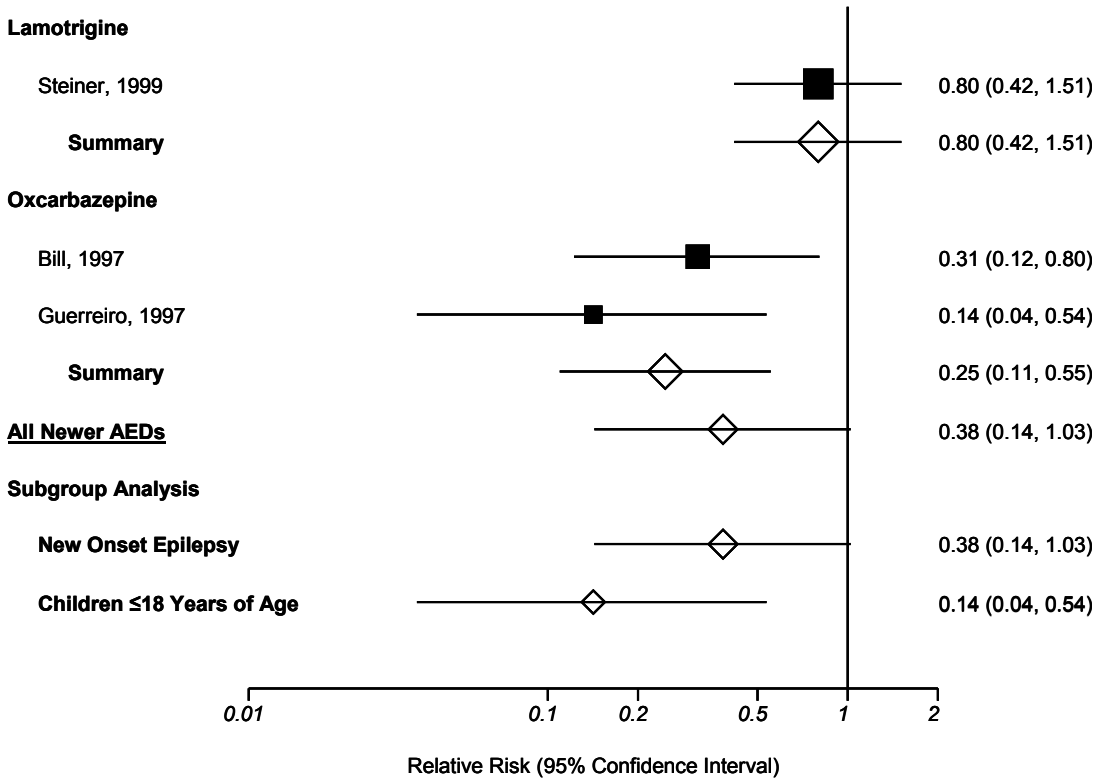
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 39. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared to controlled or sustained release carbamazepine in controlled clinical trials



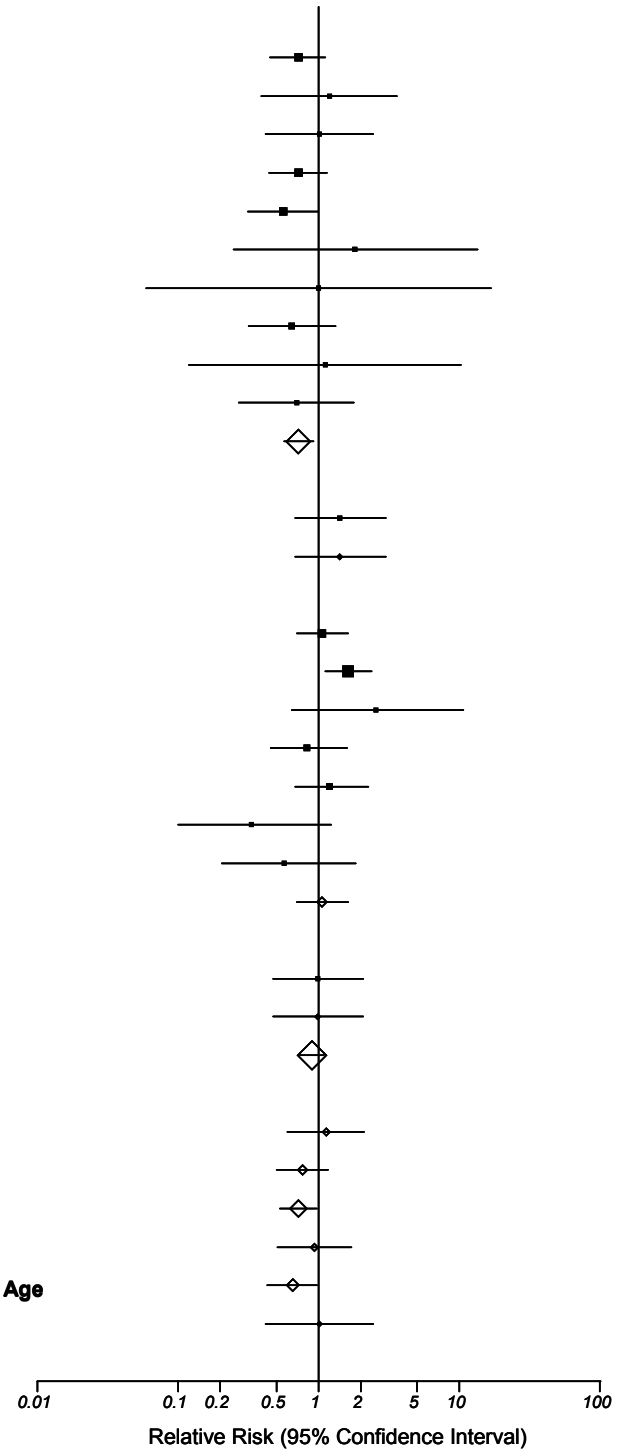
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 40. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

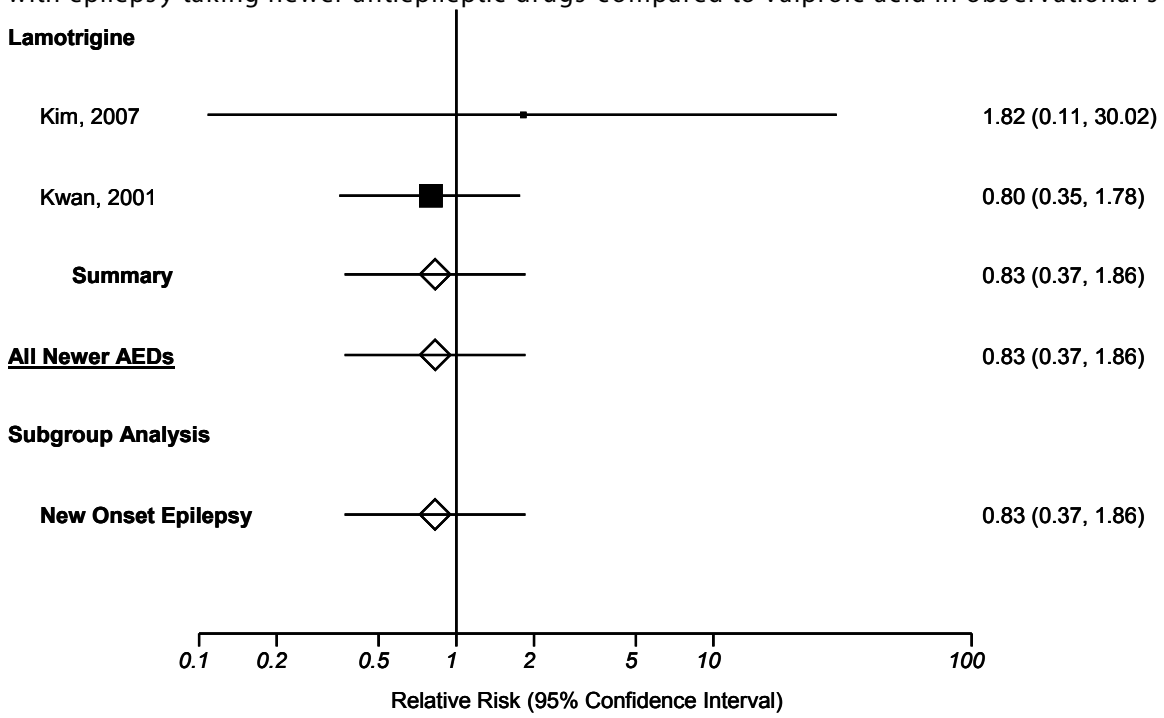
Figure 41. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs, GE=generalized epilepsy

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

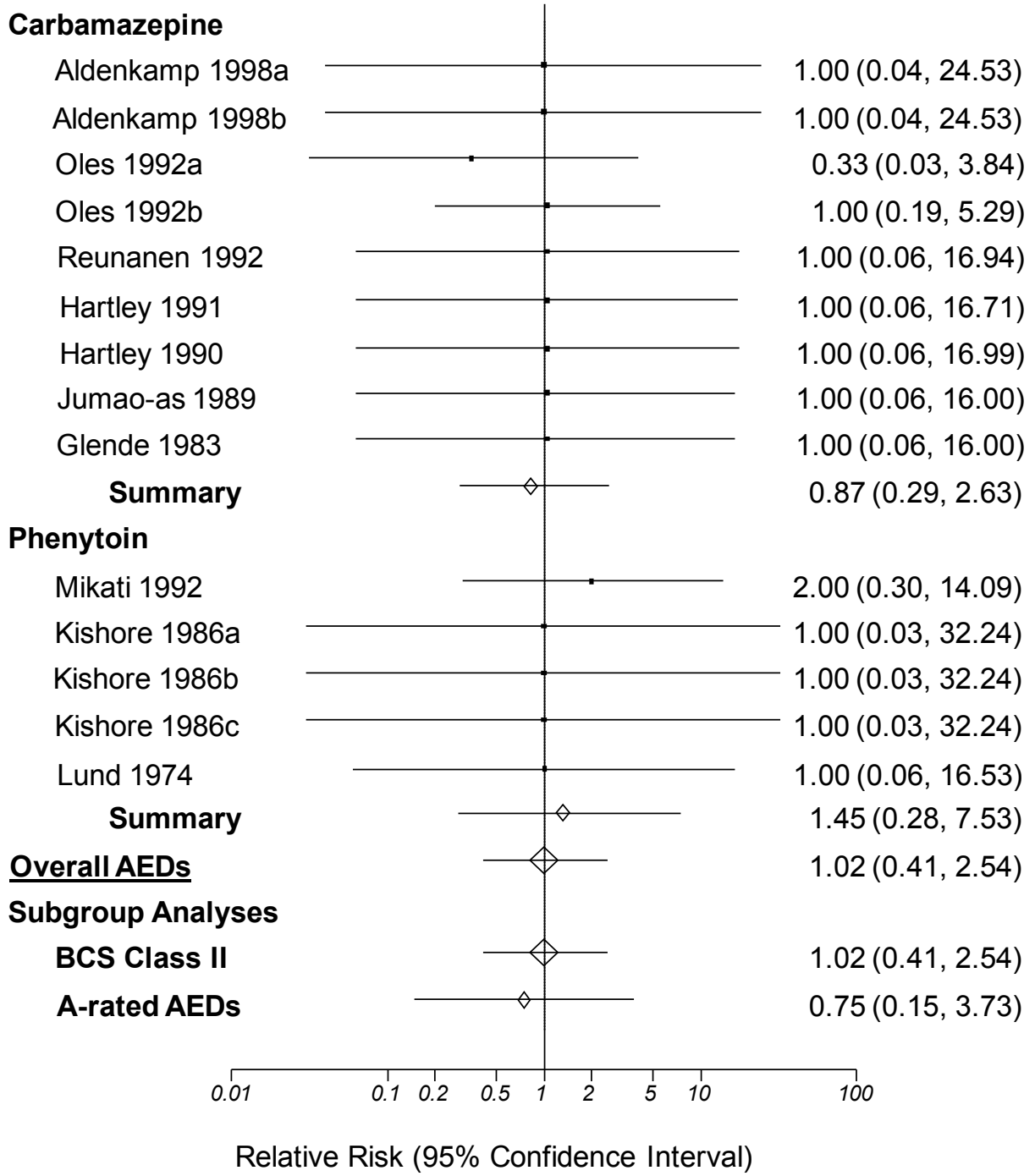
Figure 42. Composite forest plot of meta-analysis of withdrawal due to adverse events in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



Legend: AEDs=antiepileptic drugs

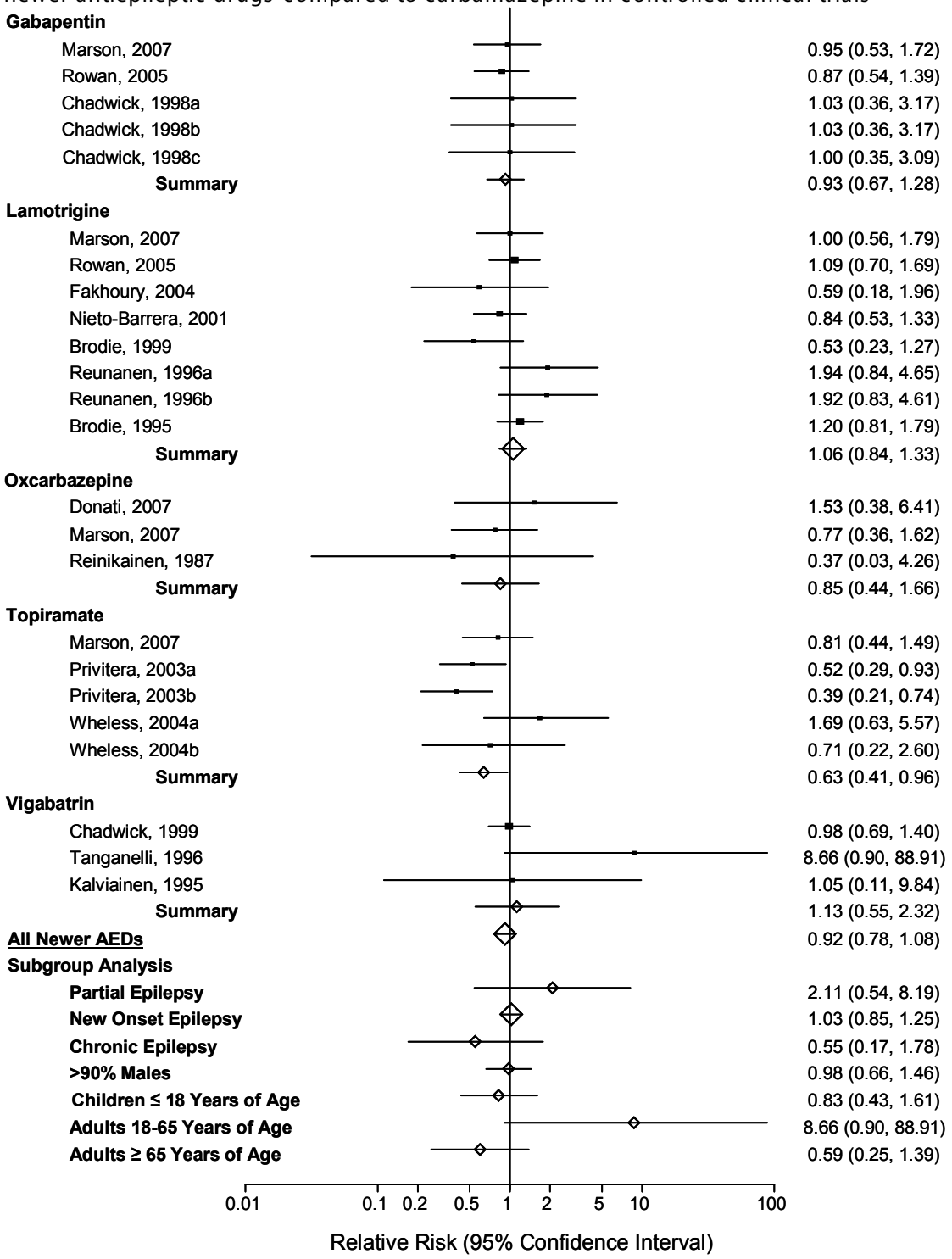
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 43. Composite forest plot of meta-analysis of withdrawals due to adverse events in patients with epilepsy taking generic antiepileptic drugs compared to the corresponding innovator antiepileptic drug



Legend: AEDs=antiepileptic drugs; BCS=biopharmaceutics classification system
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

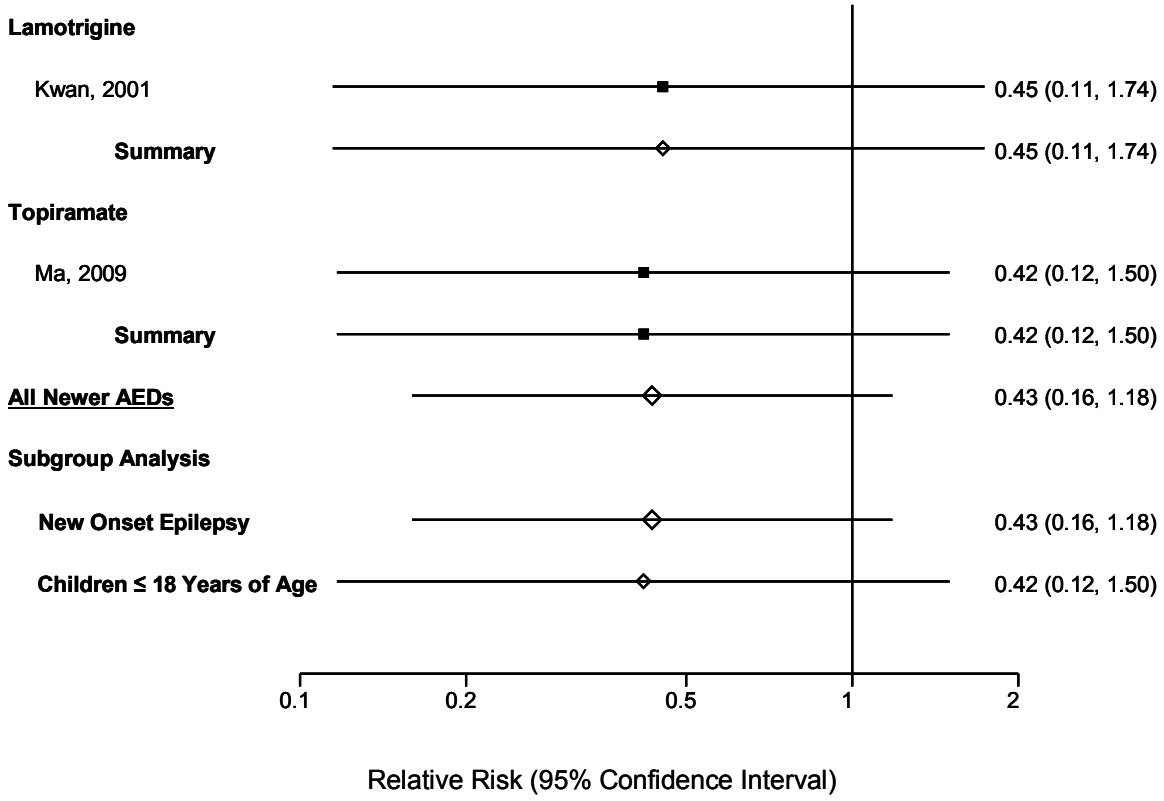
Figure 44. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

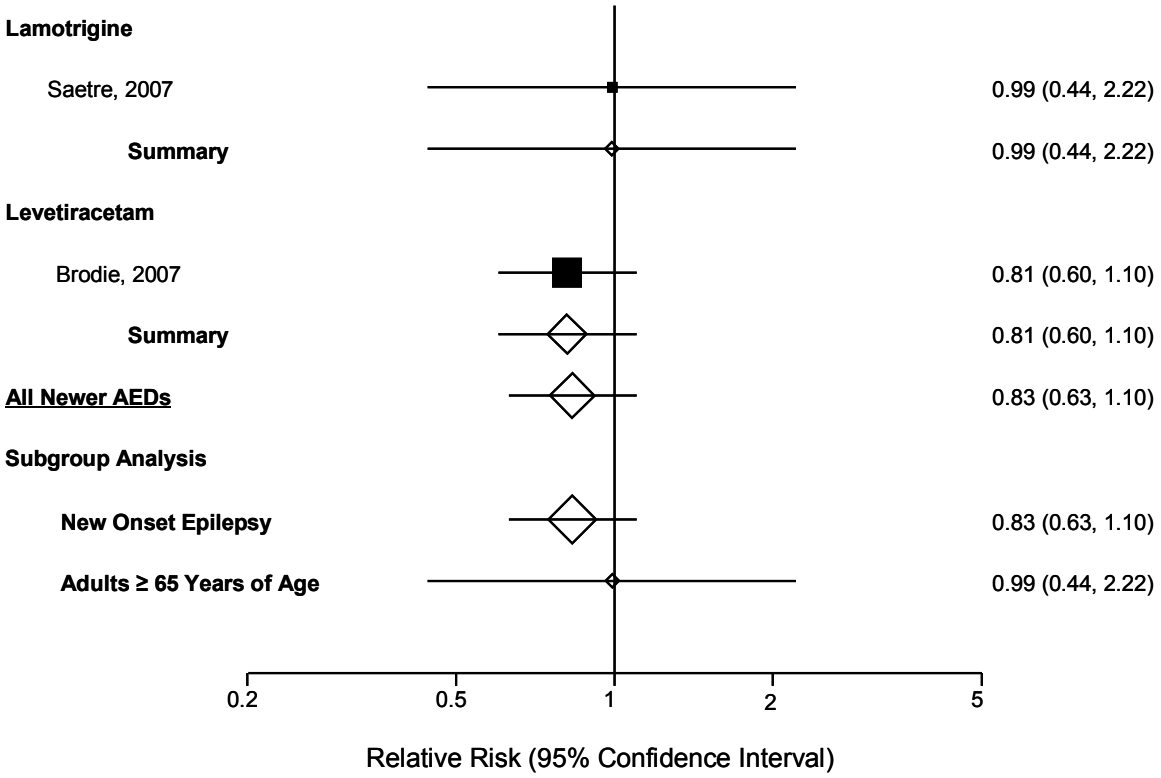
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters following author name and study year represent study arms within the same trial.

Figure 45. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



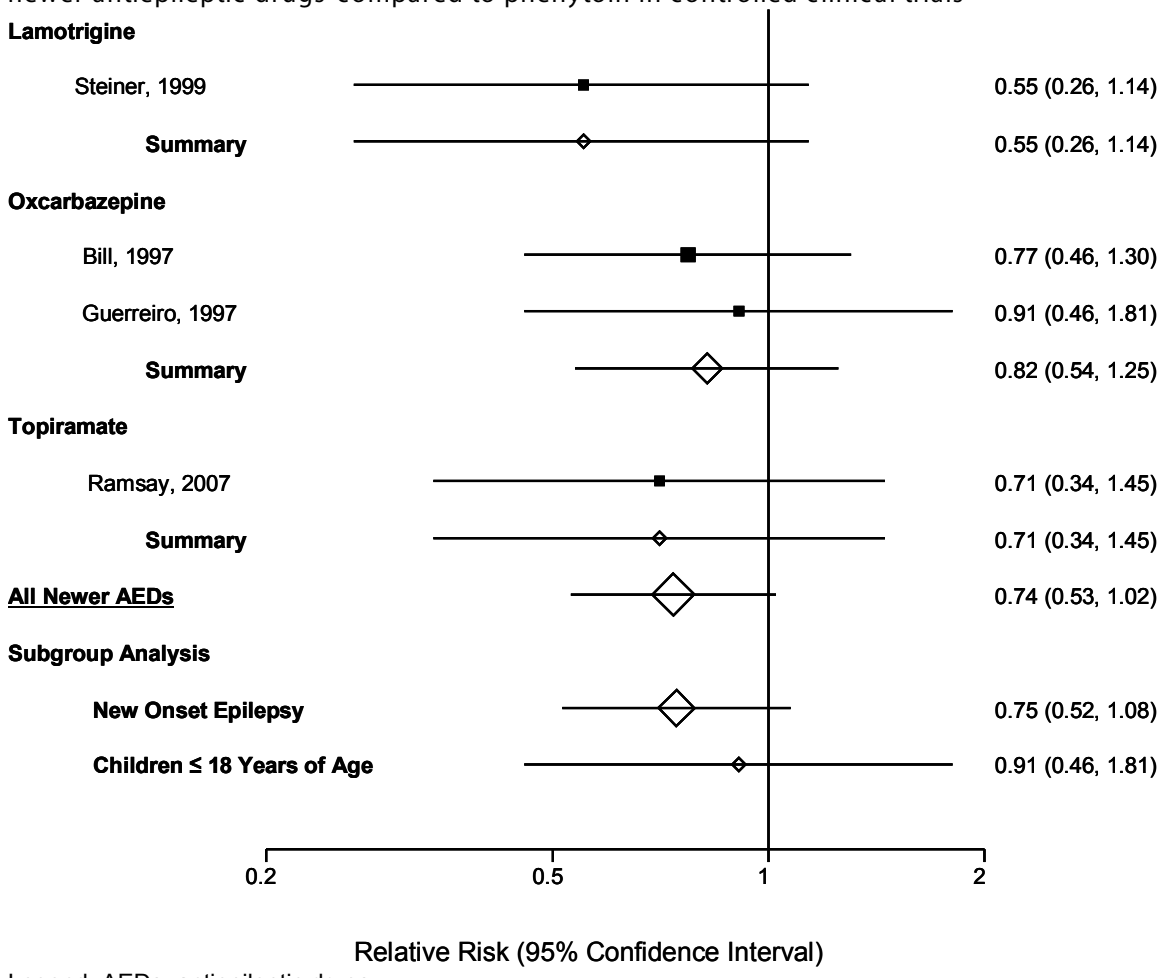
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

Figure 46. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared to controlled or sustained release carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

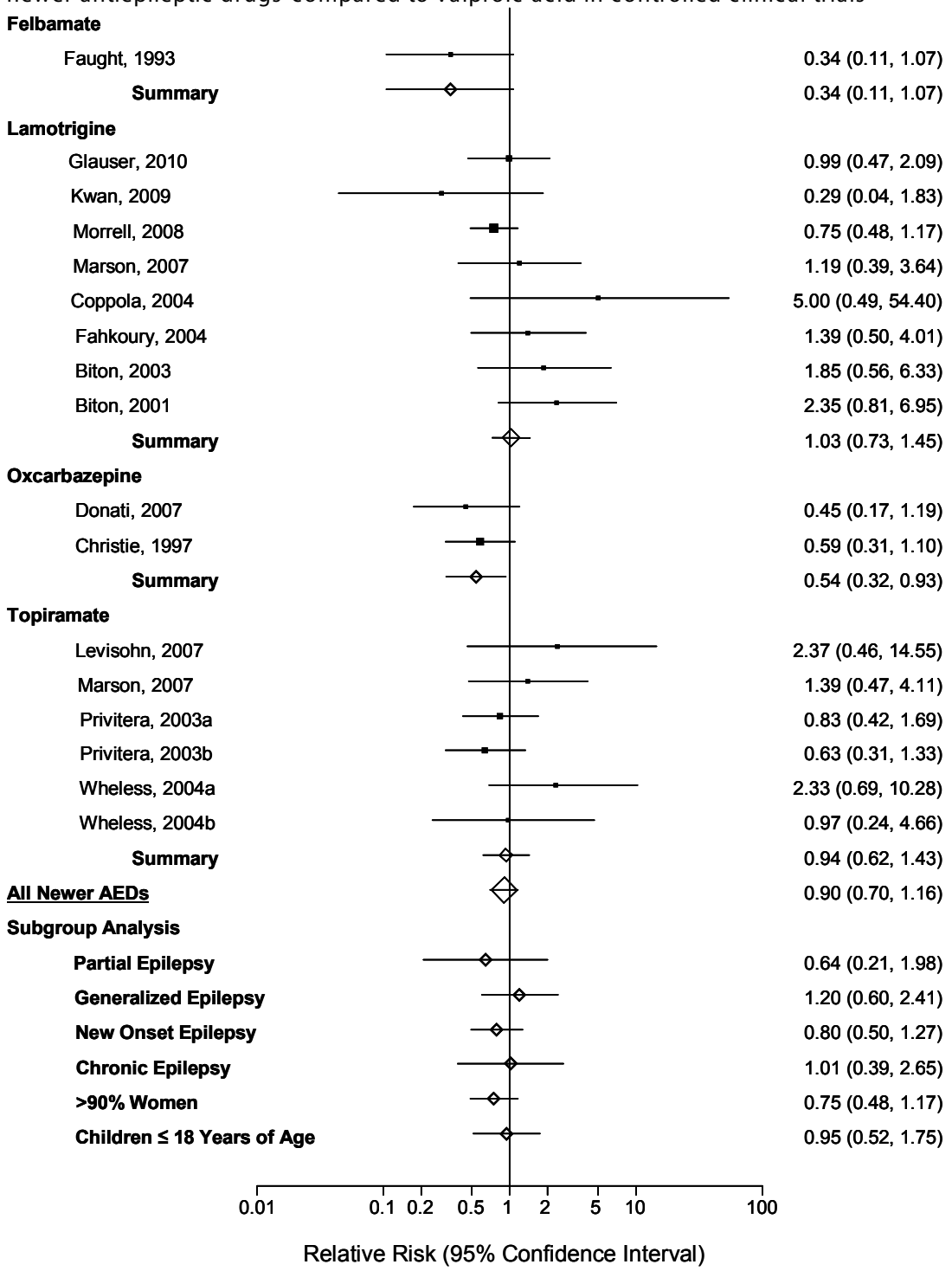
Figure 47. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

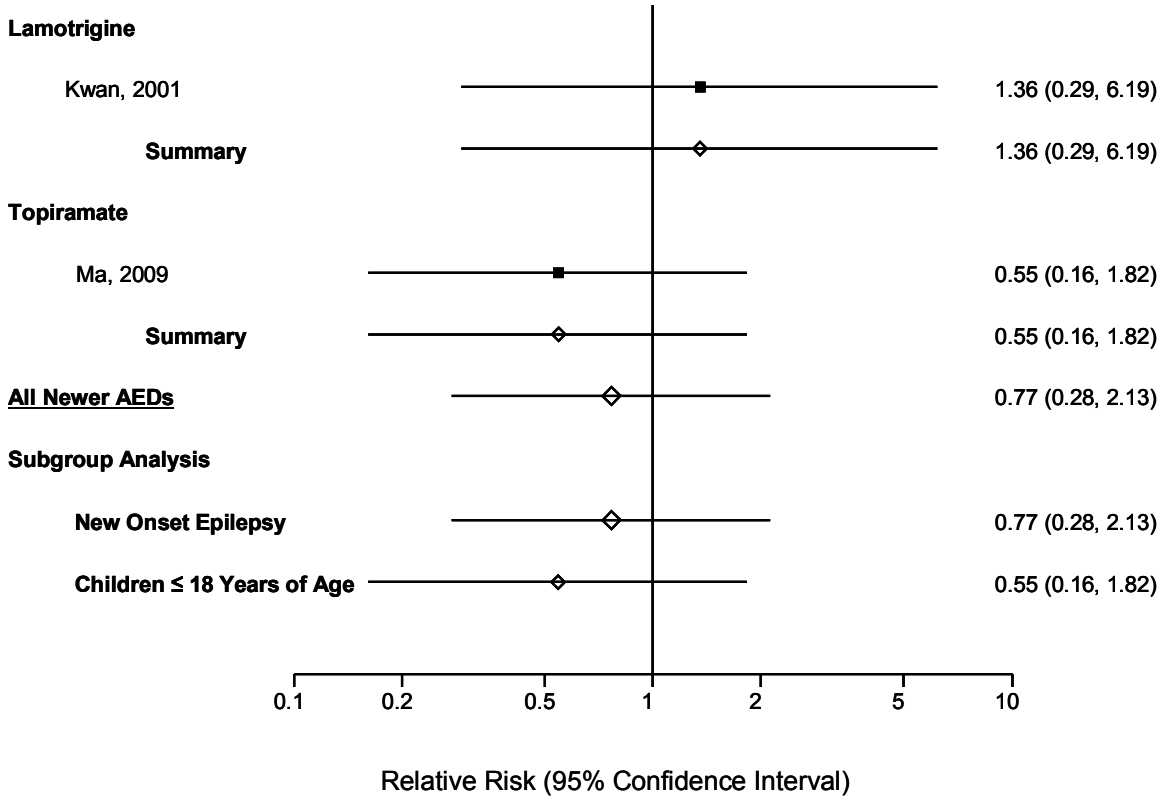
Figure 48. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

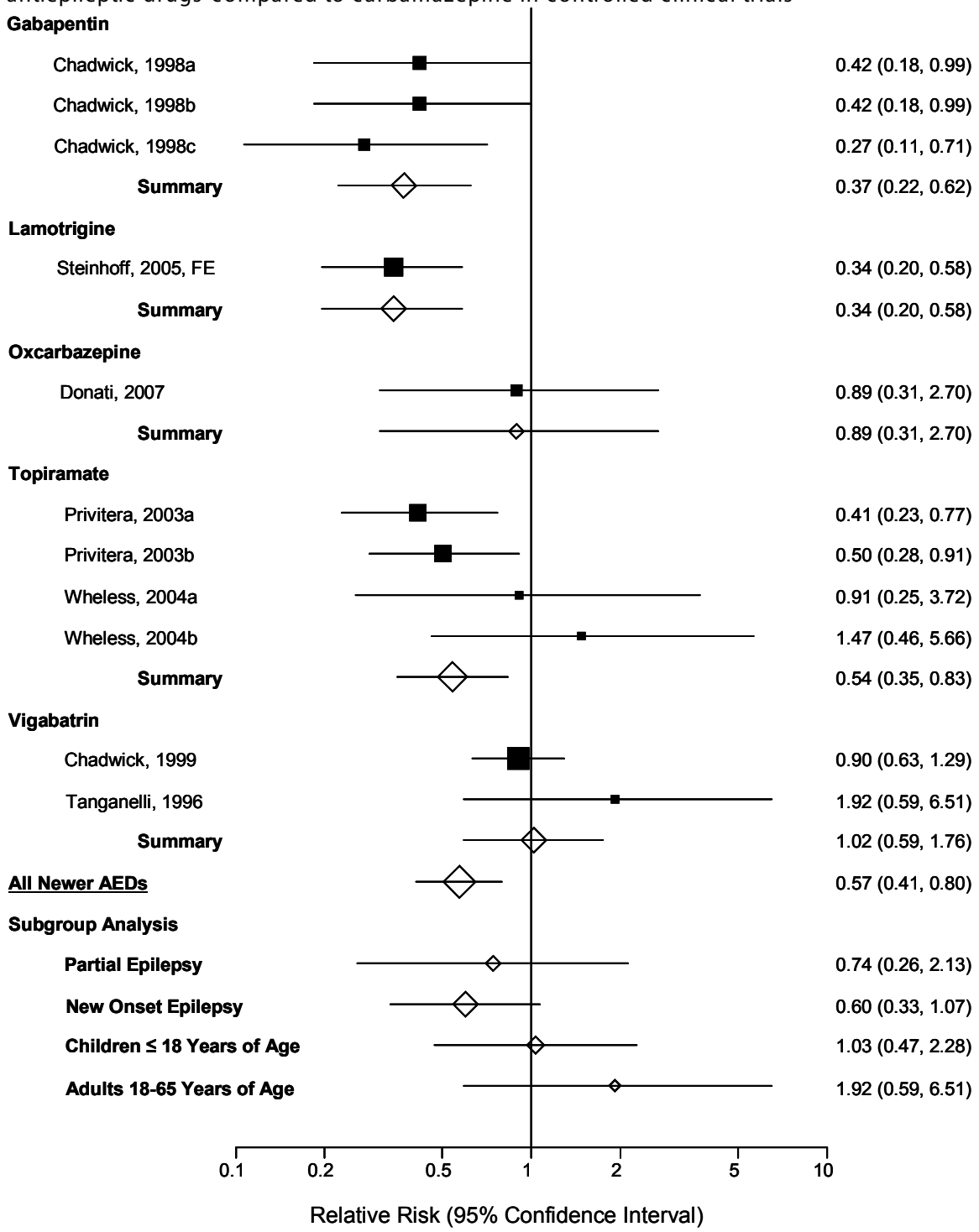
Figure 49. Composite forest plot of meta-analysis of headache in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

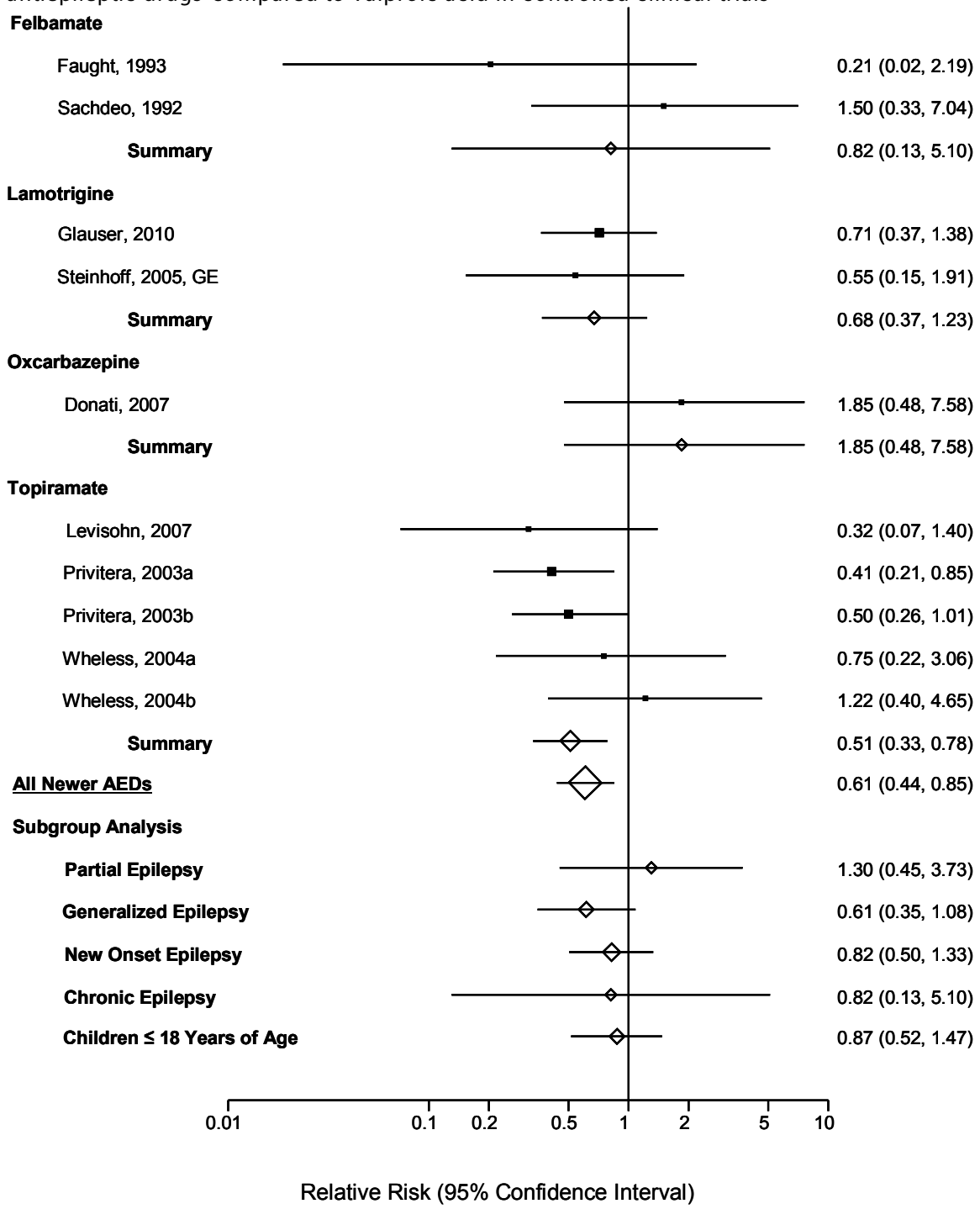
Figure 50. Composite forest plot of meta-analysis of fatigue in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

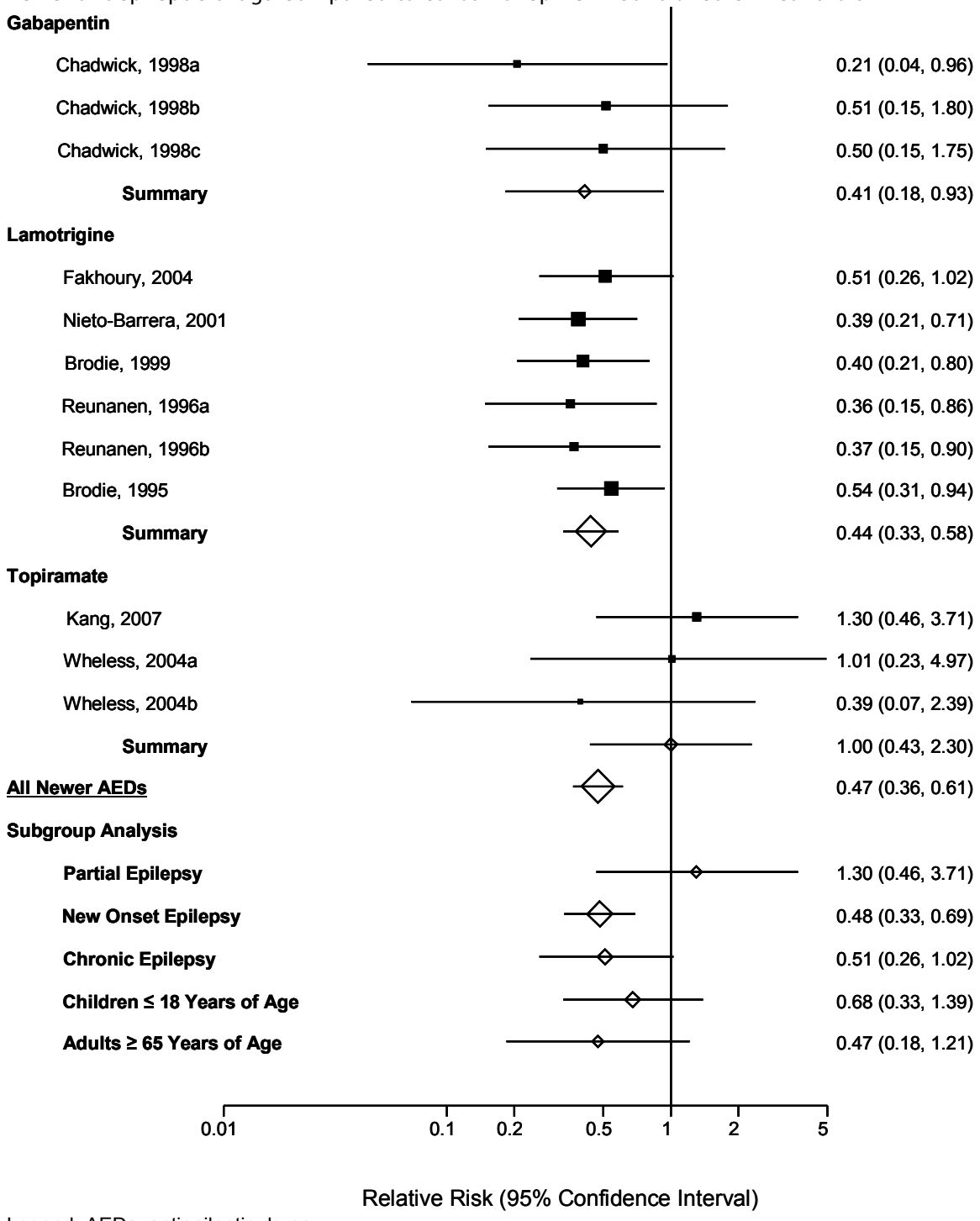
Figure 51. Composite forest plot of meta-analysis of fatigue in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

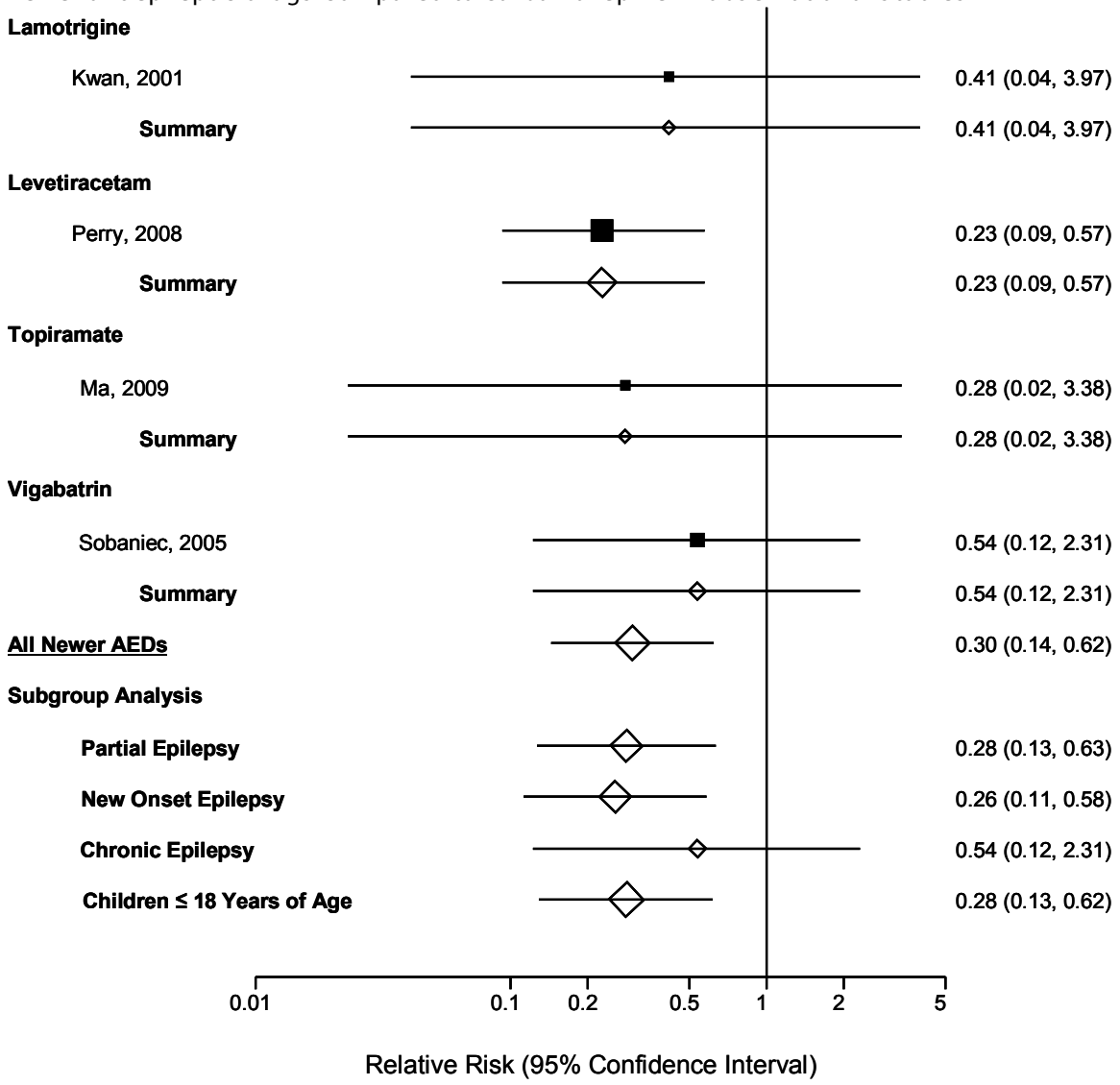
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 52. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



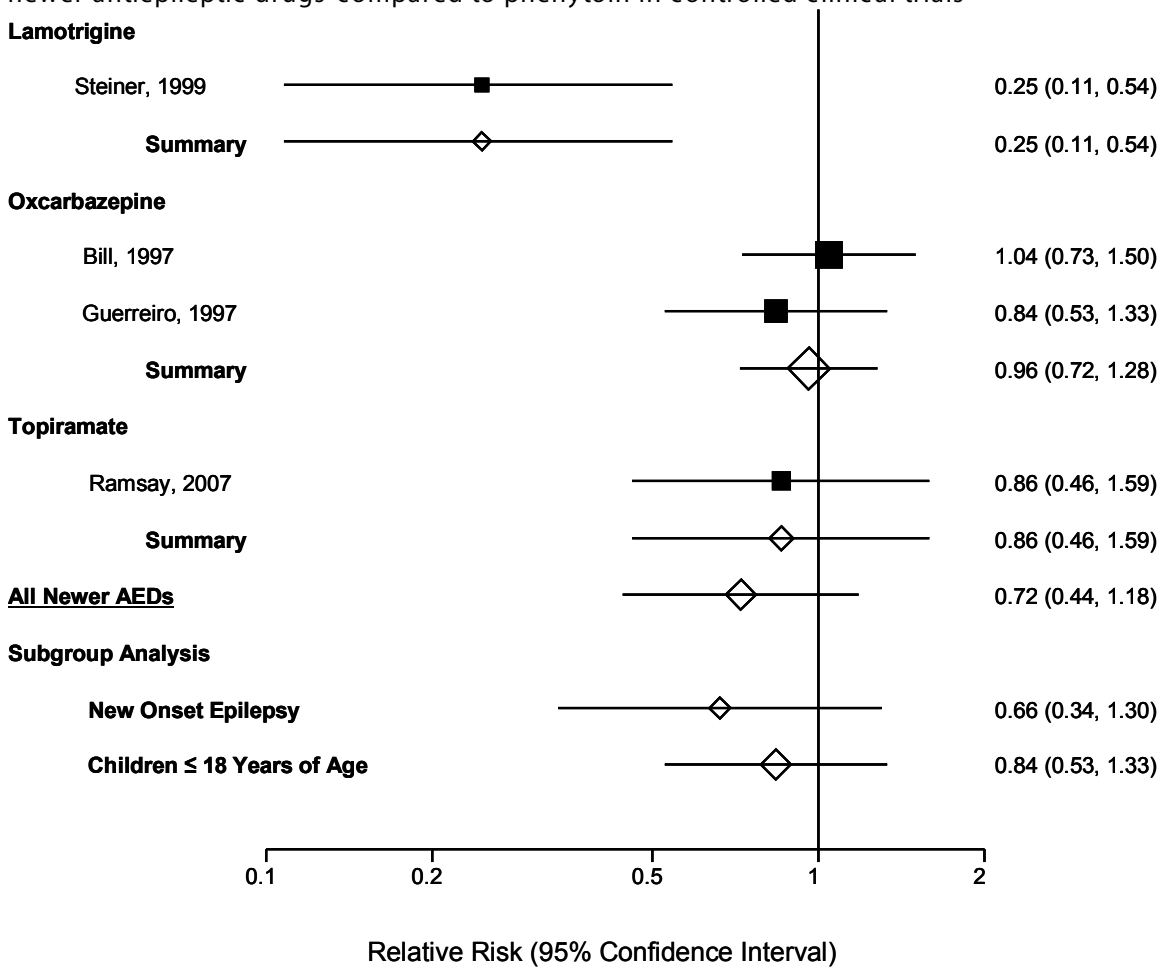
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 53. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

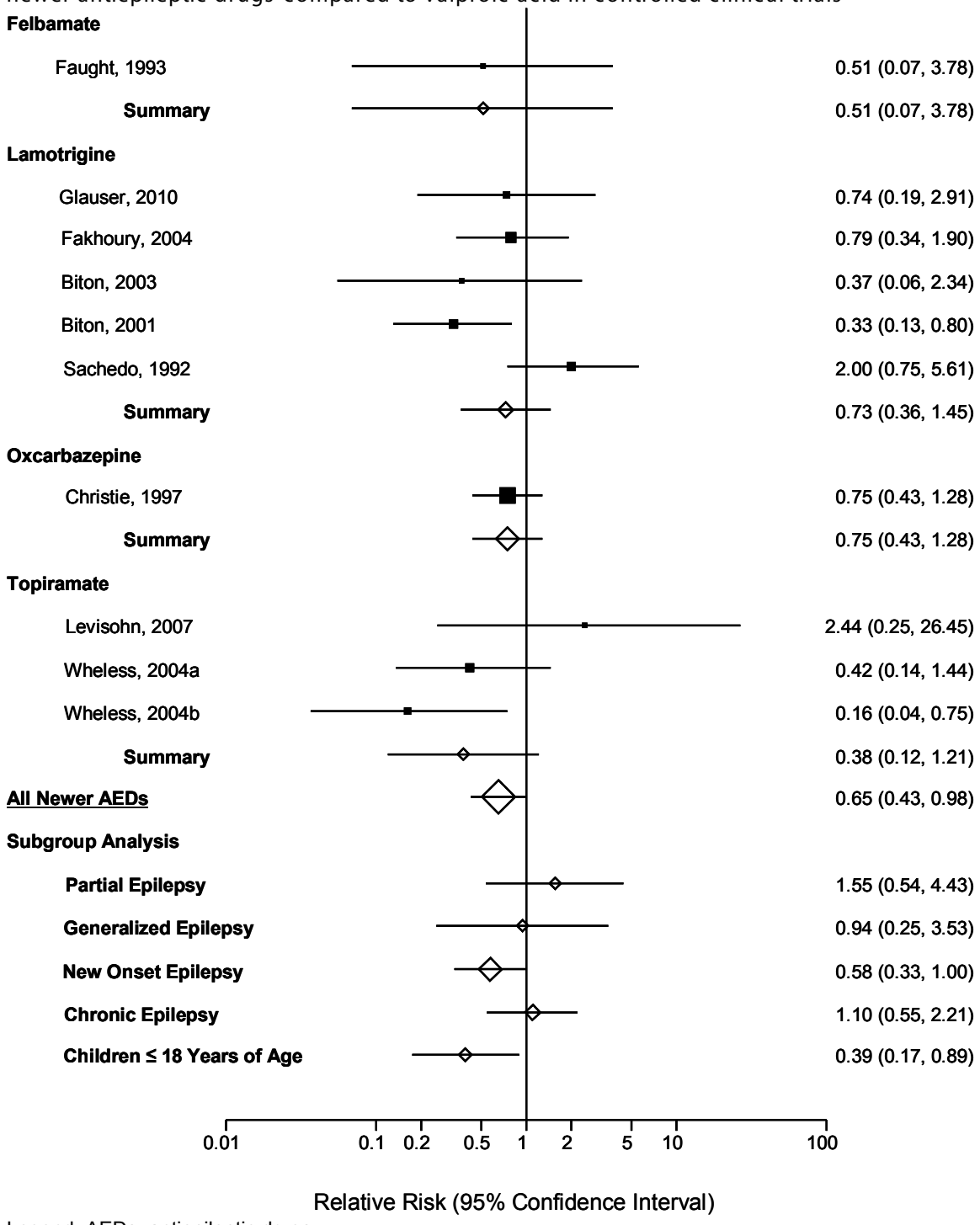
Figure 54. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

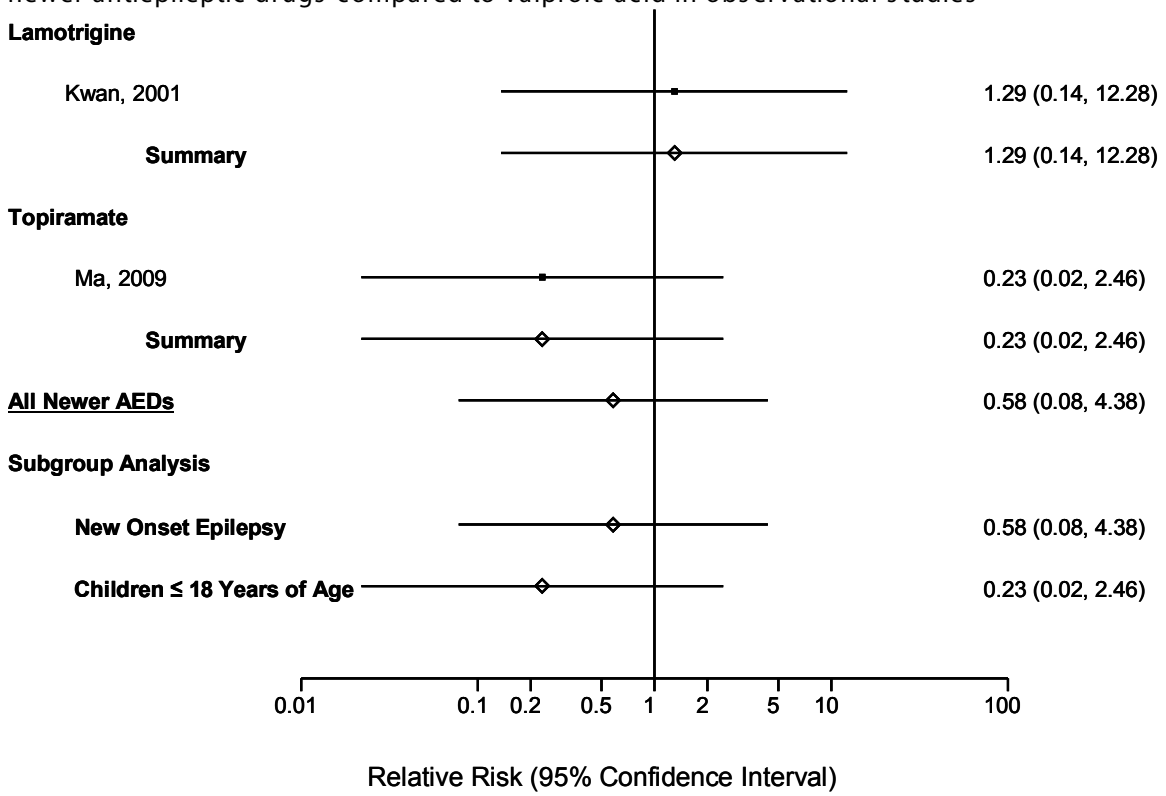
Figure 55. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

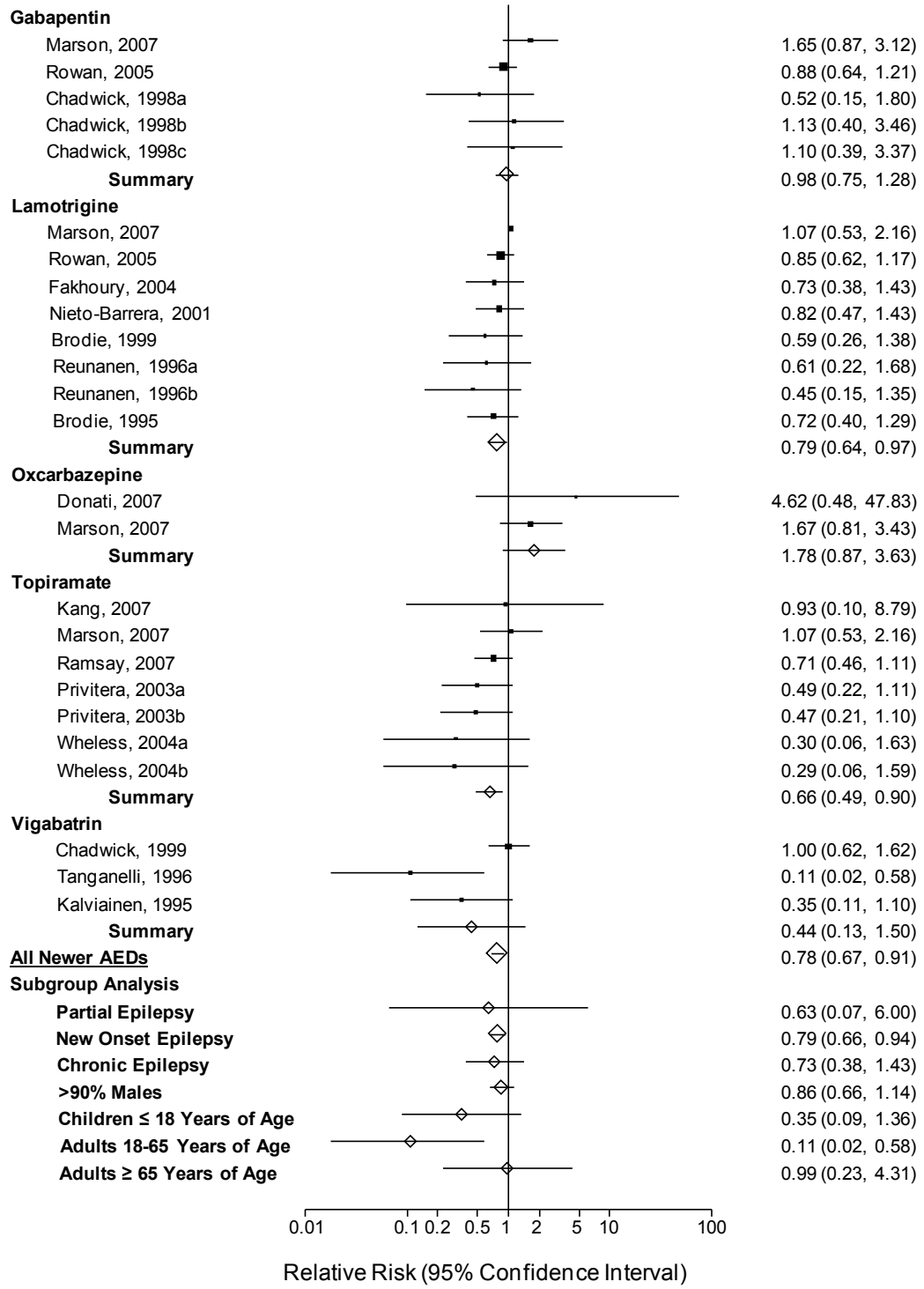
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 56. Composite forest plot of meta-analysis of somnolence in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

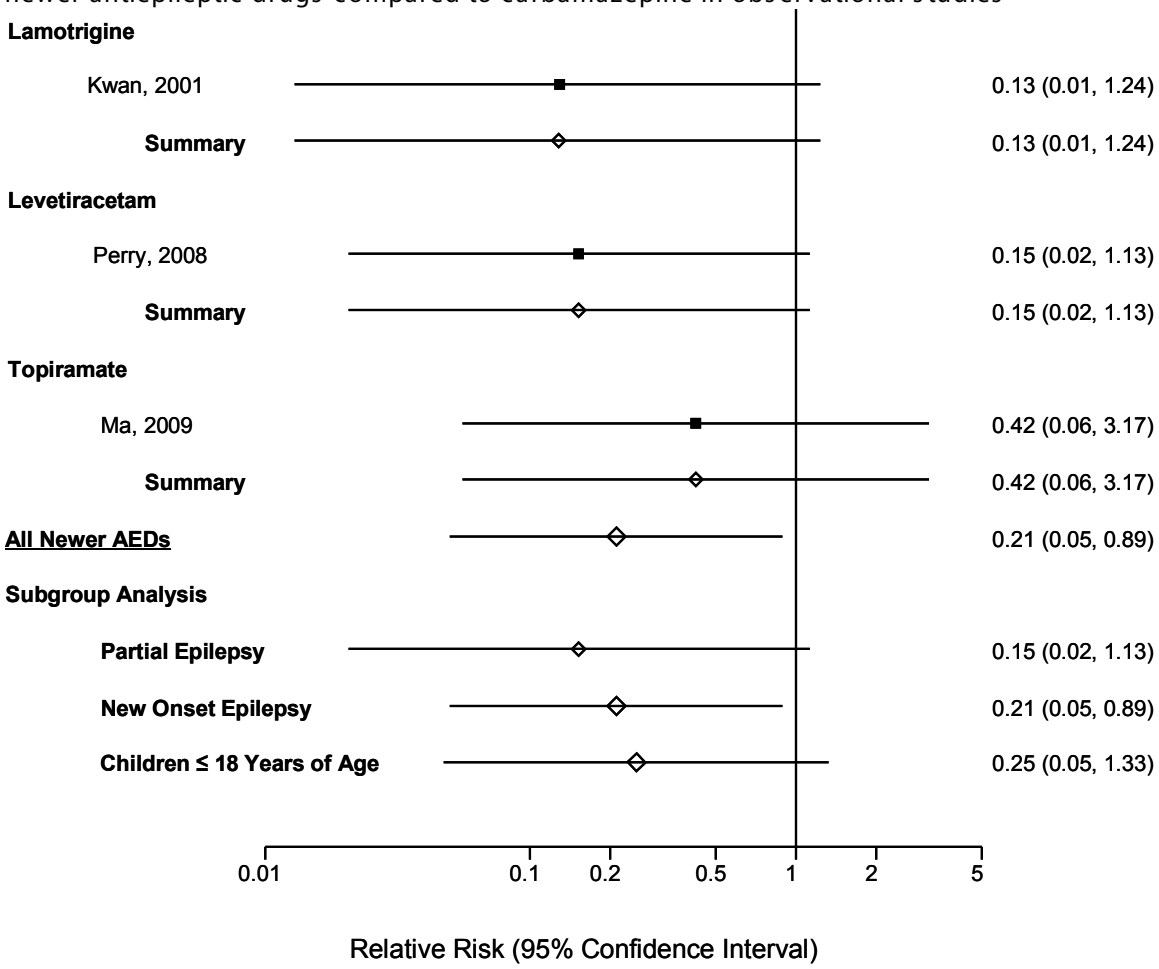
Figure 57. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

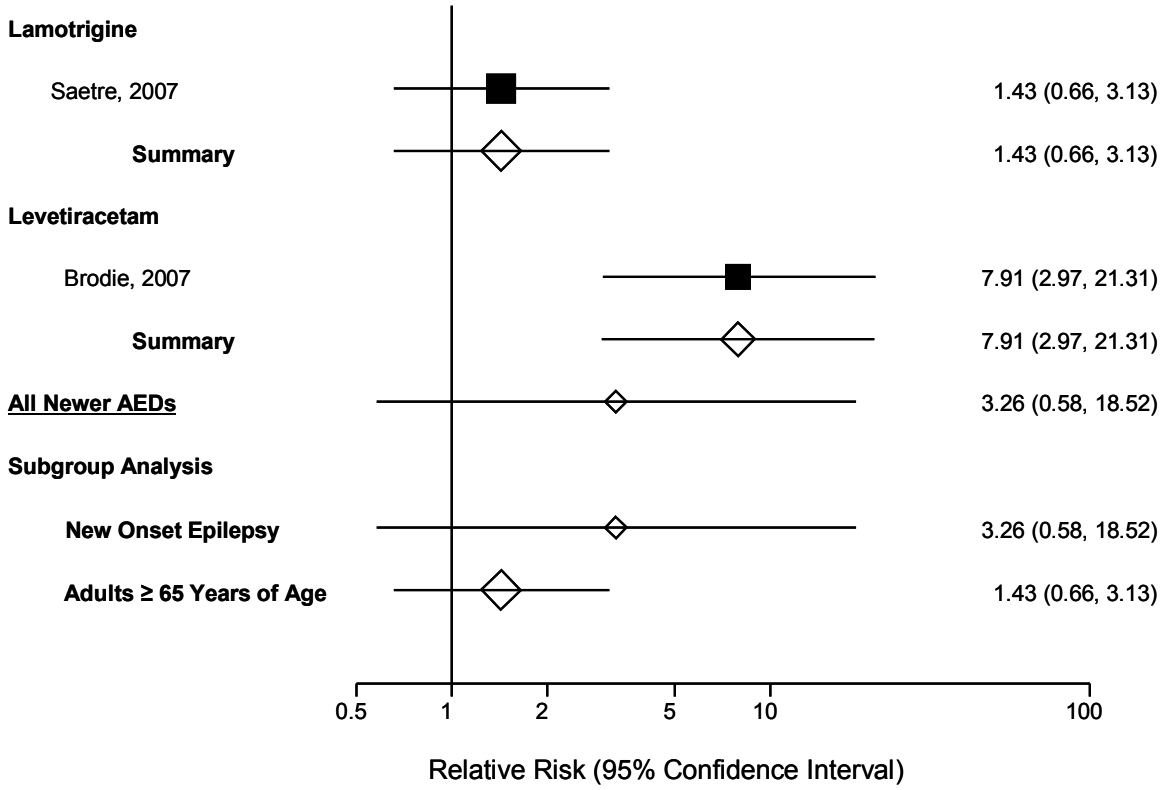
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 58. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



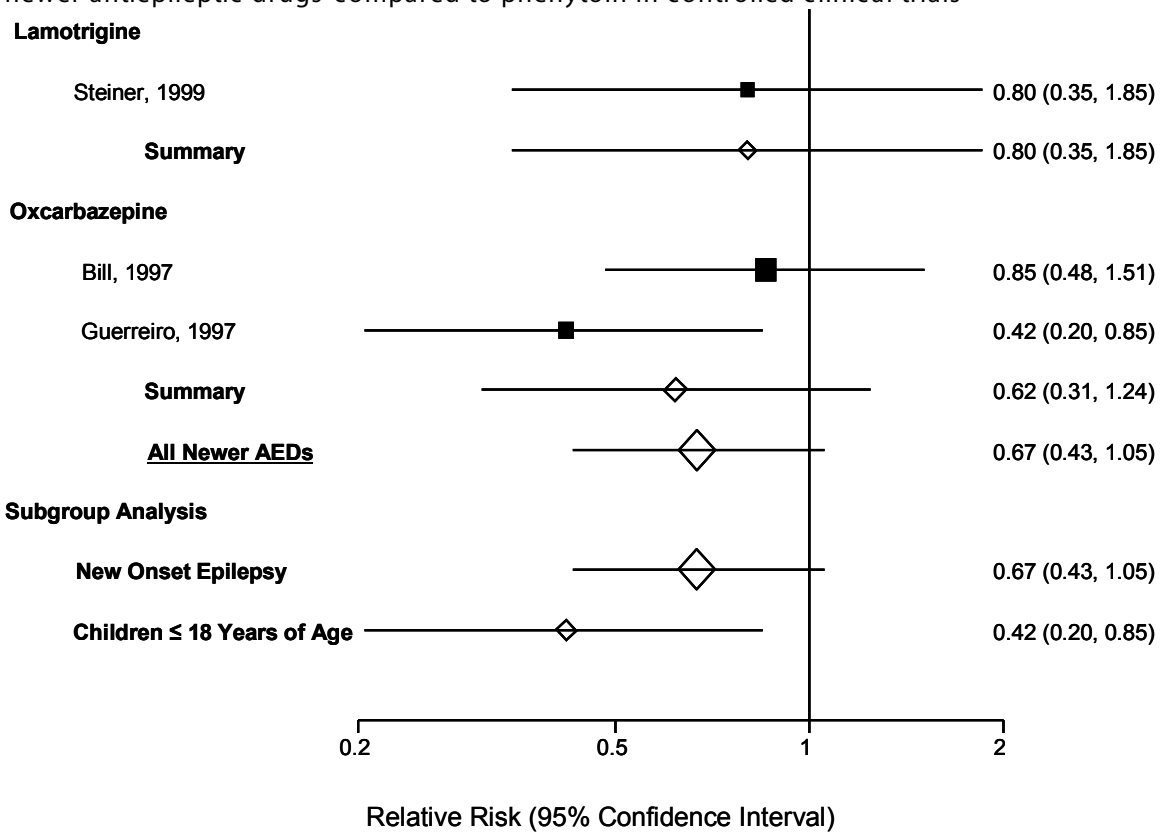
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 59. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared to controlled or sustained release carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

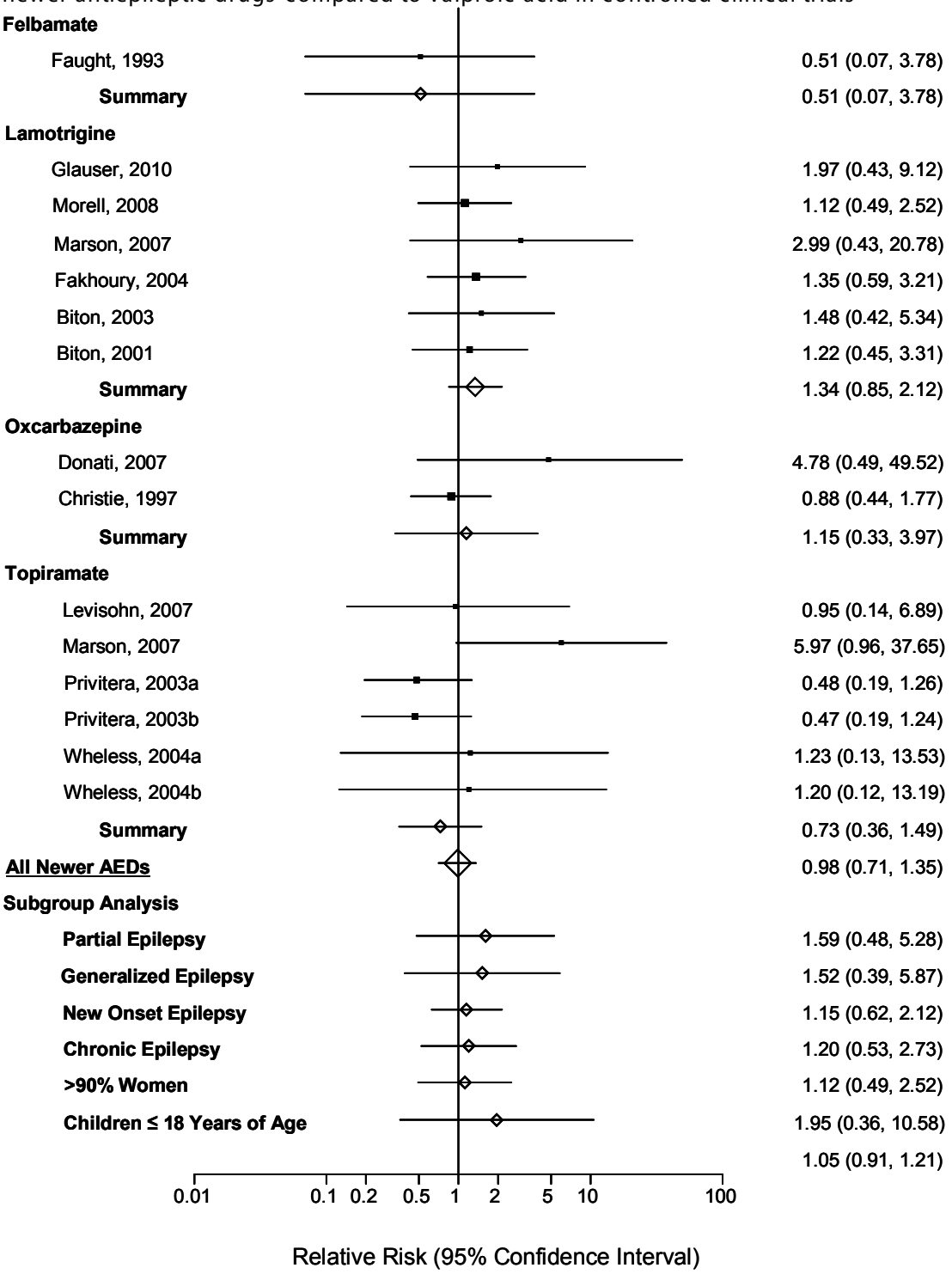
Figure 60. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

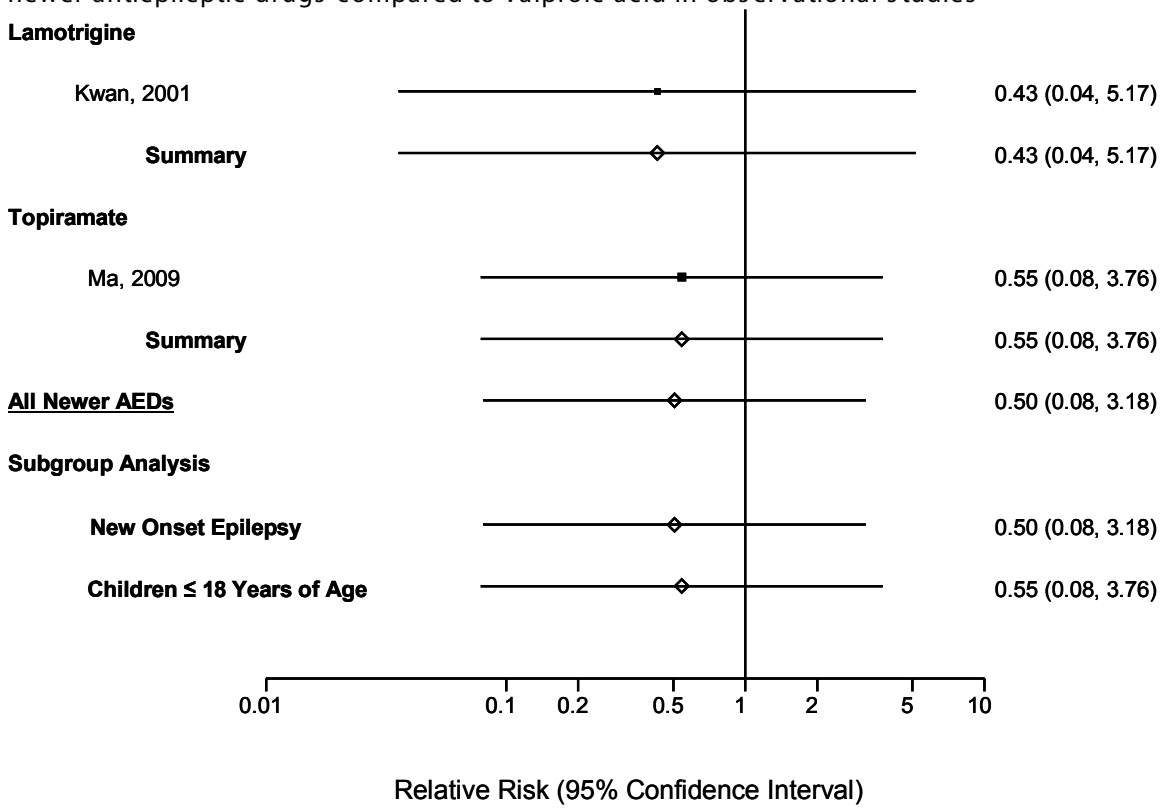
Figure 61. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

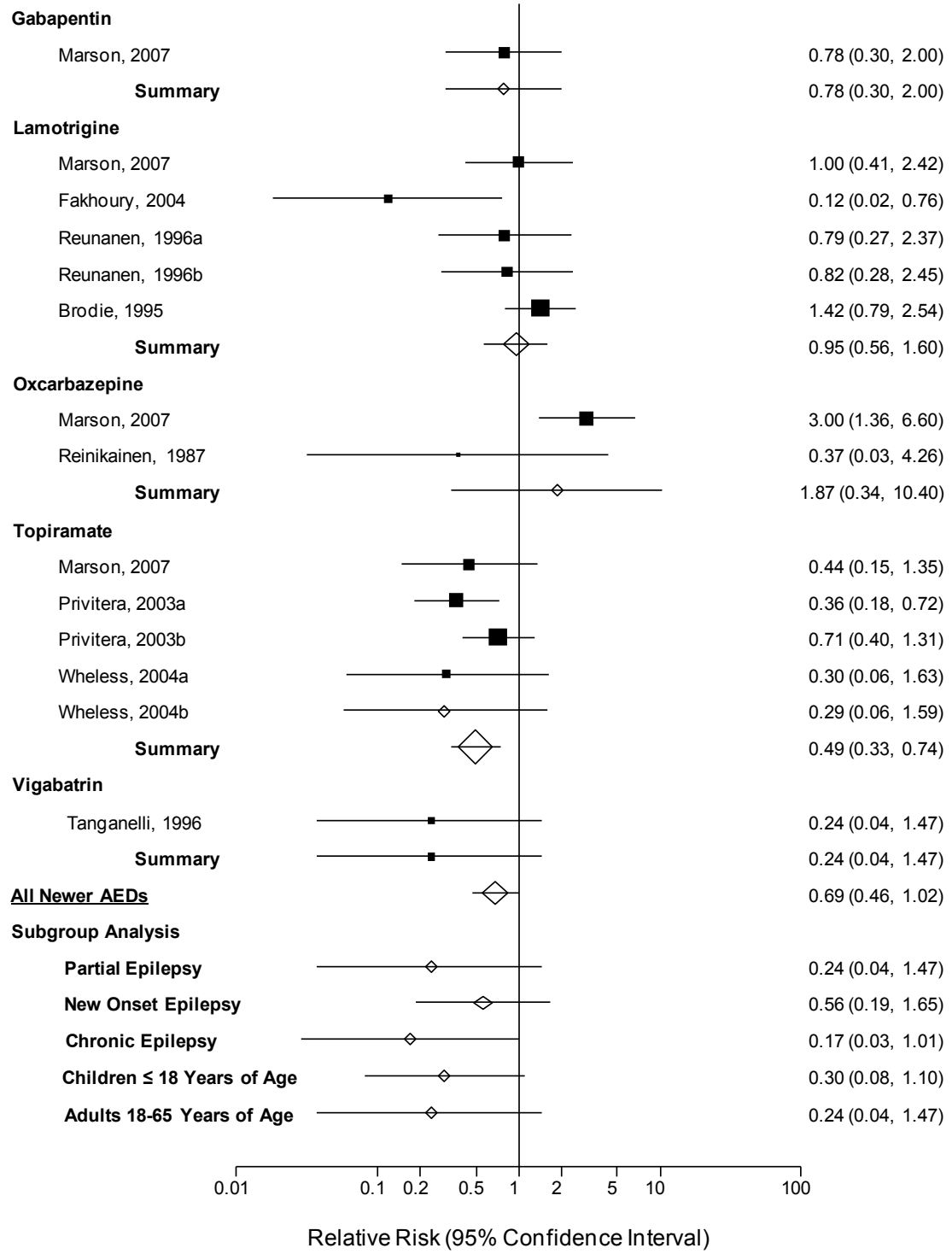
Figure 62. Composite forest plot of meta-analysis of dizziness in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

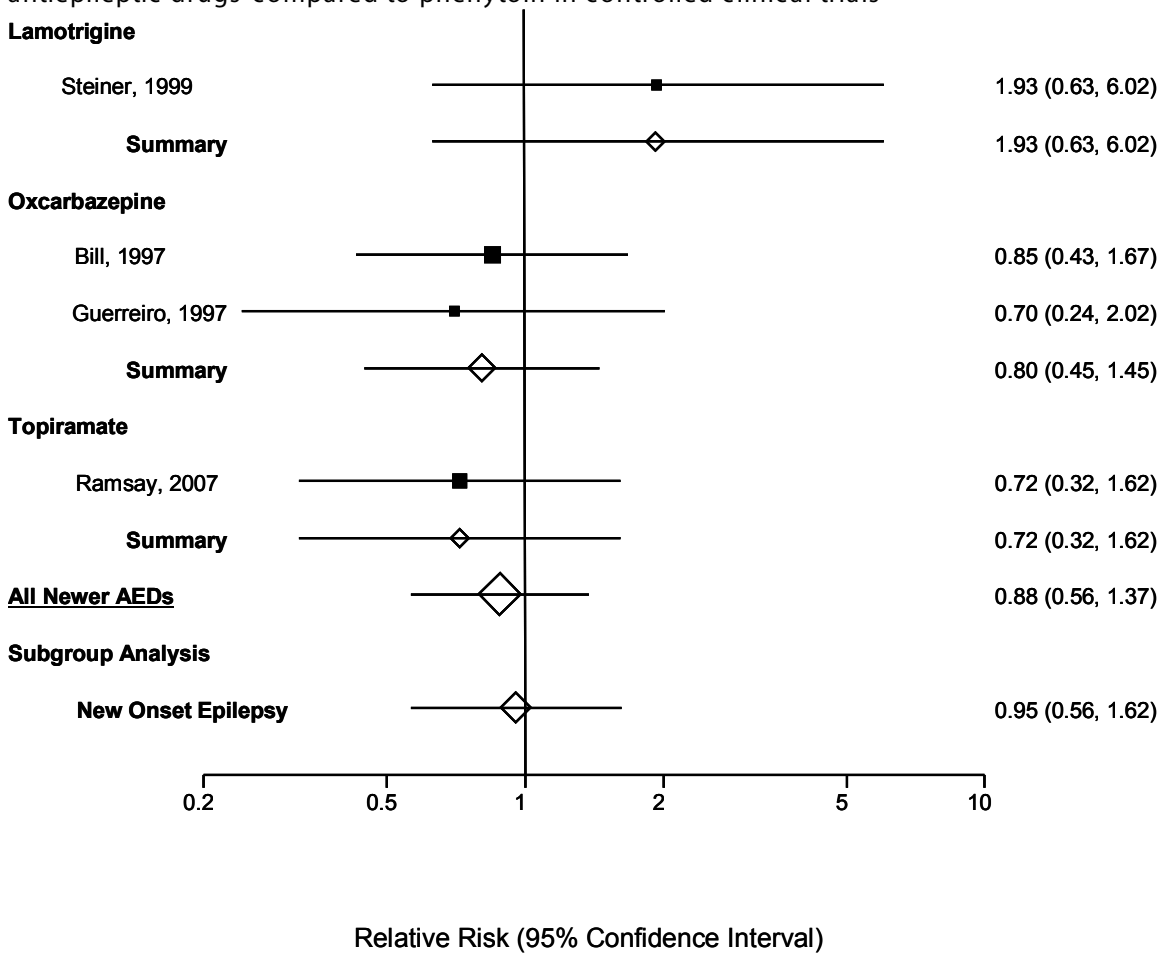
Figure 63. Composite forest plot of meta-analysis of nausea in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

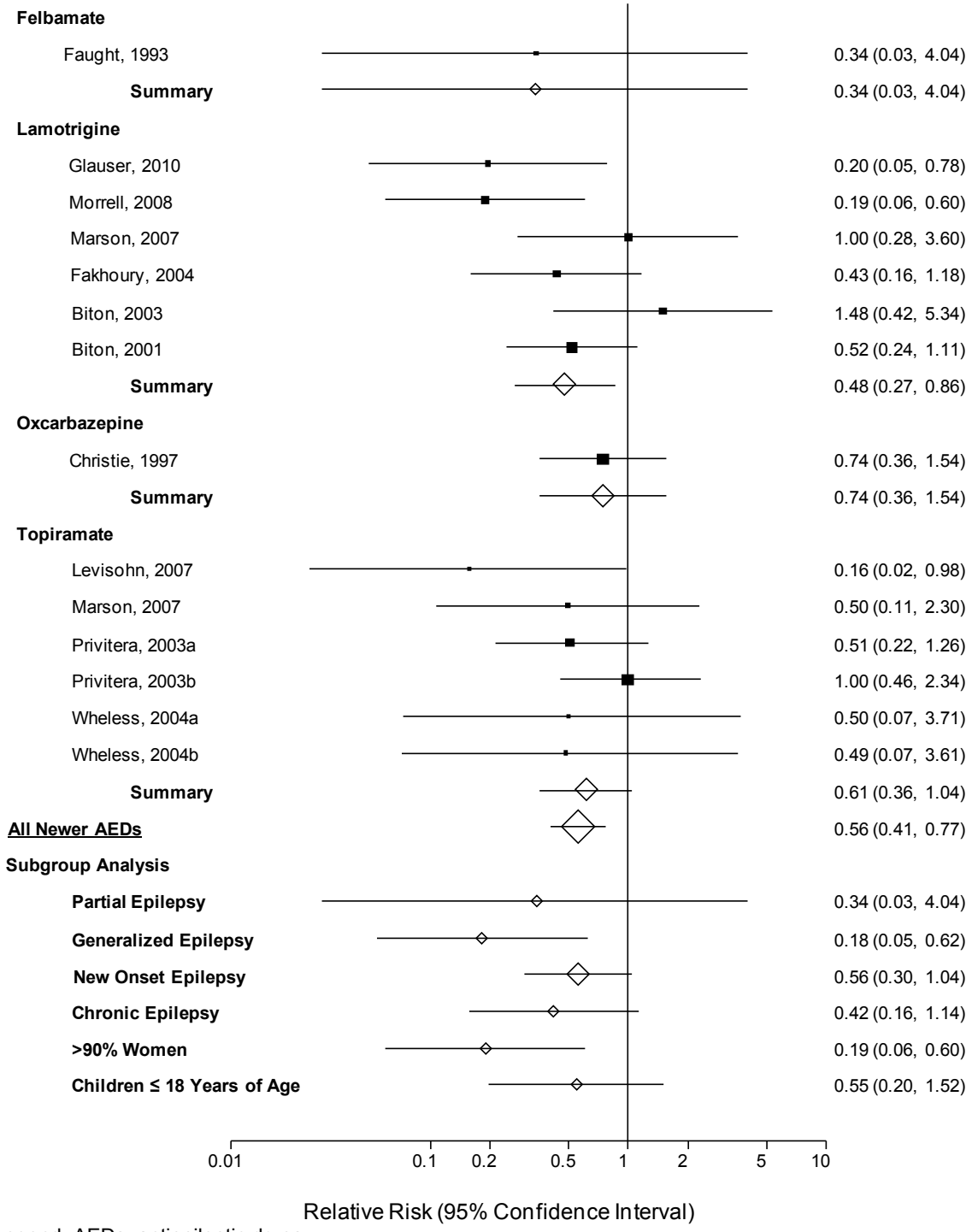
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 64. Composite forest plot of meta-analysis of nausea in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

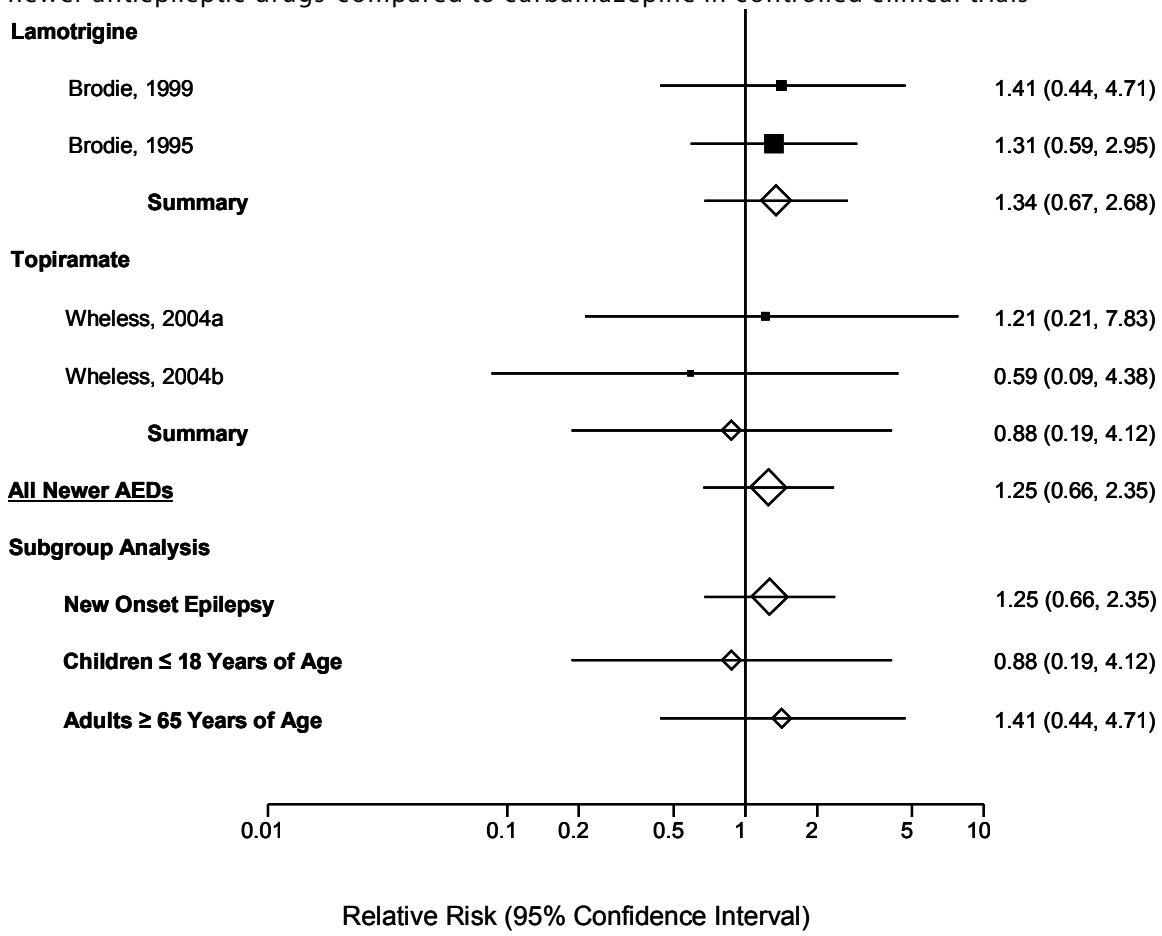
Figure 65. Composite forest plot of meta-analysis of nausea in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

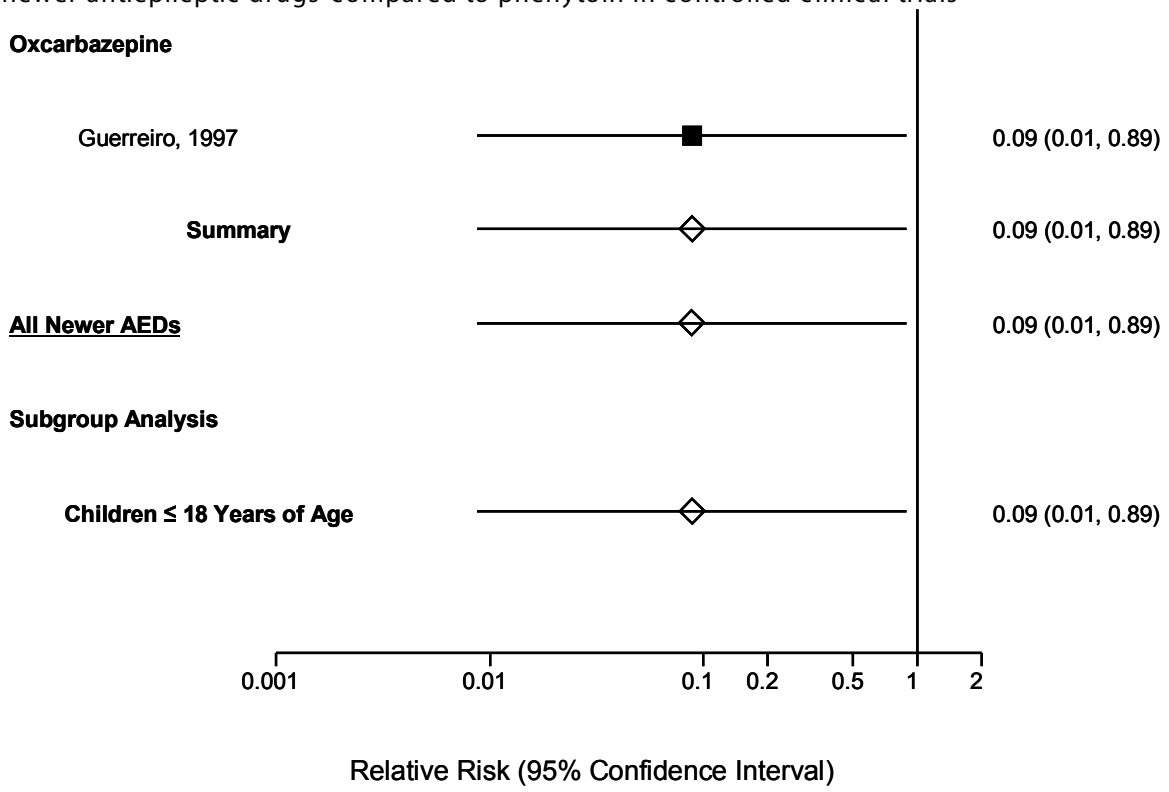
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 66. Composite forest plot of meta-analysis of vomiting in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



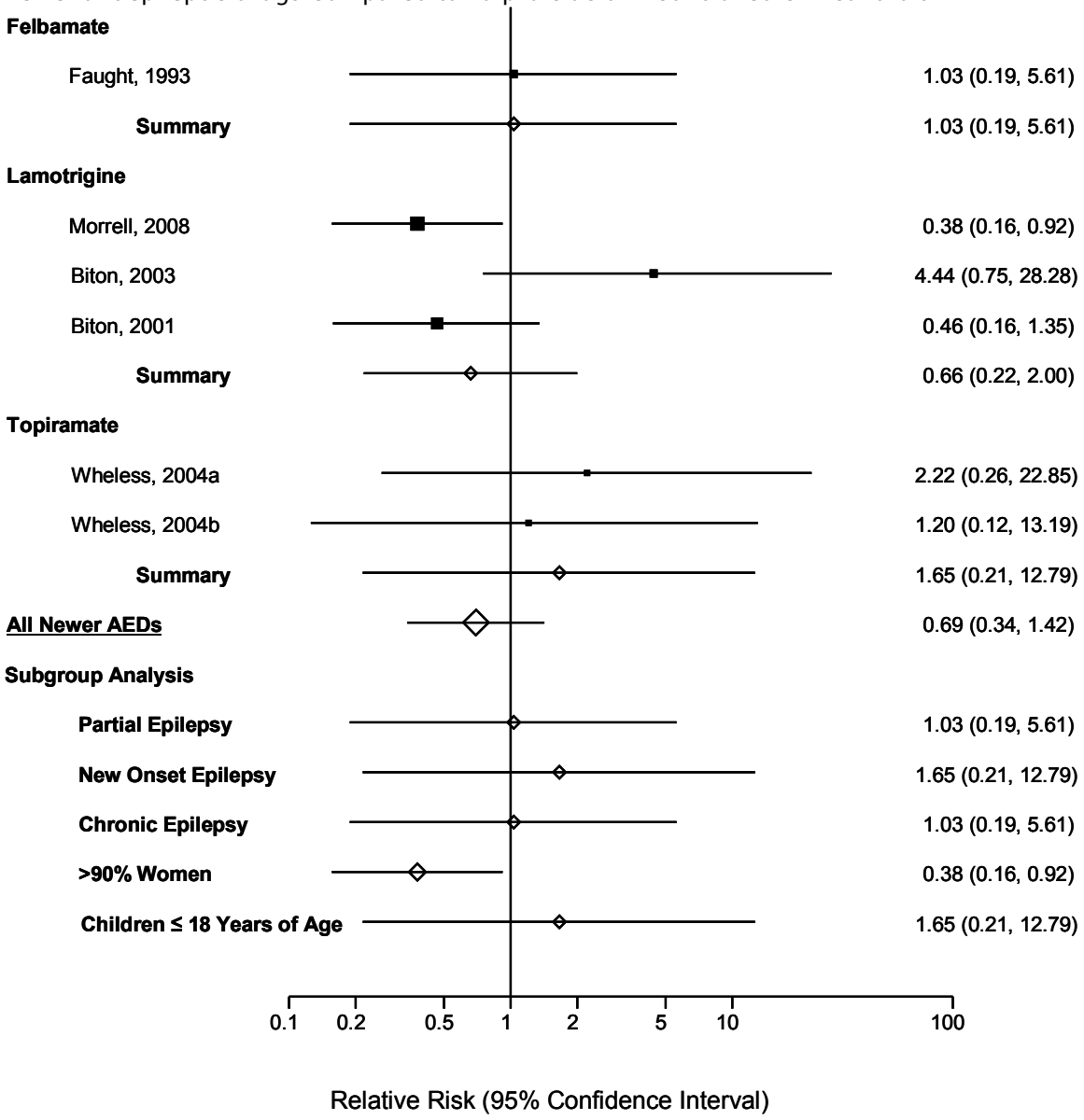
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 67. Composite forest plot of meta-analysis of vomiting in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value.

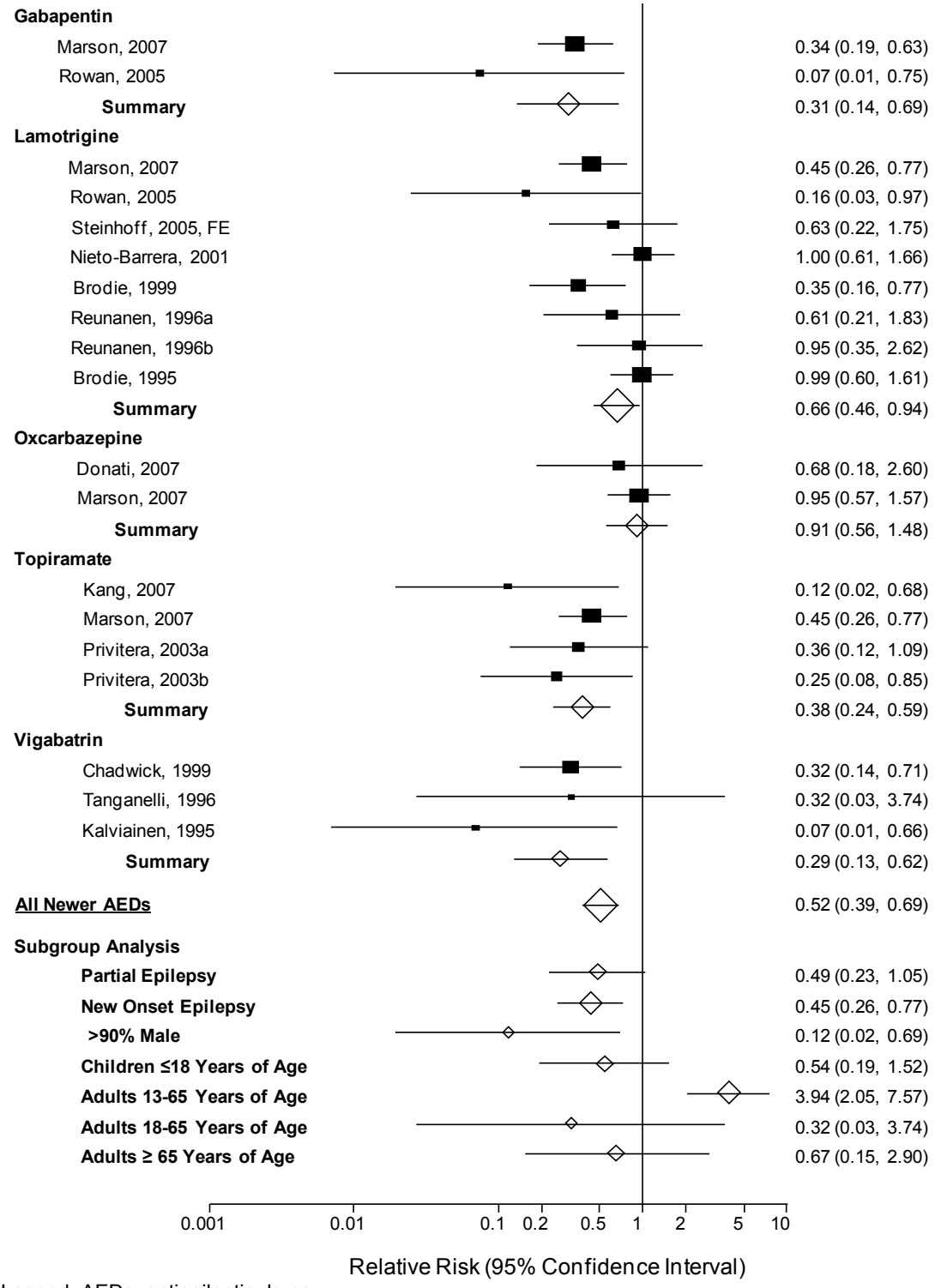
Figure 68. Composite forest plot of meta-analysis of vomiting in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

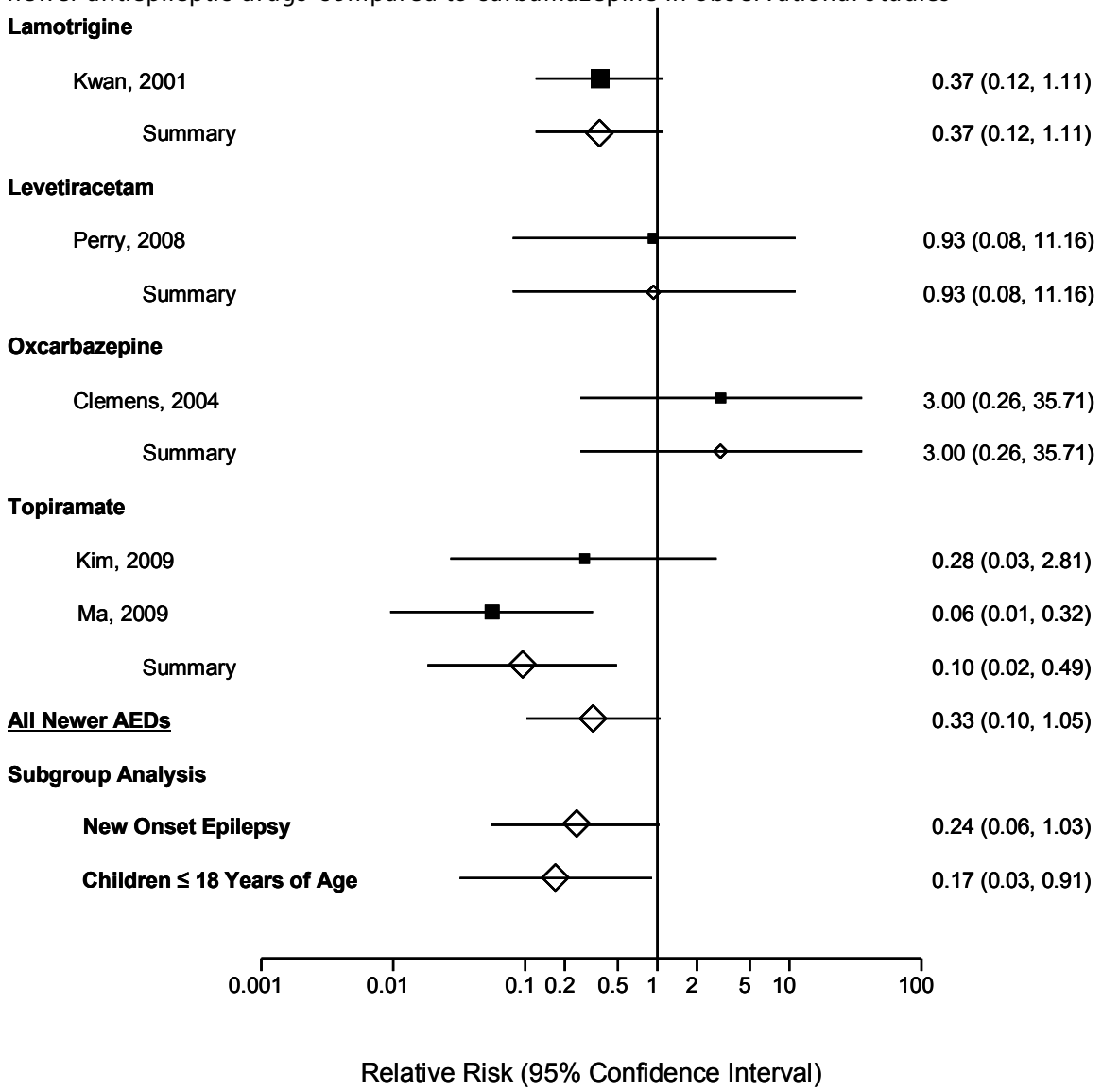
Figure 69. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



Legend: AEDs=antiepileptic drugs

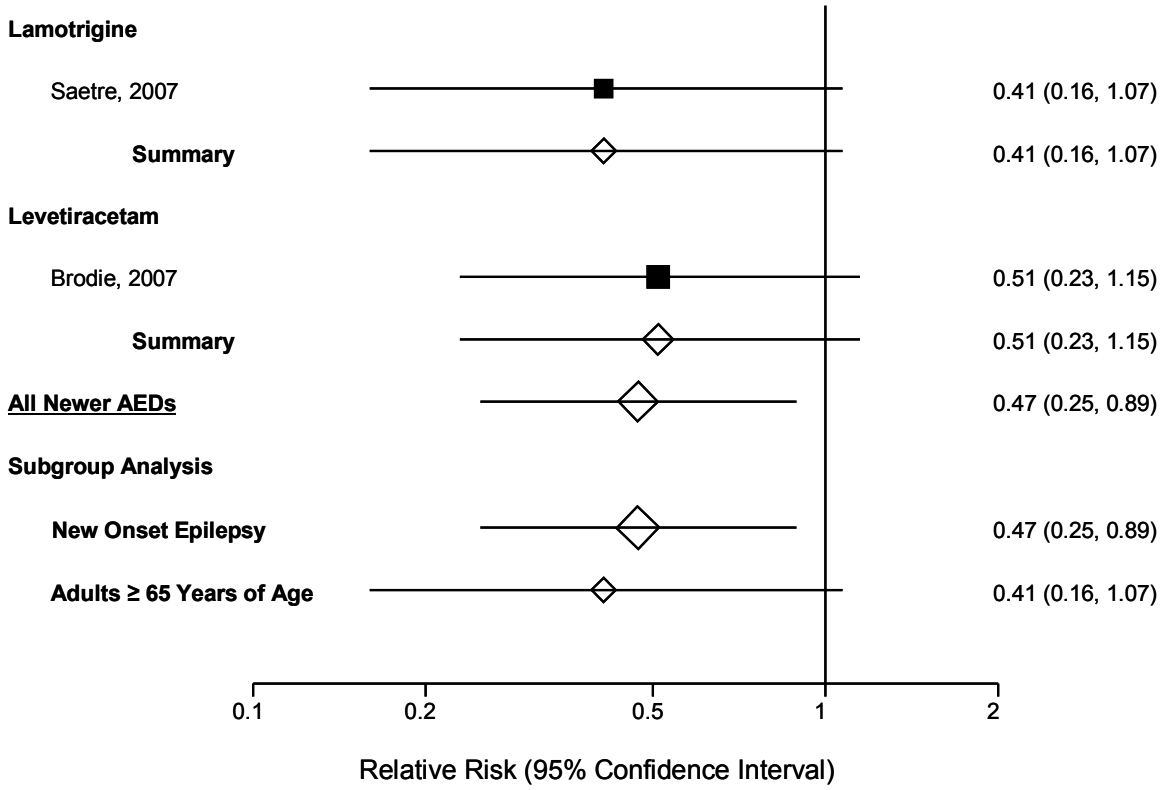
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 70. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in observational studies



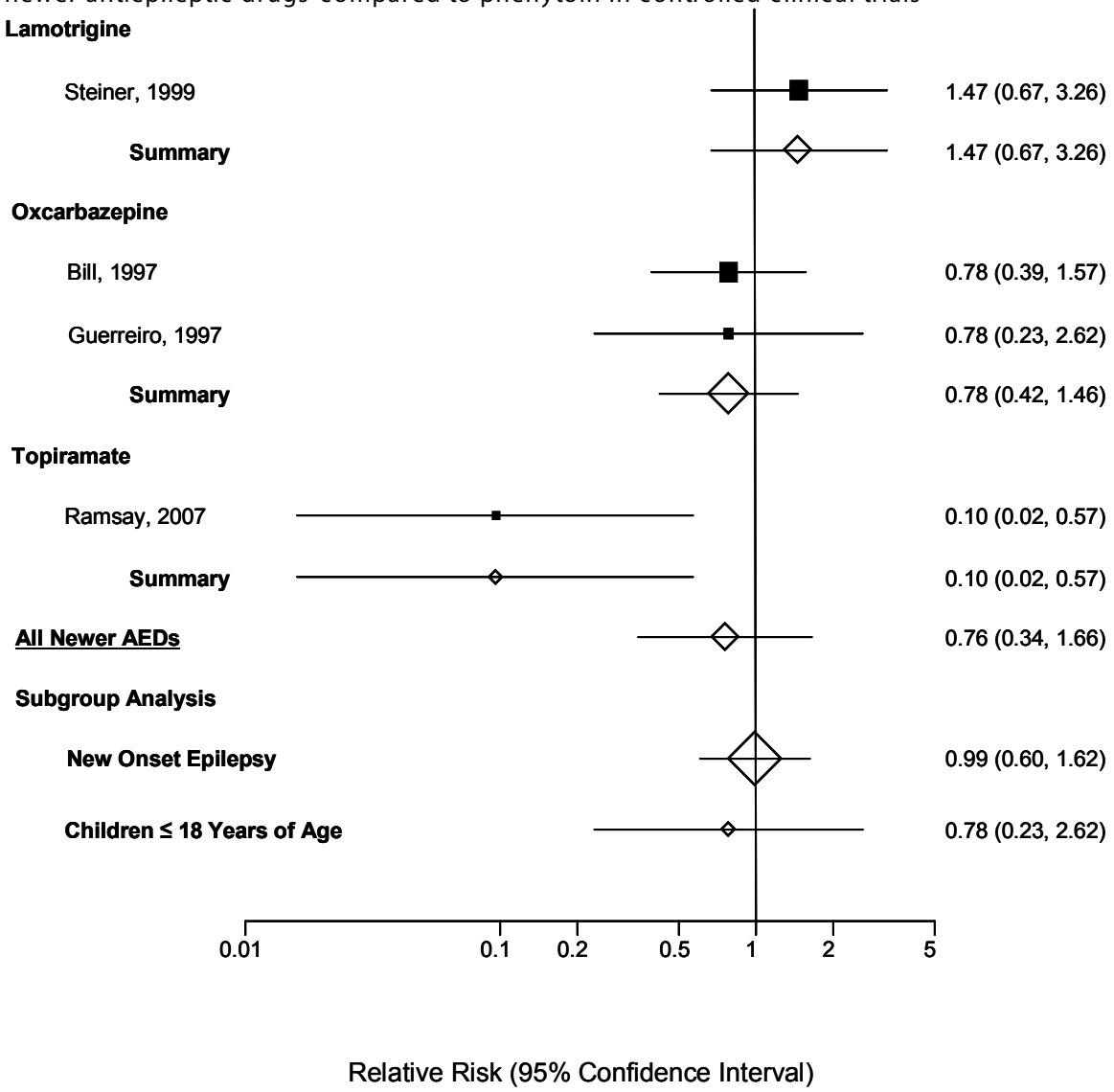
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 71. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared to controlled or sustained release carbamazepine in controlled clinical trials



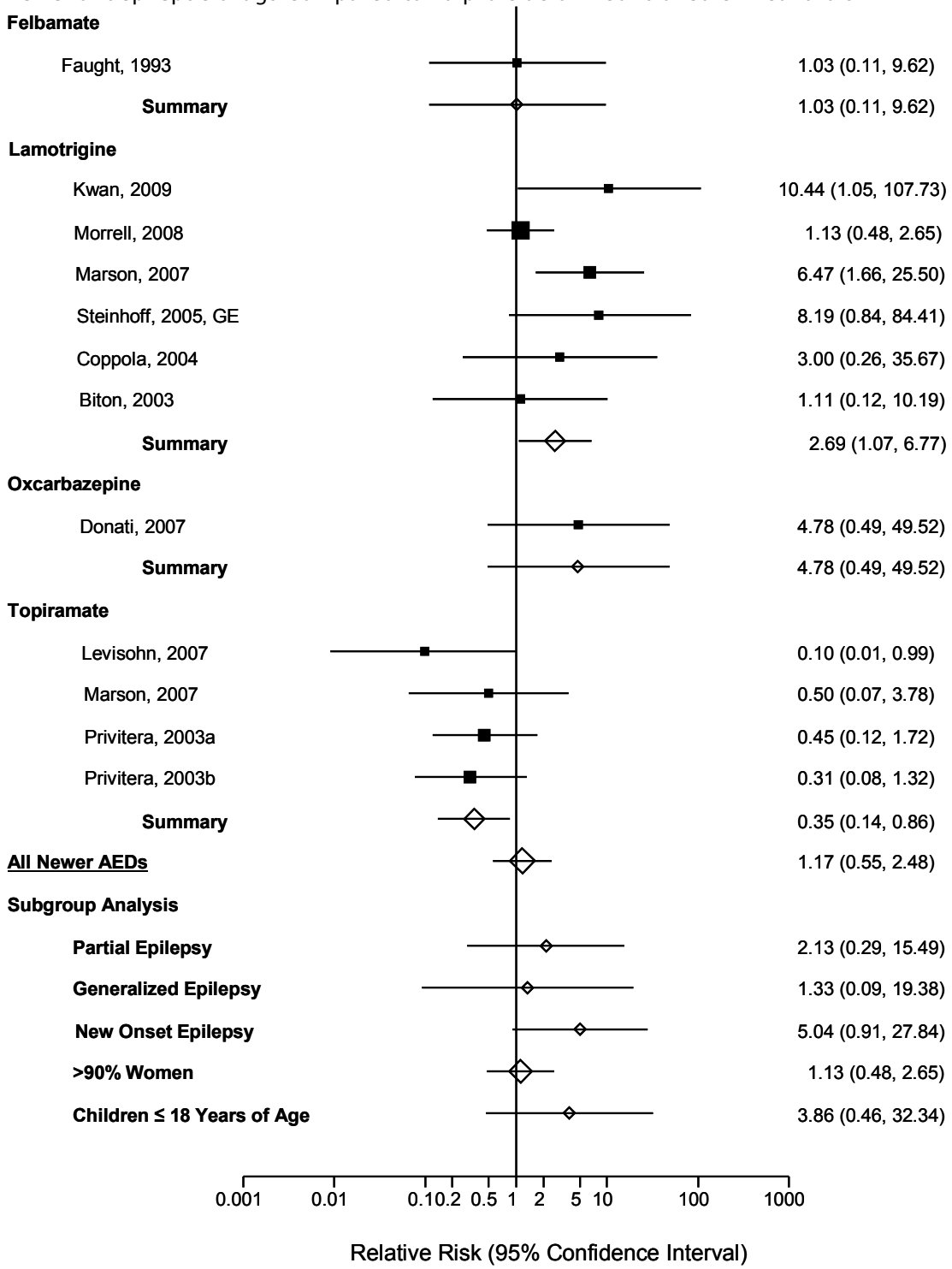
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 72. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

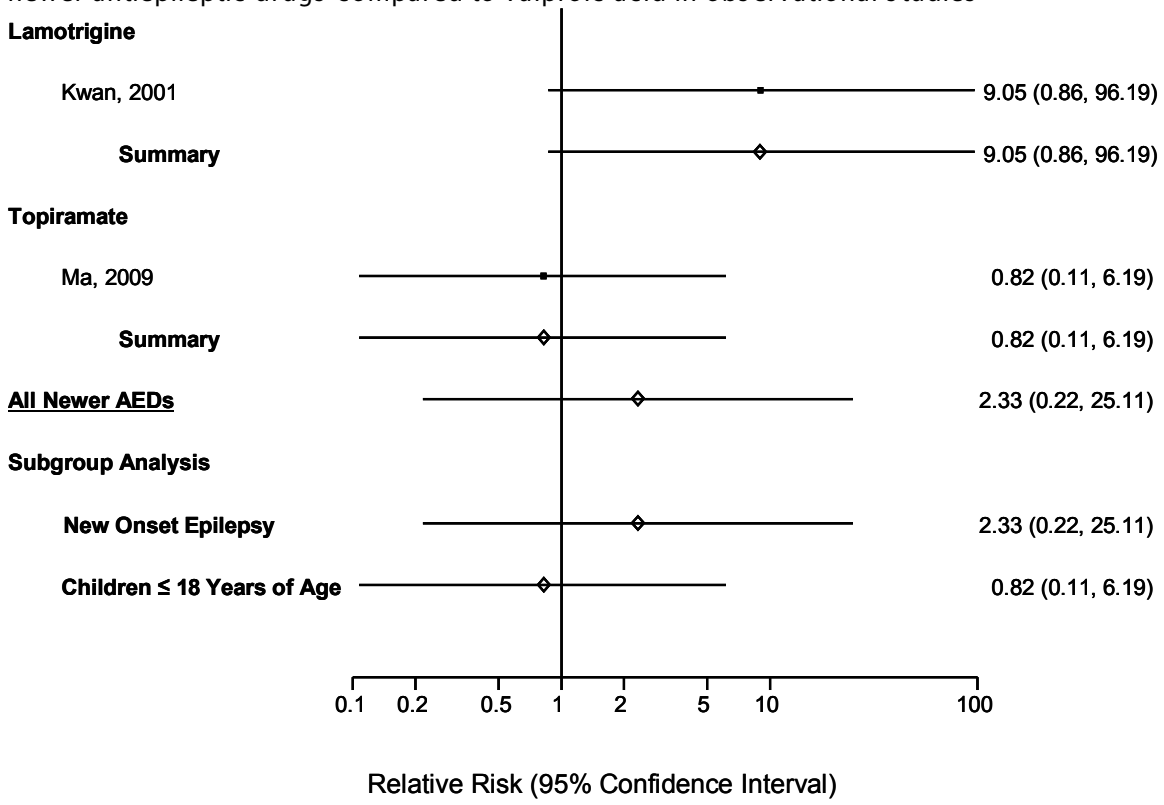
Figure 73. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs

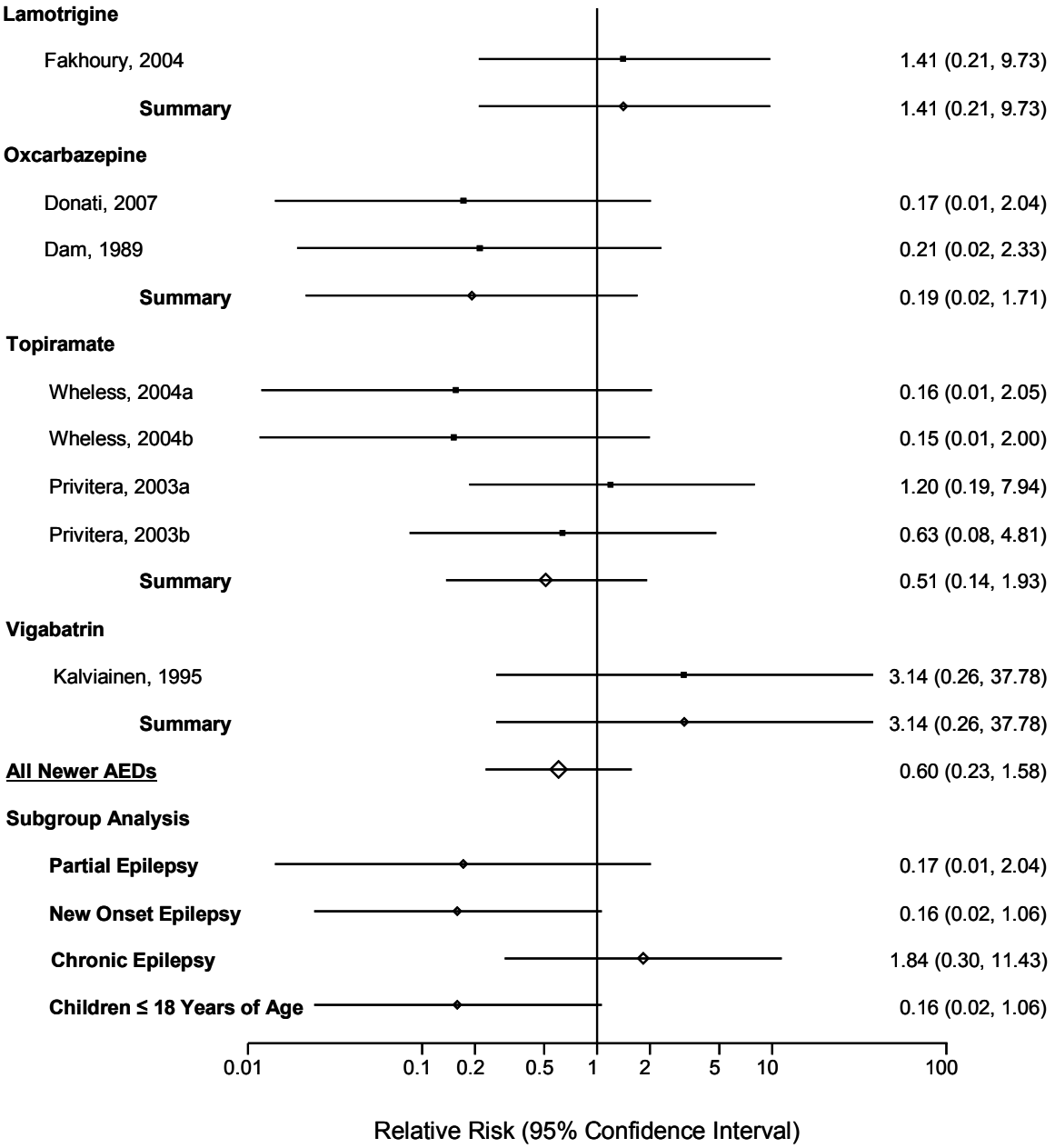
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 74. Composite forest plot of meta-analysis of skin rash in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in observational studies



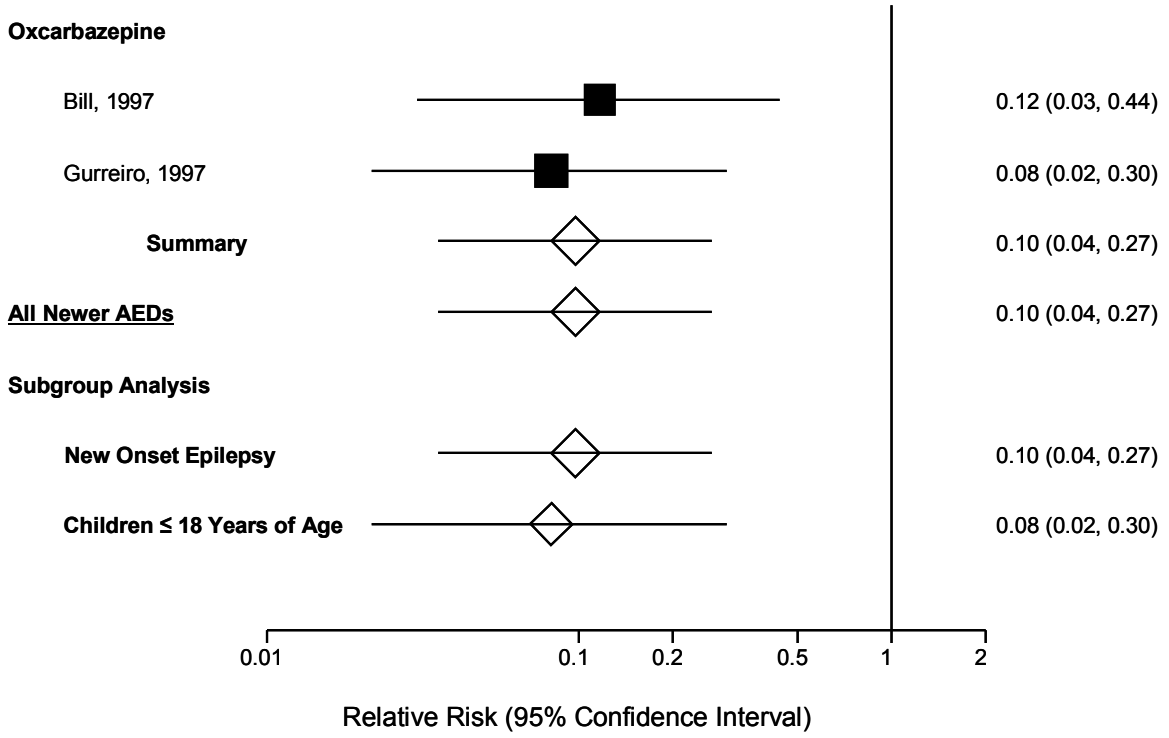
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 75. Composite forest plot of meta-analysis of alopecia in patients with epilepsy taking newer antiepileptic drugs compared to carbamazepine in controlled clinical trials



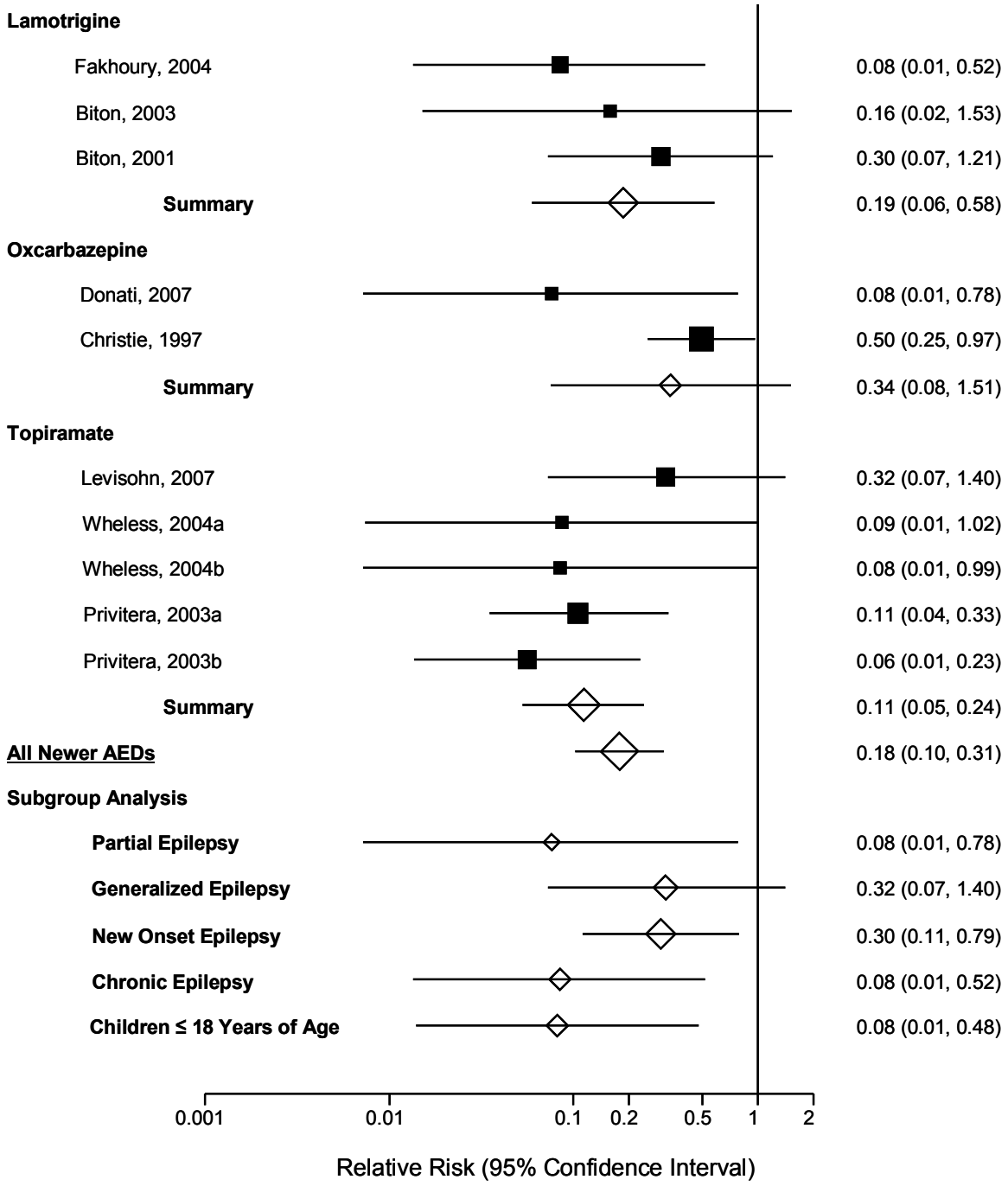
Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 76. Composite forest plot of meta-analysis of gum hyperplasia in patients with epilepsy taking oxcarbazepine compared to phenytoin in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.

Figure 77. Composite forest plot of meta-analysis of alopecia in patients with epilepsy taking newer antiepileptic drugs compared to valproic acid in controlled clinical trials



Legend: AEDs=antiepileptic drugs
Note: The squares represent individual point estimates. The size of the square represents the weight given to each study in the meta-analysis. Horizontal lines through each square represent 95 percent confidence intervals. The diamond represents the combined results. The solid vertical line extending from 1 is the null value. Lowercase letters represent study arms within the same trial.